

As. 126.101

Señor

**DIRECTOR DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

E.

S.

D.

REF: Expediente No. **13 -264.524-** solicitud de patente de invención a favor de **ABBOTT HEALTHCARE PVT. LTD.** Título: **COMPOSICIÓN ORAL LÍQUIDA QUE COMPRENDE SODIO DIVALPROEX Y PROCESO PARA PREPARAR LA MISMA.**

RECURSO DE REPOSICIÓN

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante, manifiesto a usted que debidamente notificado de la Resolución No. 64597 del 17 de Septiembre de 2015, interpongo contra ella en debido término, **RECURSO DE REPOSICIÓN**, para que sea revocada en su totalidad, y en su lugar se conceda el Privilegio de Patente, para el objeto de la solicitud en referencia.

Respaldo el RECURSO en los siguientes

HECHOS

1. La resolución No. 64597 arriba citada niega el Privilegio exclusivo de Patente de Invención para el objeto de la solicitud de la referencia, considerando que el capítulo reivindicatorio carece de novedad y nivel inventivo. Lo anterior, de acuerdo con las siguientes consideraciones.

i. Determinación del Estado de la Técnica

Consultadas las fuentes de información con que se cuenta se encontraron los siguientes documentos, que anticipan el objeto de esta solicitud.

No	Documento	Título	Fecha de publicación
D1	US2002115718	"Divalproex sodium tablets"	22/agosto/2002
D2	WO2009142968	"Valproic acid salts"	26/noviembre/2009

Considera el examinador que la presente invención no cumple con los requisitos de novedad y nivel inventivo en vista de los documentos D1 y D2.

RESUELVE

ARTÍCULO PRIMERO: Denegar la patente de invención a la creación titulada **"COMPOSICIÓN ORAL LÍQUIDA QUE COMPRENDE SODIO DIVALPROEX Y PROCESO PARA PREPARAR LA MISMA".**

FUNDAMENTOS

Nos permitimos mostrar nuestro total desacuerdo frente a todas y cada una de las objeciones de la Resolución No. 64597 toda vez que en dicho análisis no se demostró de manera concluyente que la invención carecía de novedad y/o nivel inventivo. A continuación, me permito desvirtuar todas y cada una de las afirmaciones de su Despacho en contra de la novedad y el nivel inventivo de la invención y expuestas en la Resolución No. 64597.

Como primera medida es de notar que dadas las insistentes objeciones del señor Examinador en contra de la patentabilidad de la presente invención, el pliego reivindicatorio anteriormente vigente fue modificado. Por esta razón, remitimos a su Despacho un nuevo pliego reivindicatorio que consta de diez (10) reivindicaciones, las cuales han sido modificadas limitando el alcance de la materia anteriormente reclamada.

Debido a que dicho nuevo pliego reivindicatorio no excede de ninguna manera el alcance de las divulgaciones del capítulo descriptivo de la presente solicitud, solicitamos sea admitido a trámite y estudiado de ahora en adelante.

Así pues, nos permitimos señalar que tras la eliminación de las reivindicaciones 1 a 15, la nueva reivindicación independiente 1 define la invención de la siguiente manera:

“Una composición estable, caracterizada porque comprende:

- a) divalproex sódico de 2% p/v hasta 15% p/v de la composición;*
 - b) conservador de 0.01% p/v hasta 1.5% p/v de la composición;*
 - c) agente de amortiguador de 0.05% p/v hasta 1.5% p/v de la composición;*
 - d) edulcorante de 0.1% p/v hasta 85% p/v de la composición;*
 - e) opcionalmente, uno o más agentes de coloración y/o saborización;*
- y en donde dicha composición está en forma oral líquida.”*

Adaptado del nuevo pliego reivindicatorio

Tal y como podrá notar el señor Examinador, la composición ahora reivindicada define tanto los componentes como la proporción de los mismos, alcanzando de esta manera una caracterización muy precisa y en todo caso distinguible de las divulgaciones del estado de la técnica.

Adicionalmente, vale la pena destacar que el preámbulo de la invención fue modificando, trasladando la expresión ***“y en donde dicha composición está en forma oral líquida”*** a la parte caracterizante de la reivindicación pues la misma representa una característica técnica esencial y distintiva de la invención, como será comentado más adelante.

Aclarado lo anterior, nos permitimos expresar que la composición descrita en esta nueva reivindicación 1 no se ve de ninguna manera anticipada por las enseñanzas del documento D1, referencia citada como arte previo capaz de afectar la novedad de la presente invención.

Más específicamente, insistimos en que la materia revelada en el documento D1 no es siquiera comparable con la presente invención pues, en lugar de divulgar una **composición oral líquida**, esta anterioridad da a conocer una **tableta de divalproex sódico**, la cual evidentemente representa una forma farmacéutica distinta a la que atañe a la composición reivindicada.

En este sentido, nos permitimos expresar que las enseñanzas de esta anterioridad se enfocan en describir un **protocolo para formular una tableta de liberación retardada**, tal y como demuestra el siguiente fragmento:

EXAMPLE 1

Divalproex Sodium Delayed Release Tablets

[0061] 1. Preparation of Neutralized Divalproex Sodium Solution

[0062] Neutralized divalproex sodium solution is prepared by dissolving 260 kg of divalproex sodium in about 189.49 kg purified water with 33.51 kg of sodium hydroxide. The solution is adjusted to pH 10.8 ± 0.3 with 20% sodium hydroxide solution and adjusted to 483 kg with additional purified water to yield divalproex sodium solution with $50 \pm 3\%$ valproic acid activity.

[0063] 2. Preparation Divalproex Sodium Granules

[0064] 11.52 kg of the neutralized divalproex sodium solution is diluted with 14.57 kg of isopropyl alcohol. The diluted solution is then sprayed onto 5.15 kg anhydrous lactose in a fluid bed processor with a Wurster apparatus at product temperature of $42-48^\circ \text{C}$. and spray rate of 40-80 ml/min to form divalproex sodium granules. The granules are sized through a sifter equipped with 16 mesh screen.

[0065] 3. Blending and Tableting

[0066] The sifted divalproex sodium granules, 102.51 kg, are blended with 3.987 kg crospovidone, 5.695 kg anhydrous lactose, 0.57 kg colloidal silicon dioxide and 1.139 magnesium stearate to yield divalproex sodium blend. The divalproex sodium blend is then compressed to yield divalproex sodium tablets having a weight of 871 to 983 mg, with 500 mg valproic acid activity.

[0067] 4. Seal Coating and Enteric Coating

[0068] The divalproex sodium tablet cores, 108.3 kg, are seal coated in a coating pan with a suspension of 1.34 kg hydroxypropylmethylcellulose, 1.34 kg hydroxypropylcellulose and 0.67 kg magnesium stearate in 30.15 kg ethanol. The seal coated tablets, 110.71 kg, are coated in a coating pan with a solution of 7.181 kg cellacefate (CAP) and 1.795 kg diethyl phthalate in 31.42 kg isopropyl alcohol and 31.42 kg acetone to yield enteric coated, delayed-release divalproex sodium tablets.

[0069] 5. Color Coating and Polishing

[0070] The enteric coated tablets, 118.51 kg, are color coated with a solution of 3.291 kg Opadry Blue and 0.037 kg Vanillin in 29.62 kg water. The color coated tablets are then polished by sprinkling 0.037 kg candelilla wax powder onto the tablets while the pan is rotating to yield color-coated divalproex sodium delayed-release tablets, with 500 mg valproic acid activity.

Adaptado del documento D1; Ejemplo 1, párrafos [0061] a [0070]

A partir de esta información tomada del documento D1, resulta evidente que:

- El Ejemplo 1 de dicha anterioridad se encuentra dirigido al desarrollo de una **tableta de liberación retardada de divalproex sódico**;
- La etapa citada por el señor Examinador (párrafo [0062]) corresponde a la preparación de una solución neutralizada de divalproex sódico, la cual representa el primer paso del protocolo en mención;
- El párrafo [0064] aborda la preparación de gránulos de divalproex sódico;
- El párrafo [0066] aborda las etapas de mezcla y tableteado;
- El párrafo [0068] aborda las etapas de recubrimiento de sellado y recubrimiento entérico; y
- El párrafo [0070] aborda las etapas de recubrimiento de color y pulido.

Considerando lo anterior, solicitamos sea reconocido que las enseñanzas del documento D1 no guardan ninguna relación con el objeto de la presente invención puesto que la *"preparación de una solución de divalproex sódico"* representa apenas una etapa involucrada con la formulación de una tableta de liberación retardada, lo cual no es de ninguna manera equivalente o semejante al desarrollo de una composición oral líquida como se propone a lo largo de esta solicitud.

Más aún, reiteramos que el párrafo [0062] citado por el señor Examinador enseña únicamente la preparación de una solución necesaria para elaborar un granulado que, mediante la ejecución de una serie de etapas subsecuentes, será transformado en una tableta de liberación retardada de divalproex sódico y que, por tanto, **no equivale en ningún momento a una composición oral líquida** como la de la presente invención.

Asimismo, es nuestra intención señalar que la solución de divalproato sódico en hidróxido de sodio al 20% mencionada en el documento D1 no es equivalente o siquiera comparable con la **formulación líquida** de dicho fármaco que propone la presente invención, la cual evidentemente cumple con una serie de requisitos biofarmacéuticos necesarios para que su administración sea además de eficaz, segura.

Inclusive, es de notar que dicha solución de divalproato sódico en hidróxido de sodio al 20% exhibe un **pH de 10.8 ± 0.3** que de ninguna manera resulta aceptable en caso de que se tratara de una solución administrable por vía oral, hecho que demuestra que no hay ningún motivo por el cual las divulgaciones del documento D1 puedan ser comparables con la presente invención.

A pesar de esta argumentación, y asumiendo que el señor Examinador insista en que las enseñanzas del documento D1 pueden desvirtuar la novedad de la presente invención así no exista ningún vínculo entre las mismas y el objeto aquí reivindicado, llamamos la atención sobre el hecho de que, como se mencionó anteriormente, el alcance de la presente invención fue restringido a fin de establecer una distinción completamente evidente entre esta y las divulgaciones del arte previo.

Puntualmente, la nueva reivindicación 1 indica de manera explícita cada uno de los componentes de la composición junto a sus respectivas cantidades y proporciones, lo cual no se ve de ninguna manera anticipado por las enseñanzas del citado documento D1.

Teniendo en cuenta entonces que dicha referencia carece de enseñanzas relacionadas con una **composición oral líquida** que comprende:

a) ~~divalproex sódico~~ **divalproex sódico de 2% p/v hasta 15% p/v de la composición;**

- b) conservador de 0.01% p/v hasta 1.5% p/v de la composición;
- c) agente de amortiguador de 0.05% p/v hasta 1.5% p/v de la composición;
- d) edulcorante de 0.1% p/v hasta 85% p/v de la composición;
- e) opcionalmente, uno o más agentes de coloración y/o saborización;

o cualquier información que pueda ser interpretada por el señor Examinador como semejante a dicha caracterización, concluimos que el documento D1 no perjudica de ninguna manera la novedad de la presente divulgación ni representa el debido soporte documental a la objeción manifestada por su Despacho.

Así las cosas, solicitamos respetuosamente sea retirada la objeción que cuestiona la novedad de este nuevo pliego reivindicatorio en vista del documento D1, la cual en nuestro concepto carece de todo fundamento ya que, como hemos demostrado, dicha referencia ignora completamente la caracterización que da lugar a la presente invención.

Igualmente, partiendo de que ni el documento D1, ni cualquier otra referencia perteneciente al estado de la técnica anticipa una composición oral líquida de divalproex sódico como la que aquí se reivindica, ni cada una de sus características técnicas, solicitamos sea reconocida su total novedad.

Ahora bien, respecto al cumplimiento del requisito de nivel inventivo consideramos oportuno manifestar nuestro desconcierto ya que pese a haber defendido la patentabilidad de la presente invención mediante argumentos y evidencias contundentes en la pasada actuación, permanecen las objeciones en contra del mismo.

De la mano con lo anterior, insistimos en que el examen conducido por su Despacho evidencia un enfoque altamente subjetivo en donde el señor Examinador se limita a identificar las características técnicas que supuestamente dan origen a la presente invención en diferentes documentos del estado del arte, cuando en realidad no existe ninguna instrucción o motivación concreta que dirija al versado en la materia a alcanzar, de manera precisa y exacta, la materia que aquí se reivindica.

Por esta razón, nos permitimos presentar nuevamente nuestro análisis del estado de la técnica definido por los documentos D1 y D2, haciendo especial énfasis en las diferencias existentes entre tales anterioridades y la presente invención, y demostrando de este modo el cabal cumplimiento del requisito de nivel inventivo por parte de esta última.

Tomando como punto de partida la argumentación expuesta en torno a la novedad de la presente invención, es de notar que el documento D1 guarda total silencio respecto al desarrollo de una **composición oral líquida** y que los métodos allí descritos se oponen completamente a la metodología necesaria para tal fin, razón por la que afirmamos que dicha anterioridad no logra desvirtuar la patentabilidad de la presente invención.

Dicho esto, insistimos que contrario a lo afirmado por el señor Examinador, el documento D1 se encuentra orientado al diseño y desarrollo de **tabletas de liberación retardada de divalproex**, cuya realización se ejemplifica en todos y cada uno de los Ejemplos 1 a 10 de la referencia en mención, tal y como señalamos anteriormente.

En conexión con lo anterior, consideramos que la información revelada en el documento D1 no constituye una aproximación al objeto de la presente invención sino que **aleja** al versado en la materia de la misma al promover el desarrollo de formulaciones orales sólidas de divalproex, lo cual **se opone** de manera evidente a la materia reclamada a lo largo de este nuevo pliego reivindicatorio.

Además, es evidente que si el versado en la materia se basara en las enseñanzas de la referencia en mención, este contaría con todo el respaldo y motivación necesaria para crear una **tableta de liberación retardada de divalproex** y no una **composición oral líquida** como la de la presente invención, razón por la que insistimos en que el documento D1 no representa soporte documental suficiente a la insistente objeción del señor Examinador.

Dejando de lado estos hechos y centrándonos en el examen de patentabilidad llevado a cabo, encontramos que las comparaciones hechas a lo largo del mismo exponen de manera clara las deficiencias del documento D1 frente a la presente invención, dentro de las cuales se destaca lo siguiente:

- El documento D1 no menciona la presencia de un conservador;
- El documento D1 no menciona la presencia de un edulcorante;
- El documento D1 no menciona la presencia opcional de un agente de coloración y/o saborización.

Sin embargo, dada las modificaciones realizadas a la nueva reivindicación 1, es preciso señalar que la expresión ***“y en donde dicha composición está en forma oral líquida”*** representa ahora una característica técnica esencial de la presente invención, en torno a la cual es posible comprender el **aporte** que la misma representa al campo técnico del desarrollo de nuevas y mejores alternativas farmacéutica.

Con base en lo anterior, insistimos en que el documento D1 ignora completamente el concepto técnico inventivo que da lugar a la presente invención y por tanto no podría sugerir o instruir su desarrollo al versado en la materia, fallando en definitiva en perjudicar su patentabilidad.

Pese a que en nuestro concepto las diferencias existentes entre la referencia en mención y el objeto de la presente solicitud son evidentes, el señor Examinador acude a un segundo documento afirmando que este solventa las falencias del citado documento D1 y por tanto, permite al versado en la materia alcanzar la presente invención de manera obvia.

Frente a esto, es nuestra intención señalar que el documento D2 aborda el estudio de una serie de sales de ácido valproico y su utilidad en el campo farmacéutico enumerando posibles formas farmacéuticas en las cuales dicho fármaco podría adecuarse pero sin ahondar en el desarrollo de las mismas, razón por la que afirmamos que esta referencia tampoco pone a disposición del versado en la materia la información necesaria para sustentar la objeción emitida de manera insistente por su Despacho.

Del mismo modo, cabe anotar que las enseñanzas del documento D2 son muy limitadas en lo que respecta al desarrollo de diversas formas farmacéuticas pues únicamente abordan nociones básicas que pertenecen al conocimiento estándar de cualquier versado en la materia y no aportan una orientación puntual que pueda relacionarse con el objeto de la presente invención.

Por esta razón, consideramos que la anterioridad descrita en el documento D2 no solventa de ninguna manera las falencias del ya analizado documento D1 ni constituye soporte documental suficiente que permita atribuirle obviedad a la presente invención, hecho que solicitamos sea reconocido mediante el retiro de la respectiva objeción.

Así pues, dado que el documento D2 no da a conocer ninguna **composición oral líquida**; métodos para su obtención o cualquier tipo de información útil para que el versado en la materia pueda alcanzar la presente invención de manera obvia, concluimos que esta referencia no resulta relevante para el presente análisis de patentabilidad.

En resumidas cuentas, solicitamos sea reconocido que el documento D1 **aleja** al versado en la materia de la presente invención pues divulga una tableta de liberación retardada de divalproex que nada tiene que ver con el objeto de la presente solicitud, y que adicionalmente el documento D2 falla por completo en brindar instrucciones o sugerencias que motiven el desarrollo de la presente invención o que complementen de alguna manera lo divulgado en el documento D1; razones por las cuales solicitamos sea retirada la objeción por nivel inventivo que perjudica la patentabilidad de la invención ahora reivindicada.

Por lo anterior, concluimos que los documentos D1 y D2 no constituyen el debido soporte documental a la objeción del señor Examinador bajo la cual el privilegio de patente es denegado a la presente solicitud, ya que esta no podría haber sido derivada de manera obvia a partir de lo divulgado en tales referencias.

En complemento de la argumentación precedente, solicitamos sea reconocido en esta instancia el importante aporte que simboliza la presente invención al representar **la primera y única composición líquida para administración oral de valproex**, hecho que como bien reconocerá el versado en la materia, resulta benéfico y valioso en el campo técnico porque pone a disposición del mismo una forma farmacéutica mucho más favorable y que puede adecuarse a cualquier tipo de esquema terapéutico.

Concordantemente, destacamos que las **composiciones orales líquidas** gozan de beneficios y ventajas en comparación con las composiciones orales sólidas –como por ejemplo, aquellas descritas en el documento D1–, dentro de las cuales se puede mencionar:

- Mayor aceptabilidad por parte del paciente;
- Mayor facilidad de deglución, por lo que puede ser administrada tanto a bebés, adultos y ancianos, como a personas con impedimentos para deglutir como el estado de coma o condiciones gastroesofágicas sin los inconvenientes asociados a las formas farmacéuticas sólidas; y
- Mayor disponibilidad del fármaco, pues este se encuentra soluble y no debe someterse a procesos biofarmacéuticos y farmacodinámicos complejos para que el mismo sea liberado, como ocurre en el caso de las formulaciones sólidas.

A pesar de que este hecho fue expuesto en la pasada actuación, el señor Examinador afirma que la descripción de la presente solicitud no incluye información que sustente dichas ventajas ni que permita asociarlas de manera específica a la invención que aquí se reivindica.

Ante esto es preciso aclarar que las ventajas en mención constituyen apenas algunos de los aspectos favorables que representan las formulaciones orales líquidas en comparación con las formulaciones orales sólidas, lo cual es evidente a ojos de cualquier persona normalmente versada en la materia en ejercicio de la profesión farmacéutica orientada al diseño y desarrollo de nuevas y mejores formulaciones para el beneficio del hombre.

No obstante, hemos recopilado una serie de referencias (Anexos 1 a 11 adjuntos al presente memorial en medio digital) en torno a las cuales procedemos a exponer todas y cada una de las ventajas relacionadas con la presente invención, así como los desafíos y retos que su desarrollo implica en el campo farmacéutico de la formulación y adecuación de un medicamento existente en nuevas formas farmacéuticas.

Como comentario preliminar, consideramos pertinente abordar el problema técnico que enfrenta el desarrollo farmacéutico en este campo técnico particular dada la constante necesidad de disponer de diversas maneras y posibilidades para administrar un fármaco a un paciente, en línea con la diversidad propia de los grupos de personas a tratar.

En este sentido, aclaramos que más allá de proporcionar mecanismos para la entrega segura y conveniente de un fármaco en la dosis que es debida, las diferentes formas farmacéuticas cumplen con roles muy importantes y esenciales, a saber:

- Protección de la sustancia activa de la degradación o posibles daños ocasionados por el medio ambiente;
- Protección de la sustancia activa de las interacciones que tienen lugar al interior del organismo, las cuales pueden generar igualmente daño o degradación;
- Adecuación organoléptica al ocultar sabores y/u olores desagradables;
- Proporcionar un vehículo líquido para el suministro de sustancias insolubles o inestables de otro modo;
- Intervenir la tasa de entrega de la sustancia activa, modificando el tiempo de liberación de la misma;
- Optimizar el efecto de la sustancia activa en el caso en el que la administración de la misma deba tener lugar en un sitio tópico o superficial;
- Optimizar la entrega de fármacos en sitios particulares de acción, como es el caso del recto o la vagina; y
- Permitir la administración de una sustancia activa directamente en el torrente sanguíneo.

A la luz de lo anterior, solicitamos respetuosamente al señor Examinador tener en cuenta que la presente invención, al ser **la primera y única composición líquida para administración oral de valproex**, tiene un valor considerable dado el contexto aquí expuesto y por tanto, más allá de cumplir con los requisitos de novedad y nivel inventivo, resulta completamente meritoria del privilegio que aquí se solicita.

De la mano con lo anterior, afirmamos que cada una de las formas farmacéuticas disponibles en la actualidad constituye una **alternativa independiente** que goza de características físicas, químicas y farmacéutica propias, lo cual da lugar a una serie de consideraciones que la persona versada en la materia debe tener en cuenta al momento de decidir desarrollar un nuevo producto farmacéutico.

El siguiente fragmento enuncia de manera breve los principales aspectos a tener en cuenta en el desarrollo general de nuevas formas farmacéuticas:

“El correcto diseño y formulación de una forma de dosificación requiere consideración de los aspectos físicos, químicos y biológicos característicos de todas las sustancias medicinales e ingredientes farmacéuticos a ser utilizados en la fabricación del producto. Los materiales medicinales y farmacéuticos deben ser compatibles uno con el otro para producir un medicamento que sea estable, eficaz, atractivo, fácil de administrar, y seguro. El producto debe ser fabricado con las medidas apropiadas de control de calidad y envasados en recipientes que mantengan la estabilidad del producto.”

Adaptado del Anexo 1, página 90

De acuerdo con lo anterior, afirmamos que el proceso de formulación de una nueva forma farmacéutica para un medicamento determinado implica definitiva y necesariamente la aplicación de la habilidad inventiva propia del versado en la materia, la cual rodea todos los procedimientos relacionados con asegurar la **estabilidad, eficacia, aceptabilidad y seguridad** de dicha nueva forma, tal y como describen Zhou y Qiu (2010) (Anexo 2) en el siguiente fragmento:

“La estabilidad es un atributo crítico de la calidad del producto que se relaciona directamente con la potencia, pureza, eficacia, y seguridad de un producto farmacéutico a lo largo de su vida útil. Para la mayoría de sustancias farmacológicas, la estabilidad del producto farmacéutico no depende únicamente

de las propiedades del fármaco, sino también del diseño de formulación y procesamiento."

Adaptado del Anexo 2, página 79

De este modo, existen preceptos que deben ser cumplidos por todas y cada una de las formas farmacéuticas a desarrollar, los cuales son conocidos en el campo técnico como los cinco tipos de estabilidad que se exponen a continuación:

1. **Química:** Relacionada con que cada ingrediente activo se mantenga íntegro en términos químicos y demuestre una potencia congruente con la esperada dentro de los límites especificados.
2. **Física:** Las propiedades físicas de una forma farmacéutica determinada, entre ellas apariencia, palatabilidad, uniformidad, disolución y suspensibilidad, deben mantenerse.
3. **Microbiológica:** La condición de esterilidad o resistencia al crecimiento microbiano debe mantenerse dentro de los límites especificados, para lo cual es útil y válido en algunos casos hacer uso de agentes antimicrobianos.
4. **Terapéutica:** No deben haber cambios en el efecto terapéutico de una sustancia activa.
5. **Toxicológica:** No deben haber aumentos significativos del efecto tóxico atribuido a una sustancia activa.

Adaptado del Anexo 1, página 112

Es así que una de las prioridades de la persona normalmente versada en las prácticas de formulación farmacéutica es velar por cumplir y mantener los requisitos intrínsecos de dichas cinco diferentes estabilidades, lo cual a pesar de representar una labor rutinaria y de cumplimiento obligatorio, implica evidentes retos que involucran, sin lugar a dudas, la aplicación de la habilidad inventiva.

Contextualizando ahora esta introducción al estudio de la patentabilidad de la presente invención, es de notar que las divulgaciones del estado de la técnica únicamente abordan el estudio y desarrollo de composiciones orales sólidas que, a pesar de representar una alternativa terapéutica válida, vigente y de utilidad; **no logran desvirtuar la patentabilidad de la presente invención** dadas las enormes diferencias existentes en el desarrollo de las mismas.

Como muestra de ello, procedemos a analizar en detalle todas las consideraciones relacionadas con las formas farmacéuticas sólidas –es decir, aquellas conocidas en el arte previo relativo a la presente invención–, abordando posteriormente el estudio de los retos y desafíos involucrados en el desarrollo de una **forma farmacéutica líquida** como es el caso de la presente invención.

Así las cosas, definimos una formulación sólida como una mezcla compleja de múltiples componentes que conforman una variedad de fases sólidas y que son seleccionados gracias a la aplicación sistemática de principios, conceptos y procesos de diseño específicos para la naturaleza de estas composiciones.

Como parte del desarrollo de este tipo de composiciones, la persona versada en la materia tiene que tener en cuenta una serie de propiedades, tales como la **solubilidad, dosis, velocidad de disolución, permeabilidad, estabilidad, deformación, flujo y propiedades de compactación**, las cuales en definitiva definen la calidad, seguridad y eficacia de la misma.

Sin embargo, es común encontrar cierta relación entre tales propiedades de las formulaciones sólidas y las propiedades intrínsecas de las sustancias activas, las cuales por tanto pueden determinar la facilidad con que un fármaco puede ser absorbido a lo largo del tracto gastrointestinal (biodisponibilidad) o cuánto tiempo puede ser almacenado un producto (estabilidad), por mencionar algunos ejemplos.

Lastimosamente, en el campo técnico se ha encontrado que la mayoría de sustancias activas no cuentan con un perfil consistente de propiedades físicas, químicas, biofarmacéuticas y mecánicas sino que su comportamiento es más bien irregular e impredecible, siendo esta la razón principal por la que resulta imposible aplicar

conceptos simples de formulación al desarrollo de nuevas formas farmacéuticas, requiriendo por tanto de estrategias destinadas a lograr tal fin.

A este respecto, Zhou y Qiu (2010) (Anexo 2) ejemplifican los siguientes casos:

"Por ejemplo, muchos fármacos de altas dosis carecen de propiedades de fluidez y compactación aceptables. Muchos fármacos en dosis bajas (por ejemplo, miligramos o microgramos) pueden no tener la densidad de partícula, forma y distribución de tamaño deseadas para producir mezclas de polvo consistentemente uniformes especialmente a escalas mayores. Algunos fármacos pueden ser químicamente lábiles. Algunos fármacos son poco solubles en agua y desfavorecen la absorción oral. Suele ser necesario aplicar un diseño adecuado de los procesos de formulación y fabricación que abordan propiedades problemáticas de drogas."

Adaptado del Anexo 2, página 76

Como si fuera poco, el desarrollo de una nueva forma farmacéutica sólida también debe considerar que cada uno de los excipientes incorporados en pro de la adecuación de la misma cuenta con propiedades físicas, químicas y mecánicas características y únicas que, evidentemente, deben ser analizadas durante el proceso de formulación pues también influyen sobre la calidad, seguridad y eficacia del producto final.

Debido a esto, se hace necesario implantar mecanismos racionales de formulación y diseño de procesos que permitan entender las propiedades –solubilidad, velocidad de disolución, permeabilidad, estabilidad y propiedades mecánicas– los componentes a incluir en una nueva composición, es decir, de ingredientes activos y excipientes, haciendo posible entender a manera en como dichas propiedades influyen la **calidad, desempeño y procesamiento** de las formas farmacéuticas sólidas.

Ahora bien, dejando de lado las consideraciones farmacotécnicas que atañen a las formas farmacéuticas sólidas, es preciso destacar que las aplicaciones terapéuticas de las mismas se ven en ocasiones muy limitadas puesto que existen grupos de pacientes a quienes simplemente no les puede ser suministrada una tableta o una cápsula, limitando de este modo la utilidad de este tipo de formulaciones.

Tal es el caso de los pacientes pediátricos y geriátricos, los cuales dada su condición natural no se encuentran en la capacidad de **deglutir** una tableta o una cápsula, hecho que genera la necesidad de (i) adecuar una forma sólida para la administración a este tipo de pacientes, o bien (ii) diseñar una forma farmacéutica oral líquida *de novo*. El análisis de estas dos estrategias se desarrolla a continuación:

(i) Adecuación de formas farmacéuticas extemporáneas:

En el primer caso, la adecuación de una forma farmacéutica sólida a líquida –conocida también en el campo técnico como preparación extemporánea– surge como solución a la necesidad de proporcionar a un paciente un fármaco que no se encuentra disponible en forma de administración oral líquida.

De acuerdo con Woods (Anexo 3), los métodos más empleados en la actualidad consisten en moler un determinado número de tabletas con la ayuda de un mortero, obteniendo así un polvo fino que posteriormente es mezclado con pequeños volúmenes de agua para formar una suspensión. A dicha suspensión se le adicionan excipientes tales como conservantes antimicrobianos, agentes de suspensión y agentes saborizantes a fin de obtener un producto final medianamente aceptable.

Adicionalmente, la preparación de formulaciones extemporáneas debe afrontar serios problemas, entre ellos:

- **Inestabilidad química**, ya que la adecuación a forma líquida expone los fármacos a reacciones de degradación tales como hidrólisis, oxidación y reducción subsecuentes a los cambios de pH o temperatura, por ejemplo;
- **Inestabilidad física**, dada la facilidad que presentan las suspensiones obtenidas para sedimentar;
- **Baja solubilización del fármaco** partiendo de su pobre solubilidad, o de que la extracción a partir del material sólido sea parcial o incompleta;
- **Susceptibilidad a la contaminación microbiológica** dado su alto contenido acuoso y la modificación y manipulación de su forma farmacéutica inicial;

- **Mala apariencia**, la cual se deriva de la necesidad de suspender las partículas trituradas de la forma farmacéutica original dada la baja solubilidad del fármaco, o bien de la presencia de contaminación microbiológica;
- **Bajo tiempo de vida útil**, ocasionada por los mencionados problemas de estabilidad microbiológica, física y química que conlleva la adecuación de la forma farmacéutica inicial;
- **Falta de documentación** respecto al comportamiento de formulaciones adecuadas extemporáneamente, lo cual da lugar a desconocimiento de las propiedades de las mismas; y
- **Interacciones causadas por los excipientes**, los cuales también son susceptibles de sufrir alteraciones fisicoquímicas con la adecuación de la fórmula farmacéutica original.

Adaptado de Anexo 3, páginas 4 a 8

En relación con algunos de estos problemas, cabe anotar que hasta el momento se han llevado a cabo numerosos estudios más profundos enfocados en determinar los motivos y mecanismos involucrados con la baja estabilidad de dichas preparaciones extemporáneas, tal y como expone Gerhardt (2009) (Anexo 4) a través de su estudio sobre el impacto del agua en forma de humedad sobre un producto farmacéutico terminado.

En este sentido, Gerhardt indica que el análisis de un amplio rango de propiedades químicas, físicas y microbiológicas evaluadas a una forma farmacéutica sólida antes y después de someterle a condiciones de alta humedad permite determinar los cambios inducidos por tal situación, estableciendo por tanto la susceptibilidad de dicho producto farmacéutico frente a la presencia de agua en ambiente.

Como resultado de tales estudios, Gerhardt afirma que las interacciones causadas por la presencia de agua en contacto con formulaciones orales sólidas en forma de tabletas comprenden:

- Alteración de la estabilidad del producto;

- Compactación de la tableta;
- Granulación húmeda causada por la humedad;
- Presencia de efervescencia en la superficie de la tableta;
- Propiedades de flujo sólido; y
- Crecimiento microbiano.

Adaptado del Anexo 4, página 61

Teniendo en cuenta lo anterior, es evidente que las consecuencias y problemas derivados de la adecuación extemporánea de tabletas a suspensiones o soluciones se relaciona específicamente con el hecho de que dicha transformación implica necesariamente el uso de un **vehículo acuoso**, hecho que promueve una condición de susceptibilidad al daño físico, químico y microbiológico y que, en todo caso, resulta desfavorable.

Adicional a esto, es de notar que Patel *et al.* (2011) (Anexo 5) exponen mediante ejemplos puntuales las desventajas ocasionadas al adecuar de forma extemporánea un medicamento en forma sólida para su administración por vía oral a pacientes pediátricos. Concretamente, Patel *et al.* citan el siguiente caso:

“Stewart y Tucker encuestaron hospitales australianos y mostraron que 116 medicamentos fueron formulados extemporáneamente en 270 diferentes formulaciones para uso pediátrico. Los problemas frecuentes identificados en esta encuesta incluyen disfrazar el sabor desagradable, lograr la uniformidad de dosis y la falta de datos químicos y físicos de estabilidad. Esta falta de información sobre estabilidad es un problema común y se han publicado formularios de formulaciones extemporáneas en un intento de proporcionar alguna orientación sobre la preparación de líquidos orales pediátricos”

Adaptado de Anexo 5, página 87

Como bien se mencionó anteriormente, la estrategia de adecuar una forma farmacéutica sólida a líquida surge como respuesta a la necesidad de administrar determinados medicamentos a grupos de pacientes específicos para quienes la formulación original no resulta aplicable, como es el caso de la población pediátrica.

Tal y como indica el anterior fragmento, el **sabor desagradable, la baja uniformidad de la dosis y la falta de documentación respecto a la estabilidad de este tipo de preparaciones extemporáneas** constituyen limitaciones a la aplicabilidad de las mismas, lo cual genera a su vez la necesidad de disponer de **formas farmacéuticas de administración oral alternativas a las existentes** a fin de promover el fácil acceso a los medicamentos y terapias por parte de estas poblaciones.

En vista de la materia divulgada en los Anexos 4 y 5 correspondientes a estudios prácticos que demuestran **las limitaciones y aspectos negativos** asociados a la preparación de formulaciones extemporáneas, solicitamos sea reconocido que en el campo técnico existe la necesidad de disponer de formulaciones farmacéuticas de administración oral alternativas a las existentes, es decir, a las formas sólidas de divalproex descritas por los documentos D1 y D2; hecho que evidencia el **aporte** que simboliza la presente invención.

(ii) Desarrollo de formas farmacéuticas líquidas:

En lo que respecta a las formas farmacéuticas líquidas de administración oral como alternativa terapéutica a la administración de medicamentos en forma sólida a pacientes en las circunstancias ya comentadas, es preciso señalar que si bien las mismas cuentan con un amplio rango de ventajas –que expondremos más adelante–, su diseño y desarrollo representa en muchas ocasiones un **desafío mayor** que el que representa el desarrollo de una tableta o una cápsula.

En este orden de ideas, nos permitimos señalar que el proceso de formulación de una forma líquida oral se encuentra particularmente limitado por las propiedades intrínsecas del fármaco, las cuales definen tres grandes desafíos para el profesional dedicado a las labores de formulación farmacéutica que se resumen a continuación:

- (a) **Estabilidad** de la sustancia activa en solución;
- (b) **Solubilidad** de la sustancia activa en la medida requerida; y
- (c) **Condiciones organolépticas aceptables.**

En primer lugar, es de notar que la **estabilidad** es un factor muy relevante en la determinación del tiempo de vida útil de una composición, el cual a diferencia del caso de las formulaciones extemporáneas que se comentó anteriormente, debe ser garantizado de manera mandatoria en línea con los requerimientos de seguridad y eficacia que rigen las composiciones farmacéuticas.

Debido a esto, es labor del profesional dedicado al desarrollo de composiciones farmacéuticas proporcionar un vehículo de excipientes diseñado racionalmente que asegure que la sustancia activa no sufrirá cambios físicos o químicos una vez solubilizada en él durante todo el periodo de vida útil del producto final, lo cual no puede resultar de la simple selección y combinación de excipientes.

Por otra parte, es de notar que la **solubilidad** constituye el factor determinante tanto de la dosis como del volumen del producto final, haciendo inclusive necesaria la utilización de cosolventes o surfactantes como estrategia para lograr una composición estable, segura y eficaz.

En función de lograr una adecuada solubilización de la sustancia activa, el versado en la materia a cargo de la formulación de nuevas formas farmacéuticas líquidas debe tener en cuenta, en principio, las características físicas y químicas del fármaco, entre ellas **solubilidad, estabilidad en ciertos pHs, valores de pKa de los grupos funcionales reactivos**, las cuales representan el punto de partida para la adecuada selección de excipientes.

Más allá de lo anterior, no debe dejarse de lado que dada su naturaleza, las formulaciones líquidas orales deben mantener cierto grado de **aceptabilidad organoléptica** mediante la aplicación de estrategias de enmascaramiento de sabores desagradables, utilización de edulcorantes, colorantes y saborizantes, entre otras, ya que su administración exitosa depende principalmente de la adherencia que manifiesten los pacientes al tratamiento.

Derivado de estas consideraciones, una formulación líquida requiere de una variedad de excipientes que incluyen **vehículo, agentes solubilizantes, viscosantes, preservativos, endulcorantes, colorantes y saborizantes, buffers** o

amortiguadores, cosolventes, tensioactivos, entre otros, los cuales constituyen una mezcla compleja de agentes cuyo único objetivo es garantizar la (a) estabilidad, (b) solubilidad y (c) aceptabilidad de la forma farmacéutica final.

La finalidad de disponer de una selección tan meticulosa de ingredientes persigue el cumplimiento de un sinnúmero de funciones como el humedecimiento y solubilización del fármaco, estabilización del mismo en un vehículo líquido, ajuste de pH, ajuste de atributos como el color, el sabor y la viscosidad, por nombrar un ejemplo, manteniéndose **compatible, estable y sin dar lugar a cualquier tipo de reacción entre los mismos componentes**.

Así pues, concluimos que la selección de excipientes constituye un proceso racional guiado por las propiedades inherentes al fármaco que involucra de manera indiscutible la aplicación de la habilidad inventiva en pro de garantizar la **seguridad y eficacia de la nueva forma farmacéutica**.

A partir de este aspecto, surge una clara diferencia entre el desarrollo de las formas sólidas descritas por el arte previo y la presente invención, pues como es evidente, los documentos D1 y D2 no abordan en ningún momento el estudio de una **formulación líquida** ni mucho menos de cada uno de dichos excipientes, razón por la que los mismos no habrían podido guiar el diseño y desarrollo de la presente invención.

De hecho, llamamos la atención sobre el hecho de que el comportamiento de un fármaco en estado sólido como parte de una tableta, por ejemplo, no constituye una sugerencia sobre la **compatibilidad de dicho fármaco al ser incorporado como parte de una solución**.

A la luz de lo anterior, reiteramos que como bien se ha mencionado a lo largo del trámite de la presente solicitud, la invención aquí descrita representa **la primera y única composición líquida para administración oral de valproex** disponible actualmente, hecho que evidencia que en el arte previo no existe ningún tipo de información que el versado en la materia hubiera podido tomar como referencia para el desarrollo de la misma.

Asimismo, destacamos que en ausencia de formulaciones líquidas de valproex desarrolladas con anterioridad, el versado en la materia **no contaba con ningún tipo de instrucción o guía que sugiriera el comportamiento de este fármaco al ser incorporado en una composición líquida como la reivindicada**, razón por la que insistimos que en el campo técnico era completamente desconocido el desarrollo de esta invención.

En conexión con este hecho, solicitamos sea reconocido que el valor de la presente invención no se limita únicamente a proponer una combinación precisa de excipientes que dan lugar a una composición en forma líquida para ser administrada por vía oral; sino que gracias a ello, el campo técnico dispone ahora de información relacionada con el comportamiento de valproex al ser formulado como una composición líquida, lo cual da pie al desarrollo de muchas otras formulaciones de igual valor terapéutico.

Por lo anterior, resulta evidente que la obtención de una formulación líquida, ya sea solución, suspensión o emulsión, surge de la aplicación de esfuerzos y análisis rigurosos que involucran de manera necesaria la utilización de la habilidad inventiva pues se debe sortear un elevado número de obstáculos y desafíos para lograr cumplir con los mínimos estándares de aceptabilidad que rigen a este tipo de productos.

Consecuentemente, solicitamos al señor Examinador reconocer que la presente invención, más allá de no verse sugerida o anticipada por las enseñanzas de los documentos D1 o D2, representa un **aporte importante** al campo técnico pues implica el desarrollo de una nueva forma farmacéutica desconocida hasta el momento, la cual soluciona un problema técnico vigente hoy en día pese a la existencia de formas farmacéuticas sólidas del fármaco divalproex.

En complemento de la anterior argumentación, consideramos oportuno enumerar las **ventajas** asociadas con las formulaciones líquidas de administración oral, las cuales guardan estrecha relación con el desarrollo aquí descrito y su valor en el contexto técnico expuesto:

- Las formulaciones líquidas tienen **mayor alcance terapéutico** pues el acceso de las poblaciones geriátricas y pediátricas a las mismas no se ve de ninguna manera limitado, situación que sí ocurre en el caso de las formulaciones orales.
- La administración de un medicamento en forma líquida resulta **más conveniente** pues no hace necesario disponer de elementos adicionales, contrario a la administración de tabletas, cápsulas o grageas, las cuales deben ser necesariamente administradas con agua o algún otro líquido.
- Las formulaciones líquidas permiten un **mejor control de la dosificación** pues el fármaco se encuentra solubilizado/dispersado de manera uniforme, hecho que permite administrar cantidades precisas del fármaco independiente a la concentración del mismo en la forma farmacéutica. En el caso de las tabletas, resulta mucho más difícil dividir y re-dosificar la forma farmacéutica, lo cual limita igualmente su aplicabilidad terapéutica.
- En contraste con las formas sólidas de administración oral, las formas líquidas **no requieren de un tiempo de disolución**, por lo que estas últimas gozan de **más rápida absorción** a nivel del tracto gastrointestinal.
- Los esquemas terapéuticos fundamentados en la administración de formas farmacéuticas líquidas son por lo general preferidas por los pacientes, lo cual da lugar a **mayor adherencia terapéutica**, siendo menos probable que el paciente abandone el tratamiento.
- De la mano con lo anterior, la administración de formas farmacéuticas líquidas da lugar a su vez a un **mayor éxito terapéutico** dada la aceptabilidad del paciente por el mismo.

Adaptado del Anexo 6

A la luz de lo anterior, y considerando también cualquier otra ventaja adicional evidente a ojos del versado en la materia, asumimos demostrado por completo el valor de la presente invención, hecho que respalda por completo el cumplimiento del requisito de nivel inventivo por su parte.

Relacionado con los hechos aquí expuestos, solicitamos sea reconocido que la presente invención exhibe los siguientes indicios de la existencia de nivel inventivo, los cuales ratifican por completo la patentabilidad de la materia que aquí se reivindica:

- ***Problema técnico sin resolver antes de la invención***, dada la carencia de formulaciones líquidas de administración oral de divalproex.
- ***Superación de dificultades no resueltas por las técnicas rutinarias***, pues las estrategias de adecuación de formulaciones extemporáneas cuentan con claros problemas que ratifican la necesidad de disponer de formulaciones líquidas de administración oral de divalproex como las descritas por la presente solicitud.

Con base en lo anterior, concluimos una vez más que la objeción emitida por el señor Examinador bajo la cual se deniega el privilegio de patente a la presente solicitud carece completamente de fundamento dadas las **ventajas, aporte e indicios de nivel inventivo** que demuestra la invención aquí descrita.

Finalmente, dadas las falencias del arte previo expuestas a la luz de la argumentación aquí desarrollada, consideramos pertinente mencionar que el examen conducido por el señor Examinador evidencia un enfoque altamente subjetivo por cuanto se limita a identificar de manera aislada e inconexa los diferentes elementos que definen la composición reivindicada en dos documentos del estado de la técnica, sin que estos brinden instrucciones concretas respecto a **cómo** conseguiría el versado en la materia desarrollar una invención como la reivindicada sin la necesidad de aplicar su capacidad inventiva, más aún cuando no existe ningún vínculo entre las tabletas de liberación retardada del documento D1, las sales de ácido valproico del documento D2 y la composición oral líquida objeto de la presente solicitud.

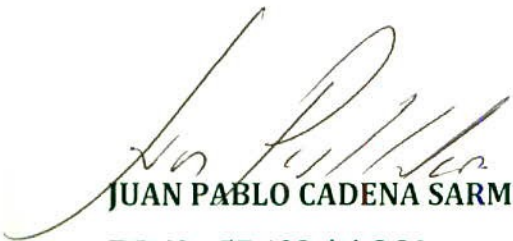
PETICIÓN

Por las razones anteriormente expuestas, solicito a ese despacho **REVOCAR** la decisión tomada mediante la Resolución No. 64597 del 17 de Septiembre de 2015 y tendiente a obtener la concesión del Privilegio de Patente de conformidad con los artículos 14 y 48 de la Decisión 486 de la comunidad Andina.

NOTIFICACIONES

Recibiré notificaciones en la Secretaría General de la Superintendencia de Industria y Comercio, o en su defecto, en mi oficina de Abogado, situada en la Calle 70ª No. 4-41 de esta ciudad de Bogotá.

Del Señor Director



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.S.J.

C.C. 80.410.337 de Usaquén

Calle 70 A No. 4 - 41

Dependencia Jerárquica: DEL PROPIEDAD INDUSTRIAL		Código	2000
Dependencia Productora: GRUPO DE NUEVAS CREACIONES		Código	2020
Tipo de Radicación: Entrada: ☒ Salida: ☐ Traslado: ☐ Convenio: ☐			
Radicador:			
DESCRIPCIÓN DE LA PRUEBA			
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Expediente: 13 - 264524 - 11 -		Solicitante / <i>Quejoso / Demandante / otros.</i>	
Prueba excluida: CO			
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SECTION II

DRUG DOSAGE FORM AND DRUG DELIVERY SYSTEM DESIGN

CHAPTER

4

Dosage Form Design: Pharmaceutical and Formulation Considerations

OBJECTIVES

After reading this chapter, the student will be able to:

1. List reasons for the incorporation of drugs into various dosage forms
2. Compare and contrast the advantages/disadvantages of various drug dosage forms
3. Describe the information needed in preformulation studies to characterize a drug substance for possible inclusion into a dosage form
4. Describe the mechanisms of drug degradation and provide examples of each
5. Describe the five types of drug instability of concern to the practicing pharmacist
6. Summarize approaches employed to stabilize drugs in pharmaceutical dosage forms
7. Calculate rate reactions for various liquid dosage forms
8. Categorize various pharmaceutical ingredients and excipients

Drug substances are seldom administered alone; rather they are given as part of a formulation in combination with one or more nonmedicinal agents that serve varied and specialized pharmaceutical functions. Selective use of these nonmedicinal agents, referred to as pharmaceutical ingredients or excipients, produces dosage forms of various types. The pharmaceutical ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medicinal agents into efficacious and appealing dosage forms. Each type of dosage form is unique in its physical and pharmaceutical characteristics. These varied preparations provide the manufacturing and compounding pharmacist with the challenges of formulation and the physician with the choice of drug and delivery system to

prescribe. The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed pharmaceutics.

The proper design and formulation of a dosage form requires consideration of the physical, chemical, and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe. The product should be manufactured with appropriate measures of quality control and packaged in containers that keep the product stable. The product should be labeled to promote correct use and be

stored under conditions that contribute to maximum shelf life.

Methods for the preparation of specific types of dosage forms and drug delivery systems are described in subsequent chapters. This chapter presents some general considerations regarding physical pharmacy, drug product formulation, and pharmaceutical ingredients.

THE NEED FOR DOSAGE FORMS

The potent nature and low dosage of most of the drugs in use today precludes any expectation that the general public could safely obtain the appropriate dose of a drug from the bulk material. Most drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive prescription or electronic analytical balance. For instance, how could the lay person accurately obtain from a bulk supply the

325 mg of aspirin found in the common tablet? Not possible. Yet compared with many other drugs, the dose of aspirin is formidable (Table 4.1). For example, the dose of ethinyl estradiol, 0.05 mg, is 1/6,500 the amount of aspirin in an aspirin tablet. To put it another way, 6,500 ethinyl estradiol tablets, each containing 0.05 mg of drug, could be made from an amount of ethinyl estradiol equal to the amount of aspirin in just one standard tablet. When the dose of the drug is minute, as with ethinyl estradiol, solid dosage forms such as tablets and capsules must be prepared with fillers or diluents so that the dosage unit is large enough to pick up with the fingertips.

Besides providing the mechanism for the safe and convenient delivery of accurate dosage, dosage forms are needed for additional reasons:

- To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampuls)

TABLE 4.1 SOME DRUGS WITH RELATIVELY LOW USUAL DOSES

DRUG	USUAL DOSE (MG)	CATEGORY
Betaxolol HCl	10.00	Antianginal
Clotrimoxazole	10.00	Antifungal
Methylphenidate HCl	10.00	CNS stimulant
Medroxyprogesterone acetate	10.00	Progestin
Mesoridazine besylate	10.00	Antipsychotic
Morphine sulfate	10.00	Narcotic analgesic
Nifedipine	10.00	Coronary vasodilator
Omeprazole	10.00	Antilcerative
Quinapril HCl	10.00	Antihypertensive
Chlorazepate dipotassium	7.50	Tranquilizer
Buspirone HCl	5.00	Antianxiety
Enalapril maleate	5.00	Antihypertensive
Hydrocodone	5.00	Narcotic analgesic
Prednisolone	5.00	Adrenocortical steroid
Albuterol sulfate	4.00	Bronchodilator
Chlorpheniramine maleate	4.00	Antihistaminic
Felodipine	2.50	Vasodilator
Glyburide	2.50	Antidiabetic
Doxazosin mesylate	2.00	Antihypertensive
Levorphanol tartrate	2.00	Narcotic analgesic
Prazosin HCl	2.00	Antihypertensive
Risperidone	2.00	Antipsychotic
Estropipate	1.25	Estrogen
Bumetanide	1.00	Diuretic
Clonazepam	1.00	Anticonvulsant
Ergoloid mesylates	1.00	Cognitive adjuvant
Alprazolam	0.50	Antianxiety
Colchicine	0.50	Gout suppressant
Nitroglycerin	0.40	Antianginal
Digoxin	0.25	Cardiotonic (maintenance)
Levothyroxine	0.10	Thyroid
Misoprostol	0.10	Antilcerative, abortifacient
Ethinyl estradiol	0.05	Estrogen

- To protect the drug substance from the destructive influence of gastric acid after oral administration (enteric-coated tablets)
- To conceal the bitter, salty, or offensive taste or odor of a drug substance (capsules, coated tablets, flavored syrups)
- To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle (suspensions)
- To provide clear liquid dosage forms of substances (syrups, solutions)
- To provide rate-controlled drug action (various controlled-release tablets, capsules, and suspensions)
- To provide optimal drug action from topical administration sites (ointments, creams, transdermal patches, and ophthalmic, ear, and nasal preparations)
- To provide for insertion of a drug into one of the body's orifices (rectal or vaginal suppositories)
- To provide for placement of drugs directly in the bloodstream or body tissues (injections)
- To provide for optimal drug action through inhalation therapy (inhalants and inhalation aerosols)

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

Before formulating a drug substance into a dosage form, the desired product type must be determined insofar as possible to establish the framework for product development. Then, various initial formulations of the product are developed and examined for desired features (e.g., drug release profile, bioavailability, clinical effectiveness) and for pilot plant studies and production scale-up. The formulation that best meets the goals for the product is selected to be its *master formula*. Each batch of product subsequently prepared must meet the specifications established in the master formula.

There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease. Most commonly, a manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease (Fig. 4.1). Before a medicinal agent is formulated into one or more dosage forms, among the factors considered are such therapeutic matters as the nature of the illness, the manner in which it is treated (locally or through systemic



FIGURE 4.1 Various forms of a drug substance marketed by a Pharmaceutical Company to meet the special requirements of the patient.

action), and the age and anticipated condition of the patient.

If the medication is intended for systemic use and oral administration is desired, tablets and/or capsules are usually prepared because they are easily handled by the patient and are most convenient in the self-administration of medication. If a drug substance has application in an emergency in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared. Many other examples of therapeutic situations affecting dosage form design could be cited, including motion sickness, nausea, and vomiting, for which tablets and skin patches are used for prevention and suppositories and injections for treatment.

The age of the intended patient also plays a role in dosage form design. For infants and children younger than 5 years of age, pharmaceutical liquids rather than solid forms are preferred for oral administration. These liquids, which are flavored aqueous solutions, syrups, or suspensions, are usually administered directly into the infant's or child's mouth by drop, spoon, or oral dispenser (Fig. 4.2) or incorporated into the child's food. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered. When a young patient has a productive cough or is vomiting, gagging, or simply rebellious, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated. In such instances, injections may be



FIGURE 4.2 Oral dosage devices to assist in measuring doses for children.

required. Infant-size rectal suppositories may also be employed, although drug absorption from the rectum is often erratic.

During childhood and even adulthood, a person may have difficulty swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets. Many of these tablets are comparable in texture to an after-dinner mint and break down into a pleasant-tasting creamy material. Newly available tablets dissolve in the mouth in about 10 to 15 seconds; this allows the patient to take a tablet but actually swallow a liquid. Capsules have been found by many to be more easily swallowed than whole tablets. If a capsule is moistened in the mouth before it is swallowed, it becomes slippery and readily slides down the throat with water. Also, a teaspoonful of gelatin dessert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them. Also, if a person has difficulty swallowing a capsule, the contents may be emptied into a spoon, mixed with jam, honey, or other similar food to mask the taste of the medication and swallowed. Medications intended for the elderly are commonly formulated into oral

liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. However, certain tablets and capsules that are designed for controlled release should not be crushed or chewed, because that would interfere with their integrity and intended performance.

Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and color of solid dosage forms, the easier is proper identification of the medications. Errors in taking medications among the elderly occur frequently because of their multiple drug therapy and impaired eyesight. Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous.

In dealing with the problem of formulating a drug substance into a proper dosage form, research pharmacists employ knowledge gained through experience with other chemically similar drugs and through the proper use of the physical, chemical, biologic, and pharmaceutical sciences. The early stages of any new formulation include studies to collect basic information on the physical and chemical characteristics of the drug substance. These basic studies are the *preformulation* work needed before actual product formulation begins.

PREFORMULATION STUDIES

Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterized. The following *preformulation studies* (1) and others provide the type of information needed to define the nature of the drug substance. This information provides the framework for the drug's combination with pharmaceutical ingredients in the fabrication of a dosage form.

Physical Description

It is important to understand the physical description of a drug substance prior to dosage form development. Most drug substances in use today are solid materials, pure chemical compounds of either crystalline or amorphous constitution. The purity of the chemical substance is essential for its identification and for evaluation of its chemical, physical, and biologic properties. Chemical properties include structure, form, and reactivity. Physical properties include such characteristics as its physical description, particle size, crystalline

structure, melting point, and solubility. Biologic properties relate to its ability to get to a site of action and elicit a biologic response.

Drugs can be used therapeutically as solids, liquids, and gases. Liquid drugs are used to a much lesser extent than solid drugs; gases, even less frequently.

Liquid drugs pose an interesting problem in the design of dosage forms and delivery systems. Many liquids are volatile and must be physically sealed from the atmosphere to prevent evaporation loss. Amyl nitrite, for example, is a clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is kept for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material. When amyl nitrite is administered, the glass is broken between the fingertips, and the liquid wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilation. Propylhexedrine is another volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for its vasoconstrictor action. A cylindrical roll of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in a suitable, usually plastic, sealed nasal inhaler. The inhaler's cap must be securely tightened each time it is used. Even then, the inhaler maintains its effectiveness for only a limited time because of the volatility of the drug.

Another problem associated with liquid drugs is that those intended for oral administration cannot generally be formulated into tablet form, the most popular form of oral medication, without chemical modification. An exception to this is the liquid drug nitroglycerin, which is formulated into sublingual tablets that disintegrate within seconds after placement under the tongue. However, because the drug is volatile, it has a tendency to escape from the tablets during storage, and it is critical that the tablets be stored in a tightly sealed glass container. For the most part, when a liquid drug is to be administered orally and a solid dosage form is desired, one of two approaches is used. First, the liquid substance may be sealed in a soft gelatin capsule. Vitamins A, D, and E, cyclosporin (Neoral, Sandimmune), and ergoloid mesylates (Hydergine LC) are liquids commercially available in capsule form. Second, the liquid drug may be developed into a solid ester or salt form that will be suitable for tablets or drug capsules. For instance, scopol-

amine hydrobromide is a solid salt of the liquid drug scopolamine and is easily pressed into tablets. Another approach to formulate liquids into solids is by mixing the drug with a solid or melted semisolid material, such as a high-molecular-weight polyethylene glycol. The melted mixture is poured into hard gelatin capsules to harden and the capsules sealed.

For certain liquid drugs, especially those taken orally in large doses or applied topically, their liquid nature may have some advantage in therapy. For example, 15-mL doses of mineral oil may be administered conveniently as such. Also, the liquid nature of undecylenic acid certainly does not hinder but rather enhances its use topically in the treatment of fungus infections of the skin. However, for the most part, pharmacists prefer solid materials in formulation work because they can easily form them into tablets and capsules.

Formulation and stability difficulties arise less frequently with solid dosage forms than with liquid preparations, and for this reason many new drugs first reach the market as tablets or dry-filled capsules. Later, when the pharmaceutical problems are resolved, a liquid form of the same drug may be marketed. This procedure is doubly advantageous, because for the most part physicians and patients alike prefer small, generally tasteless, accurately dosed tablets or capsules to the analogous liquid forms. Therefore, marketing a drug in solid form first is more practical for the manufacturer and suits most patients. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

Microscopic Examination

Microscopic examination of the raw drug substance is an important step in preformulation work. It gives an indication of particle size and size range of the raw material along with the crystal structure. Photomicrographs of the initial and subsequent batch lots of the drug substance can provide important information in case of problems in formulation processing attributable to changes in particle or crystal characteristics of the drug. During some processing procedures, the solid drug powders must flow freely and not become entangled. Spherical and oval powders flow more easily than needle-shaped powders and make processing easier.

Heat of Vaporization

The use of vapor pressure is important in the operation of implantable pumps delivering medications as well as in aerosol dosage forms. Another application is the use of nasal inhalants (propylhexedrine with menthol and lavender oil-Benzedrex) for treating nasal congestion. In this latter dosage form, the quantity of drug required for effectiveness and a reasonable estimate of time of usefulness can be determined. Also, in the case of spills in inaccessible places, the time to evaporation of a substance can also be calculated. Some volatile drugs can even migrate within a tablet dosage form so the distribution may not be uniform any longer. This may have an impact in tablets that are scored for dosing where the drug in one portion may be higher or lower than in the other portion.

Exposure of personnel to hazardous drugs due to handling, spilling, or aerosolizing of drugs that may vaporize (oncology agents) is another application as the increase in mobility of the hazardous drug molecules may be related to temperature of the environment. Some drugs, such as carmustine, experience greater vapor pressures with increased temperature as compared

to cyclophosphamide, etoposide, cisplatin, and 5-fluorouracil, as illustrated in Physical Pharmacy Capsule 4.1, Heat of Vaporization.

Melting Point Depression

A characteristic of a pure substance is a defined melting point or melting range. If not pure, the substance will exhibit a change in melting point. This phenomenon is commonly used to determine the purity of a drug substance and in some cases the compatibility of various substances before inclusion in the same dosage form. This characteristic is further described in Physical Pharmacy Capsule 4.2, Melting Point Depression.

The Phase Rule

Phase diagrams are often constructed to provide a visual picture of the existence and extent of the presence of solid and liquid phases in binary, ternary, and other mixtures. Phase diagrams are normally two-component (binary) representations, as shown in Physical Pharmacy Capsule 4.3, The Phase Rule, but can also be three-component representations, as shown in Physical Pharmacy Capsule 4.4, Triangular Phase Diagram.



PHYSICAL PHARMACY CAPSULE 4.1

Heat of Vaporization

The amount of heat absorbed when 1 g of a liquid vaporizes is known as the heat of vaporization of that liquid and is measured in calories. The heat of vaporization of water at 100°C is 540 cal/g or about 9.720 cal/mole. This is the same quantity of heat energy that is released when 1 g of steam condenses to water at 100°C. This energy exchange is important in processes like steam sterilization as it is this energy transfer that results in death of microorganisms.

The movement of molecules varies with temperature. In liquids, this results in a tendency of the molecules to escape the liquid environment into a gaseous environment and possibly loss of the liquid. In the case of solids that sublime, the movement of the molecules is from the solid state to the vapor state. As an example, if one looks at an older bottle containing aspirin, there may be crystals of aspirin on the inside walls of the container. With ibuprofen, the walls of the container may become cloudy as the ibuprofen sublimates.

The use of vapor pressure is important in the operation of implantable pumps delivering medications as well as in aerosol dosage forms. Exposure of personnel to hazardous drugs due to handling, spilling, or aerosolizing of drugs that may vaporize (oncology agents) is another application as the increase in mobility of the hazardous drug molecules may be related to temperature of the environment. Some drugs, such as carmustine, experience greater vapor pressures with increased temperature as compared to cyclophosphamide, etoposide, cisplatin and 5-fluorouracil, as illustrated in the table below. Particle size affects vapor pressure; the smaller the particle size, the greater the vapor pressure. This demonstrates the importance of personnel protection with working with micronized hazardous powders. The time to evaporation of a substance can also be calculated.

PHYSICAL PHARMACY CAPSULE 4.1 CONT.

The variation of vapor pressure with temperature is described by the form of the Clausius–Clapeyron equation, as follows:

$$\frac{d \ln P}{dT} = \frac{\Delta H_{\text{vap}}}{RT^2}$$

assuming that ΔH_{vap} is constant, integration of the equation gives:

$$\log P = \frac{-\Delta H_{\text{vap}}}{2.303 RT} + \text{constant}$$

A plot of the log of the vapor pressure versus $1/T$ should be linear and the slope will equal $-\Delta H_{\text{vap}}/2.303R$ from which the enthalpy of vaporization can be calculated. With data obtained from Kiffmeyer TK, Kube C, Opiolka S, et al. Pharm J 2002;268:331, the following table can be constructed:

COMPOUND	MEASURED VAPOR PRESSURE (Pa)	
	20°C	40°C
Carmustine	0.019	0.530
Cisplatin	0.0018	0.0031
Cyclophosphamide	0.0033	0.0090
Etoposide	0.0026	0.0038
Fluorouracil	0.0014	0.0039

PHYSICAL PHARMACY CAPSULE 4.2

Melting Point Depression

The *melting point*, or *freezing point*, of a pure crystalline solid is defined as the temperature at which the pure liquid and solid exist in equilibrium. Drugs with a low melting point may soften during a processing step in which heat is generated, such as particle size reduction, compression, sintering, and so on. Also, the melting point or range of a drug can be used as an indicator of purity of chemical substances (a pure substance is ordinarily characterized by a very sharp melting peak). An altered peak or a peak at a different temperature may indicate an adulterated or impure drug. This is explained as follows.

The *latent heat of fusion* is the quantity of heat absorbed when 1 g of a solid melts; the molar heat of fusion (ΔH_f) is the quantity of heat absorbed when 1 mole of a solid melts. High-melting-point substances have high heat of fusion, and low-melting-point substances have low heat of fusion. These characteristics are related to the types of bonding in the specific substance. For example, ionic materials have high heats of fusion (NaCl melts at 801°C with a heat of fusion of 124 cal/g), and those with weaker van der Waals forces have low heats of fusion (paraffin melts at 52°C with a heat of fusion of 35.1 cal/g). Ice, with weaker hydrogen bonding, has a melting point of 0°C and a heat of fusion of 80 cal/g.

The addition of a second component to a pure compound (A), resulting in a mixture, will result in a melting point that is lower than that of the pure compound. The degree to which the melting point is lowered is proportional to the mole fraction (N_A) of the second component that is added. This can be expressed thus:

$$\Delta T = \frac{2.303 RT T_0}{\Delta H_f} \log N_A$$

where

ΔH_f is the molar heat of fusion,

T is the absolute equilibrium temperature,

T_0 is the melting point of pure A, and

R is the gas constant.

PHYSICAL PHARMACY CAPSULE 4.2 CONT.

Two noteworthy things contribute to the extent of lowering of the melting point:

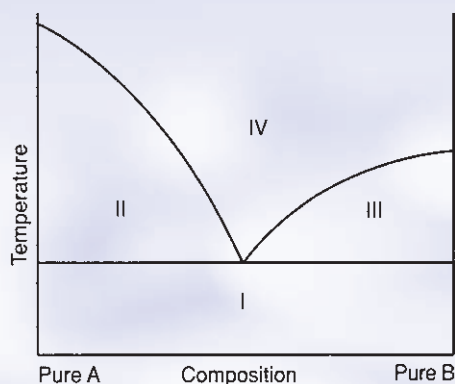
1. Evident from this relationship is the inverse proportion between the melting point and the heat of fusion. When a second ingredient is added to a compound with a low molar heat of fusion, a large lowering of the melting point is observed; substances with a high molar heat of fusion will show little change in melting point with the addition of a second component.
2. The extent of lowering of the melting point is also related to the melting point itself. Compounds with low melting points are affected to a greater extent than compounds with high melting points upon the addition of a second component (i.e., low-melting-point compounds will result in a greater lowering of the melting point than those with high melting points).

PHYSICAL PHARMACY CAPSULE 4.3

The Phase Rule

A phase diagram, or temperature-composition diagram, represents the melting point as a function of composition of two or three component systems. The figure is an example of such a representation for a two-component mixture.

This phase diagram depicts a two-component mixture in which the components are completely miscible in the molten state and no solid solution or addition compound is formed in the solid state. As is evident, starting from the extremes of either pure component A or pure component B, as the second component is added, the melting point of the pure component decreases. There is a point on this phase diagram at which a minimum melting point occurs (i.e., the eutectic point). As is evident, four regions, or phases, in this diagram, represent the following:



- I Solid A + solid B
- II Solid A + melt
- III Solid B + melt
- IV Melt

Each phase is a homogenous part of the system, physically separated by distinct boundaries.

A description of the conditions under which these phases can exist is called the *Phase Rule*, which can be presented thus:

$$F = C - P + X$$

where

F is the number of degrees of freedom,

C is the number of components,

P is the number of phases, and

X is a variable dependent upon selected considerations of the phase diagram (1, 2, or 3).

C describes the minimum number of chemical components to be specified to define the phases. F is the number of independent variables that must be specified to define the complete system (e.g., temperature, pressure, concentration).

PHYSICAL PHARMACY CAPSULE 4.3 CONT.

EXAMPLE 1

In a mixture of menthol and thymol, a phase diagram similar to that illustrated can be obtained. To describe the number of degrees of freedom in the part of the graph moving from the curved line starting at pure A, progressing downward to the eutectic point, and then following an increasing melting point to pure B, it is evident from this presentation that either temperature or composition will describe this system, since it is assumed in this instance that pressure is constant. Therefore, the number of degrees of freedom to describe this portion of the phase diagram is given thus:

$$F = 2 - 2 + 1 = 1$$

In other words, along this line either temperature or composition will describe the system.

EXAMPLE 2

When in the area of a single phase of the diagram, such as the melt (IV), the system can be described thus:

$$F = 2 - 1 + 1 = 2$$

In this portion of the phase diagram, two factors, temperature and composition, can be varied without a change in the number of phases in the system.

EXAMPLE 3

At the eutectic point,

$$F = 2 - 3 + 1 = 0$$

and any change in the concentration or temperature may cause disappearance of one of the two solid phases or the liquid phase.

Phase diagrams are valuable for interpreting interactions between two or more components, relating not only to melting point depression and possible liquefaction at room temperature but also the formation of solid solutions, coprecipitates, and other solid-state interactions.



PHYSICAL PHARMACY CAPSULE 4.4

Triangular (Three-component) Phase Diagram

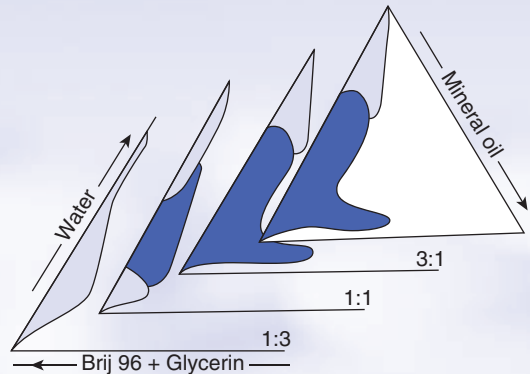
A three-component phase diagram has four degrees of freedom: $F = 3 - 1 + 2 = 4$. In this case, temperature and pressure are two of the conditions and the concentrations of two of the three components make up the rest. Only two concentrations are required because the third will be the difference between 100% and the sum of the other two components.

These systems are used for determining miscibility/solubility, coacervation regions, gel-forming regions for multicomponent mixtures, etc. To read a 3-phase diagram, each of the three corners of the triangle represent 100% by weight of one of the components (A, B, C) and 0% by weight of the other two (A, B, C). The lines joining the corner points forming the triangle each represent two component mixtures of the three possible combinations (AB, BC, and CA). If two of the components are known, the third is known by difference. Any combination of the three components is described by a single point on the diagram. Combining different proportions of the three components and observing for an end point (solubility, gel-formation, haziness, etc.), the phase differences can be visualized, as follows.

PHYSICAL PHARMACY CAPSULE 4.4 CONT.

The following is a stack of four separate pseudoternary phase diagrams for a quaternary system composed of Brij 96, glycerin, mineral oil, and water. The Brij 96:glycerin ratio is noted on the diagram and is considered one of three components. The shaded regions represent gel systems while the clear regions represent fluid systems.

In addition to observing the phase changes in a single plane, the use of stacked ternary phase diagrams enables one to visualize the change using different ratios of one of the components (in this case, the Brij 96:glycerin ratios). Constructions like this enable a pharmaceutical scientist to select the best ratios and combinations of components for a formulation.



Particle Size

Certain physical and chemical properties of drug substances, including dissolution rate, bioavailability, content uniformity, taste, texture, color, and stability, are affected by the particle size distribution. In addition, flow characteristics and sedimentation rates, among other properties, are important factors related to particle size. It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and efficacy. Of special interest is the effect of particle size on absorption. Particle size significantly influences the oral absorption profiles of certain drugs, including griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin. Also, satisfactory con-

tent uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation. Particle size is discussed further in Chapter 6. Figure 4.3 shows a particle size analyzer.

Polymorphism

An important factor on formulation is the crystal or amorphous form of the drug substance. Polymorphic forms usually exhibit different physicochemical properties, including melting point and solubility. Polymorphic forms in drugs are relatively common. It has been estimated that at least one third of all organic compounds exhibit polymorphism.

In addition to polymorphic forms, compounds may occur in noncrystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than is required to escape from an amorphous powder. Therefore, the amorphous form of a compound is always more soluble than a corresponding crystal form.

Evaluation of crystal structure, polymorphism, and solvate form is an important preformulation activity. The changes in crystal characteristics can influence bioavailability and chemical and physical stability and can have important implications in dosage form process functions. For example, it can be a significant factor relating to tablet formation because of flow and compaction



FIGURE 4.3 Mastersizer 2000E particle size analyzer. (Courtesy of Malvern Instruments Ltd.)

behaviors, among others. Various techniques are used to determine crystal properties. The most widely used methods are hot stage microscopy, thermal analysis, infrared spectroscopy, and X-ray diffraction.

Solubility

An important physicochemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation and exert a therapeutic effect, it must first be in solution. Relatively insoluble compounds often exhibit incomplete or erratic absorption. If the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility. The methods to accomplish this depend on the chemical nature of the drug and the type of drug product under consideration. Chemical modification of the drug into salt or ester forms is frequently used to increase solubility.

A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. Chemical analysis of the drug content in solution is performed to determine degree of solubility.

Solubility and Particle Size

Although solubility is normally considered a physicochemical constant, small increases in solubility can be accomplished by particle size reduction as described in the Physical Pharmacy Capsule 4.5, Solubility and Particle Size.

Solubility and pH

Another technique, if the drug is to be formulated into a liquid product, is adjustment of the pH of the solvent to enhance solubility. However, for many drug substances pH adjustment is not an effective means of improving

PHYSICAL PHARMACY CAPSULE 4.5

Solubility and Particle Size

The particle size and surface area of a drug exposed to a medium can affect actual solubility within reason, for example, in the following relationship:

$$\log \frac{S}{S_0} = \frac{2\gamma V}{2.303 R T r}$$

where

- S is the solubility of the small particles,
- S_0 is the solubility of the large particles,
- γ is the surface tension,
- V is the molar volume,
- R is the gas constant,
- T is the absolute temperature, and
- r is the radius of the small particles.

The equation can be used to estimate the decrease in particle size required to increase solubility. For example, a desired increase in solubility of 5% would require an increase in the S/S_0 ratio to 1.05; that is, the left term in the equation would become $\log 1.05$. If a powder has a surface tension of 125 dynes per centimeter, molar volume of 45 cm^3 , and temperature of 27°C , what is the particle size required to obtain the 5% increase in solubility?

$$\begin{aligned} \log 1.05 &= \frac{(2)(125)(45)}{(2.303)(8.314 \times 10^7)(300)r} \\ r &= 9.238 \times 10^{-6} \text{ cm or } 0.09238 \mu \end{aligned}$$

A number of factors are involved in actual solubility enhancement, and this is only an introduction to the general effects of particle size reduction.

solubility. Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients. Adjustment of pH usually has little effect on the solubility of substances other than electrolytes. In many cases, it is desirable to use cosolvents or other techniques such as complexation, micronization, or solid dispersion to improve

aqueous solubility. A review of pH is provided in Physical Pharmacy Capsule 4.6, Principles of pH. The effect of pH on solubility is illustrated in Physical Pharmacy Capsule 4.7, Solubility and pH.

In recent years, more and more physicochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important



PHYSICAL PHARMACY CAPSULE 4.6

Principles of pH

pH is a critical variable in pharmaceuticals, and a basic understanding of its principles and measurement are important. Let's begin with a definition of the term pH. The p comes from the word power. The H, of course, is the symbol for hydrogen. Together, the term pH means the hydrogen ion exponent.

The pH of a substance is a measure of its acidity, just as a degree is a measure of temperature. A specific pH value tells the exact acidity. Rather than stating general ideas, such as cherry syrup is acidic or the water is hot, a specific pH value gives the same relative point of reference, thus providing more exact communication. "The cherry juice has a pH of 3.5" or "the water is at 80°C" provides an exact common language.

pH is defined in terms of the hydrogen ion activity:

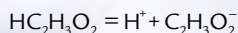
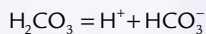
$$\text{pH} = -\log_{10} a_{\text{H}^+} \text{ or } 10^{-\text{pH}} = a_{\text{H}^+}$$

pH equals the negative logarithm of the hydrogen ion activity, or the activity of the hydrogen ion is 10 raised to the exponent $-\text{pH}$. The latter expression renders the use of the p exponent more obvious. The activity is the effective concentration of the hydrogen ion in solution. The difference between effective and actual concentration decreases as one moves toward more dilute solutions, in which ionic interaction becomes progressively less important.

Normally, reference is made to the hydrogen ion when reference should be made to the hydronium ion (H_3O^+). It is a matter of convenience and brevity that only the hydrogen ion is mentioned, even though it is normally in its solvated form:



The complexing of the hydrogen ion by water affects activity and applies to other ions, which partially complex or establish an equilibrium with the hydrogen ion. In other words, equilibrium such as



complexes the hydrogen ion so that it is not sensed by the pH measuring system. This is why an acid-base titration is performed if the total concentration of acid (H^+) is needed. These effects on hydrogen ion activity are obvious, but other more subtle effects are involved in the correlation of activity and concentration.

The activity of the hydrogen ion can be defined by its relation to concentration (C_{H^+} , molality) and the activity coefficient f_{H^+} :

$$a_{\text{H}^+} = f_{\text{H}^+} \cdot C_{\text{H}^+}$$

If the activity coefficient is unity, activity is equal to concentration. This is nearly the case in dilute solutions, whose ionic strength is low. Since the objective of most pH measurements is to find a stable and reproducible reading that can be correlated to the results of some process, it is important to know what influences the activity coefficient and therefore the pH measurement.

PHYSICAL PHARMACY CAPSULE 4.6 CONT.

The factors that affect the activity coefficient are the temperature (T), the ionic strength (μ), the dielectric constant (ϵ), the ion charge (Z_i), the size of the ion in angstroms ($\text{\AA}$), and the density of the solvent (d). All of these factors are characteristics of the solution that relate the activity to the concentration by two main effects: the salt effect and the medium effect; the latter relates the influence that the solvent can have on the hydrogen ion activity. Thus, hydrogen activity is related to concentration through a salt effect and a solvent effect. Because of these influences, a sample pH value cannot be extrapolated to another temperature or dilution. If the pH value of a particular solution is known at 40°C , it is not automatically known at 25°C .

THE pH SCALE

In pure water, hydrogen and hydroxyl ion concentrations are equal at 10^{-7} M at 25°C . This is a neutral solution. Since most samples encountered have less than 1 M H^+ or OH^- , the extremes of pH 0 for acids and pH 14 for bases are established. Of course, with strong acids or bases, pH values below 0 and above 14 are possible but infrequently measured.

MEASUREMENT OF pH

The activity of the hydrogen ion in solution is measured with a glass electrode, a reference electrode, and a pH meter.

COMBINATION ELECTRODES

A combination electrode is a combination of the glass and reference electrodes into a single probe. The main advantage in using a combination electrode is with the measurement of small volume samples or samples in limited-access containers.



PHYSICAL PHARMACY CAPSULE 4.7

Solubility and pH

pH is one of the most important factors in the formulation process. Two areas of critical importance are the effects of pH on solubility and stability. The effect of pH on solubility is critical in the formulation of liquid dosage forms, from oral and topical solutions to intravenous solutions and admixtures.

The solubility of a weak acid or base is often pH dependent. The total quantity of a monoprotic weak acid (HA) in solution at a specific pH is the sum of the concentrations of both the free acid and salt (A^-) forms. If excess drug is present, the quantity of free acid in solution is maximized and constant because of its saturation solubility. As the pH of the solution increases, the quantity of drug in solution increases because the water-soluble ionizable salt is formed. The expression is



where K_a is the dissociation constant.

There may be a certain pH level reached where the total solubility (S_T) of the drug solution is saturated with respect to both the salt and acid forms of the drug, that is, the pH_{max} . The solution can be saturated with respect to the salt at pH values higher than this, but not with respect to the acid. Also, at pH values

PHYSICAL PHARMACY CAPSULE 4.7 CONT.

less than this, the solution can be saturated with respect to the acid but not to the salt. This is illustrated in the accompanying figure.

To calculate the total quantity of drug that can be maintained in solution at a selected pH, either of two equations can be used, depending on whether the product is to be in a pH region above or below the pH_{max} . The following equation is used when below the pH_{max} :

$$S_T = S_a \left(1 + \frac{K_a}{[H^+]} \right) \quad (\text{Equation 1})$$

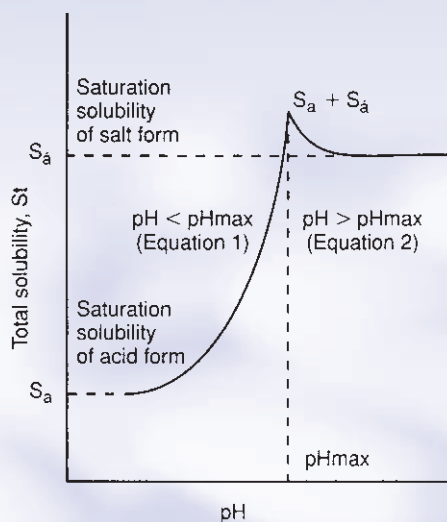
The next equation is used when above the pH_{max} :

$$S_T = S'_a \left(1 + \frac{K_a}{[H^+]} \right) \quad (\text{Equation 2})$$

where

S_a is the saturation solubility of the free acid and

S'_a is the saturation solubility of the salt form.



EXAMPLE

A pharmacist prepares a 3.0% solution of an antibiotic as an ophthalmic solution and dispenses it to a patient. A few days later the patient returns the eye drops to the pharmacist because the product contains a precipitate. The pharmacist, checking the pH of the solution and finding it to be 6.0, reasons that the problem may be pH related. The physicochemical information of interest on the antibiotic includes the following:

Molecular weight	285 (salt) 263 (free acid)
3.0% solution of the drug	0.1053 M solution
Acid form solubility (S_a)	3.1 mg/mL (0.0118 M)
K_a	5.86×10^{-6}

Using Equation 1, the pharmacist calculates the quantity of the antibiotic in solution at a pH of 6.0 (Note: $\text{pH of } 6.0 = [H^+] \text{ of } 1 \times 10^{-6}$)

$$S_T = 0.0118[1+] = 0.0809 \text{ molar}$$

From this the pharmacist knows that at a pH of 6.0, a 0.0809-M solution can be prepared. However, the concentration that was to be prepared was a 0.1053-M solution; consequently, the drug will not be in solution at that pH. The pH may have been all right initially but shifted to a lower pH over time, resulting in precipitation of the drug. The question is at what pH (hydrogen ion concentration) the drug will remain in solution. This can be calculated using the same equation and information. The S_T value is 0.1053 M.

$$0.1053 = 0.0118 \left[1 + \frac{5.86 \times 10^{-6}}{[H^+]} \right]$$

$$[H^+] = 7.333 \times 10^{-7}, \text{ or a pH of } 6.135$$

The pharmacist prepares a solution of the antibiotic, adjusting the pH to above about 6.2, using a suitable buffer system, and dispenses the solution to the patient—with positive results.

PHYSICAL PHARMACY CAPSULE 4.7 CONT.

An interesting phenomenon concerns the close relationship of pH to solubility. At a pH of 6.0, only a 0.0809-M solution could be prepared, but at a pH of 6.13 a 0.1053-M solution could be prepared. In other words, a difference of 0.13 pH units resulted in

$$\frac{0.1053 - 0.0809}{0.0809} = 30.1\%$$

more drug going into solution at the higher pH than at the lower pH. In other words, a very small change in pH resulted in about 30% more drug going into solution. According to the figure, the slope of the curve would be very steep for this example drug, and a small change in pH (x-axis) results in a large change in solubility (y-axis). From this, it can be reasoned that if one observes the pH-solubility profile of a drug, it is possible to predict the magnitude of the pH change on its solubility.

In recent years, more and more physicochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important for pharmacists in different types of practice, especially those who compound and do pharmacokinetic monitoring.

for pharmacists in different types of practice, especially those involved in compounding and pharmacokinetic monitoring.

Dissolution

Variations in the biologic activity of a drug substance may be brought about by the rate at which it becomes available to the organism. In many instances, dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in absorption. This is true for drugs administered orally in solid forms such as tablets, capsules, or suspensions, and for those administered intramuscularly. When the dissolution rate is the rate-limiting step, anything that affects it will also affect absorption. Consequently, dissolution rate can affect the onset, intensity, and duration of response and control the overall bioavailability of the drug from the dosage form, as discussed in the previous chapter.

The dissolution rate of drugs may be increased by decreasing the drug's particle size. It may also be increased by increasing its solubility in the diffusion layer. The most effective means of obtaining higher dissolution rates is to use a highly water-soluble salt of the parent substance. Although a soluble salt of a weak acid will precipitate as the free acid in the bulk phase of an acidic solution, such as gastric fluid, it will do so

in the form of fine particles with a large surface area.

The dissolution rates of chemical compounds are determined by two methods: the constant-surface method, which provides the intrinsic dissolution rate of the agent, and particulate dissolution, in which a suspension of the agent is added to a fixed amount of solvent without exact control of surface area.

The constant-surface method uses a compressed disc of known area. This method eliminates surface area and surface electrical charges as dissolution variables. The dissolution rate obtained by this method, the *intrinsic dissolution rate*, is characteristic of each solid compound and a given solvent in the fixed experimental conditions. The value is expressed as milligrams dissolved per minute per centimeters squared. It has been suggested that this value is useful in predicting probable absorption problems due to dissolution rate. In particulate dissolution, a weighed amount of powdered sample is added to the dissolution medium in a constant agitation system. This method is frequently used to study the influence of particle size, surface area, and excipients upon the active agent. Occasionally, the surface properties of the drug produce an inverse relationship of particle size to dissolution. In these instances, surface charge and/or agglomeration results in the reduced particle size form of the drug presenting

a lower effective surface area to the solvent due to incomplete wetting or agglomeration. Fick's laws describe the relationship of diffusion and dissolution of the active drug in the dosage form and when administered in the body, as shown in Physical Pharmacy Capsule 4.8, Fick's Laws of Diffusion and the Noyes–Whitney Equation.

Early formulation studies should include the effects of pharmaceutical ingredients on the dissolution characteristics of the drug substance.

Membrane Permeability

Modern preformulation studies include an early assessment of passage of drug molecules across biologic membranes. To produce a biologic response, the drug molecule must first cross a biologic membrane. The biologic membrane acts as a lipid barrier to most drugs and permits the absorption of lipid-soluble substances by passive diffusion, while lipid-insoluble



PHYSICAL PHARMACY CAPSULE 4.8

Fick's Laws of Diffusion and the Noyes-Whitney Equation

All drugs must diffuse through various barriers when administered to the body. For example, some drugs must diffuse through the skin, gastric mucosa, or some other barrier to gain access to the interior of the body. Parenteral drugs must diffuse through muscle, connective tissue, and so on, to get to the site of action; even intravenous drugs must diffuse from the blood to the site of action. Drugs must also diffuse through various barriers for metabolism and excretion.

Considering all the diffusion processes that occur in the body (passive, active, and facilitated), it is not surprising that the laws governing diffusion are important to drug delivery systems. In fact, diffusion is important not only in the body but also in some quality control procedures used to determine batch-to-batch uniformity of products (dissolution test for tablets based on the Noyes-Whitney equation, which can be derived from Fick's law).

When individual molecules move within a substance, diffusion is said to occur. This may occur as the result of a concentration gradient or by random molecular motion.

Probably the most widely used laws of diffusion are known as Fick's first and second laws. Fick's first law involving steady-state diffusion (where dc/dx does not change) is derived from the following expression for the quantity of material (M) flowing through a cross section of a barrier (S) in unit time (t) expressed as the flux (J):

$$J = dM/(Sdt)$$

Under a concentration gradient (dc/dx), Fick's first law can be expressed thus:

$$J = D[(C_1 - C_2)/h] \text{ or } J = -D(dc/dx)$$

where

J is the flux of a component across a plane of unit area,

C_1 and C_2 are the concentrations in the donor and receptor compartments,

h is the membrane thickness, and

D is the diffusion coefficient (or diffusivity).

The sign is negative, denoting that the flux is in the direction of decreasing concentration. The units of J are grams per square centimeter; C , grams per cubic centimeter; M , grams or moles; S , square centimeters; x , centimeters; and D , square centimeters per second.

D is appropriately called a diffusion coefficient, not a diffusion constant, as it is subject to change. D may change in value with increased concentrations. Also, D can be affected by temperature, pressure, solvent properties, and the chemical nature of the drug itself. To study the rate of change of the drug in the system, one needs an expression that relates the change in concentration with time at a definite location in place of the mass of drug diffusing across a unit area of barrier in unit time; this expression is known as Fick's second law. This law can be summarized as stating that the change in concentration in a particular place with time is proportional to the change in concentration gradient at that particular place in the system.

PHYSICAL PHARMACY CAPSULE 4.8 CONT.

In summary, Fick's first law relates to a steady-state flow, whereas Fick's second law relates to a change in concentration of drug with time, at any distance, or an unsteady state of flow.

The diffusion coefficients ($D \times 10^{-6}$) of various compounds in water (25°C) and other media have been determined as follows: ethanol, 12.5 cm^2 per second; glycine, 10.6 cm^2 per second; sodium lauryl sulfate, 6.2 cm^2 per second; glucose, 6.8 cm^2 per second.

The concentration of drug in the membrane can be calculated using the partition coefficient (K) and the concentration in the donor and receptor compartments.

$$K = (C_1/C_d) = (C_2/C_r)$$

where

C_1 and C_d are the concentrations in the donor compartment (g/cm^3)

and C_2 and C_r are the concentrations in the receptor compartment (g/cm^3).

K is the partition coefficient of the drug between the solution and the membrane. It can be estimated using the oil solubility of the drug versus the water solubility of the drug. Usually, the higher the partition coefficient, the more the drug will be soluble in a lipophilic substance. We can now write the expression:

$$dM/dt = [DSK(C_d - C_r)]/h$$

or in sink conditions,

$$dM/dt = DSKC_d/h = PSC_d$$

The permeability coefficient (centimeters per second) can be obtained by rearranging to:

$$P = DK/h$$

EXAMPLE 1

A drug passing through a 1-mm-thick membrane has a diffusion coefficient of $4.23 \times 10^{-7}\text{ cm}^2$ per second and an oil-water partition coefficient of 2.03. The radius of the area exposed to the solution is 2 cm, and the concentration of the drug in the donor compartment is 0.5 mg/mL. Calculate the permeability and the diffusion rate of the drug.

$$h = 1\text{ mm} = 0.1\text{ cm}$$

$$D = 4.23 \times 10^{-7}\text{ cm}^2/\text{second}$$

$$K = 2.03$$

$$r = 2\text{ cm}, S = \pi(2\text{ cm})^2 = 12.57\text{ cm}^2$$

$$C_d = 0.5\text{ mg/mL}$$

$$P = [(4.23 \times 10^{-7}\text{ cm}^2/\text{second})(2.03)]/0.1\text{ cm} = 8.59 \times 10^{-6}\text{ cm}/\text{second}$$

$$dM/dt = (8.59 \times 10^{-6}\text{ cm}/\text{second})(12.57\text{ cm}^2)(0.5\text{ mg/mL}) = 5.40 \times 10^{-5}\text{ mg}/\text{second}$$

$$(5.40 \times 10^{-5}\text{ mg}/\text{second})(3600\text{ second}/\text{hour}) = 0.19\text{ mg}/\text{hour}$$

In the dissolution of particles of drug, the dissolved molecules diffuse away from the individual particle body. An expression to describe this, derived from Fick's equations, is known as the Noyes and Whitney expression, proposed in 1897. It can be written as follows:

$$dC/dt = (DS/Vh)(C_s - C)$$

where

C is the concentration of drug dissolved at time t ,

D is the diffusion coefficient of the solute in solution,

S is the surface area of the exposed solid,

PHYSICAL PHARMACY CAPSULE 4.8 CONT.

V is the volume of solution,
 h is the thickness of the diffusion layer,
 C_s is the saturation solubility of the drug, and
 C is the concentration of solute in the bulk phase at a specific time, t.

It is common practice to use sink conditions in which C does not exceed about 20% of the solubility of the drug being investigated. Under these conditions, the expression simplifies to

$$dC/dt = (DSC_s/Vh)$$

and incorporating the volume of solution (V), the thickness of the diffusion layer (h), and the diffusivity coefficient (D) into a coefficient k (to take into account the various factors in the system), the expression becomes

$$dC/dt = kSC_s$$

As the factors are held constant, it becomes apparent that the dissolution rate of a drug can be proportional to the surface area exposed to the dissolution medium. A number of other expressions have been derived for specific application to various situations and conditions.

These relationships expressed as Fick's first and second laws and the Noyes-Whitney equation have great importance and relevance in pharmaceutical systems.

EXAMPLE 2

The following information was obtained using the USP 32-NF 27 dissolution apparatus I. The drug is soluble at 1 g in 3 mL of water, so sink conditions were maintained; the surface area of the tablet exposed was 1.5 cm² (obtained by placing the tablet in a special holder exposing only one side to the dissolution medium); and the dosage form studied was a 16-mg sustained-release tablet; the release pattern should be zero order. What is the rate of release of drug?

TIME (HOURS)	DRUG CONCENTRATION (mg/900 mL OF SOLUTION)	GRAPH OF RELEASE PROFILE
0.0	0.0	
0.5	1.0	
1.0	1.9	
2.0	4.1	
4.0	8.0	
6.0	11.8	
8.0	15.9	

In this problem, since the surface area (S) was maintained constant at 1.5 cm² and the solubility (C_s) of the drug is constant at 1 g in 3 mL of water, the plot of concentration versus time (t) yields a slope with a value of kSC_s, or k₂, expressing the rate of release of the drug as

$$dC/dt = kSC_s$$

The slope of the line = $\Delta y/\Delta x = (y_2 - y_1)/(x_2 - x_1)$
 $= (15.9 \text{ mg} - 0 \text{ mg})/(8.0 \text{ h} - 0 \text{ h})$
 $= 15.9/8 = 1.99 \text{ mg/h}$

Therefore, the rate of release of the sustained-release preparation is 1.99, or approximately 2 mg per hour. From this, the quantity of drug released at any time (t) can be calculated.

substances can diffuse across the barrier only with considerable difficulty if at all. The interrelationship of the dissociation constant, lipid solubility, and pH at the absorption site with the absorption characteristics of various drugs are the basis of the pH partition theory.

Data obtained from the basic physicochemical studies, specifically, pKa, solubility, and dissolution rate, provide an indication of absorption. To enhance these data, a technique using the everted intestinal sac may be used to evaluate absorption characteristics of drug substances. In this method, a piece of intestine is removed from an intact animal, is everted, and is filled with a solution of the drug substance, and the degree and rate of passage of the drug through the membrane sac are determined. This method allows evaluation of both passive and active transport.

In the latter stages of preformulation testing or early formulation studies, animals and humans must be studied to assess the absorption efficiency and pharmacokinetic parameters and to establish possible in vitro and in vivo correlation for dissolution and bioavailability.

Partition Coefficient

The use of the partition coefficient is described in some detail in Physical Pharmacy Capsule 4.9, Partition Coefficient. Inherent in this procedure is the selection of appropriate extraction solvents, drug stability, use of salting-out additives, and environmental concerns. The octanol–water partition coefficient is commonly used in formulation development. Following the illustrations provided earlier, it is defined as

$$P = \frac{(\text{Conc. of drug in octanol})}{(\text{Conc. of drug in water})}$$

P depends on the drug concentration only if the drug molecules have a tendency to associate in solution. For an ionizable drug, the following equation is applicable:

$$P = \frac{(\text{Conc. of drug in octanol})}{[1 - \alpha](\text{Conc. of drug in water})}$$

where α equals the degree of ionization.



PHYSICAL PHARMACY CAPSULE 4.9

Partition Coefficient

The oil–water partition coefficient is a measure of a molecule's lipophilic character; that is, its preference for the hydrophilic or lipophilic phase. If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach an equilibrium at a constant temperature. The distribution of the solute (unaggregated and undissociated) between the two immiscible layers can be described thus:

$$K = C_U / C_L$$

where

- K is the distribution constant or partition constant,
- C_U is the concentration of the drug in the upper phase, and
- C_L is the concentration of the drug in the lower phase.

This information can be effectively used in the

1. Extraction of crude drugs
2. Recovery of antibiotics from fermentation broth
3. Recovery of biotechnology-derived drugs from bacterial cultures
4. Extraction of drugs from biologic fluids for therapeutic drug monitoring
5. Absorption of drugs from dosage forms (ointments, suppositories, transdermal patches)
6. Study of the distribution of flavoring oil between oil and water phases of emulsions
7. In other applications

PHYSICAL PHARMACY CAPSULE 4.9 CONT.

This basic relationship can be used to calculate the quantity of drug extracted from or remaining behind in a given layer and to calculate the number of extractions required to remove a drug from a mixture.

The concentration of drug found in the upper layer (U) of two immiscible layers is given thus:

$$U = Kr/(Kr + 1)$$

where

K is the distribution partition constant and

r is V_u/V_l , or the ratio of the volume of upper and lower phases.

The concentration of drug remaining in the lower layer (L) is given thus:

$$L = 1/(Kr + 1)$$

If the lower phase is successively extracted again with n equal volumes of the upper layer, each upper (U_n) contains the following fraction of the drug:

$$U_n = Kr/(Kr + 1)^n$$

where

U_n is the fraction contained in the n th extraction and

n is the n th successive volume.

The fraction of solute remaining in the lower layer (L_n) is given thus:

$$L_n = 1/(Kr + 1)^n$$

More efficient extractions are obtained using successive small volumes of the extraction solvent than single larger volumes. This can be calculated as follows when the same volume of extracting solvent is used in divided portions. For example, the fraction L_n remaining after the n th extraction:

$$L_n = \frac{1}{\left(\frac{Kr}{n} + 1\right)^n}$$

EXAMPLE 1

At 25°C and pH 6.8, the K for a second generation cephalosporin is 0.7 between equal volumes of butanol and the fermentation broth. Calculate the U, L, and L_n (using the same volume divided into fourths).

$$U = 0.7/(0.7 + 1) = 0.41, \text{ the fraction of drug extracted into the upper layer}$$

$$L = 1/(0.7 + 1) = 0.59, \text{ the fraction of drug remaining in the lower layer}$$

The total of the fractions in the U and L = $0.41 + 0.59 = 1$.

If the fermentation broth is extracted with four successive extractions accomplished by dividing the quantity of butanol used into fourths, the quantity of drug remaining after the fourth extraction is

$$L_{4th} = \frac{1}{\left(\frac{0.7 \times 1}{4} + 1\right)^4} = 0.525$$

From this, the quantity remaining after a single volume, single extraction is 0.59, but when the single volume is divided into fourths and four successive extractions are done, the quantity remaining is 0.525; therefore, more was extracted using divided portions of the extracting solvent. Inherent in this procedure is the selection of appropriate extraction solvents, drug stability, use of salting-out additives, and environmental concerns.

pKa/Dissociation Constants

Among the physicochemical characteristics of interest is the extent of dissociation or ionization of drug substances. This is important because the extent of ionization has an important effect on the formulation and pharmacokinetic parameters of the drug. The extent of dissociation or ionization in many cases is highly dependent on the pH of the medium containing the drug. In formulation, often the vehicle is adjusted to a certain pH to obtain a certain level of ionization of the drug for solubility and stability. In the pharmacokinetic area, the extent of ionization of a drug has a strong effect on its extent of absorption,

distribution, and elimination. The dissociation constant, or pKa, is usually determined by potentiometric titration. For the practicing pharmacist, it is important in predicting precipitation in admixtures and in calculating the solubility of drugs at certain pH values. Physical Pharmacy Capsule 4.10, pKa/Dissociation Constants, presents a brief summary of dissociation and ionization concepts.

DRUG AND DRUG PRODUCT STABILITY

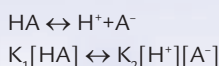
One of the most important activities of preformulation work is evaluation of the physical and chemical stability of the pure drug substance. It



PHYSICAL PHARMACY CAPSULE 4.10

pKa/Dissociation Constants

The dissociation of a weak acid in water is given by this expression:



At equilibrium, the reaction rate constants K_1 and K_2 are equal. This can be rearranged, and the dissociation constant defined as

$$K_a = \frac{K_1}{K_2} = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]}$$

where K_a is the acid dissociation constant.

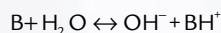
For the dissociation of a weak base that does not contain a hydroxyl group, the following relationship can be used:



The dissociation constant is described by

$$K_a = \frac{[\text{H}^+][\text{B}]}{[\text{BH}^+]}$$

The dissociation of a hydroxyl-containing weak base,



The dissociation constant is described by

$$K_b = \frac{[\text{OH}^-][\text{BH}^+]}{[\text{B}]}$$

The hydrogen ion concentrations can be calculated for the solution of a weak acid using

$$[\text{H}^+] = \sqrt{K_a C}$$

Similarly, the hydroxyl ion concentration for a solution of a weak base is approximated by

$$[\text{OH}^-] = \sqrt{K_b C}$$

PHYSICAL PHARMACY CAPSULE 4.10 CONT.

Some practical applications of these equations are as follows.

EXAMPLE 1

The K_a of lactic acid is 1.387×10^{-4} at 25°C . What is the hydrogen ion concentration of a 0.02 M solution?

$$[\text{H}^+] = \sqrt{1.387 \times 10^{-4} \times 0.02} = 1.665 \times 10^{-3} \text{ G-ion/L}$$

EXAMPLE 2

The K_b of morphine is 7.4×10^{-7} . What is the hydroxyl ion concentration of a 0.02 M solution?

$$[\text{OH}^-] = \sqrt{7.4 \times 10^{-7} \times 0.02} = 1.216 \times 10^{-4} \text{ G-ion/L}$$

is essential that these initial studies be conducted using drug samples of known purity. The presence of impurities can lead to erroneous conclusions in such evaluations. Stability studies conducted in the preformulation phase include solid-state stability of the drug alone, solution phase stability, and stability in the presence of expected excipients. Initial investigation begins with knowledge of the drug's chemical structure, which allows the preformulation scientist to anticipate the possible degradation reactions.

Drug Stability: Mechanisms of Degradation

Chemical instability of medicinal agents may take many forms because the drugs in use today are of such diverse chemical constitution. Chemically, drug substances are alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with reactive chemical groups having different susceptibilities to chemical instability. Chemically, the most frequently encountered destructive processes are hydrolysis and oxidation.

Hydrolysis is a solvolysis process in which (drug) molecules interact with water molecules to yield breakdown products. For example, aspirin, or acetylsalicylic acid, combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid.

Hydrolysis is probably the most important single cause of drug decomposition, mainly

because a great number of medicinal agents are esters or contain such other groupings as substituted amides, lactones, and lactams, which are susceptible to the hydrolytic process (2).

Another destructive process is oxidation, which destroys many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils. Chemically, oxidation is loss of electrons from an atom or a molecule. Each electron lost is accepted by some other atom or molecule, reducing the recipient. In inorganic chemistry, oxidation is accompanied by an increase in the positive valence of an element, for example, ferrous (+2) oxidizing to ferric (+3). In organic chemistry, oxidation is frequently considered synonymous with the loss of hydrogen (dehydrogenation) from a molecule. Oxidation frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, such as molecular (atmospheric) oxygen ($\bullet\text{O}-\text{O}\bullet$) and free hydroxyl ($\bullet\text{OH}$). These radicals tend to take electrons from other chemicals, thereby oxidizing the donor.

Many of the oxidative changes in pharmaceutical preparations have the character of autooxidations. Autooxidations occur spontaneously under the initial influence of atmospheric oxygen and proceed slowly at first and then more rapidly. The process has been described as a type of chain reaction commencing with the union of oxygen with the drug molecule and continuing with a free radical of this oxidized molecule participating in the destruction of other drug molecules and so forth.

In drug product formulation work, steps are taken to reduce or prevent deterioration due to hydrolysis, oxidation, and other processes. These techniques are discussed later.

Drug and Drug Product Stability: Kinetics and Shelf Life

Stability is the extent to which a product retains within specified limits and throughout its period of storage and use (i.e., its shelf life) the same properties and characteristics that it possessed at the time of its manufacture.

Five types of stability concern pharmacists:

1. *Chemical*: Each active ingredient retains its chemical integrity and labeled potency within the specified limits.
2. *Physical*: The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
3. *Microbiologic*: Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
4. *Therapeutic*: The therapeutic effect remains unchanged.
5. *Toxicologic*: No significant increase in toxicity occurs.

Chemical stability is important for selecting storage conditions (temperature, light, humidity), selecting the proper container for dispensing (glass vs. plastic, clear vs. amber or opaque, cap liners), and anticipating interactions when mixing drugs and dosage forms. Stability and expiration dating are based on reaction kinetics, that is, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical species and by factors such as solvent, pressure, and temperature.

In considering chemical stability of a pharmaceutical, one must know the reaction order and reaction rate. The reaction order may be the overall order (the sum of the exponents of the concentration terms of the rate expression), or the order with respect to each reactant (the exponent of the individual concentration term in the rate expression).

Rate Reactions

The reaction rate is a description of the drug concentration with respect to time. Most commonly,

zero-order and first-order reactions are encountered in pharmacy. These are presented in Physical Pharmacy Capsule 4.11, Rate Reactions, along with some appropriate examples.

Q_{10} Method of Shelf Life Estimation

The Q_{10} method of shelf life estimation lets the pharmacist estimate shelf life for a product that has been stored or is going to be stored under a different set of conditions. It is explained in Physical Pharmacy Capsule 4.12, Q_{10} Method of Shelf Life Estimation.

Enhancing Stability of Drug Products

Many pharmaceutical ingredients may be used to prepare the desired dosage form of a drug substance. Some of these agents may be used to achieve the desired physical and chemical characteristics of the product or to enhance its appearance, odor, and taste. Other substances may be used to increase the stability of the drug substance, particularly against hydrolysis and oxidation. In each instance, the added pharmaceutical ingredient must be compatible with and must not detract from the stability of the drug substance.

There are several approaches to the stabilization of pharmaceutical preparations containing drugs subject to hydrolysis. Perhaps the most obvious is the reduction or elimination of water from the pharmaceutical system. Even solid dosage forms containing water-labile drugs must be protected from humidity in the atmosphere. This may be accomplished by applying a waterproof protective coating over tablets or by keeping the drug in a tightly closed container. It is fairly common to detect hydrolyzed aspirin by noticing an odor of acetic acid upon opening a bottle of aspirin tablets. In liquid preparations, water can frequently be replaced or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol, and alcohol. In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.

Decomposition by hydrolysis may be prevented in other liquid drugs by suspending them in a nonaqueous vehicle rather than dissolving them in an aqueous solvent. In still other instances, particularly for certain unstable

PHYSICAL PHARMACY CAPSULE 4.11

Rate Reactions

ZERO-ORDER RATE REACTIONS

If the loss of drug is independent of the concentration of the reactants and constant with respect to time (i.e., 1 mg/mL/hour), the rate is called zero order. The mathematical expression is

$$\frac{-dC}{dt} = k_0$$

where k_0 is the zero-order rate constant [concentration(C)/time(t)].

The integrated and more useful form of the equation:

$$C = -k_0t + C_0$$

where C_0 is the initial concentration of the drug.

The units for a zero rate constant k_0 are concentration per unit time, such as moles per liter-second or milligrams per milliliter per minute.

It is meaningless to attempt to describe the time required for *all* material in a reaction to decompose, that is, infinity. Therefore, reaction rates are commonly described by k or by their half-life, $t_{1/2}$.

The half-life equation for a zero-order reaction:

$$t_{1/2} = (1/2)(C_0/k_0)$$

If the C_0 changes, the $t_{1/2}$ changes. There is an inverse relationship between the $t_{1/2}$ and k .

EXAMPLE 1

A drug suspension (125 mg/mL) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/mL/hour. What is the concentration of intact drug remaining after 3 days (72 hours), and what is its $t_{1/2}$?

$$C = -(0.5 \text{ mg/mL/hour})(72 \text{ hour}) + 125 \text{ mg/mL}$$

$$C = 89 \text{ mg/mL after 3 days}$$

$$t_{1/2} = 1/2(125 \text{ mg/mL})/(0.5 \text{ mg/mL/hour})$$

$$t_{1/2} = 125 \text{ hours}$$

EXAMPLE 2

How long will it take for the suspension to reach 90% of its original concentration?

$$90\% \times 125 \text{ mg/mL} = 112.5 \text{ mg/mL}$$

$$t = \frac{C - C_0}{-k_0} = \frac{112.5 \text{ mg/mL} - 125 \text{ mg/mL}}{-0.5 \text{ mg/mL/hour}} = 25 \text{ hours}$$

Drug suspensions are examples of pharmaceuticals that ordinarily follow zero-order kinetics for degradation.

FIRST-ORDER RATE REACTIONS

If the loss of drug is directly proportional to the concentration remaining with respect to time, it is called a first-order reaction and has the units of reciprocal time, that is, time^{-1} . The mathematical expression is

$$\frac{-dC}{dt} = kC$$

where

C is the concentration of intact drug remaining,

t is time,

(dC/dt) is the rate at which the intact drug degrades, and

k is the specific reaction rate constant.

PHYSICAL PHARMACY CAPSULE 4.11 CONT.

The integrated and more useful form of the equation:

$$\log C = \frac{-kt}{2.303} + \log C_0$$

where C_0 is the initial concentration of the drug.

In natural log form, the equation is

$$\ln C = -kt + \ln C_0$$

The units of k for a first-order reaction are per unit of time, such as per second.

The half-life equation for a first-order reaction is

$$t_{1/2} = 0.693/k$$

and can be easily derived from the first-order equation by substituting values of $C = 50\%$ and $C_0 = 100\%$, representing a decrease in concentration by 50%.

EXAMPLE 3

An ophthalmic solution of a mydriatic drug at 5 mg/mL exhibits first-order degradation with a rate of 0.0005/day. How much drug will remain after 120 days, and what is its half-life?

$$\ln C = -(0.0005/\text{day})(120) + \ln(5 \text{ mg/mL})$$

$$\ln C = -0.06 + 1.609$$

$$\ln C = 1.549$$

$$C = 4.71 \text{ mg/mL}$$

$$t_{1/2} = 0.693/0.0005/\text{day}$$

$$t_{1/2} = 1,386 \text{ days}$$

EXAMPLE 4

In Example 3, how long will it take for the drug to degrade to 90% of its original concentration?

$$90\% \text{ of } 5 \text{ mg/mL} = 4.5 \text{ mg/mL}$$

$$\ln 4.5 \text{ mg/mL} = -(0.0005/\text{day})t + \ln(5 \text{ mg/mL})$$

$$t = \frac{\ln 4.5 \text{ mg/mL} - \ln 5 \text{ mg/mL}}{-0.0005/\text{day}}$$

$$t = 210 \text{ days}$$

ENERGY OF ACTIVATION: ARRHENIUS EQUATION

Stability projections for shelf life (t_{90} , or the time required for 10% of the drug to degrade with 90% of the intact drug remaining) are commonly based on the Arrhenius equation:

$$\log \frac{k_2}{k_1} = \frac{E_a(T_2 - T_1)}{2.3RT_1T_2}$$

which relates the reaction rate constants (k) to temperatures (T) with the gas constant (R) and the energy of activation (E_a).

The relationship of the reaction rate constants at two different temperatures provides the energy of activation for the degradation. By performing the reactions at elevated temperatures instead of allowing the process to proceed slowly at room temperature, the E_a can be calculated and a k value for room temperature determined with the Arrhenius equation.

PHYSICAL PHARMACY CAPSULE 4.11 CONT.

EXAMPLE 5

The degradation of a new cancer drug follows first-order kinetics and has first-order degradation rate constants of 0.0001 per hour at 60°C and 0.0009 at 80°C. What is its E_a ?

$$\log = \frac{(0.0009)}{(0.0001)} = \frac{E_a(353 - 333)}{(2.3)(1.987)(353)(333)}$$

$$E_a = 25,651 \text{ kcal/mol}$$



PHYSICAL PHARMACY CAPSULE 4.12

Q₁₀ Method of Shelf Life Estimation

The Q_{10} approach, based on E_a , which is independent of reaction order, is described as

$$Q_{10} = e^{\{(E_a/R)[(1/T + 10) - (1/T)]\}}$$

where

E_a is the energy of activation,
 R is the gas constant, and
 T is the absolute temperature.

In usable terms, Q_{10} , the ratio of two different reaction rate constants, is defined thus:

$$Q_{10} = \frac{K_{(T+10)}}{K_T}$$

The commonly used Q values of 2, 3, and 4 relate to the energies of activations of the reactions for temperatures around room temperature (25°C). For example, a Q value of 2 corresponds to an E_a (kcal/mol) of 12.2, a Q value of 3 corresponds to an E_a of 19.4, and a Q value of 4 corresponds to an E_a of 24.5. Reasonable estimates can often be made using the value of 3.

The equation for Q_{10} shelf life estimates is

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

where

$t_{90} T_2$ is the estimated shelf life,
 $t_{90} T_1$ is the given shelf life at a given temperature, and
 ΔT is the difference in the temperatures T_1 and T_2 .

As is evident from this relationship, an increase in ΔT will decrease the shelf life and a decrease in ΔT will increase shelf life. This is the same as saying that storing at a warmer temperature will shorten the life of the drug and storing at a cooler temperature will increase the life of the drug.

EXAMPLE 1

An antibiotic solution has a shelf life of 48 hours in the refrigerator (5°C). What is its estimated shelf life at room temperature (25°C)?

Using a Q value of 3, we set up the relationship as follows:

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} = \frac{48}{3^{[(25-5)/10]}} = \frac{48}{3^2} = 5.33 \text{ hours}$$

PHYSICAL PHARMACY CAPSULE 4.12 CONT.

EXAMPLE 2

An ophthalmic solution has a shelf life of 6 hours at room temperature (25°C). What is the estimated shelf life in a refrigerator at 5°C? (Note: Since the temperature is decreasing, ΔT will be negative.)

$$t_{90}(T_2) = \frac{6}{3^{[(5-25)/10]}} = \frac{6}{3^{-2}} = 6 \times 3^2 = 54 \text{ hours}$$

These are estimates, and actual energies of activation can often be obtained from the literature for more exact calculations.

antibiotic drugs, when an aqueous preparation is desired, the drug may be supplied to the pharmacist in a dry form for *reconstitution* by adding a specified volume of purified water just before dispensing. The dry powder is actually a mixture of the antibiotic, suspending agents, flavorants, and colorants; when reconstituted by the pharmacist, it remains stable for the period over which the preparation is normally consumed. Refrigeration is advisable for most preparations considered subject to hydrolysis. Together with temperature, pH is a major determinant of the stability of a drug prone to hydrolytic decomposition. Hydrolysis of most drugs depends on the relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolyzable drugs, optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, through judicious use of buffering agents, the stability of otherwise unstable compounds can be increased. Buffers are used to maintain a certain pH, as described in Physical Pharmacy Capsule 4.13, Buffer Capacity.

Pharmaceutically, oxidation of a susceptible drug substance is most likely to occur when it is not kept dry in the presence of oxygen or when it is exposed to light or combined with other chemical agents without proper regard to their influence on oxidation. Oxidation of a chemical in a pharmaceutical preparation is usually accompanied by an alteration in the color of that preparation. It may also result in precipitation or a change in odor.

The oxidative process is diverted and the stability of the drug is preserved by agents called *antioxidants*, which react with one or more compounds in the drug to prevent progress of the chain reaction. In general, antioxidants act by

providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Various antioxidants are employed in pharmacy. Among those most frequently used in aqueous preparations are sodium sulfite (Na_2SO_3 , at high pH values), sodium bisulfite (NaHSO_3 , at intermediate pH values), sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$ at low pH values), hypophosphorous acid (H_3PO_2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alpha-tocopherol, butyl hydroxy anisole, and ascorbyl palmitate find application.

In June 1987, U.S. Food and Drug Administration (FDA) labeling regulations went into effect requiring a warning about possible allergic-type reactions, including anaphylaxis, in the package insert for prescription drugs to whose final dosage form sulfites have been added. Sulfites are used as preservatives in many injectable drugs, such as antibiotics and local anesthetics. Some inhalants and ophthalmic preparations also contain sulfites, but relatively few oral drugs contain these chemicals. The purpose of the regulation is to protect the estimated 0.2% of the population who are subject to allergic reactions to the chemicals. Many sulfite-sensitive persons have asthma or other allergic conditions. Previous to the regulations dealing with prescription medication, the FDA issued regulations for the use of sulfites in food. Asthmatics and other patients who may be sulfite sensitive should be reminded to read the labels of packaged foods and medications to check for the presence of these agents. Sulfite agents covered by the regulations are potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide. The FDA permits the use of



PHYSICAL PHARMACY CAPSULE 4.13

Buffer Capacity

pH, buffers, and buffer capacity are especially important in drug product formulation, since they affect the drug's solubility, activity, absorption, and stability and the patient's comfort.

A buffer is a system, usually an aqueous solution, that can resist changes in pH upon addition of an acid or base. Buffers are composed of a weak acid and its conjugate base or a weak base and its conjugate acid. Buffers are prepared by one of these processes:

1. Mixing a weak acid and its conjugate base or a weak base and its conjugate acid
2. Mixing a weak acid and a strong base to form the conjugate base or a weak base and a strong acid to form the conjugate acid

Using the Henderson-Hasselbach equation:

$$\text{pH} = \text{pK}_a + \log (\text{base/acid})$$

Remember that the acid is the proton donor and the base is the proton acceptor.

EXAMPLE 1

A buffer is prepared by mixing 100 mL of 0.2 M phosphoric acid with 200 mL of 0.08 M sodium phosphate monobasic. What is the pH of this buffer? (K_a of phosphoric acid = 7.5×10^{-3})

$$\text{Moles acid} = (0.2 \text{ mol}/1000 \text{ mL})(100 \text{ mL}) = 0.02 \text{ mol}; (0.02 \text{ mol})/(0.3 \text{ L}) = 0.067 \text{ M}$$

$$\text{Moles base} = (0.08 \text{ mol}/1000 \text{ mL})(200 \text{ mL}) = 0.016 \text{ mol}; (0.016 \text{ mol})/(0.3 \text{ L}) = 0.053 \text{ M}$$

$$\text{pK}_a = -\log 7.5 \times 10^{-3} = 2.125$$

$$\text{pH} = 2.125 + \log (0.016 \text{ mol}/0.02 \text{ mol}) = 2.028$$

EXAMPLE 2

Determine the pH of the buffer prepared as shown:

Sodium acetate 50 g

Conc. HCl 10 mL

Water q.s. 2 L

Helpful numbers:

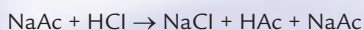
pK_a acetic acid = 4.76

m.w. sodium acetate = 82.08

m.w. acetic acid = 60.05

m.w. HCl = 36.45

Conc. HCl, 44% HCl w/v



$$(0.609 \text{ mol}) \quad (0.121 \text{ mol}) \quad (0.121 \text{ mol}) \quad (0.121 \text{ mol}) \quad (0.488 \text{ mol})$$

$$\text{HCl: } \{(10 \text{ mL}) [(44 \text{ g})/(100 \text{ mL})] (1 \text{ mol})/(36.45 \text{ g})\} = 0.121 \text{ mol}$$

$$\text{NaAc: } \{(50 \text{ g})[(1 \text{ mol})/(82.08 \text{ g})] = 0.609 \text{ mol} (0.609 \text{ mol}) - (0.121 \text{ mol}) = 0.488 \text{ mol}$$

$$\text{pH} = 4.76 + \log (0.488 \text{ mol})/(0.121 \text{ mol}) = 5.367$$

The ability of a buffer solution to resist changes in pH upon the addition of an acid or a base is called buffer capacity (β) and is defined thus:

$$\beta = \Delta B / \Delta \text{pH}$$

where

ΔB is molar concentration of acid or base added,

ΔpH is change in pH due to addition of acid or base, and

ΔpH can be determined experimentally or calculated using the Henderson-Hasselbach equation.

PHYSICAL PHARMACY CAPSULE 4.13 CONT.

EXAMPLE 3

If 0.2 mole of HCl is added to a 0.015 M solution of ammonium hydroxide and the pH falls from 9.5 to 8.9, what is the buffer capacity?

$$\begin{aligned}\Delta\text{pH} &= 9.5 - 8.9 = 0.6 \\ \Delta B &= 0.2 \text{ mol/L} = 0.2 \text{ M} \\ \beta &= 0.2 \text{ M}/0.6 = 0.33 \text{ M}\end{aligned}$$

EXAMPLE 4

If 0.002 mole of HCl is added to the buffer in Example 1, what is its buffer capacity? After adding 0.002 mole HCl:

$$\begin{aligned}\text{H}_3\text{PO}_4 &: 0.02 \text{ mol} + 0.002 \text{ mol} = 0.022 \text{ mol} \\ \text{NaH}_2\text{PO}_4 &: 0.016 \text{ mol} - 0.002 \text{ mol} = 0.014 \text{ mol} \\ \text{pH} &= 2.125 + \log (0.014 \text{ mol}/0.022 \text{ mol}) = 1.929 \\ \Delta\text{pH} &= 2.028 - 1.929 = 0.099 \\ \Delta AB &= 0.002 \text{ mol}/0.3 \text{ L} = 0.0067 \text{ M} \\ \beta &= 0.0067 \text{ M}/0.099 = 0.067 \text{ M}\end{aligned}$$

Another approach to calculating buffer capacity involves the use of Van Slyke's equation:

$$\beta = 2.3C \{K_a[H^+]/(K_a[H^+])^2\}$$

where

C is the sum of the molar concentrations of the acid and base, and $[H^+] = 10^{-\text{pH}}$.

EXAMPLE 5

What is the Van Slyke buffer capacity of the buffer prepared in Example 1?

$$\begin{aligned}C &= 0.0067 \text{ M} + 0.0053 \text{ M} = 0.12 \text{ M} \\ K_a &= 7.5 \times 10^{-3} \\ [H^+] &= 10^{-2.028} = 9.38 \times 10^{-3} \text{ M} \\ \beta &= 2.3(0.12 \text{ M})\{[(7.5 \times 10^{-3} \text{ M})(9.38 \times 10^{-3} \text{ M})]/[(7.5 \times 10^{-3} \text{ M})/(9.38 \times 10^{-3} \text{ M})^2]\} = 0.68 \text{ M}\end{aligned}$$

sulfites in prescription products, with the proper labeling, because there are no generally suitable substitutes for sulfites to maintain potency in certain medications. Some but not all epinephrine injections contain sulfites.

The proper use of antioxidants permits their specific application only after appropriate biomedical and pharmaceutical studies. In certain instances, other pharmaceutical additives can inactivate a given antioxidant. In other cases, certain antioxidants can react chemically with the drugs they were intended to stabilize without a noticeable change in the appearance of the preparation.

Because oxygen may adversely affect their stability, certain pharmaceuticals require an oxygen-free atmosphere during preparation and storage. Oxygen may be present in pharmaceutical liquids in the airspace within the container or may be dissolved in the liquid vehicle. To avoid these exposures, oxygen-sensitive drugs may be prepared in the dry state and packaged in sealed containers with the air replaced by an inert gas such as nitrogen, as may liquid preparations. This is common practice in commercial production of vials and ampuls of easily oxidizable preparations intended for parenteral use.

TABLE 4.2 SOME USP DRUGS AND PREPARATIONS ESPECIALLY SUBJECT TO CHEMICAL OR PHYSICAL DETERIORATION

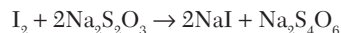
PREPARATION	CATEGORY	MONOGRAPH OR LABEL WARNING
Epinephrine bitartrate ophthalmic solution	Adrenergic	Do not use inhalation, injection, nasal, or ophthalmic solution if it is brown or contains a precipitate
Epinephrine inhalation solution		
Epinephrine injection		
Epinephrine nasal solution		
Epinephrine ophthalmic solution		
Isoproterenol sulfate inhalation, solution	Adrenergic (bronchodilator)	Do not use inhalation or injection if it is pink to brown or contains a precipitate
Isoproterenol inhalation solution		
Nitroglycerin tablets	Antianginal	To prevent loss of potency, keep in original container or supplemental container specifically labeled suitable for nitroglycerin tablets
Paraldehyde	Hypnotic	Subject to oxidation to form acetic acid

Trace metals originating in the drug, solvent, container, or stopper are a constant source of difficulty in preparing stable solutions of oxidizable drugs. The rate of formation of color in epinephrine solutions, for instance, is greatly increased by the presence of ferric, ferrous, cupric, and chromic ions. Great care must be taken to eliminate these trace metals from labile preparations by thorough purification of the source of the contaminant or by chemically complexing or binding the metal through the use of specialized agents that make it chemically unavailable for participation in the oxidative process. These chelating agents are exemplified by calcium disodium edetate and ethylenediaminetetraacetic acid.

Light can also act as a catalyst to oxidation reactions, transferring its energy (photons) to drug molecules, making the latter more reactive through increased energy capability. As a precaution against acceleration of oxidation, sensitive preparations are packaged in light-resistant or opaque containers.

Because most drug degradations proceed more rapidly as temperature increases, it is also advisable to maintain oxidizable drugs in a cool place. Another factor that can affect the stability of an oxidizable drug in solution is the pH of the preparation. Each drug must be maintained in solution at the pH most favorable to its stability. This varies from preparation to preparation and must be determined on an individual basis for the drug in question.

Statements in the United States Pharmacopeia (USP), as with those in Table 4.2, warn of the oxidative decomposition of drugs and preparations. In some instances, the specific agent to employ as a stabilizer is mentioned in the monograph, and in others the term “suitable stabilizer” is used. An example in which a particular agent is designated for use is in the monograph for potassium iodide oral solution, USP. Potassium iodide in solution is prone to photocatalyzed oxidation and the release of free iodine, with a resultant yellow-to-brown discoloration of the solution. The use of light-resistant containers is essential to its stability. As a further precaution against decomposition if the solution is not to be used within a short time, the USP recommends the addition of 0.5 mg of sodium thiosulfate for each gram of potassium iodide. In the event free iodine is released during storage, the sodium thiosulfate converts it to colorless and soluble sodium iodide:



In summary, for easily oxidizable drugs, the formulation pharmacist may stabilize the preparation by the selective exclusion from the system of oxygen, oxidizing agents, trace metals, light, heat, and other chemical catalysts to the oxidation process. Antioxidants, chelating agents, and buffering agents may be added to create and maintain a favorable pH.

In addition to oxidation and hydrolysis, destructive processes include polymerization,

chemical decarboxylation, and deamination. However, these processes occur less frequently and are peculiar to only small groups of chemical substances. Polymerization is a reaction between two or more identical molecules that forms a new and generally larger molecule. Formaldehyde is an example of a drug capable of polymerization. In solution it may polymerize to paraformaldehyde $(\text{CH}_2\text{O})_n$, a slowly soluble white crystalline substance that may cloud the solution. The formation of paraformaldehyde is enhanced by cool storage, especially in solutions with high concentrations of formaldehyde. The official formaldehyde solution contains approximately 37% formaldehyde and according to the USP, should be stored at temperatures not below 15°C (59°F). If the solution becomes cloudy upon standing in a cool place, it usually may be cleared by gentle warming. Formaldehyde is prepared by the limited oxidation of methanol (methyl alcohol), and the USP permits a residual amount of this material to remain in the final product, since it can retard the formation of paraformaldehyde. Formaldehyde solution must be maintained in a tight container because oxidation of the formaldehyde yields formic acid.



Other organic drug molecules may be degraded through processes in which one or more of their active chemical groups are removed. These processes may involve various catalysts, including light and enzymes. Decarboxylation and deamination are examples of such processes; the former is decomposition of an organic acid ($\text{R}\cdot\text{COOH}$) and release of carbon dioxide gas, and the latter is removal of the nitrogen-containing group from an organic amine. For example, insulin, a protein, deteriorates rapidly in acid solutions as a result of extensive deamination (3). Thus, most preparations of insulin are neutralized to reduce the rate of decomposition.

Stability Testing

FDA's Current Good Manufacturing Practice regulations include sections on stability and stability testing of pharmaceutical components and finished pharmaceutical products. In addition, FDA and International Conference on

Harmonization guidelines and guidances provide working recommendations to support the regulatory requirements. Among these are the following (4):

- "Stability Testing of New Drug Substances and Products"
- "Quality of Biotechnological Products: Stability Testing of Biotechnology/Biological Drug Products"
- "Photostability Testing of New Drug Substances and Products"
- "Stability Testing of New Dosage Forms"

Drug and drug product stability testing during every stage of development is critical to the quality of the product. Drug stability is important during preclinical testing and in clinical (human) trials to obtain a true and accurate assessment of the product being evaluated. For a marketed drug product, assurance of stability is vital to its safety and effectiveness during the course of its shelf life and use.

The FDA-required demonstration of drug stability is necessarily different for each stage of drug development, such as for a 2-week preclinical study, an early Phase I study, a limited Phase II trial, a pivotal Phase III clinical study, or for a new drug application. As a drug development program progresses, so do the requisite data to demonstrate and document the product's stability profile. Before approval for marketing, a product's stability must be assessed with regard to its formulation; the influence of its pharmaceutical ingredients; the influence of the container and closure; the manufacturing and processing conditions (e.g., heat); packaging components; conditions of storage; anticipated conditions of shipping, temperature, light, and humidity; and anticipated duration and conditions of pharmacy shelf life and patient use. Holding intermediate product components (such as drug granulations for tablets) for long periods before processing into finished pharmaceutical products can affect the stability of both the intermediate component and the finished product. Therefore, in-process stability testing, including retesting of intermediate components, is important.

Product containers, closures, and other packaging features must be considered in stability testing. For instance, tablets or capsules packaged in glass or plastic bottles require different stability test protocols from those for blister packs or strip packaging. Drugs particularly subject to

hydrolysis or oxidative decomposition must be evaluated accordingly. And sterile products must meet sterility test standards to ensure protection against microbial contamination. All preservatives must be tested for effectiveness in the finished product.

As noted elsewhere in this section, drug products must meet stability standards for long-term storage at room temperature and relative humidity. Products are also subjected to accelerated stability studies as an indication of shelf life stability. It is an FDA requirement that if the data are not submitted in the approved application, the first three postapproval production batches of a drug substance must be subjected to long-term stability studies and the first three postapproval production batches of drug product must be subjected to both long-term and accelerated stability studies (5, 6).

Drug instability in pharmaceutical formulations may be detected in some instances by a change in the physical appearance, color, odor, taste, or texture of the formulation, whereas in other instances chemical changes may not be self-evident and may be ascertained only through chemical analysis. Scientific data pertaining to the stability of a formulation can lead to prediction of the expected shelf life of the proposed product, and when necessary to redesign of the drug (e.g., into more stable salt or ester form) and to reformulation of the dosage form. Obviously, the rate at which a drug product degrades is of prime importance. The study of the rate of chemical change and the way it is influenced by such factors as the concentration of the drug or reactant, the solvent, temperature and pressure, and other chemical agents in the formulation is reaction kinetics.

In general, a kinetic study begins by measuring the concentration of the drug at given intervals under a specific set of conditions including temperature, pH, ionic strength, light intensity, and drug concentration. The measurement of the drug's concentration at the various times reveals the stability or instability of the drug under the specified conditions with the passage of time. From this starting point, each of the original conditions may be varied to determine the influence of such changes on the drug's stability. For example, the pH of the solution may be changed while the temperature, light intensity, and original drug concentration are held constant.

The findings may be presented graphically, by plotting the drug concentration as a function of time. From the experimental data, the reaction rate may be determined and a rate constant and half-life calculated.

The use of exaggerated conditions of temperature, humidity, light, and others to test the stability of drug formulations is termed accelerated stability testing. Accelerated temperature stability studies, for example, may be conducted for 6 months at 40°C with 75% relative humidity. If a significant change in the product occurs under these conditions, lesser temperature and humidity may be used, such as 30°C and 60% relative humidity. Short-term accelerated studies are used to determine the most stable of the proposed formulations for a drug product. In stress testing, temperature elevations in 10°C increments higher than used in accelerated studies are employed until chemical or physical degradation. Once the most stable formulation is ascertained, its long-term stability is predicted from the data generated from continuing stability studies. Depending on the types and severity of conditions employed, it is fairly common to maintain samples under exaggerated conditions of both temperature and varying humidity for 6 to 12 months. Such studies lead to the prediction of shelf life for a drug product.

In addition to the accelerated stability studies, drug products are subjected to long-term stability studies under the usual conditions of transport and storage expected during product distribution. In conducting these studies, the different national and international climate zones to which the product may be subjected must be borne in mind and expected variances in conditions of temperature and humidity included in the study design. Geographic regions are defined by zones: zone I, temperate; zone II, subtropical; zone III, hot and dry; and zone IV, hot and humid. A given drug product may encounter more than a single zone of temperature and humidity variations during its production and shelf life. Furthermore, it may be warehoused, transported, placed on a pharmacy's shelf, and subsequently in the patient's medicine cabinet, over a varying time course and at a wide range of temperature and humidity. In general, however, the long-term (12 months minimum) testing of new drug entities is conducted at 25°C $\pm$ 2°C and at a relative humidity of 60% $\pm$ 5%.

Samples maintained under these conditions may be retained for 5 years or longer, during which time they are observed for physical signs of deterioration and chemically assayed. These studies, considered with the accelerated stability studies previously performed, lead to a more precise determination of drug product stability, actual shelf life, and the possible extension of expiration dating.

When chemical degradation products are detected, the FDA requires the manufacturer to report their chemical identity, including structure, mechanism of formation, physical and chemical properties, procedures for isolation and purification, specifications and directions for determination at levels expected to be present in the pharmaceutical product, and their pharmacologic action and biologic significance, if any.

Physical Pharmacy Capsule 4.14 Analytical Methods and Standard Curves discusses some analytical methods and standard curve construction used in studies of this type.

In addition, signs of degradation of the specific dosage forms must be observed and reported. For the various dosage forms, this includes the following (1):

Tablets: Appearance (cracking, chipping, mottling), friability, hardness, color, odor, moisture content, clumping, disintegration, and dissolution.

Capsules: Moisture tackiness, color, appearance, shape, brittleness, and dissolution.

Oral solutions and suspensions: Appearance, precipitation, pH, color, odor, redispersibility (suspensions), and clarity (solutions).

Oral powders: Appearance, color, odor, and moisture.

Metered-dose inhalation aerosols: Delivered dose per actuation, number of metered doses, color, particle size distribution, loss of propellant, pressure, valve corrosion, spray pattern, and absence of pathogenic microorganisms.

Topical nonmetered aerosols: Appearance, odor, pressure, weight loss, net weight dispensed, delivery rate, and spray pattern.

Topical creams, ointments, lotions, solutions, and gels: Appearance, color, homogeneity, odor, pH, resuspend-



PHYSICAL PHARMACY CAPSULE 4.14

Analytical Methods and Standard Curves

Any study involving concentration of a drug requires an analytical method and the development of standard curves. There are numerous analytical methods used in pharmacy. It is important for pharmacists to have a basic understanding of pharmaceutical analysis to ensure that valid results are obtained when tests are being conducted. It is important to know (a) when to test, (b) what to test, (c) what method(s) to use, (d) how to interpret the results, (e) the limits of the test, and (f) the importance of analytical testing in the overall quality program in pharmacy.

The goal in analytical testing is to produce results as accurately, efficiently, and quickly as possible. Any analytical method used should have accuracy, speed, reproducibility, and specificity. No single analytical method is ideally suited for all drugs; each method has its own strengths and weaknesses, and there are a number of factors that determine the validity and reliability of results.

SELECTION OF AN ANALYTICAL METHOD

One general consideration in analytical method selection is the type of information that is needed; quantitative (potency, concentration), semiquantitative (where a “cutoff” level is involved, as in endotoxin levels) or qualitative (yes/no type of testing, including substance identification, sterility). Another consideration involves the physical and chemical characteristics of the analyte, including its solubility, partition coefficient, dissociation constant (pKa), volatility, binding, and the quantity present.

One must consider the degree of quantitative measurement in the validation process, for example accuracy, repeatability/reproducibility, and precision are required; generally, the greater the level that is required, the more sophisticated and expensive the analytical methods that must be used. This is also governed by the types of instrumentation that are on hand or available and the standards available for comparison.

PHYSICAL PHARMACY CAPSULE 4.14 CONT.

FACTORS INVOLVED IN METHODS SELECTION

The ultimate analytical method selected depends upon a number of factors, including sample requirements, sample handling/preparation/purification requirements, type of data needed, and levels of specificity and accuracy required.

SAMPLING REQUIREMENTS

In any analytical method, there may be certain sample requirements that impact one's choice, such as the number of samples needed, the difficulty in obtaining a representative sample, the physical state of the sample (solid, liquid or gas), the type of container required for collection and storage of the sample (some analytes may sorb to the walls or cap liner of the sample containers), and leaching of the container material into the sample, if a liquid, may occur. All these may cause problems in analysis. In the event of sorption, siliconization of the sample vials may sometimes help.

The storage requirements for the sample after collection must be specified (type of container, material used, UV protection, latex contamination, etc.). The effects of air, such as oxidation of the sample ingredients, the presence of carbon dioxide and the formation of insoluble carbonates, pH changes, free versus bound drug, etc., must be considered. The sample must be stored at the proper temperature (refrigerated, frozen or controlled room) prior to shipment and during shipment. Procedures to follow if the sample is accidentally frozen or experiences a freeze-thaw cycle should be detailed.

In considering the chemical and physical stability of the sample, the effects of water must also be considered. If the sample must be maintained in a dry environment, including a desiccant, this should be detailed. The stability of the sample during storage, extraction, and preparation must be determined. The potential for enzymatic breakdown, or other adverse effects of pH, temperature, solvents, bacterial growth, etc., must be addressed. If volatile solvents are required, special handling must be implemented to prevent evaporation because if some of the solvent is allowed to evaporate, the resulting concentration may be falsely elevated.

The sample matrix effects must be determined. Any effects caused by sample viscosity (pipetting, aspiration), ionic strength (immunoassays, dialysis), buffers (ionized/unionized ratio can alter the extraction efficiency of an analyte prior to analysis), and vapor pressure, where drug can be lost must be considered. If any sample pretreatment is required prior to shipment or working in-house, consider any inaccuracies that may occur from pipetting, which is one of the most common sources of analytical errors when working with small volumes.

There must be a consideration of any physical methods of separation and purification that might be used. Most analytical methods require some degree of sample pretreatment to prepare it for analysis. These may include crystallization from solution, distillation, sublimation, solvent extraction, solid-phase extraction, chromatography, centrifugation; the proper choice of separation and purification depends upon the physical and chemical properties of the sample, including its solubility, volatility, binding, quantity present, etc. The effect of any substances in the formulation that may interfere or alter the results must be known beforehand.

DATA INTERPRETATION REQUIREMENTS

The collection of raw data from the analytical process must be done appropriately. One must ensure that appropriate and valid descriptive statistics are used to analyze the data, and that the operating parameters of the analytical instruments are well established. Reference values, if available, should be provided with the analytical results. A description of the analytical controls used by the laboratory is important for documentation, as well as the source of reference standards used to establish standard curves.

PHYSICAL PHARMACY CAPSULE 4.14 CONT.

ANALYTICAL METHODS

In pharmaceutical analysis, analytical methods can be generally divided into physical testing methods, methods that interact with electromagnetic radiation, conductometric techniques, immunoassay methods, separation techniques and others.

Nonspecific methods generally include melting, freezing and boiling points, density, refractive index, polarimetry, ultraviolet/visible spectroscopy, and pH. Methods that are somewhat more specific include infrared spectroscopic, mass spectroscopy, ion selective electrodes, immunoassay methods, and chromatographic methods (high performance liquid chromatography [HPLC] and gas chromatography [GC]), provided proper standards are used.

Methods that can be routinely used for testing incoming bulk materials, whether active or excipients, include melting, freezing and boiling points, density, refractive index, UV/Visible spectroscopy, infrared spectroscopy, polarimetry, pH, and the separation methods. Final products may generally require a method such as HPLC or GC. A classification of analytical methods follows along with suggested analytical methods that can be used for different dosage forms.

CLASSIFICATION OF ANALYTICAL AND MICROBIOLOGICAL METHODS**Physical testing procedures**

- Melting point
- Freezing point
- Boiling point
- Density
- Refractive index
- Optical rotation (Polarimetry)
- Thermal analysis
- Color change
- Precipitate formation
- Viscosity change

Interaction of electromagnetic radiation

- Ultraviolet/Visible spectroscopy
- Infrared spectroscopy
- Fluorescence/Phosphorescence spectroscopy
- Raman spectroscopy
- X-ray spectroscopy
- Flame emission and Atomic absorption spectroscopy
- Polarimetry
- Refractometry
- Interferometry

Conductance methods

- pH
- Ion selective electrodes
- Polarography

Immunoassay

- Radioimmunosassay
- Enzyme multiplied immunoassay technique
- Enzyme linked immunosorbent assay
- Fluorescent immunoassay

PHYSICAL PHARMACY CAPSULE 4.14 CONT.

Separation techniques

HPLC

GC

Thin layer chromatography

Paper chromatography

Column chromatography

Gravimetric

Balance

Others

Osmolality

Microbiological methods

Sterility testing

Endotoxin testing

Preservative effectiveness testing

Suggested analytical methods for various dosage forms, depending upon the active drug:

DOSAGE		ANALYTICAL METHOD												
Form	Wt	Vol	pH	Osm	RI	Sp Gr	MP	UV/vis	HPLC	GC	IR	Steril	Endo	
Bulk substances	—	—	*	—	*	—	*	*	*	*	*	—	—	
Powders	*	—	—	—	—	—	—	—	*	*	—	—	—	
Capsules	*	—	—	—	—	—	—	—	*	*	—	—	—	
Tablets		*	—	—	—	—	—	—	—	*	*	—	—	
Lozenges	*	—	—	—	—	—	—	—	*	*	—	—	—	
Suppositories	*	—	—	—	—	*	*	—	*	*	—	—	—	
Sticks	*	—	—	—	—	*	*	—	*	*	—	—	—	
Solutions	*	*	*	*	*	*	—	*	*	*	—	—	—	
Suspensions	*	*	*	—	—	*	—	—	*	*	—	—	—	
Emulsions	*	*	*	—	—	*	—	—	*	*	—	—	—	
Semisolids	*	—	—	—	—	*	*	—	*	*	—	—	—	
Gels	*	*	*	—	*	*	—	—	*	*	—	—	—	
Ophthalmics, Otics & Nasals	*	*	*	*	*	*	—	*	*	*	—	*(Oph. only)	—	
Inhalations	*	*	*	*	*	—	—	*	*	*	—		*	—
Injections	*	*	*	*	*	*	—	*	*	*	—		*	*

CONSTRUCTION OF A STANDARD CURVE

A standard curve is constructed by analyzing samples (standards) of known composition, generally in increasing concentrations. As each standard is analyzed, an instrumental response (Absorbance, Peak Height, Peak Area, Other Numerical Value) will be obtained. The standard concentrations are plotted as the “x” axis on a graph and the instrumental responses are plotted on the “y” axis. As an example,

The following table represents the results from an HPLC analytical method of methotrexate.

Concentration (µg/mL)	0	10	20	30
Response (Peak Height in units)	0	2600	5190	7780

PHYSICAL PHARMACY CAPSULE 4.14 CONT.

When plotted on a graph, one obtains the following:

The next step involves analyzing the unknown sample to obtain a response from the instrument. For example, if the unknown sample provided an instrumental response of 3895, checking that value on the y-axis and moving toward the right on the graph until it intersects the plotted line and dropping down to the x-axis, we can read a value of 15 $\mu\text{g/mL}$ of the methotrexate. As an option,

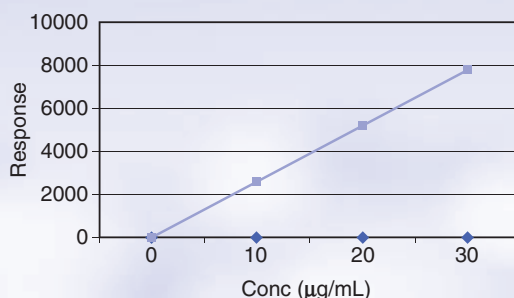
the equation of the line can be calculated and the concentration determined by substituting the values of “y” and “b” with the slope of the line to obtain the drug concentration, as follows:

$$m = \Delta y / \Delta x = (7780 - 0) / (30 - 0) = 7780 / 30 = 259.3$$

$$y = mx + b$$

$$3895 = 259.3 \times x + 0$$

$$x = 15.02 \mu\text{g/mL}$$



ability (lotions), consistency, particle-size distribution, strength, and weight loss.

Ophthalmic and nasal and oral inhalation preparations: Appearance, color, consistency, pH, clarity (solutions), particle size and resuspendability (suspensions, ointments), strength, and sterility.

Small-volume parenterals: Appearance, color, particulate matter, dispersibility (suspensions), pH, sterility, pyrogenicity, and closure integrity.

Large-volume parenterals: Appearance, color, clarity, particulate matter, pH, volume and extractables (when plastic containers are used), sterility, pyrogenicity, and closure integrity.

Suppositories: Softening range, appearance, and melting.

Emulsions: Appearance (such as phase separation), color, odor, pH, and viscosity.

Controlled-release membrane drug delivery systems: Seal strength of the drug reservoir, decomposition products, membrane integrity, drug strength, and drug release rate.

Under usual circumstances, most manufactured products must have a shelf life of 2 or more years to ensure stability at the time of consumption. Commercial products must bear an appropriate expiration date that sets out the time during which the product may be expected to maintain its potency and remain stable under the designated storage conditions. The expiration date limits the time during which the product may be dispensed by the pharmacist or used by the patient.

Prescriptions requiring extemporaneous compounding by the pharmacist do not require the extended shelf life that commercially manufactured and distributed products do because they are intended to be used immediately on receipt by the patient and used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of use, and the compounding pharmacist must employ formulative components and techniques that will result in a stable product (7).

In years past, pharmacists were confronted primarily with innocuous topical prescriptions that required extemporaneous formulation. However, in recent years there has been a need to compound other drug delivery systems, for example, progesterone vaginal suppositories and oral suspensions, from tablets or capsules. When presented with a prescription that requires extemporaneous compounding, the pharmacist is confronted with a difficult situation, because the potency and stability of these prescriptions is a serious matter. Occasionally, the results of compatibility and stability studies on such prescriptions are published in scientific and professional journals. These are very useful; however, for some prescriptions stability and compatibility information is not readily available. In these instances, it behooves the pharmacist to contact the manufacturer of the active

ingredient or ingredients to solicit stability information. Also, a compilation of published stability information is included in *Trissel's Stability of Compounded Formulations* (8). The published stability data are applicable only to products that are prepared identically to the products that are reported.

USP guidelines on stability of extemporaneous compounded formulations state that in the absence of stability information applicable to a specific drug and preparation, the following guidelines can be used: nonaqueous liquids and solid formulations in which the manufactured drug is the source of the active ingredient, not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier; nonaqueous liquids and solid formulations in which a USP or National Formulary (NF) substance is the source of active ingredient, a beyond-use date of 6 months; for water-containing formulations prepared from ingredients in solid form, a beyond-use date not later than 14 days in storage at cold temperatures; for all other formulations, a beyond-use date of the intended duration of therapy or 30 days, whichever is earlier (7). Thus, if an oral aqueous liquid preparation is made from a tablet or capsule formulation, the pharmacist should make up only at most 14 days' supply, and it must be stored in a refrigerator. Furthermore, the pharmacist must dispense the medication in a container conducive to stability and use and must advise the patient of the proper method of use and conditions of storage of the medication.

Finally, when compounding on the basis of extrapolated or less than concrete information, the pharmacist is well advised to keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription.

PHARMACEUTICAL INGREDIENTS AND EXCIPIENTS

DEFINITIONS AND TYPES

To produce a drug substance in a final dosage form requires pharmaceutical ingredients. For example, in the preparation of solutions, one or more *solvents* are used to dissolve the drug substance, *flavors* and *sweeteners* are used to make the product more palatable, *colorants* are added to enhance appeal, *preservatives* may be added

to prevent microbial growth, and *stabilizers*, such as antioxidants and chelating agents, may be used to prevent decomposition, as previously discussed. In the preparation of tablets, *diluents* or *fillers* are commonly added to increase the bulk of the formulation, *binders* to cause adhesion of the powdered drug and pharmaceutical substances, *antiadherents* or *lubricants* to assist smooth tablet formation, *disintegrating agents* to promote tablet breakup after administration, and coatings to improve stability, control disintegration, or enhance appearance. Ointments, creams, and suppositories acquire their characteristic features from their pharmaceutical bases. Thus, for each dosage form, the pharmaceutical ingredients establish the primary features of the product and contribute to the physical form, texture, stability, taste, and overall appearance.

Table 4.3 presents the principal categories of pharmaceutical ingredients, listing some of the official and commercial agents in use. Additional discussion of many ingredients may be found in the chapters where they are most relevant; for example, pharmaceutical materials used in tablet and capsule formulations are discussed in Chapters 7 and 8 and those used in modified-release solid oral dosage forms and drug delivery systems in Chapter 9.

HANDBOOK OF PHARMACEUTICAL EXCIPIENTS AND FOOD AND CHEMICALS CODEX

The *Handbook of Pharmaceutical Excipients* (9) presents monographs on more than 250 excipients used in dosage form preparation. Each monograph includes such information as nonproprietary, chemical, and commercial names; empirical and chemical formulas and molecular weight; pharmaceutical specifications and chemical and physical properties; incompatibilities and interactions with other excipients and drug substances; regulatory status; and applications in pharmaceutical formulation or technology. Additional excipients commonly used are listed in the Food Chemicals Codex (FCC), now owned and published by the USP. The Codex contains information on general provisions and requirements applying to specifications, tests and assays of the FCC, monograph specifications, flavor chemicals, infrared spectra, and general tests and assays.

TABLE 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Acidifying agent</i>	Used in liquid preparations to provide acidic medium for product stability	Citric acid Acetic acid Fumaric acid Hydrochloric acid Nitric acid
<i>Alkalinizing agent</i>	Used in liquid preparations to provide alkaline medium for product stability	Ammonia solution Ammonium carbonate Diethanolamine Monoethanolamine Potassium hydroxide Sodium bicarbonate Sodium borate Sodium carbonate Sodium hydroxide Trolamine
<i>Adsorbent</i>	An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means	Powdered cellulose Activated charcoal
<i>Aerosol propellant</i>	Agent responsible for developing the pressure within an aerosol container and expelling the product when the valve is opened	Carbon dioxide Dichlorodifluoromethane Dichlorotetrafluoroethane Trichloromonofluoromethane
<i>Air displacement</i>	Agent employed to displace air in a hermetically sealed container to enhance product stability	Nitrogen Carbon dioxide
<i>Antifungal preservative</i>	Used in liquid and semisolid preparations to prevent growth of fungi. Effectiveness of parabens is usually enhanced by use in combination	Butylparaben Ethylparaben Methylparaben Benzoic acid Propylparaben Sodium benzoate Sodium propionate
<i>Antimicrobial preservative</i>	Used in liquid and semisolid preparations to prevent growth of microorganisms	Benzalkonium chloride
<i>Antioxidant</i>	Used to prevent deterioration of preparations by oxidation	Ascorbic acid Ascorbyl palmitate Butylated hydroxyanisole Butylated hydroxytoluene Hypophosphorous acid Monothioglycerol Propyl gallate Sodium ascorbate Sodium bisulfite Sodium formaldehyde Sulfoxylate Sodium metabisulfite
<i>Buffering agent</i>	Used to resist change in pH upon dilution or addition of acid or alkali	Potassium metaphosphate Potassium phosphate, monobasic Sodium acetate Sodium citrate, anhydrous and dihydrate
<i>Chelating agent</i>	Substance that forms stable water-soluble complexes (chelates) with metals; used in some liquid pharmaceuticals as stabilizers to complex heavy metals that might promote instability. In such use, they are also called <i>sequestering agents</i>	Edetic acid Edetate disodium

(continued)

TABLE 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Colorant</i>	Used to impart color to liquid and solid (e.g., tablets and capsules) preparations	FD&C Red No. 3 FD&C Red No. 20 FD&C Yellow No. 6 FD&C Blue No. 2 D&C Green No. 5 D&C Orange No. 5 D&C Red No. 8 Caramel Ferric oxide, red
<i>Clarifying agent</i>	Used as a filtering aid for its adsorbent qualities	Bentonite
<i>Emulsifying agent</i>	Used to promote and maintain dispersion of finely subdivided particles of liquid in a vehicle in which it is immiscible. End product may be a liquid emulsion or semisolid emulsion (e.g., a cream)	Acacia Cetomacrogol Cetyl alcohol Glyceryl monostearate Sorbitan monooleate Polyoxyethylene 50 stearate
<i>Encapsulating agent</i>	Used to form thin shells to enclose a drug for ease of administration	Gelatin
<i>Flavorant</i>	Used to impart a pleasant flavor and often odor to a preparation. In addition to the natural flavorants listed, many synthetic ones are used	Anise oil Cinnamon oil Cocoa Menthol Orange oil Peppermint oil Vanillin
<i>Humectant</i>	Used to prevent drying of preparations, particularly ointments and creams	Glycerin Propylene glycol Sorbitol
<i>Levigating agent</i>	Liquid used as an intervening agent to reduce the particle size of a powder by grinding, usually in a mortar	Mineral oil Glycerin Propylene glycol
<i>Ointment base</i>	Semisolid vehicle for medicated ointments	Lanolin Hydrophilic ointment Polyethylene glycol ointment Petrolatum Hydrophilic petrolatum White ointment Yellow ointment Rose water ointment
<i>Plasticizer</i>	Component of film-coating solutions to make film more pliable, enhance spread of coat over tablets, beads, and granules	Diethyl phthalate Glycerin
<i>Solvent</i>	Used to dissolve another substance in preparation of a solution; may be aqueous or not (e.g., oleaginous). Cosolvents, such as water and alcohol (hydroalcoholic) and water and glycerin, may be used when needed. Sterile solvents are used in certain preparations (e.g., injections)	Alcohol Corn oil Cottonseed oil Glycerin Isopropyl alcohol Mineral oil Oleic acid Peanut oil Purified water Water for injection Sterile water for injection Sterile water for irrigation

(continued)

TABLE 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Stiffening agent</i>	Used to increase thickness or hardness of a preparation, usually an ointment	Cetyl alcohol Cetyl esters wax Microcrystalline wax Paraffin Stearyl alcohol White wax Yellow wax
<i>Suppository base</i>	Vehicle for suppositories	Cocoa butter Polyethylene glycols (mixtures) PEG 3350
<i>Surfactant (surface active agent)</i>	Substances that absorb to surfaces or interfaces to reduce surface or interfacial tension. May be used as wetting agents, detergents, or emulsifying agents	Benzalkonium chloride Nonoxynol 10 Octoxynol 9 Polysorbate 80 Sodium lauryl sulfate Sorbitan monopalmitate
<i>Suspending agent</i>	Viscosity-increasing agent used to reduce sedimentation rate of particles in a vehicle in which they are not soluble; suspension may be formulated for oral, parenteral, ophthalmic, topical, or other route	Agar Bentonite Carbomer (e.g., Carbopol) Carboxymethylcellulose sodium Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Kaolin Methylcellulose Tragacanth Veegum
<i>Sweetening agent</i>	Used to impart sweetness to a preparation	Aspartame Dextrose Glycerin Mannitol Saccharin sodium Sorbitol Sucrose
<i>Tablet antiadherents</i>	Prevent tablet ingredients from sticking to punches and dies during production	Magnesium stearate
<i>Tablet binders</i>	Substances used to cause adhesion of powder particles in tablet granulations	Acacia Alginic acid Carboxymethylcellulose sodium Compressible sugar (e.g., Nu-Tab) Ethylcellulose Gelatin Liquid glucose Methylcellulose Povidone Pregelatinized starch
<i>Tablet and capsule diluent</i>	Inert filler to create desired bulk, flow properties, and compression characteristics of tablets and capsules	Dibasic calcium phosphate Kaolin Lactose Mannitol Microcrystalline cellulose Powdered cellulose Precipitated calcium carbonate Sorbitol Starch

(continued)

TABLE 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Tablet coating agent</i>	Used to coat a tablet to protect against decomposition by atmospheric oxygen or humidity, to provide a desired release pattern, to mask taste or odor, or for aesthetic purposes. Coating may be sugar, film, or thick covering around a tablet. Sugar-coated tablets generally start to break up in the stomach. Film forms a thin cover around a formed tablet or bead. Unless it is enteric, film dissolves in the stomach. Enteric coating passes through the stomach to break up in the intestines. Some water-insoluble coatings (e.g., ethylcellulose) are used to slow the release of drug in the gastrointestinal tract	
<i>Sugar coating</i>		Liquid glucose Sucrose
<i>Film coating</i>		Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Methylcellulose (e.g., Methocel) Ethylcellulose (e.g., Ethocel)
<i>Enteric coating</i>		Cellulose acetate phthalate Shellac (35% in alcohol, pharmaceutical glaze)
<i>Tablet direct compression excipient</i>	Used in direct compression tablet formulations	Dibasic calcium phosphate (e.g., Datab)
<i>Tablet disintegrant</i>	Used in solid forms to promote disruption of the mass into smaller particles more readily dispersed or dissolved	Alginate acid Polacrillin potassium (e.g., Amberlite) Sodium alginate Sodium starch glycolate Starch
<i>Tablet glidant</i>	Used in tablet and capsule formulations to improve flow properties of the powder mixture	Colloidal silica Cornstarch Talc
<i>Tablet lubricant</i>	Used in tablet formulations to reduce friction during tablet compression	Calcium stearate Magnesium stearate Mineral oil Stearic acid Zinc stearate
<i>Tablet or capsule opaquant</i>	Used to render a coating opaque. May be used alone or with a colorant	Titanium dioxide
<i>Tablet polishing agent</i>	Used to impart an attractive sheen to coated tablets	Carnauba wax White wax
<i>Tonicity agent</i>	Used to render solution similar in osmotic-dextrose characteristics to physiologic fluids, e.g., in ophthalmic, parenteral, and irrigation fluids	Sodium chloride
<i>Vehicle</i>	Carrying agent used in formulating a variety of liquids for oral and parenteral administration Generally, oral liquids are aqueous (e.g., syrups) or hydroalcoholic (e.g., elixirs). Solutions for intravenous use are aqueous, whereas intramuscular injections may be aqueous or oleaginous	

(continued)

TABLE 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
Flavored, sweetened		Acacia syrup Aromatic syrup Aromatic elixir Cherry syrup Cocoa syrup Orange syrup Syrup
Oleaginous		Corn oil Mineral oil Peanut oil Sesame oil
Sterile		Bacteriostatic sodium chloride injection
Viscosity-increasing agent	Used to render preparations more resistant to flow. Used in suspensions to deter sedimentation, in ophthalmic solutions to enhance contact time (e.g., methylcellulose), to thicken topical creams, etc.	Alginic acid Bentonite Carbomer Carboxymethylcellulose Sodium Methylcellulose Povidone Sodium alginate Tragacanth

HARMONIZATION OF STANDARDS

There is great interest in the international harmonization of standards applicable to pharmaceutical excipients. This is because the pharmaceutical industry is multinational, with major companies having facilities in more than a single country, with products sold in markets worldwide, and with regulatory approval for these products required in each country. Standards for each drug substance and excipient used in pharmaceuticals are contained in pharmacopeias—or for new agents, in an application for regulatory approval by the relevant governing authority. The four pharmacopeias with the largest international use are the *United States Pharmacopeia–National Formulary* (USP–NF), *British Pharmacopeia*, *European Pharmacopeia*, and *Japanese Pharmacopeia*. Uniform standards for excipients in these and other pharmacopeias would facilitate production efficiency, enable the marketing of a single formulation of a product internationally, and enhance regulatory approval of pharmaceutical products worldwide. The goal of harmonization is an ongoing effort by corporate representatives and international regulatory authorities.

A few of the more common and widely used pharmaceutical excipients, including sweeteners,

flavors, colors, and preservatives, are discussed here.

APPEARANCE AND PALATABILITY

Although most drug substances in use today are unpalatable and unattractive in their natural state, their preparations present them to the patient as colorful, flavorful formulations attractive to the sight, smell, and taste. These qualities, which are the rule rather than the exception, have virtually eliminated the natural reluctance of many patients to take medications because of disagreeable odor or taste. In fact, the inherent attractiveness of today's pharmaceuticals has caused them to acquire the dubious distinction of being a source of accidental poisonings in the home, particularly among children who are lured by their organoleptic appeal.

There is some psychologic basis to drug therapy, and the odor, taste, and color of a pharmaceutical preparation can play a part. An appropriate drug has its most beneficial effect when it is accepted and taken properly by the patient. The proper combination of flavor, fragrance, and color in a pharmaceutical product contributes to its acceptance.

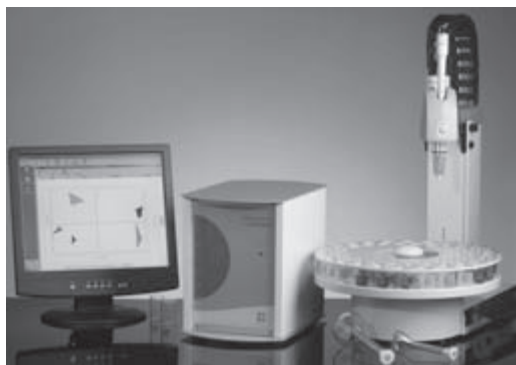


FIGURE 4.4 Electronic tongue to assist in formulation development. (Courtesy of Alpha MOS.)

An “electronic tongue” is used to aid in providing a global “taste fingerprint” during formulation development. It provides information on bitterness levels and the stability of flavors in terms of taste (Figure 4.4).

Flavoring Pharmaceuticals

The flavoring of pharmaceuticals applies primarily to liquids intended for oral administration. The 10,000 taste buds on the tongue, roof of the mouth, cheeks, and throat have 60 to 100 receptor cells each (10). These receptor cells interact with molecules dissolved in the saliva and produce a positive or negative taste sensation. Medication in liquid form comes into immediate and direct contact with these taste buds. The addition of flavoring agents to liquid medication can mask the disagreeable taste. Drugs placed in capsules or prepared as coated tablets may be easily swallowed with no contact between the drug and the taste buds. Tablets containing drugs that are not especially distasteful may remain uncoated and unflavored. Swallowing them with water usually is sufficient to avoid undesirable taste sensations. However, chewable tablets, such as certain antacid and vitamin products, usually are sweetened and flavored to improve acceptance.

The flavor sensation of a food or pharmaceutical is actually a complex blend of taste and smell, with lesser influences of texture, temperature, and even sight. In flavor-formulating a pharmaceutical product, the pharmacist must give consideration to the color, odor, texture, and taste of the preparation. It would be incongruous, for example, to color a liquid pharmaceutical

red and give it a banana taste and a mint odor. The color of a pharmaceutical must have a psychogenic balance with the taste, and the odor must also enhance that taste. Odor greatly affects the flavor of a preparation or foodstuff. If one's sense of smell is impaired, as during a head cold, the usual flavor sensation of food is similarly diminished.

The medicinal chemist and the formulation pharmacist are well acquainted with the taste characteristics of certain chemical types of drugs and strive to mask the unwanted taste through the appropriate use of flavoring agents. Although there are no rules for unerringly predicting the taste sensation of a drug based on its chemical constitution, experience permits the presentation of several observations. For instance, although we recognize and assume the salty taste of sodium chloride, the formulation pharmacist knows that not all salts are salty but that their taste is a function of both cation and anion. Whereas salty tastes are evoked by chlorides of sodium, potassium, and ammonium and by sodium bromide, bromides of potassium and ammonium elicit bitter and salty sensations, and potassium iodide and magnesium sulfate (Epsom salt) are predominantly bitter. In general, low-molecular-weight salts are salty, and high-molecular-weight salts are bitter.

With organic compounds, an increase in the number of hydroxyl groups (—OH) seems to increase the sweetness of the compound. Sucrose, which has eight hydroxyl groups, is sweeter than glycerin, another pharmaceutical sweetener, which has but three hydroxyl groups. In general, the organic esters, alcohols, and aldehydes are pleasant to the taste, and since many of them are volatile, they also contribute to the odor and thus the flavor of preparations in which they are used. Many nitrogen-containing compounds, especially the plant alkaloids (e.g., quinine) are extremely bitter, but certain other nitrogen-containing compounds (e.g., aspartame) are extremely sweet. The medicinal chemist recognizes that even the most simple structural change in an organic compound can alter its taste. D-Glucose is sweet, but L-glucose has a slightly salty taste; saccharin is very sweet, but N-methyl-saccharin is tasteless (11).

Thus, prediction of the taste characteristics of a new drug is only speculative. However, it is soon learned and the formulation pharmacist is

then put to the task of increasing the drug's palatability in the environment of other formulative agents. The selection of an appropriate flavoring agent depends on several factors, primarily the taste of the drug substance itself. Certain flavoring materials are more effective than others in masking or disguising the particular bitter, salty, sour, or otherwise undesirable taste of medicinal agents. Although individuals' tastes and flavor preferences differ, cocoa-flavored vehicles are considered effective for masking the taste of bitter drugs. Fruit or citrus flavors are frequently used to combat sour or acid-tasting drugs, and cinnamon, orange, raspberry, and other flavors have been successfully used to make preparations of salty drugs more palatable.

The age of the intended patient should also be considered in the selection of the flavoring agent, because certain age groups seem to prefer certain flavors. Children prefer sweet candy-like preparations with fruity flavors, but adults seem to prefer less sweet preparations with a tart rather than a fruit flavor.

Flavors can consist of oil- or water-soluble liquids and dry powders; most are diluted in carriers. Oil-soluble carriers include soybean and other edible oils; water-soluble carriers include water, ethanol, propylene glycol, glycerin, and emulsifiers. Dry carriers include maltodextrins, corn syrup solids, modified starches, gum arabic, salt, sugars, and whey protein. Flavors can degrade as a result of exposure to light, temperature, head space oxygen, water, enzymes, contaminants, and other product components, so they must be carefully selected and checked for stability.

The different types of flavors include natural, artificial, and spice:

Natural flavor: Essential oil, oleoresin, essence or extractive, protein hydrolysate, distillate, or any product of roasting, heating, or enzymolysis, which contains the flavoring constituents derived from a spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf or similar plant material, meat, seafood, poultry, eggs, dairy products, or fermentation products thereof whose significant function in food is flavoring rather than nutritional. [CFR 101.22(a)(3)] In "all natural" flavors, one doesn't necessarily know the exact chemical composition.

Artificial flavor: Any substance used to impart flavor that is not derived from a spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf or similar plant material, meat, fish, poultry, eggs, dairy products, or fermentation products thereof. [CFR 101.22(a)(1)]

Spice: Any aromatic vegetable substance in whole, broken, or ground form, except substances traditionally regarded as foods, such as onions, garlic, and celery; whose significant function in food is seasoning rather than nutritional; that is true to name; and from which no portion of any volatile oil or other flavoring principle has been removed. [CFR 101.22(a)(2)]

In addition to the types of flavors, you should be aware of commercial flavor designations, including the following (*Note:* ABCD would be the flavor name, e.g., cherry):

Natural ABCD flavor	All components derived from ABCD.
ABCD flavor, natural	At least one component and artificial-derived from ABCD. No definition of natural to artificial ratio.
ABCD flavor, WONF*	All components natural. At least one component derived from ABCD.
Natural flavor, ABCD type	All components natural. No components derived from ABCD.
ABCD flavor, artificial	All components are artificial.
Conceptual flavors	May contain artificial flavors. No reference point. May only have to declare in ingredient declaration.

*WONF, with other natural flavors.

A general guide to using flavors is to start as follows (keep in mind it is usually possible to add more flavor, but once it is added, it is too late to remove it).

Water-soluble flavors	Generally start at 0.2% for artificial and 1%–2% for natural flavors.
Oil-soluble flavors	Generally start at 0.1% in finished product for artificial flavors and 0.2% for natural flavors.
Powdered flavors	Generally start at 0.1% in finished product for artificial flavors and 0.75% for natural flavors.

Sweetening Pharmaceuticals

In addition to sucrose, a number of artificial sweetening agents have been used in foods and pharmaceuticals over the years. Some of these, including aspartame, saccharin, and cyclamate, have faced challenges over their safety by the FDA and restrictions to their use and sale; in fact, in 1969, FDA banned cyclamates from use in the United States.

The introduction of diet soft drinks in the 1950s provided the spark for the widespread use of artificial sweeteners today. Besides dieters, patients with diabetes are regular users of artificial sweeteners. Over the years, each of the artificial sweeteners has undergone long periods of review and debate. Critical to the evaluation of food additives are issues of metabolism and toxicity. For example, almost none of the saccharin a person consumes is metabolized; it is excreted by the kidneys virtually unchanged. Cyclamate, on the other hand, is metabolized, or processed, in the digestive tract, and its by-products are excreted by the kidneys. Aspartame breaks down in the body into three basic components: the amino acids phenylalanine and aspartic acid, and methanol. These three components, which also occur naturally in various foods, are in turn metabolized through regular pathways in the body. Because of its metabolism to phenylalanine, the use of aspartame by persons with phenylketonuria (PKU) is discouraged, and diet foods and drinks must bear an appropriate label warning indicating that the particular foodstuff not be consumed by such individuals. They cannot metabolize phenylalanine adequately, so they undergo an increase in the serum levels of the amino acid (hyperphenylalaninemia). This can result in mental retardation and can affect the fetus of a pregnant woman who has PKU.

Passage in 1958 of the Food Additives Amendment to the Food, Drug, and Cosmetic Act produced a major change in how the federal government regulates food additives. For one thing, no new food additive may be used if animal feeding studies or other appropriate tests showed that it caused cancer. This is the famous Delaney Clause. The *amount* of the substance one would have to consume to induce cancer is not significant under the Delaney Clause.

Another critical feature of the 1958 amendment was that it did not apply to additives that were generally recognized by experts as safe for their intended uses. Saccharin, cyclamate, and a long list of other substances were being used in foods before the amendment's passage and were "generally recognized as safe"—or what is known today as GRAS. Aspartame, on the other hand, was the first artificial sweetener to fall under the 1958 amendment's requirement for premarketing proof of safety, because the first petition to FDA for its approval was filed in 1973. In 1968, the Committee on Food Protection of the National

Academy of Sciences issued an interim report on the safety of nonnutritive sweeteners, including saccharin. In the early 1970s, FDA began a major review of hundreds of food additives on the GRAS list to determine whether current studies justified their safe status. In 1972, with new studies under way, FDA decided to take saccharin off the GRAS and establish interim limits that would permit its continued use until additional studies were completed. (Previous studies indicated that male and female rats fed doses of saccharin developed a significant incidence of bladder tumors.) In November 1977, Congress passed the Saccharin Study and Labeling Act, which permitted saccharin's continued availability while mandating that warning labels be used to advise consumers that saccharin caused cancer in animals. The law also directed FDA to arrange further studies of carcinogens and toxic substances in foods.

Cyclamate was introduced into beverages and foods in the 1950s and dominated the artificial sweetener market in the 1960s. After much controversy regarding its safety, the FDA issued a final ruling in 1980 stating that safety has not been demonstrated. Since that date, scientific studies have continued the search for conclusive support or rejection of the FDA decision. At question is cyclamate's possible carcinogenicity and its possible causation of genetic damage and testicular atrophy. See the indicated references for a review of the recent history of sweeteners, including saccharin, cyclamate, fructose, polyalcohols, sucrose, and aspartame (12–15).

Acesulfame potassium, a nonnutritive sweetener discovered in 1967, was approved in 1992 by the FDA. It previously was used in a number of other countries. Structurally similar to saccharin, it is 130 times as sweet as sucrose and is excreted unchanged in the urine. Acesulfame is more stable than aspartame at elevated temperatures and FDA initially approved it for use in candy, chewing gum, confectionery, and instant coffee and tea.

A relatively new sweetening agent in U.S. commerce is Stevia powder, the extract from the leaves of the plant *Stevia rebaudiana bertonii*. It is natural, nontoxic, safe, and about 30 times as sweet as cane sugar, or sucrose. It can be used in both hot and cold preparations. Table 4.4 compares three of the most commonly used sweeteners in the food and drug industry.

Most large pharmaceutical manufacturers have special laboratories for taste-testing

TABLE 4.4 COMPARISON OF SWEETENERS

	SUCROSE	SACCHARIN	ASPARTAME
Source	Sugar cane; sugar beet	Chemical synthesis; phthalic anhydride, a petroleum product	Chemical synthesis; methyl ester dipeptide of phenylalanine and aspartic acid
Relative	1	300	180–200 sweetness
Bitterness	None	Moderate to strong	None
Aftertaste	None	Moderate to strong; sometimes metallic or bitter	None
Calories	4/g	0	4/g
Acid stability	Good	Excellent	Fair
Heat stability	Good	Excellent	Poor

proposed formulations of their products. Panels of employees or interested community participants participate in evaluating the various formulations, and their assessments become the basis for the firm's flavoring decisions.

The flavoring agent in liquid pharmaceutical products is added to the solvent or vehicle component of the formulation in which it is most soluble or miscible. That is, water-soluble flavorants are added to the aqueous component of a formulation and poorly water-soluble flavorants are added to the alcoholic or other non-aqueous solvent component of the formulation. In a hydroalcoholic or other multisolvent system, care must be exercised to maintain the flavorant in solution. This is accomplished by maintaining a sufficient level of the flavorant's solvent.

Coloring Pharmaceuticals

Coloring agents are used in pharmaceutical preparations for esthetics. A distinction should be made between agents that have inherent color and those that are employed as colorants. Certain agents—sulfur (yellow), riboflavin (yellow), cupric sulfate (blue), ferrous sulfate (bluish green), cyanocobalamin (red), and red mercuric iodide (vivid red)—have inherent color and are not thought of as pharmaceutical colorants in the usual sense of the term.

Although most pharmaceutical colorants in use today are synthetic, a few are obtained from natural mineral and plant sources. For example, red ferric oxide is mixed in small proportions with zinc oxide powder to give calamine its characteristic pink color, which is intended to match the skin tone upon application.

The synthetic coloring agents used in pharmaceutical products were first prepared in the middle of the 19th century from principles of coal tar. Coal tar (*pix carbonis*), a thick, black viscid liquid, is a by-product of the destructive distillation of coal. Its composition is extremely complex, and many of its constituents may be separated by fractional distillation. Among its products are anthracene, benzene, naphtha, creosote, phenol, and pitch. About 90% of the dyes used in the products FDA regulates are synthesized from a single colorless derivative of benzene called aniline. These aniline dyes are also known as synthetic organic dyes or as coal tar dyes, since aniline was originally obtained from bituminous coal. Aniline dyes today come mainly from petroleum.

Many coal tar dyes were originally used indiscriminately in foods and beverages to enhance their appeal without regard to their toxic potential. It was only after careful scrutiny that some dyes were found to be hazardous to health because of either their own chemical nature or the impurities they carried. As more dyestuffs became available, some expert guidance and regulation were needed to ensure the safety of the public. After passage of the Food and Drug Act in 1906, the U.S. Department of Agriculture established regulations by which a few colorants were *permitted* or *certified* for use in certain products. Today, the FDA regulates the use of color additives in foods, drugs, and cosmetics through the provisions of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1960 with the Color Additive Amendments. Lists of color additives *exempt* from certification and those *subject* to certification are codified into law and regulated by the FDA (16). Certified color

additives are classified according to their approved use: (a) FD&C color additives, which may be used in foods, drugs, and cosmetics; (b) D&C color additives, some of which are approved for use in drugs, some in cosmetics, and some in medical devices; and (c) external D&C color additives, the use of which is restricted to external parts of the body, not including the lips or any other body surface covered by mucous membrane. Each certification category has a variety of basic colors and shades for coloring pharmaceuticals. One may select from a variety of FD&C, D&C, and external D&C reds, yellows, oranges, greens, blues, and violets. By selective combinations of the colorants one can create distinctive colors (Table 4.5).

TABLE 4.5 EXAMPLES OF COLOR FORMULATIONS

SHADE OR COLOR	FD&C DYE	% OF BLEND
Orange	Yellow No. 6	100
	or	
	Yellow No. 5	95
Cherry	Red No. 40	5
	Red No. 40	99
	Blue No. 1	1
Strawberry	Red No. 40	100
	or	
	Red No. 40	95
Lemon	Red No. 3	5
	Yellow No. 5	100
	Blue No. 1	5
Lime	Yellow No. 5	95
	Blue No. 1	5
Grape	Red No. 40	80
	Blue No. 1	20
Raspberry	Red No. 3	75
	Yellow No. 6	20
	Blue No. 1	5
Butterscotch	Yellow No. 5	74
	Red No. 40	24
	Blue No. 1	2
Chocolate	Red No. 40	52
	Yellow No. 5	40
	Blue No. 1	8
Caramel	Yellow No. 5	64
	Red No. 3	21
	Yellow No. 6	9
	Blue No. 1	6
Cinnamon	Yellow No. 5	60
	Red No. 40	35
	Blue No. 1	5

From literature of Warner-Jenkinson Co., St. Louis, Mo.

As a part of the National Toxicology Program of the U.S. Department of Health and Human Services, various substances, including color additives, are studied for toxicity and carcinogenesis. For color additives, the study protocols usually call for a 2-year study in which groups of male and female mice and rats are fed diets containing various quantities of the colorant. The killed and surviving animals are examined for evidence of long-term toxicity and carcinogenesis. Five categories of evidence of carcinogenic activity are used in reporting observations: (a) “clear evidence” of carcinogenic activity; (b) “some evidence”; (c) “equivocal evidence,” indicating uncertainty; (d) “no evidence,” indicating no observable effect; and (e) “inadequate study,” for studies that cannot be evaluated because of major flaws.

The certification status of the colorants is continually reviewed, and changes are made in the list of certified colors in accordance with toxicology findings. These changes may be (a) the withdrawal of certification, (b) the transfer of a colorant from one certification category to another, or (c) the addition of new colors to the list. Before gaining certification, a color additive must be demonstrated to be safe. In the case of pharmaceutical preparations, color additives, as with all additives, must not interfere with therapeutic efficacy, nor may they interfere with the prescribed assay procedure for the preparation.

In the 1970s, concern and scientific questioning of the safety of some color additives heightened. A color that drew particular attention was FD&C Red No. 2, because of its extensive use in foods, drugs, and cosmetics. Researchers in Russia reported that this color, also known as amaranth, caused cancer in rats. Although the FDA was never able to determine the purity of the amaranth tested in Russia, these reports led to FDA investigations and a series of tests that eventually resulted in withdrawal of FD&C Red No. 2 from the FDA certified list in 1976 because its sponsors were unable to prove safety. That year, FDA also terminated approval for use of FD&C Red No. 4 in maraschino cherries and ingested drugs because of unresolved safety questions. FD&C Red No. 4 is now permitted only in externally applied drugs and cosmetics.

FD&C Yellow No. 5 (also known as tartrazine) causes allergic-type reactions in many people. People who are allergic to aspirin are also

likely to be allergic to this dye. As a result, the FDA requires listing of this dye by name on the labels of foods (e.g., butter, cheese, ice cream) and ingested drugs containing it.

A colorant becomes an integral part of a pharmaceutical formulation, and its exact quantitative amount must be reproducible each time the formulation is prepared, or else the preparation would have a different appearance from batch to batch. This requires a high degree of skill, for the amount of colorant generally added to liquid preparations ranges from 0.0005% to 0.001% depending upon the colorant and the depth of color desired. Because of their color potency, dyes generally are added to pharmaceutical preparations in the form of diluted solutions rather than as concentrated dry powders. This permits greater accuracy in measurement and more consistent color production.

In addition to liquid dyes in the coloring of pharmaceuticals, lake pigments may also be used. Whereas a chemical material exhibits coloring power or tinctorial strength when dissolved, pigment is an insoluble material that colors by dispersion. An FD&C lake is a pigment consisting of a substratum of alumina hydrate on which the dye is adsorbed or precipitated. Having aluminum hydroxide as the substrate, the lakes are insoluble in nearly all solvents. FD&C lakes are subject to certification and must be made from certified dyes. Lakes do not have a specified dye content; they range from 10% to 40% pure dye. By their nature, lakes are suitable for coloring products in which the moisture levels are low.

Lakes in pharmaceuticals are commonly used in the form of fine dispersions or suspensions. The pigment particles may range in size from less than 1 μm up to 30 μm . The finer the particle, the less chance for color speckling in the finished product. Blends of various lake pigments may be used to achieve a variety of colors, and various vehicles, such as glycerin, propylene glycol, and sucrose-based syrup, may be employed to disperse the colorants.

Colored empty gelatin capsule shells may be used to hold a powdered drug mixture. Many commercial capsules are prepared with a capsule body of one color and a cap of a different color, resulting in a two-colored capsule. This makes certain commercial products more readily identifiable than solid-colored capsules. For powdered drugs dispensed as such or compressed into tab-

lets, a generally larger proportion of dye is required (about 0.1%) to achieve the desired hue than with liquid preparations.

Both dyes and lakes are used to color sugar-coated tablets, film-coated tablets, direct-compression tablets, pharmaceutical suspensions, and other dosage forms (17). Traditionally, sugar-coated tablets have been colored with syrup solutions containing varying amounts of the water-soluble dyes, starting with very dilute solutions, working up to concentrated color syrup solutions. As many as 30 to 60 coats are common. With the lakes, fewer color coats are used. Appealing tablets have been made with as few as 8 to 12 coats using lakes dispersed in syrup. Water-soluble dyes in aqueous vehicles or lakes dispersed in organic solvents may be effectively sprayed on tablets to produce attractive film coatings. There is continued interest today in chewable tablets, because of the availability of many direct-compression materials such as dextrose, sucrose, mannitol, sorbitol, and spray-dried lactose. The direct-compression colored chewable tablets may be prepared with 1 lb of lake per 1,000 lb of tablet mix. For aqueous suspensions, FD&C water-soluble colors or lakes may be satisfactory. In other suspensions, FD&C lakes are necessary. The lakes, added to either the aqueous or nonaqueous phase, generally at a level of 1 lb of color per 1,000 lb of suspension, require homogenization or mechanical blending to achieve uniform coloring.

For the most part, ointments, suppositories, and ophthalmic and parenteral products assume the color of their ingredients and do not contain color additives. Should a dye lose the certification status it held when a product was first formulated, manufactured, and marketed, the manufacturer must reformulate within a reasonable length of time, using only color additives certified at the new date of manufacture.

In addition to esthetics and the certification status of a dye, a formulation pharmacist must select the dyes to be used in a particular formula on the basis of their physical and chemical properties. Of prime importance is the solubility of a prospective dye in the vehicle to be used for a liquid formulation or in a solvent to be employed during a pharmaceutical process, as when the dye is sprayed on a batch of tablets. In general, most dyes are broadly grouped into those that are water soluble and those that are oil soluble; few if any dyes are both. Usually, a water-soluble

dye is also adequately soluble in commonly used pharmaceutical liquids like glycerin, alcohol, and glycol ethers. Oil-soluble dyes may also be soluble to some extent in these solvents and in liquid petrolatum (mineral oil), fatty acids, fixed oils, and waxes. No great deal of solubility is required, since the concentration of dye in a given preparation is minimal.

Another important consideration when selecting a dye for use in a liquid pharmaceutical is the pH and pH stability of the preparation to be colored. Dyes can change color with a change in pH, and the dye must be selected so that no anticipated pH change will alter the color during the usual shelf life. The dye also must be chemically stable in the presence of the other formula-tive ingredients and must not interfere with the stability of the other agents. To maintain their original colors, FD&C dyes must be protected from oxidizing agents, reducing agents (especially metals, including iron, aluminum, zinc, and tin), strong acids and alkalis, and excessive heating. Dyes must also be reasonably photo-stable; that is, they must not change color when exposed to light of anticipated intensities and wavelengths under the usual conditions of shelf storage. Certain medicinal agents, particularly those prepared in liquid form, must be protected from light to maintain their chemical stability and their therapeutic effectiveness. These preparations are generally kept in dark amber or opaque containers. For solid dosage forms of photolabile drugs, a colored or opaque capsule shell may enhance the drug's stability by shielding out light rays.

PRESERVATIVES

In addition to the stabilization of pharmaceutical preparations against chemical and physical degradation due to changed environmental conditions within a formulation, certain liquid and semisolid preparations must be preserved against microbial contamination.

Sterilization and Preservation

Although some types of pharmaceutical products, for example, ophthalmic and injectable preparations, are sterilized by physical methods (autoclaving for 20 minutes at 15 lb pressure and 121°C, dry heat at 180°C for 1 hour, or bacterial filtration) during manufacture, many of them

also require an antimicrobial preservative to maintain their aseptic condition throughout storage and use. Other types of preparations that are not sterilized during their preparation but are particularly susceptible to microbial growth because of the nature of their ingredients are protected by the addition of an antimicrobial preservative. Preparations that provide excellent growth media for microbes are most aqueous preparations, especially syrups, emulsions, suspensions, and some semisolid preparations, particularly creams. Certain hydroalcoholic and most alcoholic preparations may not require the addition of a chemical preservative when the alcoholic content is sufficient to prevent microbial growth. Generally, 15% V/V alcohol will prevent microbial growth in acid media and 18% V/V in alkaline media. Most alcohol-containing pharmaceuticals, such as elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation. The same applies to other individual pharmaceuticals that by virtue of their vehicle or other formula-tive agents may not permit the growth of microorganisms.

Preservative Selection

When experience or shelf storage experiments indicate that a preservative is required in a pharmaceutical preparation, its selection is based on many considerations, including some of the following:

- The preservative prevents the growth of the type of microorganisms considered the most likely contaminants of the preparation.
- The preservative is soluble enough in water to achieve adequate concentrations in the aqueous phase of a system with two or more phases.
- The proportion of preservative remaining undissociated at the pH of the preparation makes it capable of penetrating the microorganism and destroying its integrity.
- The required concentration of the preservative does not affect the safety or comfort of the patient when the pharmaceutical preparation is administered by the usual or intended route; that is, it is nonirritating, nonsensitizing, and nontoxic.
- The preservative has adequate stability and will not be reduced in concentration by chemical decomposition or volatilization during the desired shelf life of the preparation.

- The preservative is completely compatible with all other formulative ingredients and does not interfere with them, nor do they interfere with the effectiveness of the preservative agent.
- The preservative does not adversely affect the preparation's container or closure.

General Preservative Considerations

Microorganisms include molds, yeasts, and bacteria, with bacteria generally favoring a slightly alkaline medium and the others an acid medium. Although few microorganisms can grow below pH 3 or above pH 9, most aqueous pharmaceutical preparations are within the favorable pH range and therefore must be protected against microbial growth. To be effective, a preservative agent must be dissolved in sufficient concentration in the aqueous phase of a preparation. Furthermore, only the undissociated fraction or molecular form of a preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism. Thus, the preservative selected must be largely undissociated at the pH of the formulation being prepared. Acidic preservatives like benzoic, boric, and sorbic acids are more undissociated and thus more effective as the medium is made more acid. Conversely, alkaline preservatives are less effective in acid or neutral media and more effective in alkaline media. Thus, it is meaningless to suggest preservative effectiveness at specific concentrations unless the pH of the system is mentioned and the undissociated concentration of the agent is calculated or otherwise determined. Also, if formulative materials interfere with the solubility or availability of the preservative agent, its chemical concentration may be misleading, because it may not be a true measure of the effective concentration. Many incompatible combinations of preservative agents and other pharmaceutical adjuncts have been discovered in recent years, and undoubtedly many more will be uncovered in the future as new preservatives, pharmaceutical adjuncts, and therapeutic agents are combined for the first time. Many of the recognized incompatible combinations that inactivate the preservative contain macromolecules, including various cellulose derivatives, polyethylene glycols, and natural gums. These include tragacanth, which can attract and hold preservative agents, such as the parabens and phenolic compounds, rendering

them unavailable for their preservative function. It is essential for the research pharmacist to examine all formulative ingredients as one affects the other to ensure that each agent is free to do its job. In addition, the preservative must not interact with a container, such as a metal ointment tube or a plastic medication bottle, or with an enclosure, such as a rubber or plastic cap or liner. Such an interaction could result in decomposition of the preservative or the container closure or both, causing decomposition and contamination. Appropriate tests should be devised and conducted to prevent this type of preservative interaction.

Mode of Action

Preservatives interfere with microbial growth, multiplication, and metabolism through one or more of the following mechanisms:

- Modification of cell membrane permeability and leakage of cell constituents (partial lysis)
- Lysis and cytoplasmic leakage
- Irreversible coagulation of cytoplasmic constituents (e.g., protein precipitation)
- Inhibition of cellular metabolism, such as by interfering with enzyme systems or inhibition of cell wall synthesis
- Oxidation of cellular constituents
- Hydrolysis

A few of the commonly used pharmaceutical preservatives and their probable modes of action are presented in Table 4.6.

Preservative Utilization

Suitable substances may be added to a pharmaceutical preparation to enhance its permanency or usefulness. Such additives are suitable only if they are nontoxic and harmless in the amounts administered and do not interfere with the therapeutic efficacy or tests or assays of the preparation. Certain intravenous preparations given in large volumes as blood replenishers or as nutrients are not permitted to contain bacteriostatic additives, because the amounts required to preserve such large volumes would constitute a health hazard when administered to the patient. Thus preparations like dextrose injection, USP, and others commonly given as fluid and nutrient replenishers by intravenous injections in amounts of 500 to 1,000 mL may not contain antibacterial preservatives. On the other hand, injectable preparations

TABLE 4.6 PROBABLE MODES OF ACTION OF SOME PRESERVATIVES

PRESERVATIVE	PROBABLE MODES OF ACTION
Benzoic acid, boric acid, p-hydroxybenzoates	Denaturation of proteins
Phenols and chlorinated phenolic compounds	Lytic and denaturation action on cytoplasmic membranes and for chlorinated preservatives, also by oxidation of enzymes
Alcohols	Lytic and denaturation action on membranes
Quaternary compounds	Lytic action on membranes
Mercurials	Denaturation of enzymes by combining with thiol (-SH) groups)

given in small volumes—for example, morphine sulfate injection, USP, which provides a therapeutic amount of morphine sulfate in approximately a 1-mL volume—can be preserved with a suitable preservative without the danger of the patient receiving an excessive amount of the preservative.

Examples of the preservatives and their concentrations commonly employed in pharmaceutical preparations are benzoic acid (0.1% to 0.2%), sodium benzoate (0.1% to 0.2%), alcohol (15% to 20%), phenylmercuric nitrate and acetate (0.002% to 0.01%), phenol (0.1% to 0.5%), cresol (0.1% to 0.5%), chlorobutanol (0.5%), benzalkonium chloride (0.002% to 0.01%), and combinations of methylparaben and propylparaben (0.1% to 0.2%), the latter being especially good against fungus. The required proportion

varies with the pH, dissociation, and other factors already indicated as well with the presence of other formulative ingredients with inherent preservative capabilities.

For each type of preparation to be preserved, the research pharmacist must consider the influence of the preservative on the comfort of the patient. For instance, a preservative in an ophthalmic preparation must have an extremely low degree of irritant qualities, which is characteristic of chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate, frequently used in ophthalmic preparations. In all instances, the preserved preparation must be biologically tested to determine its safety and efficacy and shelf-tested to determine its stability for the intended shelf life of the product.

APPLYING THE PRINCIPLES AND CONCEPTS

GROUP ACTIVITIES

1. Develop a listing of examples where patients misunderstand the intent of the administration of a pharmaceutical dosage form.
2. Develop a listing of examples where patients misuse/abuse a pharmaceutical dosage form.
3. Explain the appropriate use of specific dosage forms for different patient types, e.g., geriatric, pediatric, visually impaired, hearing impaired.
4. Identify four ophthalmic products with differing preservative agents and provide a rationale for the selection of the specific preservative in the product.
5. Identify elixir dosage form products that contain minimal or no alcohol content. Explain the reasons for this misnomer.

INDIVIDUAL ACTIVITIES

1. Given a specific dosage form, list the signs of degradation a pharmacist might observe indicating product instability.
2. Given a concentration of drug in a liquid dosage form, determine its type of degradation rate and calculate its half life and when its concentration will be 90% of the labeled amount.
3. Compare and contrast a zero-order rate of degradation and a first-order rate of degradation.
4. Make a listing of drugs that follow a zero-order rate of degradation in a liquid dosage form.
5. Make a listing of drugs that follow first-order rates of degradation in a liquid dosage form

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Understanding Drug Properties in Formulation and Process Design of Solid Oral Products

Deliang Zhou and Yihong Qiu

"Product and Process Design" discusses scientific and technical principles associated with pharmaceutical product development useful to practitioners in validation and compliance. We intend this column to be a useful resource for daily work applications. The primary objective for this feature: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator Yihong Qiu at qiu.yihong@abbott.com or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed:

- A solid dosage form is a complex mixture of multiple solid components. A systematic application of scientific principles to formulation and process design results in an increased level of product and process understanding. This approach enables higher levels of assuring assurance of product quality and performance, more robust manufacturing processes, improved efficiency, and other benefits. This approach is consistent with the basic principle of quality by design (QbD).
- The goal of product design is to consistently deliver the intended dose of a drug in a bioavailable, safe, and efficacious manner.

- Most drug substances do not possess desirable or consistent physical, chemical, biopharmaceutical, and mechanical properties to allow for a straightforward application of simple formulation and process. Proper design of enabling formulation and manufacturing processes is usually necessary.
- Rational formulation and process design starts with understanding drug properties such as solubility, dissolution rate, permeability, stability, and mechanical properties, and how they may influence product quality, performance, and manufacturing.
- Properties and required dose of a drug substance generally affect formulation and process design, including selection of dosage form, mode of drug release, bioavailability, stability, manufacturing process and manufacturability.
- In selecting formulation composition and processing technology, it is important not only to aim at achieving predefined product quality attributes, but also to strive for understanding and anticipating how the selected composition and process may influence product quality and performance. Further, variability in the chosen materials and processes must be effectively controlled and monitored such that formulation or process can consistently yield desired quality attributes throughout the product lifecycle.

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- A unified approach to formulation and process development should be adopted in order to achieve desired product quality attributes, improve formulation and process understanding, anticipate the impacts of formulation and process on product quality and performance, and consistently produce products with pre-defined quality.
- The primary objectives in the preformulation studies are to elucidate various drug properties, identify potential barriers, and evaluate strategies to overcome such barriers.
- Drug properties, required dose, and mode of drug delivery usually dictate the choice of the type of dosage form to be developed. Options comprise immediate release (IR) and modified release. Modified release includes delayed release (DR) and extended release (ER).
- The *in vivo* performance of a drug product in terms of bioavailability is an important product quality that provides a link to the clinical performance of the product. The active pharmaceutical ingredient (API) is categorized using the biopharmaceutics classification system (BCS).
- Different solid forms, such as polymorphs, hydrates, amorphous, and salts are known to exhibit different properties that often affect solubility, stability, and processing behavior. Selection of an appropriate solid form with desired properties is also an integral part of formulation and process design.
- Chemical and physical stability is a critical product quality attribute that is directly linked to potency, purity, efficacy, and safety of a drug product throughout its shelf life. Common drug degradation pathways include thermolytic (e.g., hydrolysis), oxidative, and photolytic. Physical stability refers to changes in the physical characteristics of the formulation ingredients of a drug product such as phase transformation of the drug or excipients. The degradation susceptibility of a drug molecule can often be predicted to a large extent from the knowledge of the drug, its molecular structure, past experience, and theoretical calculations.
- Designing effective, efficient, and robust manufacturing processes plays an important role in achieving and assuring product quality and performance in accordance with QbD.
- It is important for validation and compliance personnel to have a general understanding of the

principles of rational formulation and process development, the potential impacts of changes in drug properties, formulation, process, and their interplays in order to gain better product understanding, to ensure quality product, and to facilitate changes and continuous improvement post product launch.

- Two case studies demonstrating the importance of understanding API properties are discussed. One study addressed API physical changes in wet granulation. The other optimized the product pH to achieve maximum product stability.
- By systematically applying multidisciplinary knowledge and understanding drug properties, formulation and processing technologies and their interactions, a product and a robust manufacturing process can be developed. An increased level of understanding will assure product quality and performance, define product and process control, develop risk management strategy, improve efficiency and streamline post approval changes, and offer opportunities for continual improvement post product launch.

INTRODUCTION

A solid dosage form (i.e., tablets, capsules, powders, and similar products) is a complex mixture of multiple solid components consisting of many solid phases. Because of the challenges in applying the principles of basic and applied sciences in understanding such systems, various approaches have been utilized in solid product design. Some scientists may tend to rely more heavily on empirical or even “shotgun” approaches that often result in low efficiency or poorly understood product and process. Others use a more rational approach by systematically applying scientific principles to formulation and process design for an increased level of product and process understanding. Adopting the latter approach can result in many benefits for the patients, industry, and the regulatory bodies such as higher levels of assurance of product quality and performance, more robust manufacturing process and control, improved efficiency, increased cost savings, and enhanced opportunities for first cycle regulatory approval. It can also help develop risk management strategy, streamline post approval changes, and offer opportunities for continual improvement post product launch. In fact, this approach is consistent with the basic principle of quality by design (QbD).

Product and Process Design.

Rational formulation and process design should start with understanding drug properties that play a critical role in determining whether or not a specific target product profile (TPP) can be achieved. Among the most important properties that should be considered during formulation and process design are solubility, dose, dissolution rate, permeability, stability, deformation, flow, and compaction properties. These properties have been discussed in previous columns (1-5). This column discusses considerations and application of these properties in formulation and process design.

SELECTION OF FORMULATION COMPONENTS AND PROCESSING TECHNOLOGY

The goal of product design is to consistently deliver the intended dose of a drug in a bioavailable, safe, and efficacious manner. One of the key components in rational formulation and process design is to acquire and utilize knowledge of drug properties to facilitate the application of various basic and applied sciences, such as pharmaceutical sciences, various branches of chemistry, biological sciences, engineering principles, and statistics in the product development process. Properties of a drug molecule often dictate how readily the drug is absorbed from the gastrointestinal (GI) tract (bioavailability), how long the product can be stored (stability), and whether the drug product can be manufactured consistently on a commercial scale (manufacturability) especially when drug loading is relatively high or very low. Potential challenges and barriers to the development of a drug product with desired quality and performance can be identified and evaluated through the assessment of drug properties. Hence, understanding drug properties in relation to formulation and process characteristics and biopharmaceutics is essential to the successful design of a high quality product with predefined delivery and pharmacokinetic performance.

Most drug substances do not possess desirable or consistent physical, chemical, biopharmaceutical, and mechanical properties to allow for a straightforward application of simple formulation and process development including direct compression or direct blending for capsule filling. For example, many high-dose drugs lack acceptable flow and compaction properties. Many low-dose drugs (e.g., milligram or micrograms) may not have desired particle density, shape, and size distribution for producing consistently uniform powder blends especially at larger scales. Some drugs

may be chemically labile. Some drugs are poorly water soluble and unfavorable to oral absorption. Proper design of formulation and manufacturing processes that address problematic drug properties is usually necessary. To illustrate how a formulation is assembled and an associated manufacturing process is selected, conventional immediate release (IR) tablet dosage forms are considered.

Design of an IR Dosage Form

Composition of an IR tablet formulation typically consists of the active drug (from <1% to > 50%), fillers or diluents, binder, disintegrant, lubricant or glidant, and other inactive ingredients as needed (e.g., stabilizer, dissolution enhancer, processing aid, etc.).

Various excipients and grades of the same excipients are available to serve similar or same functions in a tablet formulation. However, each excipient has its unique physical, chemical, and mechanical characteristics that require consideration. Common process options for manufacturing the tablets include direct compression, wet granulation, dry granulation, and melt granulation. Each of these includes several unit operations such as milling, sizing, blending, compaction, coating, and so on. Furthermore, processing operations of each type of the processes also vary with equipment used. For example, wet granulation processing conditions are different for a fluid bed and a high-shear granulator. Unit operations and process parameters of a melt granulation process differ depending on whether higher shear, spray-congealing, or melt-extrusion method is used. The general aspects of solid dosage forms, excipients, related formulation and processing technologies can be found in commonly used textbooks and reference books (6). In many cases, tablets with similar quality attributes can be prepared using different combinations of formulation and manufacturing processes. However, consistency, scalability, efficiency, and robustness of different formulations and processes often depend on whether the design of a product and associated manufacturing process is based on an empirical or a science-based rational approach.

In selecting formulation composition and processing technology, it is important not only to aim at achieving predefined product quality attributes, but also to strive for understanding and anticipating how the selected composition and process may influence product quality and performance. Further, variability in the chosen materials and processes must be effectively controlled and monitored such that formula-

tion or process can consistently yield desired quality attributes throughout the product lifecycle. To achieve these objectives, formulation and process should not be selected in isolation. Instead, a unified view of formulation and process development should be adopted and knowledge of drug properties and their interrelations with formulation and manufacturing process should be utilized. For example, designing formulation composition requires consideration of the properties, functionality, and processing characteristics of its ingredients with respect to product quality and performance and possible material-process interactions. Selection of the process train needs to consider how each unit operation may affect material characteristics and product quality and performance. An integrated formulation and process design based on understanding of drug properties is essential to the development of robust product and manufacturing processes. It also helps ensure optimal efficiency and productivity, and minimize potential material-related processing issues or process-related performance and quality problems.

CONSIDERATIONS OF DRUG PROPERTIES IN FORMULATION AND PROCESS DESIGN

Design of a drug product should start with the end in mind (i.e., formulation and process design should be centered on a predefined quality target product profile [QTPP]) (7). International Conference on Harmonisation (ICH) Q8 defines QTPP as the prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, safety, and efficacy of the drug product. QTPP forms the basis of design for the development of a new product. QTPP generally includes route of administration, dosage strength, dosage form, container closure system, product quality attributes (e.g., purity, stability, and drug release), and predefined delivery and pharmacokinetic performance. Additional factors that also require consideration include production, commercial needs, intellectual property, etc.

Dosage form development involves design and development of formulation and its manufacturing process. With a predefined QTPP, the first step in formulation and process design is to gain knowledge of the drug substance including its physicochemical, biopharmaceutics and mechanical properties, and compatibility with excipients through preformulation investigation or literature search. The next step is to design the formulation and evaluate process feasibility

and options. Because there are often more than one ways to produce a solid dosage form with predefined quality attributes, selection of appropriate formulation components and manufacture process should be based on scientific knowledge and technological, economical, and practical considerations. More specifically, choice of formulation ingredients requires systematic understanding of their functionality, properties, and processing behaviors in relation to the drug substance and in the context of a specific process train. Selection of a manufacturing process requires consideration of existing processing technologies, characteristics of drug substance and excipients, development cost and time, process complexity, robustness, scale-up challenges, manufacturability and control, commercial production cost, capacity and efficiency, along with equipment availability, facility, and environmental impact.

It has been well established that drug properties, such as solubility, permeability, purity, stability, solid form, morphology, particle size and distribution, surface properties, and mechanical properties, can potentially impact quality and processing behaviors of drug products. The primary objectives in the preformulation studies are to elucidate various drug properties, identify potential barriers, and evaluate strategies to overcome such barriers. For example, low or erratic oral bioavailability that is often observed with poorly soluble drugs may be overcome by designing a solid dispersion containing amorphous drug. For a moisture-sensitive drug, tablets can be prepared using dry granulation or a direct compression manufacturing process, or a more stable solid form of the drug substance. To facilitate formulation and process design and ensure consistent product quality, a drug substance with reproducible characteristics should be used. In the following sections, the influence of drug properties on formulation and process design is discussed in the context of certain key components of product QTPP and manufacturability.

Dosage Forms and Mode of Drug Release

Drug properties, required dose, and mode of drug delivery usually dictate the choice of the type of dosage form and determine the overall approach to formulation and process design. Main formulation components and technologies for drug delivery and product manufacturing process may be selected once a specific mode of drug release and type of dosage form are defined.

Immediate release. Immediate release (IR) dosage forms are designed to render drug molecules

available for absorption immediately following administration. The focus of formulation and process design is generally on drug properties that influence dissolution, stability or processing behaviors (e.g., flow and compaction) depending on the amount of the drug substance in each dosage unit (drug loading), and potential impact of a particular process train on the physical and chemical characteristics of the drug substance.

Modified release. A modified-release (MR) dosage form is designed to provide drug-release characteristics that are chosen to accomplish therapeutic or convenience objectives not offered by an IR dosage form. These include both delayed and extended release drug products (8).

Delayed release. Delayed release (DR) dosage forms are designed to release a drug at a time other than immediately following oral administration. The need for a DR delivery usually varies with the physicochemical or biopharmaceutical properties of drug molecules. For instance, certain drug molecules that are acid-labile require a delay of drug release in the acidic stomach until it reaches the small intestine. Some drugs intended for treating local condition in the lower GI tract (e.g., colon) are also designed as a DR dosage form. In most cases, delayed release dosage forms are manufactured by coating single unit or multi-particulates using an enteric polymer. Enteric polymers are insoluble at gastric pH and dissolve at intestinal pH. Depending on drug properties and design objective (e.g., the extent of release delay), different polymers or different amount of a polymer may be used. For example, Eudragit L 55 consisting of random copolymer of ethyl methacrylate (EMA) and methacrylic acid (MA) at ~ 1:1 ratio is soluble at pH > 5.5. Eudragit L 100, a copolymer of methyl methacrylate (MMA) and methacrylic acid (MA) at ~1:1 ratio, is soluble at pH > 6. Eudragit S (100) made of the same monomers but with more insoluble component (MMA : MA = 2:1) is soluble at pH > 7. These polymers may be used alone or in combination to achieve a predetermined release delay. With regard to coating dosage forms, a pan coater is often chosen for single-unit tablets containing drug with low-high required dose, while Wurster coating in a fluidized bed is generally used for multi-particulates for drugs that require low-medium dose.

Extended release. Extended-release (ER) dosage forms are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug

presented as an IR dosage form. Several types of ER delivery technologies have been commonly utilized over the years, such as a reservoir system, osmotic pump, and the hydrophilic matrix tablet. Each technology has its unique features, advantages and disadvantages. Drug properties and required dose usually play an important role in selecting appropriate ER technologies and formulation composition. For example, assessing technical feasibility and designing an extended-release dosage form should be based on an understanding of permeability and solubility of the drug substance. If a drug molecule is poorly absorbed in the lower GI tract, it is generally not a suitable candidate for developing an ER dosage form. For a drug with low solubility, a hydrophilic matrix or bilayer osmotic pump system should be used to achieve zero-order release. Reservoir delivery systems are not suitable because they require high concentration gradient (solubility) across the rate-controlling membrane as its driving force for drug release.

Oral Bioavailability

The *in vivo* performance of a drug product in terms of bioavailability (BA) is an important product quality that provides a link to the clinical performance of the product with respect to safety and efficacy. Oral bioavailability depends on properties of drug, formulation, and process design that usually determine the extent and rate at which the drug dissolves in the gastrointestinal tract. Among drug properties that are most critical to oral absorption are solubility and intestinal permeability as defined by the biopharmaceutics classification system (BCS) discussed previously (3, 4).

When designing formulation and process for an IR dosage form of BCS class I drugs with favorable solubility and permeability, oral bioavailability is often not a major concern as long as rapid dissolution can be ensured and inactive ingredients selected do not significantly affect absorption of the active ingredients. Thus, the primary focus is generally on ensuring acceptable stability and designing a robust manufacturing process based on the understanding of the physical and mechanical properties of the drug and excipients. Similar design considerations also apply to BCS III compounds, as rapid dissolution can often be achieved via conventional formulation design and intestinal permeability is normally the rate-controlling step in oral drug absorption. However, attention should be given to the excipients to ensure that they do not affect drug permeability or drug intestinal residence time.

Achieving high or consistent exposure of BCS II and IV drugs in the systemic circulation is often more challenging due to low solubility. Hence, integrated formulation and process design becomes more important for these types of drugs. Selection of enabling formulation technologies should be based on consideration of drug properties in order to enhance dissolution or bioavailability and ensure stability while designing a matching process that facilitates or is synergistic with formulation technology, does not result in negative impact on solubility or stability, and is scalable and robust. For example, the use of a small quantity of wetting agents (e.g., surfactants) is one of the formulation approaches to improve dissolution rate of an insoluble compound through increasing effective surface area. The effectiveness of such approach depends on the manufacturing process. When the small amount of wetting agent incorporated in the formulation is dissolved in the granulation fluid in a wet granulation process, its efficiency can be greatly enhanced via coating on the surface of drug particles following drying operation when compared to dry mixing the surfactant(s) with drug and excipients or using a direct compression or dry granulation process.

API polymorphism and other solid forms.

Different solid forms, such as polymorphs, hydrates, amorphous, and salts are known to exhibit different properties that often affect solubility, stability, and processing behavior. Thus, selection of an appropriate solid form with desired properties is also an integral part of formulation and process design. In fact, improving solubility and dissolution via selection of an optimal solid form has become an essential part of drug product development, especially for BCS II or IV drugs. For example, among various solid forms, amorphous drug is known to have the highest apparent solubility or dissolution rate as a result of its high free energy compared to the crystalline counterparts. With increased understanding of amorphous materials in pharmaceutical development over the past decade, amorphous solid dispersion (ASD) has become one of the most important technologies for improving bioavailability of poorly water soluble compounds. However, the amorphous phase is thermodynamically unstable and will eventually revert to a crystalline phase if uncontrolled, negating its intended benefit. As a result, physical stability of amorphous solid dispersions often represents a significant challenge in formulation and process design. In recent years, significant progress has been made in understanding the physical stability of amorphous drugs and amorphous

solid dispersions. It has been found that molecular motion provides a necessary condition for physical or chemical instability and mobility is a key determining factor. Studies have also suggested that configurational entropy of the amorphous phase plays an important role (9). ASD contains amorphous drug substance dispersed in a polymeric matrix. In designing amorphous dispersions, proper selection of formulation components provides an opportunity to control and inhibit the crystallization tendency of the drug. For example, physical stability can be enhanced by using a dispersion containing both polymer and surfactants (e.g., Tween and Span) to improve solubilization of the drug substance, thereby reducing thermodynamic driving force for crystallization as compared to the use of pure amorphous drugs. Furthermore, selection of an appropriate polymer that may inhibit crystallization of the amorphous phase during storage and during *in vivo* dissolution is also an important consideration in achieving acceptable shelf life and bioavailability. In many cases, polymers that are typically used as an ASD carrier (e.g., Kollidone, PVP, HPMC, HPMCAS) also increase the glass transition temperature (T_g), resulting in decreased molecular mobility. All these factors should be considered during formulation and process design in order to optimize its physical stability.

Chemical and Physical Stability

Stability is a critical product quality attribute that is directly linked to potency, purity, efficacy, and safety of a drug product throughout its shelf-life. For most drug substances, the stability of the drug product depends not only on properties of drug, but also on formulation and process design.

Chemical stability—hydrolysis, oxidation, and photolysis. When a drug molecule is chemically unstable, the first step in product design should be to understand the intrinsic stability of the drug molecule and its degradation mechanisms. Common drug degradation pathways include thermolytic (e.g., hydrolysis), oxidative, and photolytic. Among them, the photolytic degradation can be usually mitigated by reducing or eliminating light exposure using coating or appropriate container closure system. The most prevalent drug degradation pathway is hydrolysis, followed by oxidation. Hydrolysis is a well understood pathway that can be found in many standard organic chemistry textbooks. Oxidative degradation is more complex and has been less understood until more recently (10). In general, three mechanisms exist for oxidation: Nucleophilic/electrophilic, electron

transfer, and autoxidation. Nucleophilic/electrophilic process occurs between drug and peroxide. Electron transfer often proceeds via the catalysis of transition metals, such as Fe^{3+} and Cu^{2+} . Autoxidation is mediated by free-radicals. Oxidative degradation is usually exacerbated by minor impurities such as peroxides and metals that often exist in various excipients.

Drug degradation in crystalline solids is often initiated by defects (i.e., the non-crystalline [amorphous] regions) and various other crystal imperfections such as surface imperfections. Most of these reactions are mediated by moisture because a pure topochemical reaction is rare for drug degradation. Water can be involved directly in a reaction such as hydrolysis. The presence of moisture may form a thin layer of solution on the crystal surface or can plasticize the amorphous regions (11), resulting in increased molecular mobility and reactivity. The presence of moisture may also facilitate the creation of a microenvironment that enhances drug degradation.

Drug degradation is more complex in a formulated product, a multi-component heterogeneous system. Some commonly-used excipients are known to interact directly with certain drug molecules. A well-known example is the Maillard reaction between a primary or secondary amine and a reducing sugar (e.g., lactose/glucose). However, many interactions between drug molecules and excipients are non-specific and not well understood. This type of non-specific drug-excipient interactions may sometimes lead to significant stability problems in formulation while the drug substance alone is stable. In such cases, level of degradation is often linked to drug loading rather than the absolute amount of drug. More significant degradation is usually associated with lower drug loading in the formulation due to higher excipient-to-drug ratio. Drug degradation may also be enhanced due to the change of microenvironment pH created by the excipients present in the formulation. In addition, excipients can be a source of various impurities such as peroxide and metal ions that have been linked to increased drug oxidation. It is known that peroxides exist in a number of excipients such as povidone, crospovidone, polyethylene glycol, polysorbates, and other modified excipients containing polyoxyethylene moieties. Therefore, rational selection of formulation components based on understanding of properties of drug and excipient as well as and their interaction is essential.

Physical stability. Physical stability refers to changes in the physical characteristics of the formu-

lation ingredients of a drug product such as phase transformation of the drug or excipients. Typical phase transformations include polymorphic conversion, hydration or dehydration, crystallization or amorphization, salt-to-parent form conversion, glass transition, and other mechanisms. Because the physical, chemical, and mechanical properties may differ significantly among various solid forms, these phase transformations can potentially alter the quality attributes and processing behaviors of a drug product. For example, partial or complete phase transformation may occur during processing operations (12) resulting in increased levels of defect or formation of amorphous phase that can be detrimental to chemical stability. Therefore, rational design of a manufacturing process should be based on understanding of properties of drug substance and its interplay with each unit operation.

Predicting drug stability. The degradation susceptibility of a drug molecule can often be predicted to a large extent from the knowledge of the drug, its molecular structure, past experience, and theoretical calculations. Thus, formulation and process should be designed to resolve or control chemical or physical instability problems through understanding of the drug substance. For example, to minimize hydrolysis, control of moisture and microenvironment pH in the formulation, incorporation of desiccants in the container closure system, or selection of a dry manufacturing process may be considered during the product design. To mitigate oxidative degradation, an antioxidant and oxygen scavenger may be incorporated into a formulation or container closure system. To avoid or control process-induced phase transition, proper selection of the unit operation or ingredient(s) that inhibit phase changes may be considered. In certain case, appropriate solid form may be selected to reduce or minimize degradation such that no additional stability remedies via the formulation, processing, and packaging are necessary.

Manufacturability

Designing effective, efficient, and robust manufacturing processes plays an important role in achieving and assuring product quality and performance according to QbD. It forms the foundation for consistent production of quality products, process control, overall plant performance, efficiency improvements and cost reductions while maintaining regulatory compliance. To prevent or mitigate the risk of producing an inconsistent or low quality product, process design

should be based on considerations of both engineering aspects of a chosen process train and properties of the drug substance and excipients. More specifically, it requires an increased level of scientific understanding of how formulation and process factors as well as interactions between raw materials and processing operations affect product quality and performance, process capability, and process control.

Capsule and tablets are the most common solid dosage forms. The most important material properties to consider in the process design are powder flow and powder compaction, both of which are a function of physical and mechanical properties of the drug and excipients. Many drug substances are not suitable candidates for simpler manufacturing process, such as direct blending or compression due to a lack of adequate flowability or favorable compaction properties. Thus, enabling or improving manufacturability via an appropriate formulation and process design is usually necessary, especially for products with high drug or low drug loading. Granulation processing technology is most commonly used to improve the flow, compaction properties, or content uniformity and to prevent powder segregation during powder handling. Excipients with complementary powder consolidation mechanisms or favorable flow properties are also used in designing a drug product. For example, starch and microcrystalline cellulose primarily undergo plastic deformation, while lactose and dicalcium phosphate are less sensitive to strain rate during compaction. A combination of these excipients is often used to aid the design of a product with a robust manufacturing process. In designing a bilayer tablet, choice of ingredients of the two layers requires consideration of bonding properties, deformation mechanisms, and strain-rate sensitivity of both the drug substance and the excipients. Use of materials with significantly different strain-stress behaviors between layers can result in time-dependent delamination of the bilayer tablet.

Other properties of the drug substance that require consideration during process design include solubility, stability, solid form, deformation property, morphology, particle size, density, melting point and their interactions with excipients. Different solid phases usually have different processing characteristics. Thus, solid form selection of the drug substance may be used to modify drug properties for overcoming processing problems or for improving manufacturability. For instance, crystal forms of acetaminophen are known to exhibit different compressibility. Form II has been

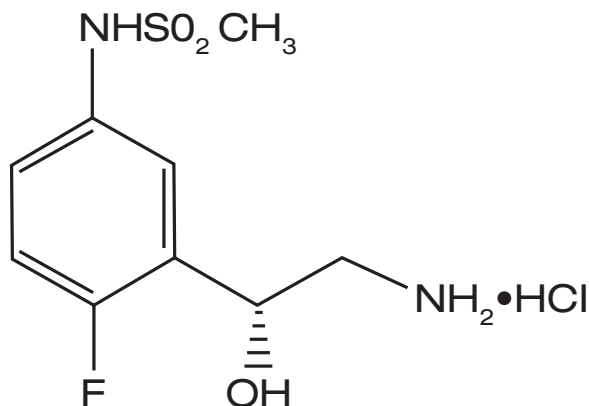
reported to have improved tableting properties and can be used in direct compression due to the presence of slip planes (13). Drugs or solid forms with low melting points are often undesirable due to their propensity to cause problems during unit operations such as milling, drying, and compaction. One of the approaches to solve this problem is by forming a salt with stronger crystal packing if feasible. However, for melt extrusion process, a lower melting solid form is sometimes preferred over a high crystalline, high melting salt form. Solid phase transformation induced by manufacturing process is known to potentially affect quality attributes and processing behaviors of a drug product. For example, solid-state transition (recrystallization) of amorphous or metastable form of an active or excipient formed during processing (e.g., granulation, compaction) may take place slowly over time, especially during storage under increased temperature or humidity. This type of transition may lead to increasing hardness of a tablet and decreasing dissolution rate over time for an IR tablet.

IMPLICATIONS OF PRODUCT AND PROCESS UNDERSTANDING IN VALIDATION AND COMPLIANCE

The information discussed in this article is fundamental to the rational design of formulation and manufacturing process for solid oral dosage forms. Validation and compliance personnel should have a general understanding of the properties of the drug and their role in the drug product and process design. Specifically, they should be very aware of the drugs that may interact with excipients and manufacturing processes as well as processes that may potentially impact drug properties with respect to solubility, dissolution, and stability. They should be especially vigilant of formulation and manufacturing changes that may impact product quality and manufacturability. Validation protocols developed in response to such changes should require appropriate sampling and testing in support of the changes. Knowledge of the principle of formulation and process design must also be considered in determining appropriate validation testing.

Special attention should be paid to drugs of which the properties are most susceptible to changes in manufacturing process and excipients (i.e., source, grade, properties, etc.). Validation and compliance personnel should be watchful of changes in unit operations with potential to impact the solid form of drugs and excipients as well as other physicochemical

Figure 1: Chemical structure of ABT-232.



and mechanical properties known to affect solubility, stability, and processing behaviors. Consultation with development scientists is encouraged to thoroughly evaluate any proposed changes in formulation and manufacturing processes.

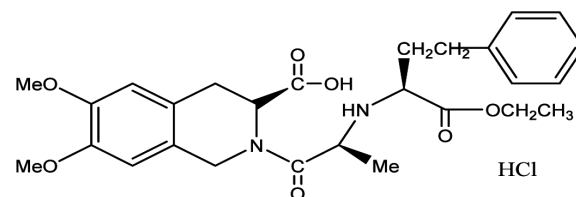
CASE STUDIES

ABT-232

ABT-232 (see Figure 1) is a compound selected for development as a potent uroselective $\alpha 1A$ agonist (14). Preformulation studies showed that it is highly water-soluble, and chemically stable in the crystalline solid state as anhydrate or monohydrate. An amorphous form was also isolated, but it is highly hygroscopic and rapidly reverted to the crystalline form under ambient conditions in less than 10 minutes. No incompatibility was identified with a range of standard excipients except for lactose (Maillard reaction).

Solid dosage forms were developed to support clinical trials. Given the chemical stability and high solubility of ABT-232, a conventional IR tablet dosage form was prepared using commonly used functional excipients discussed previously. An ER matrix tablet formulation was also designed to evaluate effect of changing release rate on bioavailability. In the design of both formulations, drug loading was low due to the low dose (0.5 – 2 mg). To ensure content uniformity of low dose formulations, a wet granulation process was selected. However, upon storage under accelerated conditions, significant loss in potency (e.g., up to 15% under 40°C/75% RH for 6 months) and an increase in related substances were observed for the IR tablet. This finding appeared to be inconsistent with the results of the excipient compatibility study. Further investigations indicated that the drug was

Figure 2: Chemical structure of moexipril hydrochloride.



rendered mostly amorphous after granulation and drying operations. Because of the high water solubility and low dose, ABT-232 in the formulation was first dissolved during the wet granulation process and subsequently converted to amorphous drug upon drying. Unlike the pure drug substance, the resulting amorphous API in the formulation did not re-crystallize during the drying, likely due to the inhibitory effects on re-crystallization by polymeric excipients present in the formulation. The process-induced phase transformation was indirectly confirmed in an investigation using a model granulation containing higher drug loading (30%) which showed that, even after six weeks of storage at 40°C/75% RH, ~60% of the total drug substance in the granulation still remained amorphous. To overcome this chemical stability problem caused by solid phase transformation, direct compression tablets were designed. Acceptable content uniformity was achieved through selecting excipients with desirable flow properties and physical properties to prevent segregation. It should be noted that chemical instability was not observed with the ER matrix tablets based on hydroxypropyl methylcellulose (HPMC) though the same manufacturing process and similar drug loading were used. This is likely related to the type and quantity of polymers used in the ER formulation. This example highlights the importance of understanding properties of materials, their interactions with each other, and with manufacturing process in formulation and process design.

Moexipril Hydrochloride

Moexipril (Figure 2) is a dipeptide angiotensin-converting enzyme (ACE) inhibitor. The compound has two ionizable groups: the carboxylic acid group with $pK_{a1} = 3.0$ (25°C), and the amino group with $pK_{a2} = 5.4$ (25°C). Preformulation studies indicated that moexipril is highly water soluble but stability may be of concern (15). The compound undergoes intramolecular aminolysis leading a diketopiperazine

(DKP) formation at pH < 4, hydrolysis at pH > 5, and epimerization in addition to hydrolysis at pH > 7. The pH-rate profile is shown in Figure 3. The effect of ionization on the overall reactivity is evident and the most stable region is pH 4-5.

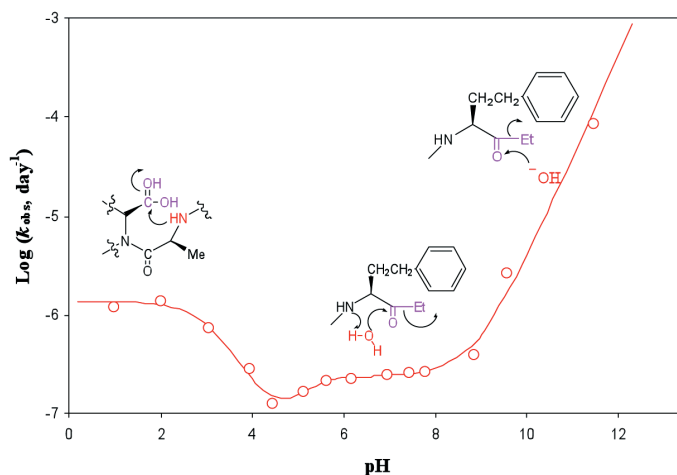
A compatibility study of moexipril hydrochloride and various excipients was conducted to support product development and to address the potential stability issue (16). The study confirmed the challenging nature of the stability problem, particularly when the drug is exposed to moisture. Based on the pKa's of moexipril, the saturated solution of the drug substance, a hydrochloride salt, is expected to have a pH of approximately 2, which falls within the unstable region of the pH-rate profile. Thus, the sensitivity of the drug to moisture can be attributed to the low pH of the solution on the surface of the solid drug substance. In general, for this type of drug, manufacturing process involving water should be avoided and moisture level of the dosage form should be controlled. However, it was also found in a further study that product stability could, in fact, be enhanced by wet granulating moexipril hydrochloride with basic excipients. The improved stability is likely a result of increased microenvironment pH in the formulation by incorporation of basic excipients (e.g., sodium bicarbonate, sodium carbonate, calcium carbonate).

It should be pointed out that based on pKa, the free base of moexipril is expected to result in a pH of approximately 4.2 on the solid surface, which falls within the stable region of the pH-rate profile. Therefore, the free base, instead of salt, should be selected for product development from the standpoint of chemical stability. If solubility enhancement of the free base is required, approaches other than salt formation may be used (e.g., amorphous solid dispersion). If solubility of the drug needs to be improved through salt formation, a counter ion should be chosen based on consideration of both solubility and stability. This example illustrates the importance of comprehensive evaluation of drug properties in the rational design of formulation and manufacturing process.

SUMMARY

One of the most critical aspects in rational design of solid product and manufacturing process is understanding the properties of the drug substance. Drug properties play a crucial role in determining how components and processing steps should be selected and whether a specific target product profile can be

Figure 3: Rate-pH profile for moexipril in aqueous solutions.



achieved. Among the most important properties that require consideration are physicochemical, biopharmaceutical, and mechanical properties.

By systematically applying multidisciplinary knowledge and understanding drug properties and formulation and processing technologies and their interactions, a product and a robust manufacturing process can be developed. An increased level of understanding will assure product quality and performance, define product and process control, develop risk management strategy, improve efficiency and streamline post approval changes, and offer opportunities for continual improvement post product launch.

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ARTICLE ACRONYM LISTING

ACE	Angiotensin-converting Enzyme
API	Active Pharmaceutical Ingredient
ASD	Amorphous Solid Dispersion
BCS	Biopharmaceutics Classification System
DKP	Diketopiperazine
DR	Delayed Release
EMA	Ethyl Methacrylate
ER	Extended Release
GI	Gastrointestinal
IR	Immediate Release
MA	Methacrylic Acid
MMA	Methyl Methacrylate
MR	Modified Release
QbD	Quality by Design
QTPP	Quality Target Product Profile
TPP	Target Product Profile

Extemporaneous formulations of Oral Liquids

A Guide

David J Woods

1. Introduction

Pharmacists and paediatricians are often faced with the problem of modifying an oral dose form intended for adult use into a suitable form for paediatric administration. Texts and research papers freely describe paediatric doses without exploring the logistics of dose administration. Tablets and capsules are generally unsuitable for administration to children aged under four years and a suitable tablet strength might not be available for use in older children. The range of commercially available paediatric oral liquids and tablets is narrow because the relatively specialised use of these products makes industrial product development, manufacture and registration financially unattractive. Availability varies between countries and very few products are available in countries which constitute a small market. There are, however, anomalies to this theory in that some oral liquids (for example, captopril liquid, metronidazole suspension and rifampicin suspension) that are not available in North America are freely available in other countries such as New Zealand.

In the absence of a ready-made product a frequent approach by pharmacists is to prepare an oral liquid from tablets, capsules or powdered drug dispersed or dissolved in a suitable base. These are often referred to as extemporaneously prepared formulations and the practice occurs on an international scale. A survey of 210 pharmacists in the USA identified the eleven most frequently compounded preparations and the authors concluded that efforts by manufacturers and professional associations are required to supply pharmacists with information on the compounding and stability of extemporaneous preparations.¹ Stewart and Tucker² surveyed Australian hospitals and showed that 116 drugs were extemporaneously compounded into 270 different formulations for paediatric use. Frequent problems identified in this survey included disguising unpleasant taste, achieving dose uniformity and a lack of chemical and physical stability data. This lack of stability information is a common problem and formularies of extemporaneous formulations have been published in an attempt to provide some guidance on the preparation of paediatric oral liquids. The first widely available book was published in the UK in 1978³ and is mainly a collation of individual

hospitals' formulas and recommendations made by pharmaceutical companies with little reference to published data. This publication is now considered outdated and obsolete. Over the last 20 years researchers have studied the stability of many extemporaneous formulations and these are summarised in three formularies which have been published in North America.^{4,5,6} However, the authors of these publications still describe a significant number of formulations which are not based on previously published data which indicates the requirement for further research. Recently more comprehensive books have been published which give much more detail of published stability studies, physicochemical stability data on each drug and some discussion on alternative methods of preparing paediatric doses.^{7,8}

The formulation of an oral liquid for paediatric use requires careful consideration of many factors to ensure that the product is of optimum quality and efficacy. Compounding an oral liquid from crushed tablets should only be considered if there are adequate stability data and it should be recognised that there are often simpler or more reliable methods of preparing the dose. Before discussing the formulation of oral liquids it is important to briefly consider these alternatives some of which are perhaps under utilised.

2. Alternatives to formulation of oral liquids

(i) An alternative drug which is available commercially in liquid form could be selected.

For example, it is usually preferable to use captopril oral solution rather than prepare enalapril solution from tablets.

(ii) Tablet dispersion

The practice of crushing tablets or opening capsules and adding the powder to a palatable drink or sprinkling onto solid food is a time-honoured alternative, but there are few circumstances when this method is appropriate or necessary. It is difficult to ensure that a complete dose has been taken and the practice of nurses or carers handling powdered drug may present health concerns.⁹ Tablet dispersion is a simpler, more reliable and potentially safer method.^{9,10}

If the tablet disperses in water, it can be dispersed in a small volume and the dose given when a suspension is formed, mixed with a flavoured vehicle if required. Not all tablets disperse readily but some form a suspension in seconds.¹⁰

If the tablet disperses readily and the drug is soluble, dispersing the tablet in a known volume of water allows a fractional dose to be accurately measured with a syringe as in the case of captopril.¹¹ As extraction of soluble drug from the tablet excipients may be incomplete^{12,13} the suspension should be shaken or stirred prior to measuring the dose and not filtered unless it has been established that active drug is not removed. In the case of an insoluble drug, the measurement of a fractional dose by taking an aliquot from a suspension formed in this way cannot be recommended due to probable rapid sedimentation of insoluble drug and resultant dosage inaccuracy. Tablet dispersion may not always be practical for infants when the doses required are the equivalent of small tablet fractions.

(iii) Oral administration of the injection

This is possible for some drugs but there are important factors which must be considered when evaluating whether the injection is suitable for oral use. This can be illustrated with some examples.

- (a) If the injectable form of the drug is the same as the oral form (for example labetalol hydrochloride, ondansetron hydrochloride) it can be assumed that the drug will be absorbed from the injectable formulation. However, as the drug is in solution more rapid absorption and higher peak levels may occur compared to slower absorption from a solid dose form.
- (b) Some injectable drug forms are produced by reaction of the insoluble oral form with sodium hydroxide to give a soluble salt (for example acetazolamide sodium, sodium folate). In the acidic conditions of the stomach the oral form (acetazolamide, folic acid) will be generated.
- (c) The injectable form of drugs which are chemically degraded by gastric acid (for example omeprazole) are unsuitable for oral administration.

- (d) The oral use of the injectable form of a drug which is subjected to extensive first-pass metabolism, resulting in poor oral bioavailability, may be impractical due to the large volume required. For example, a volume of 15 mL (15 ampoules) of 1 mg per mL is required if propranolol injection is used to give an oral dose of 15 mg.
- (e) Drugs such as cefuroxime and enalaprilat which are administered orally as pro-drugs (cefuroxime axetil and enalapril maleate) have relatively poor bioavailability and are not suitable for oral administration.
- (f) Injections may contain excipients and adjuvants that are undesirable in some patients. For example propylene glycol and ethanol.¹⁴
- (g) The cost of using the injectable form orally may be prohibitive. For example, the cost of giving dantrolene injection orally is approximately 60 times the cost (per mg of drug) of using the oral form.

(v) Powder Papers or Repacked Capsules

Fractional doses can be prepared by repacking dosage aliquots of powdered tablets or capsule contents, or mixing with a diluent such as starch or lactose prior to repacking into powder papers or empty capsules. This method can be used for drugs which are unstable in aqueous solution and was used to prepare paediatric doses of captopril before a stabilised solution was made commercially available.¹⁵ These methods can still significantly compromise drug stability and extreme care must be taken in ensuring uniform drug distribution. Further limitations are the time and cost of the operation and inflexibility of dosage. There are few situations where this option is necessary.

3. Preparation of Oral Liquids; Practices and Problems.

If alternatives are not possible or the convenience and flexibility of a ready prepared product is preferred an extemporaneously compounded oral liquid might be considered.

The most frequently used method is to grind the required number of tablets to a fine powder in a mortar and form a slurry by adding a small volume of water. Excipients such as antimicrobial preservatives, suspending agents and flavouring agents are added to make the final product. A frequently used base is a mixture of glycerol or syrup, a suspending agent

such as methylcellulose, and para-hydroxybenzoates (parabens) as a preservative. Other agents sometimes added include alternative solvents such ethanol, particularly when the drug is poorly soluble in water, and buffer systems to provide the optimum pH for drug stability or activity of the antimicrobial preservative. Whilst ostensibly simple, such formulations can be complex comprising a mixture of the base and a suspension or solution (usually a combination of both) of tablet excipients and active drug. If the drug is water soluble there is a temptation to filter out the insoluble tablet excipients to leave a clear solution but filtration can remove significant amounts of drug if extraction from tablets is incomplete.^{12,13} Insoluble tablet excipients are in suspension and may compromise product appearance whereas soluble excipients may reduce drug stability, for example, by altering the pH of the preparation.¹⁶ Thus there may be several advantages in using pure drug powder instead of tablets but the powder may not be easily obtainable.

The expiry date or “shelf-life” of an extemporaneously prepared oral liquid is assigned empirically or based on published information on a particular formulation. A conservative approach must be adopted when assigning an expiry date because of lack of information on drug stability or limitations in either the design or the conclusions of a published report. Also, it may be impractical to entirely reproduce the conditions of a study which was performed in another institution or country under the controlled conditions of an experiment rather than clinical use. Most studies base their expiry date recommendation on chemical stability but do not address possible physical or microbiological spoilage which may be significant during actual use of the product. For these reasons it is the author’s opinion that extemporaneously prepared oral liquids should only be used for a maximum of one month from the date of preparation to minimise any unrecognised product deterioration. Longer expiry dates may be applied if more extensive testing is performed.

Finally, when deciding on a formulation it is important to consider any possible adverse effects of the “inactive” components of the preparation. Sucrose (in syrup) can promote the formation of dental caries, ethanol can cause hypoglycaemia and para-hydroxybenzoates can cause hypersensitivity reactions and exacerbate the symptoms of asthma.¹⁴ It has also been suggested that benzoates and para-hydroxybenzoates can aggravate neonatal hyperbilirubinaemia by displacing bilirubin which is bound to plasma proteins but this effect has not been demonstrated *in vivo*¹⁴ and the amounts present in oral formulations are

unlikely to pose any risk.¹⁷ Limits for the inclusion of ethanol in paediatric formulations have been proposed by the American Academy of Pediatrics.¹⁸

Deterioration of an oral liquid may be due to chemical, physical or microbiological instability which can lead to a sub-therapeutic dose of drug, exposure to toxic degradation products or ingestion of unacceptable numbers of micro-organisms. It is important for pharmacists, clinicians and nursing staff to be aware of potential problems caused by instability to ensure that drug therapy is effective and safe.

Chemical instability

Drugs in extemporaneously prepared liquids may be susceptible to chemical reactions leading to degradation. The most common reactions are hydrolysis, oxidation and reduction.¹⁹ Usually the reaction rate or type is influenced by pH, for example, azathioprine is rapidly hydrolysed to 6-mercaptopurine at alkaline pH but is relatively stable in acidic or neutral conditions.²⁰ Other factors which may increase the rate of reaction include the presence of trace metals which catalyse the oxidation of captopril,²¹ methyldopa²² or exposure to light which catalyses the oxidative degradation of 6-mercaptopurine.²³ The rate of chemical degradation usually increases with temperature, a factor which is the basis for accelerated stability trials of pharmaceutical formulations. Preparations made from tablets contain excipients such as binders and disintegrating agents in addition to the active drug. These excipients may reduce chemical stability by changing the pH to a value at which more rapid degradation occurs. This probably explains why amiloride solution prepared from pure drug is more stable than an oral liquid prepared from tablets.¹⁶

The drug in the preparation may be totally or partially in solution or predominantly in the solid state as a suspension. Drugs in solution are more susceptible to chemical degradation than drugs in the solid state (ie. suspensions), thus suspensions of acetazolamide and chlorothiazide are more stable than solutions.^{24,25} However it cannot be assumed in all cases that an extemporaneously prepared suspension is more stable than a solution. In a suspension, an equilibrium exists between drug in the solid state and drug in solution and even though the amount of drug dissolved may be minimal the conditions could be optimal

for degradation. Frusemide is a notable example which undergoes hydrolysis in acidic conditions where the solid state is predominant, but is much more stable at alkaline pH where it is totally in solution.²⁶

Microbiological Instability

Microbial growth in an oral liquid may cause foul odour and turbidity and adversely effect palatability and appearance. High titres of micro-organisms may be hazardous to health especially in very young or immunocompromised patients. By-products of microbial metabolism may cause a change in the pH of the preparation and reduce the chemical stability or solubility of the drug. Microbial contamination during preparation must be minimised by using clean equipment, sterile water (Water for Irrigation BP) and avoiding contaminated raw materials and containers. If sodium benzoate or benzoic acid are used as antimicrobial preservatives the final pH must be less than 5 so that the active unionised form is predominant.²⁷ Consequently the drug must also be stable at this pH.

Effective preservative systems require rigorous evaluation which is seldom performed on extemporaneous formulations. Many factors can reduce the effectiveness of the preservative including use of contaminated materials, chemical degradation, binding of preservative to suspending agents or tablet excipients, incorrect storage or unhygienic use of the final product..

Physical Instability

Extemporaneously prepared oral suspensions may be susceptible to sedimentation of insoluble drug causing caking. Difficulty in re-suspending the drug or rapid sedimentation following shaking can lead to erratic dosage measurement as demonstrated with chlorothiazide suspension²⁸ and this inherent problem with extemporaneously prepared formulations is of considerable concern. Some spironolactone suspensions have been reported to be excessively thick and almost un-pourable.²⁹ Refrigeration, whilst usually desirable to maximise chemical stability and reduce microbial growth, can also increase the viscosity of a suspension making re-suspension more difficult³⁰ or cause the precipitation of active drug or preservatives. It is important to consider the effect on pH of all components of the formulation and the possible impact on stability. Syrup, for example, is relatively acidic

and if used in phenobarbitone sodium oral solution it will cause the precipitation of unionised phenobarbitone.

4. Conclusions

The guide (see below) is an attempt to summarise the many complex issues that have been described and to highlight some of the factors for pharmacists and paediatricians to consider in order to optimise drug therapy. Information sources such as specialised formularies, drug stability texts and the advice of pharmaceutical companies are invaluable. Most pharmaceutical companies will attempt to provide stability information and can sometimes recommend a specific formulation. Practitioners must continue to lobby for the development and availability of more paediatric oral liquids and paediatric strength tablets some of which may be obtainable in other countries. In order to make information more accessible investigators of clinical drug use should describe the formulation details of the preparation used in their research. This information is often omitted from the publication and can be extremely difficult to source especially when required rapidly. Investigators engaged in stability studies should aim to make the results of their research universally acceptable by designing simple formulations and avoiding the use of unnecessary or difficult to use ingredients. Valid protocol design for the stability study is essential^{31,32} and ideally the study should be carried out on formulations prepared from pure drug as well as tablets and the pure drug formulation used in practice whenever possible.

Finally, sharing information on paediatric formulations and research collaboration should be further encouraged especially between major paediatric hospitals and research centres to ensure that our patients receive the highest quality drug therapy.

Preparation of a Paediatric Oral Liquid-A Guide

- Consider an alternative drug
- Consider an alternative method, for example, tablet dispersion or oral administration of the injection
- Consult the latest information data-bases and publications. Prepare a formulation according to a published study and follow the conditions of this study as closely as possible. Modifications to published formulations are only appropriate if there are no

detrimental effects on stability. A maximum expiry date of one month from preparation is recommended and liquids without an antimicrobial preservative should be given a shorter expiry date.

- If there are no data from a published study consult pharmaceutical manufacturers, other paediatric hospitals and research centres.
- It may be possible to adapt existing information from drug stability texts (e.g. solubility, pH stability profile) or from the formulation details of the injection or oral liquid available elsewhere.
- Monitor use of the product and observe for any signs of physical instability such as colour change or difficulty in re-suspension.
- Provide information to carers to ensure correct use of the product (e.g. storage conditions, use of an oral syringe, shaking before administration).
- Ensure that formulations details are available to all practitioners involved in the patients care to ensure that the product is consistent in appearance and quality. Prescriptions could contain full details of the formula and hospital pharmacists could provide details to their community colleagues.

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Moisture Effects on Solid Dosage Forms—Formulation, Processing, and Stability

Armin H. Gerhardt



“Pharmaceutical Processes” discusses scientific and technical principles associated with pharmaceutical unit operations useful to practitioners in compliance and validation. We intend this column to be a useful resource for daily work applications.

Reader comments, questions, and suggestions are needed to help us fulfill our objectives. Suggestions for future discussion topics or questions to be addressed are requested. Case studies submitted by readers are also most welcome. We need your help to make “Pharmaceutical Processes” a useful resource. Please send your comments and suggestions to column coordinator Armin Gerhardt at arminhg@comcast.net or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS DISCUSSED

The following key points are discussed:

- Moisture may have a significant impact on a wide range of chemical, physical, and microbial properties of the finished pharmaceutical product
- Moisture in dosage forms comes from many sources including bulk drug, inactive excipients, manufacturing processes, and environmental conditions, and is a result of a variety of causes
- Water may interact in distinct ways including surface adsorption, as a crystal hydrate, by deliquescence, and by capillary condensation. Examples of these interactions are discussed.
- Water may have significant effects on product stability, tablet compaction, wet granulation, powder flow properties, and microbial growth
- Compliance personnel must be knowledgeable of areas with potential for moisture problems. Change control of these areas is especially important to maintain compliant manufacturing. Be prepared for potential problems.
- The effects of moisture should be considered in troubleshooting investigations and root cause analyses.

INTRODUCTION

The moisture content of drugs, excipients combined with the drugs to manufacture a final dosage form (i.e., compressed tablets), and/or processing manipulations involving moisture may have a significant impact on a wide range of chemical and physical properties of the finished product. Properties such as powder compressibility, flow rate, compactability, drug degradation, and microbial growth may be affected. Various processing steps require water (or other solvent) to accomplish their intended result. These include wet granulation, particle or film coating, spray drying, lyophilization, and crystallization. Control of these operations is best accomplished when the underlying mechanisms of water's interactions with solid particles are recognized. Quality and compliance practitioners must be aware of the potential deleterious effects of moisture on tablet products and manufacturing processes.

Sources of Moisture

Moisture in tablet products comes from many sources. Moisture may come from the bulk drug or inactive excipients in the formulation. In pure chemicals, moisture may be present as water of crystallization and/or as adsorbed water. The amount of moisture in these ingredients should be controlled by specification, but may vary within acceptable limits. Additional sources of water come from the various manufacturing processes. For example, significant amounts of water may be added in the wet granulation process. This water is then essentially removed during the drying process. Water may also be added and removed in the tablet coating process. Water may come from the environmental conditions of manufacturing (i.e., the relative humidity of the manufacturing and packaging areas). Certain formulation ingredients function to attract water and swell upon contact with moisture—and can do so when exposed to high atmospheric humidity. Water also may contact the product by transfer through packaging materials. Tablet products may be packaged in bottles with desiccants to prevent moisture uptake by the product and subsequent potential negative

effects. Moisture vapor transmission through films used in blister packaging has been quantitated. All these sources of moisture may impact the stability of susceptible products.

RELEVANT CHARACTERISTICS OF WATER

At low concentration, water possesses a number of traits that combine to make it very effective at increasing molecular mobility (i.e., a plasticizer). It has a low molecular weight (18 daltons), small size, low density, high dielectric constant, and high ability to form hydrogen bonds (1). It may move via the vapor phase to localized molecular regions with charged and polar groups and concentrate there, thus reducing hydrogen bonding between adjoining molecules, increasing the free volume by dilution, and reducing the viscosity and glass transition temperature. Defined as the point at which a solid material converts from a rigid structure to a more flexible rubbery material, the glass transition temperature is important because of its correlation with chemical reactivity. In terms of physical behavior, these effects include material softening; its viscosity is reduced; and there is a reduction in mechanical strength as measured by either the tensile strength or Young's Modulus.

Water is commonly present at low concentration on or within solid phase pharmaceutical materials, such as less than 1.5% w/w. Though water acts as a solvent when it is the predominant component as in a dilute solution, water is present in a very limited proportion in typical pharmaceutical solids systems. Under these conditions, water may be viewed as dissolving within void spaces or regions of individual particles or sorbing to their surface; it is in these situations that water exhibits its potential to be a highly effective plasticizer. At the molecular level, water increases torsion of side groups or end segments, and macromolecular chain segments or chains have increased mobility.

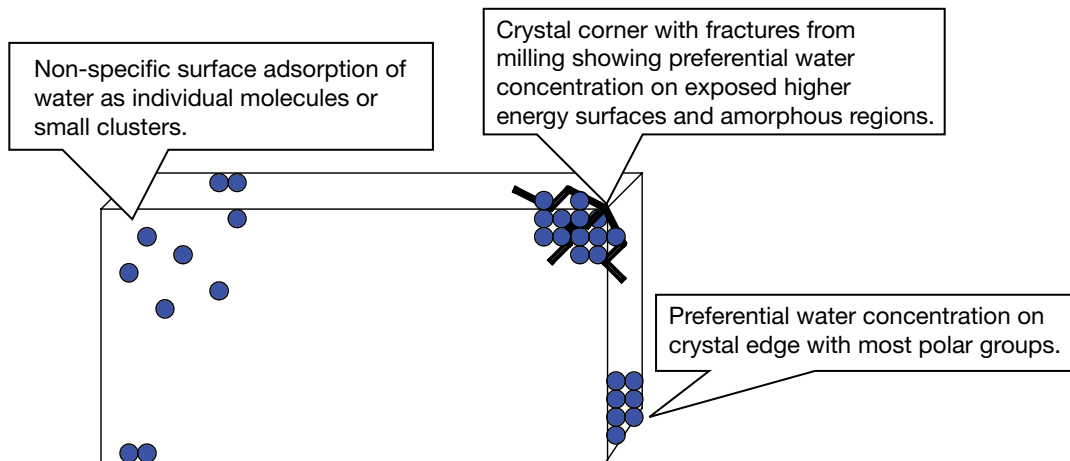
MECHANISMS OF WATER INTERACTIONS

For crystalline solids, water may interact in the following four distinct ways (2):

- It may adsorb to the surface
- It may be present within the crystalline lat-

Figure:

A plate-shaped crystalline particle with partial surface adsorption of water and preferential concentration at a corner with crack defects and on a hydrophilic edge.



tice in a stoichiometric quantity (i.e., crystal hydrate)

- The crystalline solid may deliquesce (i.e., liquefaction of the solid to form a solution by continued water vapor adsorption)
- Capillary condensation may occur when micro-porous regions are present in the solid.

Adsorbed water on the solid surface is generally hydrogen bonded to the surface. There may be an additional two to three layers possible when high relative humidity is present, all of which is readily reversible by small temperature increases or small decreases in relative humidity (3). While the water of a crystal hydrate is found at predictable locations within the solid and is held in place by hydrogen bonds, it is not generally available to reactions.

With amorphous solids, long-range ordered structure is not present. This produces localized empty voids which allow for the possibility of water to dissolve in the solid (see Figure). Though the vast majority of material in an individual solid particle may be crystalline, imperfections in the regularly repeating arrangement of atoms and molecules may also be present, and it is in these zones of disorder that significantly higher rates or reactivity may be found. Processes within the pharmaceutical indus-

try such as mechanical milling, lyophilization, spray drying, or rapid removal of solvent may produce significant quantities of amorphous material. These zones are potentially more reactive, and may produce significant increases of molecular mobility when water concentrates in them. Whereas adsorption to a crystalline solid is limited to the available surface area, water uptake of an amorphous material is limited to the quantity of amorphous solid. Polymeric materials, by virtue of their irregular chain length and myriad configurations possible in a solution, are difficult to crystallize. During a drying step, solvent removal takes place rapidly and does not permit sufficient time for individual molecules to align in a crystalline pattern; they are predominantly amorphous in structure when solvent removal is completed. Materials such as polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and starch are free-flowing powders that are predominantly amorphous.

Model calculations have been made to link this qualitative picture with relevant examples (Tables I and II). Table I depicts the situation for spherical sucrose particles in the size range from 1 to 100 μm with their specific surface area. Assuming 0.1% w/w water is at the particle surface, the calculated number of water layers ranges from 1.1 to 110.

Practical experience with pharmaceutical materials of 100 μm size (roughly 140 US mesh size) with 0.1% water would not suggest the presence of 110 layers of surface water. This indicates that a significant portion of the water is dissolved within the disordered regions in addition to water present on the surface.

Further to this example, Table II shows the calculated amount of water found in varying quantities of the amorphous regions of sucrose with either 0.1% or 0.5% moisture content. With the assumption that all water is preferentially found in the amorphous regions, the range of values is from 2% (for 5% amorphous material with 0.1% water) to 50% (for 0.5% amorphous material and 0.5% water). Connecting this to the results for the glass transition temperature, it was calculated to be in the range of -73 to 49°C [the glass transition temperature for pure water is -108°C (4)]. For sucrose with 2.5% amorphous material holding 0.5% water, the resultant glass transition temperature of 9°C is below room temperature conditions. Thus molecular mobility may be enhanced and permit reactions such as chemical degradation or re-crystallization.

EFFECTS OF WATER ON TABLET FORMULATIONS

Water may significantly affect the chemical, physical, and microbial properties of tablets. Examples of these interactions include the following:

- Product stability
- Tablet compaction
- Moisture-activated dry granulation
- Wet granulation
- Effervescent tablets
- Solids flow properties
- Microbial growth.

Product Stability

Product stability considerations comprise two areas: Drug potency and drug dissolution. When formulations are considered, the water present in excipients or employed in processing may preferentially concentrate in amorphous regions of the drug. This may occur via the vapor phase, or water concentrated regions may be brought in direct contact with the drug. Depending on the drug properties, this moisture might then increase the rate of drug

TABLE I: Sucrose sphere specific surface area and the theoretical number of water layers on the surface when 0.1% moisture is adsorbed (Adapted from Reference 2).

Particle Size (μm)	Specific Surface Area (cm^2/g)	Number of water layers
1	38,000	1.1
10	3,800	11
38	1,000	42
100	380	110

TABLE II: Moisture content in amorphous region and glass transition temperature when either 0.1% or 0.5% moisture is sorbed (Adapted from Reference 2).

Moisture Amount (%)	Amount of Amorphous Material (%)	Moisture content in amorphous zone (mg water/100mg solid)	Glass Transition Temperature (°C)
0.1	0.5	20	9
	1	10	27
	2.5	4	45
	5	2	49
0.5	0.5	100	-73
	1	50	-36
	2.5	20	9
	5	10	27

degradation. Hydrolysis is a well-known mechanism for drug degradation reactions. High moisture levels might also cause drug dissolution to be adversely affected, potentially resulting in reduced drug bioavailability. In this case, the drug would be fully potent, but would not dissolve as needed for absorption and product therapeutic efficacy.

Tablet Compaction

Moisture is an important factor in compaction of blended powders or dried granulation to form tablets. Tensile strength is generally low at low

moisture content (approximately 0.1 to 0.2% w/w). As the moisture level increases, the compact tensile strength also increases to a maximum level; higher moisture contents then lead to decreased compact tensile strength (5). Due to stability requirements, moisture levels above 1.5% w/w are seldom found in compressed tablets. Possible mechanisms for increasing the tensile strength are adsorbed water may alter surface structure such that there are more solid bridges, or immobile water at a particle surface may enhance interactions between particles. With the presence of relatively more surface moisture, it is possible for permeation into the particle, which may plasticize or soften the material. During compression, there are increased bonding surfaces as particles yield and flow under the pressure applied by the tablet press. Actual results are dependent on the material(s) being compacted. A wide range of materials have been studied and occasional anomalous results have been found. Each product requires a solid foundation of data from which to select the appropriate balance range for moisture that delivers robust compaction and stability throughout the product expiry period.

Moisture-Activated Dry Granulation

The technique of moisture-activated dry granulation provides the advantages of wet granulation while the drying step is eliminated. This process is composed of two distinct stages including agglomeration followed by moisture adsorption (6). Agglomeration is accomplished by the addition of a relatively small amount of water, roughly 1-4%, to the combination of drug substance, binder, and filler. This is then followed by the moisture adsorption step of addition and mixing microcrystalline cellulose, potato starch, or a combination of these materials.

Wet Granulation

Wet granulation is an important process in tablet manufacturing. It has been shown that the compressibility of both microcrystalline cellulose and silicified microcrystalline cellulose are progressively reduced with increasing quantities of water when

wet granulated (7). Using a laboratory scale high-shear granulator and varying the amount of water from zero to 100% w/w of the powder, both materials produced compacts of approximately 3.8 MPa tensile strength at a compression force of 50 MPa. However, when 100% water was used the maximum compact tensile strength was 1.0 MPa at the much higher compression pressure of 180MPa. At the more typical wet granulation condition where 20% water was used, there was also a significant decline in compact tensile strength. Reduction of 3.8 MPa to 1.5 MPa at compression pressure of 50 MPa was observed, a 39% loss of compact tensile strength.

For microcrystalline cellulose, the presence of low quantities of moisture has been shown to produce an antiplasticization effect (8). Specifications for this material set the moisture limit to less than 5%; a typical lot may have water content in the range of 3 to 4%. Based on the water sorption isotherm, the equilibrium moisture content for this material at commonly found manufacturing environments of 20% and 40% relative humidity is approximately 3.2% and 4.3%, respectively. Study results indicate maximal compact tensile strength at a moisture content of approximately 4.2%; however, the dried MCC compacts had less than half this tensile strength (Table III). The authors of the study attributed the reduced compact tensile strength at low moisture content to an antiplasticization effect, in essence the presence of a small quantity of water makes MCC more ductile and improves bonding. Beyond roughly 4% water content, there is reduction in bond strength as the plasticization effect weakens or limits bonding.

Effervescent Tablets

One specialty dosage form requiring exquisite control of moisture in processing is the effervescent tablet (9). This dosage form offers distinct advantages in terms of the following:

- Capacity to accommodate large dose drug within a typical 2,000 mg tablet
- No requirement to swallow the dosage form
- Buffering the acid environment of the stomach with carbonation and induction of rapid

emptying that aids drugs susceptible to acidic degradation

- The foil packaging required for stability offers protection for drugs sensitive to light, oxygen, or moisture.

Selection of formulation components requires the presence of an organic acid and metal carbonate that release carbon dioxide when exposed to water. Because this reaction is autocatalytic (i.e., it also produces water that further speeds the reaction) there is a requirement for strict relative humidity control and processing steps during all phases of production and packaging. Environmental processing conditions are typically 10% relative humidity. Minimal quantities of water are employed during granulation and spray nozzles deliver this over a large powder bed surface to minimize local concentrations.

Solids Flow Properties

Excessive moisture in blended solids may be the result of incomplete drying, the presence of large blocks of granulated material that retain moisture in their core, or permeation through poor barrier materials during storage. These occurrences may cause significant effect on the flow properties of solids in processing.

Within a powder bed, the forces of cohesion, adhesion, and friction may impact the rate of flow. Cohesion and adhesion are a mutual attraction and resistance to separation between the same material and different materials, respectively; friction originates from points of direct contact between particles and is a resistance of one particle's movement caused by other particle(s). Moisture may impact these interactions by adsorbing to the surface of particles and altering their surface energy or surface electrostatic charge. Moisture may condense from the atmosphere to porous or amorphous regions at the area of contact to soften a material and allow greater areas of contact. With the majority of materials, a relative increase in the moisture content will diminish flow rates due to an increase in the forces of cohesion and adhesion. There can be a significant range of moisture content in which

TABLE III: Microcrystalline cellulose.

Water content (% w/w)	Compact Tensile strength (MPa)	Crystallinity index
0	1.5	2.3
1.6	2.6	2.7
4.2	3.3	3.2
5.2	2.8	3.3
10.8	2.6	3.4
12.0	2.4	3.3

there appears to be little impact on flow properties, particularly at the lowest moisture values (less than 0.5% w/w). Each formulation requires sufficient data to justify its optimal moisture content range.

Materials that have been micronized or produced by other techniques such that their size is less than approximately 5 μm are particularly sensitive to the effects of electrostatic charge accumulation. This is frequently observed when fine powders cling to plastic storage materials. There may be varying quantities of material retained in the container during transfer steps in processing, which may be operator or seasonally dependent. For those items present in small quantities (e.g., potent drugs), it may be necessary to include a second step in which the empty plastic bag has a second type of material added to it with agitation or shaking to free the charged particles and permit a quantitative transfer to the product. This technique essentially becomes a rinse step for the container that uses a second component of the formulation. Process vessels made of metal serve to effectively ground a material and dissipate the electrostatic charges. Also, increasing the moisture content of a material generally results in reduced static charge accumulation. During material movement operations with large volumes of air (e.g., fluid bed drying and vacuum loading), static charges may build to significant levels, and they may produce sparks that have the potential to cause explosions. Many of the powdered organic solids found in pharmaceutical prod-

ucts have the capability to support an explosion should it be initiated. Although this is a rare event, it is important to ensure equipment is adequately grounded and enforce all safety precautions. This is particularly important where organic solvents are used near moving powder materials (e.g., transfer of powder from a plastic bag into a vessel with organic or mixed organic-aqueous solvents). The organic vapors may spread along equipment surfaces and ignite with the smallest electrical discharge.

Microbial Growth

The presence of moisture is also important to microbiological stability. The food industry has made extensive use of testing water activity to control microbial growth and monitor chemical stability (10). Water activity measurements differ from water content in that water activity reflects the energy status of water in a system. Water activity is defined as the vapor pressure of water above the sample divided by the vapor pressure of pure water at the same temperature. Values range from 0 for totally dry samples to 1.0 for pure water. Use of water activity testing has begun being adapted within the pharmaceutical industry, in part because of the introduction of US Pharmacopeia <1112> “Application of Water Activity Determination to Nonsterile Pharmaceutical Products.” Water quantitative determination is based on either a Karl Fischer titration or loss on drying in most pharmacopeial monographs. The Karl Fischer method requires meticulous analytical technique to yield accurate results; side reactions are possible and stringent drying of methanol is necessary. Most importantly, results from either technique may not be predictive of product stability outcomes. Among the advantages of water activity testing are the simplicity of this non-destructive assay, reduced likelihood of handling problems, and comparable or improved correlation to physical and chemical changes. Typical water activity values range from 0.3 to 0.5 for oral solid dosage forms. Most microbial growth is inhibited at values less than approximately 0.91, and yeasts and molds generally cease growing below 0.87 and 0.80, respectively.

IMPLICATIONS FOR COMPLIANCE, TROUBLESHOOTING, AND ROOT CAUSE ANALYSIS

The significant effects of moisture on solids processing and tablet products as described above indicate the need for good control of moisture in development and routine manufacturing and packaging. The following are potential areas of concern:

- Active drug and excipient ingredients moisture content
- Product characteristics
- Manufacturing processes
- Environmental controls
- Packaging materials.

Change in moisture levels of all associated with these areas of concern is critically important. Changes may be unintended, such as seasonal variation of environmental conditions. Changes may also be planned, such as with a new source of raw material with different moisture content. Change control of planned changes is critically important. Changes in moisture levels, both increased and decreased levels, should be considered as possible causes of manufacturing or stability problems in troubleshooting and root cause analysis.

Active Drug and Excipient Ingredients Moisture Content

The moisture content of all ingredients in the formulation should be known, including the active drug and all excipients. Also important are the specification limits for incoming materials. For example, one supplier of an excipient may reliably provide material containing 0.5% moisture. Less expensive material from a new vendor may be obtained. The new material may contain higher moisture—still within acceptable limits—but with potential for affecting product stability, processing, compaction, or other properties. Any changes to incoming materials with changes in moisture content must be carefully monitored for susceptible products.

Product Characteristics

Product characteristics impacted by the effects of moisture should be known. Products with an active drug that is chemically sensitive to moisture

or products with sensitive dissolution performance must be carefully monitored regarding exposure to moisture or to changes in moisture content. An effervescent tablet formulation containing acid and base components will be stable in a low-moisture-content environment, but is highly likely to undergo the effervescent acid-base reaction prematurely in the presence of even relatively low levels of environmental moisture.

Manufacturing Processes

Any manufacturing process that may impact the product moisture content of susceptible products should be carefully monitored. For example, there may be seasonal changes in the efficiency of drying processes caused by high humidity conditions in summer and dry air conditions in winter; air conditioning units need to have sufficient capacity to control processing within specifications. Tablet compressing problems may occur when the granulation moisture content is too high or too low. Manually controlled processes such as granulation and drying should be carefully monitored. Compliance personnel must be mindful of changes to equipment associated with manufacturing processes associated with moisture content.

Environmental Controls

Environmental conditions for moisture-sensitive materials and products must be carefully controlled. Seasonal humidity variation may impact product quality during manufacturing or packaging processes. A manufacturing area may easily run below facility limits during low humidity seasons, but may struggle to be compliant during the rainy season. Compliance personnel must be watchful of changes to equipment associated with environmental controls.

Packaging Materials and Processes

Packaging materials used for moisture sensitive products must be carefully monitored. Blister films may have widely differing moisture permeability. Data on moisture vapor permeation through flat sheets of polymeric materials (e.g., PVC, HDPE) are

readily available from the supplier for comparison. In addition to the flat sheet permeation data, it is important to realize the heating and cavity formation process may stretch and diminish the thickness in the region of bends by as much as 75%, thereby significantly reducing its moisture barrier protection in the relatively thin film regions. Metal foil materials are significantly better moisture barriers than the organic polymers, though they are more susceptible to punctures or tears that destroy their barrier function. Equipment changes which may affect the sealing of blister packages or foil pouches may cause problems with package integrity and product stability.

Change Control

Any changes affecting materials, products, manufacturing processes, environment controls, packaging materials, and packaging processes for susceptible products must be carefully evaluated. A thorough and comprehensive change control program will facilitate monitoring of change.

Troubleshooting and Root Cause Analysis

When it is necessary to troubleshoot a manufacturing challenge or out-of-specification analytical result, a practical understanding of the many ways water may impact the product can be of significant benefit in establishing a root cause with optimal remedial actions. The insight gained by asking the question "what impact did water have in causing this situation?" can be very helpful. Trace the data reported on the moisture content of materials at key points and ensure sufficient samples have been obtained to establish confidence in their accuracy and reliability. For example, tablet hardness, thickness, weight variation, compression force, ejection force, frequency of sticking to punches, disintegration, dissolution and chemical stability may be significantly different with moisture content variation of as little as 0.3% w/w. Low granulation moisture levels are well known to cause problems in tablet compressing. Water is found in nearly all pharmaceutical powders, it plays a vital role in granulation, compaction, and coating operations, yet it may have

a deleterious effect during the product's shelf life. It is essential that the effects of moisture be understood and controlled.

CONCLUSIONS

Water is present in nearly every pharmaceutical powder. It functions as a highly effective plasticizer to increase molecular mobility when present in low concentrations and may localize in surprisingly high quantities at regions of amorphous structure. Water is utilized to great benefit in granulation, compaction, and coating processes, yet may have a deleterious impact during a product's shelf life via an increase in chemical degradation or support of microbial growth. Controlling the impact of water begins with specifications and testing of all components, controlling the manufacturing and packaging processes along with the environment, selection and testing of packaging materials, and vigilance during the product's life cycle. Changes in component or product moisture content, either unintended such as those in seasonal variation or planned moisture changes such as with new sources of excipients, must be carefully monitored by compliance practitioners. In addition, understanding the myriad capabilities of water often offers valuable insight to determining root cause and corrective actions when troubleshooting.

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Review Article

EXTEMPORANEOUS DOSAGE FORM FOR ORAL LIQUIDS

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ABSTRACT

Access to a special dosage form of a medication is essential when administration to infants and children and selected other populations is required. Some drugs necessary for pediatric patients are not commercially available in dosage forms appropriate for use in this population. These drugs may be prepared extemporaneously for use in individual patients. Physical and chemical properties of drugs and excipients should be considered when preparing extemporaneous formulations. These formulations, however, may lack studies to document stability, bioavailability, pharmacokinetics, pharmacodynamics, efficacy and tolerability.

Keywords: Extemporaneous dosage form, Paediatric preparation, Paediatric medicines, Licensed liquid, Special products, Extemporaneous preparations, Compounding.

INTRODUCTION

Drug substances are usually administered as part of a formulation in combination with; nonmedical agents (otherwise known as inactive pharmaceutical ingredients or excipients) that have varied, specialized pharmaceutical functions. The proper design and formulation of a dosage form requires consideration of the physical, chemical, and biological characteristics of all drug substances and pharmaceutical ingredients to be used in formulating the product. The drug and pharmaceutical materials

utilized must be compatible with one another to produce a drug product that is stable, efficacious, palatable, easy to administer, and well tolerated. The age of the intended patient also plays a role in dosage form design. Infants and children aged ~5 years or younger are unable to swallow a solid dosage form (eg, tablet, capsule). A solid dosage form containing a fixed dose (eg, 250 mg) would also be impractical to use in these patients because the dosage requirements vary based on body weight (eg, milligram, kilogram) or surface area (milligram/meter²). Thus, pharmaceutical liquids, rather than solid dosage

forms, are preferred for oral administration to infants and young children. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered.¹

In the absence of a ready-made product a frequent approach by pharmacists is to prepare an oral liquid from tablets, capsules or powdered drug dispersed or dissolved in a suitable base. These are often referred to as extemporaneously prepared formulations and the practice occurs on an international scale. A survey of 210 pharmacists in the USA identified the eleven most frequently compounded preparations and the authors concluded that efforts by manufacturers and professional associations are required to supply pharmacists with information on the compounding and stability of extemporaneous preparations.²

Stewart and Tucker surveyed Australian hospitals and showed that 116 drugs were extemporaneously compounded into 270 different formulations for paediatric use. Frequent problems identified in this survey included disguising unpleasant taste, achieving dose uniformity and a lack of chemical and physical stability data. This lack of stability information is a common problem and formularies of extemporaneous formulations have been published in an attempt to provide some guidance on the preparation of paediatric oral liquids.³

Lack of Commercial Products and the Implications for Infants and Children

Unless an illness largely affects infants and children, most drugs are not labeled for use in the pediatric population for a variety of reasons. These include relatively small market size (thus limiting return on investment), potential delay in marketing a drug for adults, and perception of greater legal liability and regulatory requirements for conducting studies in children instead of in adults. Consequently, nearly 75% of

the drugs available in the United States for adults have not been labeled for use in infants and children (ie, those aged <12 years), even though these drugs may be needed in this population.^{4,5} For example, seizure disorders occur in both adult and pediatric patients, but certain drugs-gabapentin, lamotrigine, tiagabine, and topiramate-were not fully labeled or available in a liquid dosage form for use in young pediatric patients (ie, those aged <12 years) at the time of their marketing for adults. Also, sildenafil was found to be effective in adults for the treatment of pulmonary hypertension, but it was not available in a liquid dosage form for use in neonates with this condition. Extemporaneous liquid formulations prepared from solid dosage forms were needed to make these drugs accessible to infants and children. 6 IV drugs (eg, morphine, phenobarbital) marketed for adults are too concentrated for accurate measurement of the small volumes (doses) needed for the treatment of neonates or infants. These drugs need to be diluted to minimize underdosing or overdosing; however, stability and sterility of these extemporaneously prepared formulations for parenteral use must be documented before administration to patients.⁶

When drugs are not commercially available in appropriate dosage forms, options include the following: delaying or omitting potentially effective therapies; using a dosage form intended for adults without alteration; contacting the manufacturer for recommendations; and preparing an extemporaneous formulation, if reasonable, based on data in the literature or in consultation with peers. Examples of drugs not commercially available in suitable dosage form (ie, a liquid formulation) for infants and young children are listed in the table.⁷

Need for Pediatric Drug Formulations

Based on a survey of 57 hospitals, with 36 to 350 licensed pediatric beds, there was a need for >100 liquid formulations for use in pediatric patients. Similarly, a United States

Pharmacopeia (USP) survey identified the need for >70 formulations for oral administration in infants and children (personal communication, Claudia Okeke, PhD, Rockville, Maryland, January 15, 2008). The need is expected to grow because the majority of newly approved drugs are not labeled for use in pediatric patients, and an appropriate formulation usually does not exist unless the drug is approved for that population.⁷

Currently Available Information for Compounding Extemporaneous Formulations

Several hundred different formulations for pediatric use are compounded in various situations, including pharmacies in hospitals, nursing homes, and the community. Some have official monographs in the USP and may be published in the peer-reviewed literature. Before any USP monograph can be developed, however, valid stability studies must be undertaken to establish a beyond-use date for the compounded preparation. Formulations have been published in the professional and peer-reviewed literature.⁶ Drops, syrups, and suspensions may be suitable for use in neonates, infants, and young children, while a tablet (eg, regular, chewable, disintegrating) or capsule may be preferable for older children and adolescents. Parenteral and rectal dosage forms can be used in all age groups. Drug absorption and bioavailability, however, may be unpredictable after oral, rectal, or IM administration of certain drugs, especially among infants.⁷

Pharmaceutical Considerations in Preparing Extemporaneous Formulations

Before the formulation of a drug substance into a dosage form is planned, it is essential that the substance be chemically and physically characterized. Preformulation studies can include physical description, particle size, solubility, pKa, pH, stability, excipients toxicity, and other characteristics that provide the information needed to define the nature of the drug substance. This information then provides the

framework for the drug's combination with pharmaceutical ingredients in the development of a dosage form. Understanding the physical description of a drug substance before dosage form development is important. The majority of drug substances used today occur as solid materials. Most of them are pure chemical compounds of either crystalline or amorphous constitution. Physical properties include such characteristics as its physical description, particle size, crystalline structure, melting point, and solubility. Biological properties relate to its ability to reach a site of action and elicit a biological response.^{7,8}

Stability

When experience or shelf-storage experiments indicate that a preservative is required in a pharmaceutical preparation, selection of that preservative is based on various factors.

For example, an effective preservative should:

- I. Inhibit growth of microorganisms likely to be involved;
- II. Be sufficiently water soluble to achieve necessary concentrations;
- III. Be in an undissociated form for penetration into microorganisms;
- IV. Be nonirritating and nonsensitizing;
- V. Have adequate stability;
- VI. Be compatible with all other formulation ingredients; and
- VII. Not adversely affect the preparation's container or the closure. When compounding, caution must be used to not alter the pH or dilute the preservative below its effective concentration to prevent microbial growth.⁹

The required preservative concentration will vary with the factors of pH and dissociation, as well as with the presence of other formulation ingredients (eg, syrup) with inherent preservative capabilities. The use of syrup contributes to the

preservation of the preparation and may lessen the amount of additional preservative needed in the formulation.⁹

Sterility and Endotoxins

Microbiologic testing for pharmacy sterile compounding may include sterility and endotoxin testing. Preservative effectiveness should also be considered for some preparations. Sterility tests can be conducted using commercial kits (QI Medical, Inc., Nevada City, California) or by developing and validating USP sterility testing protocols, which are more detailed than the commercial sterility test kits. Endotoxin tests can be conducted using commercially available kits (Associates of Cape Cod, Inc., East Falmouth, Massachusetts) or by purchasing the components separately. Endotoxin testing end points can be difficult to interpret, and in-house testing requires training.⁷

Taste, Odor, Palatability and Appearance

The proper selection of taste, odor, palatability, texture, color, and sweetness of a preparation may enhance patient adherence to the agent. Much work has been done and is ongoing on enhancing the palatability of oral drug formulations. The compounder has the option of using commercially available vehicles in which to incorporate the drug or to construct the entire preparation; this would include the use of viscosity enhancers, sweeteners, flavoring agents, preservatives, and colors.^{10, 11}

Coloring agents are used in pharmaceutical preparations for purposes of esthetics. Certain agents-sulfur (yellow), riboflavin (yellow), cupric sulfate (blue), ferrous sulfate (bluish green), and cyanocobalamin (red)-have inherent color and are not considered pharmaceutical colorants in the usual sense of the term. Although most pharmaceutical colorants in use today are of synthetic origin, some are obtained from natural mineral and plant sources.⁹

Assurance of Quality and Safety

Testing for Potency, Stability and Sterility

A quality assurance program in compounding pharmacies includes some level of testing for finished compounded preparations. It is important for the compounder to understand pharmaceutical analysis so that valid results are obtained when tests are being conducted, whether they are done in-house or outsourced. It is incumbent on the compounding pharmacist to know the following: (1) when to test; (2) what to test; (3) what method(s) to use; (4) how to interpret the results; (5) the limits of the test; and (6) the importance of analytical testing in the overall quality assurance program in the pharmacy. This does not mean that one must be a pharmaceutical or chemical analyst or a microbiologist, but there should be a basic understanding of both the testing methods that are used and the sample handling requirements so that valid results are ensured. The goal in analytical testing is to produce results as accurately, efficiently, and reproducibly as possible. Any analytical method used should be accurate, rapid, reproducible, and specific (stability-indicating). No single analytical method is ideally suited for all drugs; each method has its own strengths and weaknesses. Compounding pharmacies have two options when analytical testing is required. Some analytical methods can easily be performed in-house (in the pharmacy), but some must be outsourced to a contract laboratory. If done in-house, appropriate equipment must be obtained, validated either by the manufacturer before purchase or by the compounder on purchase, maintained, calibrated, and used properly. If outsourced, the compounder needs to determine what to outsource, how to select a laboratory, and how to "test" a laboratory; ongoing relationships should be developed with the laboratories chosen. Contract laboratories should follow USP General Chapter standards by using its official methods and techniques for preparation.⁷

Safety Considerations with Excipients

Although excipients are expected to be pharmacologically inactive, certain patients may experience a variety of adverse effects, ranging from hypersensitivity or allergic reaction associated with a coloring agent in an oral dosage form to intracranial hemorrhage with a benzyl alcohol preservative in an IV dosage form. All sweeteners containing sucrose and fructose may affect blood sugar; sorbitol and xylitol may cause osmotic diarrhea. Lactose should be avoided in patients who are lactose intolerant. Ethanol is a solvent minimally used in oral liquid formulations that has largely been replaced by other excipients. Propylene glycol is commonly used as a solvent in oral, topical, and injectable drugs (eg, phenobarbital, phenytoin, diazepam, lorazepam). This vehicle is especially useful to solubilize drugs with limited water solubility. Patients aged <4 years may accumulate propylene glycol due to decreased metabolism, and those receiving multiple drugs containing this solvent are at high risk of developing central nervous system depression and hyperosmolality. Certain extemporaneously prepared suspensions, without sufficient preservative, may pose risks associated with microbial contamination.^{1, 7}

Challenges and Limitations

Lack of Stability/Sterility Studies

The use of some extemporaneous formulations in pediatric patients is based on experience rather than data from specific stability and sterility studies.^{5,6} Furthermore, published clinical studies in pediatric patients may also lack information about the dosage forms used in those studies. Standing et al searched 10 highly cited journals (5 adult medicine and 5 pediatric medicine) for studies published over a 2-year period evaluating the use of oral medications in children aged <12 years.¹² They found that <40% of the 76 articles identified provided adequate information regarding the dosage form for the study to be

accurately reproduced. In addition, 20% of the articles neglected to provide the formulation used in the study. These results thus question the validity and reliability of pediatric trials where oral dosage forms are utilized. Because highly cited journals have allowed studies with inadequate dosage form information to be published, the investigators hypothesized that less highly cited journals may tend to provide even less specific dosage form information, further decreasing reliability and validity of results. PubMed was searched using the terms administration, and oral or oral medication, limiting those results to the English language, those in children aged 0 to 12 years, and those published in the last 6 years (2001-2006).¹³ This produced >650 citations, and the abstracts were analyzed for inclusion into the study. Initial review of the first 100 citations has produced results mirroring the findings of Standing et al and in some instances was worse; only 27% of studies provided adequate formulation information, 52% provided some, and 21% provided none. Interestingly, studies published in pediatric journals were more likely to provide no information than nonpediatric journals. More highly cited journals were no more likely to require authors to provide adequate information on the dosage form used than less-cited journals. Randomized, placebo-controlled, prospective trials did no better at reporting formulations than studies that were less rigorous. Only 43% of publications documented their administration procedure and only 14% documented education if a caregiver or parent was responsible for administration. Fifty-two percent assessed and documented adherence, and only 10% documented palatability and tolerability (taste and acceptance [not adverse effects]). Only 3 citations used extemporaneous preparations, but none have cited stability data. In no instance did impact factor have a statistically significant effect on dosage form reporting. Investigators speculated that results may show a substantial

problem in the pediatric clinical trial literature that could influence pharmacotherapy.⁹

Chemical Instability

Drugs in extemporaneously prepared liquids may be susceptible to chemical reactions leading to degradation. The most common reactions are hydrolysis, oxidation and reduction.¹⁴ Usually the reaction rate or type is influenced by pH, for example, azathioprine is rapidly hydrolyzed to 6-mercaptopurine at alkaline pH but is relatively stable in acidic or neutral conditions.¹⁵ Other factors which may increase the rate of reaction include the presence of trace metals which catalyse the oxidation of captopril.¹⁶ methyl dopa¹⁷ or exposure to light which catalyses the oxidative degradation of 6-mercaptopurine.¹⁸ The rate of chemical degradation usually increases with temperature, a factor which is the basis for accelerated stability trials of pharmaceutical formulations. Preparations made from tablets contain excipients such as binders and disintegrating agents in addition to the active drug. These excipients may reduce chemical stability by changing the pH to a value at which more rapid degradation occurs. This probably explains why amiloride solution prepared from pure drug is more stable than an oral liquid prepared from tablets.

The drug in the preparation may be totally or partially in solution or predominantly in the solid state as a suspension. Drugs in solution are more susceptible to chemical degradation than drugs in the solid state (ie. suspensions), thus suspensions of acetazolamide and chlorothiazide are more stable than solutions.^{19,20} However it cannot be assumed in all cases that an extemporaneously prepared suspension is more stable than a solution. In a suspension, equilibrium exists between drug in the solid state and drug in solution and even though the amount of drug dissolved may be minimal the conditions could be optimal for degradation. Frusemide is a notable example which undergoes hydrolysis in

acidic conditions where the solid state is predominant, but is much more stable at alkaline pH where it is totally in solution.²¹

Microbiological Instability

Microbial growth in an oral liquid may cause foul odour and turbidity and adversely effect palatability and appearance. High titres of micro-organisms may be hazardous to health especially in very young or immunocompromised patients. By-products of microbial metabolism may cause a change in the pH of the preparation and reduce the chemical stability or solubility of the drug. Microbial contamination during preparation must be minimised by using clean equipment, sterile water (Water for Irrigation BP) and avoiding contaminated raw materials and containers. If sodium benzoate or benzoic acid are used as antimicrobial preservatives the final pH must be less than 5 so that the active unionised form is predominant. Consequently the drug must also be stable at this pH. Effective preservative systems require rigorous evaluation which is seldom performed on extemporaneous formulations. Many factors can reduce the effectiveness of the preservative including use of contaminated materials, chemical degradation, binding of preservative to suspending agents or tablet excipients, incorrect storage or unhygienic use of the final product.²²

Physical Instability

Extemporaneously prepared oral suspensions may be susceptible to sedimentation of insoluble drug causing caking. Difficulty in re-suspending the drug or rapid sedimentation following shaking can lead to erratic dosage measurement as demonstrated with chlorothiazide suspension and this inherent problem with extemporaneously prepared formulations is of considerable concern. Some spironolactone suspensions have been reported to be excessively thick and almost un-pourable. Refrigeration, whilst usually desirable to maximize chemical stability and reduce microbial growth, can also

increase the viscosity of a suspension making re-suspension more difficult or cause the precipitation of active drug or preservatives. It is important to consider the effect on pH of all components of the formulation and the possible impact on stability. Syrup, for example, is relatively acidic and if used in phenobarbitone sodium oral solution it will cause the precipitation of unionized phenobarbitone.²³⁻²⁵

Lack of Bioavailability and Pharmacokinetic

/Pharmacodynamic Studies

Bioavailability and pharmacokinetic/Pharmacodynamic studies are rarely conducted for most extemporaneously prepared medications. When a tablet or capsule with regular-release characteristics is used to prepare a suspension, it is assumed that the bioavailability and pharmacokinetics /pharmacodynamics will not be compromised in patients. However, those sustained-release properties can be lost when a tablet is crushed and converted to a liquid dosage form before administration. Bioavailability, pharmacokinetic, and pharmacodynamic studies are unlikely to be performed for most extemporaneous drugs due to lack of financial resources and the complexity of performing these studies at most health care facilities. Thus, treatments involving extemporaneous formulations should be observed to monitor efficacy and tolerability of these products in patients.⁷

Efficacy and Safety Concerns

Extemporaneous formulations have generally not been evaluated in controlled trials to establish effectiveness and tolerability in patients. Because these studies are even more expensive to perform than the bioavailability, pharmacokinetic, and pharmacodynamic studies, they are unlikely to be conducted for the majority of extemporaneous drug formulations. It is most important to monitor patients receiving extemporaneously prepared medications to assure effectiveness and tolerability. Patients and

caregivers should be encouraged to contact health care practitioners to confirm that the desired outcomes were achieved with therapies.⁷

Lack of Funding for Research

Most diseases are more prevalent in adults and thus the drugs are indicated for only this population at the time of approval by the US Food and Drug Administration (FDA). Manufacturers may have less interest in conducting expensive Phase I to III studies for labeling in pediatric patients-especially in neonates, infants, and young children-due to low return on investment. They may also be reluctant to fund studies for the development of pediatric drug formulations, as such funding may be viewed by the FDA as promoting a drug's use without conducting efficacy and safety studies in pediatric patients. The manufacturers of generic drugs would have even less interest in supporting such studies by independent researchers. Experience

in the past 20 years has shown that the National Institutes of Health and many foundations may view these studies as "too applied" for consideration of funding, and funding should be provided by the individual drug companies for their specific products. A national professional association in pharmacy defined the need but could not devote financial resources to conduct studies on extemporaneous formulations.^{7,10}

Variations in Practice

The need for extemporaneous formulations at various health care facilities may be similar for selected drugs, and yet different drug concentrations, excipients, and methods may be used to prepare certain formulations. This occurs because of a lack of established or "standard" formulations or a lack of information in the literature regarding stable formulations. Lack of information about extended stability creates waste of drugs, increased costs, and inconvenience to patients and caregivers because prescriptions then have to be refilled more than

necessary. Conveniently located pharmacies may not have expertise in preparing extemporaneous formulations, and thus caregivers may have to travel to specialized pharmacies. The need for extemporaneous formulations may be unique at various facilities. In such cases, the facilities would have to make these drugs available in the desired formulation, even though the expertise to do so may not exist. This might include physicians and/or nurses preparing the formulation. If these practitioners are not well versed in the procedures, there is ample room for medication and compounding errors to occur.⁷

Poor Coordination and Sharing of Information

The efforts and activities of various health care facilities in preparing extemporaneous formulations are not generally coordinated. In addition, information and knowledge regarding these formulations may not be widely shared. Although investigators at academic institutions and health care facilities present papers and publish articles about extemporaneous formulations, most pharmacists involved daily with these activities may not do so. Thus, coordination and sharing of information must be improved to decrease duplication of efforts and to increase access to stable extemporaneous formulations for patients.⁷

Reimbursement and Payment Issues

Third-party payors do not always pay for compounded medications. They do pay for compounded medications in the hospital (eg, IV admixtures, pediatric formulations) but not always in the community pharmacy setting. This practice is undesirable for patients in the ambulatory setting, as caregivers must payout of pocket for the prescriptions when they are not covered by insurance.⁷

Adverse-Event Reporting

According to the USP compounding standards, adverse events occurring as the result of a compounded medication should be reported to the USP MEDMARX program. Some individual

state boards request that these adverse events be reported to the FDA MedWatch program. However, neither of these programs is mandatory and neither was developed specifically to handle pharmaceutical compounding adverse events; rather, they were designed to handle adverse events from manufactured drug products.⁷

What Is Wrong With Extemporaneous Formulations?

In order to provide liquid formulations to administer drugs with no liquid preparation available, or to overcome 'special' supply problems, extemporaneous formulations are needed. They can be prepared by dilution of existing liquid dosage forms (e.g. dilution of the injectable form of clonidine, Table 2) if formulation parameters such as excipients and pH are suitable orally; they can be prepared directly from raw materials/chemicals although there was no example in the cardiovascular therapeutic area. The procedure of crushing tablets and "dispensing/suspending" in water, food or beverages prior to administration is associated with the highest risk of errors in extemporaneous dispensing, mainly because they are difficult to track as there is no record or control of preparation. Extemporaneous preparations tend to have little or no compatibility study back up. Very few well-controlled stability studies are published on in vitro compatibility issues between manipulated solid dosage forms and food/beverages. Studies have been undertaken with drugs for the gastrointestinal system^{26,27} (Johnson *et al.*, 2003; Carrier *et al.*, 2004), 5HT3 antagonist drugs²⁸ (Yamreudeewong *et al.*, 1995) and labetalol for the cardiovascular system²⁹ (Nahata, 1991). Standardization of recommendations for suitable alimentary vehicles is highly problematic. For example, manufacturer may recommend that the drug is stable when tablets are dissolved in apple juice³⁰ (Imatinib SPC, 2004), but surely it cannot be

known whether the drug is stable in any apple juice or other juices, whose pH and ingredients may vary significantly between manufacturers and countries. There are few stability studies undertaken on extemporaneous products. In the literature, shelf-life is determined by chemical stability, mainly assessed by HPLC, for specials or some extemporaneous preparations formulated in pharmaceutical vehicles. Vehicles can be commercially available (e.g. Ora®plus, Ora®sweet, Keltrol®) or prepared in the dispensary (e.g. methylcellulose 1%, syrup NF). Mostly, stability testing does not include physical and microbial stability testing and does not mimic the 'in-use' stability when the preparation encounters variable temperature and frequent opening during the treatment course. The bioavailability of extemporaneous products can be unpredictable. A gross formulation obtained from crushed solid dosage forms may not be bioequivalent with the dose form swallowed whole. In the past, the priority has been to provide a formulation that children can take rather than a formulation with optimized bioavailability.³¹ Notterman *et al.* (1986) described an example of inadequate isoniazid bioavailability of crushed tablets and an extemporaneous preparation made from the injection, compared with a licensed liquid. As mentioned in Table 2, drug solubility is very important to consider in extemporaneous preparation. If the active is not soluble, it can lead to inaccuracy of dosing through a lack of dose uniformity and reproducibility. This is a major consideration when no suspending agents are used, especially when the person administering the dose is inexperienced and the dose is small (Tuleu *et al.*, in press).³² Other problems with extemporaneous dispensing include the expense of some drugs (bosentan, sildenafil, Table 2) and the consequences of production errors, which can be fatal (Anonymous, 2000).³³

Is Dosing Accuracy A Problem?

Where 'special' products are used, there is some degree of certainty that the drug will be present in the stated quantity within the expiry period. The main difference between 'specials' and licensed liquids is that their bioavailability usually remains untested. This means that the bioavailability of 'specials' may depend on the manufacturing technique used and may differ between manufacturers. There is little incentive for 'specials' manufacturers to perform bioavailability/ bioequivalence studies as, without going to the considerable expense of attempting to license the drug, dosing recommendations based on such studies cannot be legally made. Extemporaneous preparation of doses by nurses or carers is probably the least accurate method. The weight of a split tablet can range from 50 to 150% of the actual half-tablet weight³⁵ (Teng *et al.*, 2002) and accuracy does not seem to be improved by using commercially available tablet cutters (Breitkreutz *et al.*, 1999).³⁶ Insoluble drugs are often crushed and dispersed in water to give a proportion of the dose. Without the use of suspending agents, this method provides highly variable dosing especially if the dose (volume) is small. Although drug dosing in children is often based on bodyweight, this can be a poor predictor of drug clearance (Anderson *et al.*, 1997).³⁷ It is therefore questionable how much impacting inaccurate dosing will have on clinical outcomes, especially with anti-hypertensive medications where dose is titrated to response. The main problem will be with variability in dosing, which occurs most frequently when solid doses are manipulated immediately prior to administration. Warfarin is available as a special but the expense and short shelf-life along with the drug's water solubility means that it is usually administered as tablets crushed and dispersed in water. In a cohort study of paediatric patients receiving warfarin therapy, children under one year took significantly longer to achieve the target international normalized ratio (INR), needed more INR tests per month and required more

dose changes per month compared with other age groups. Children under 6 years were more likely to have INRs below the target range³⁸ (Streif *et al.*, 1999). There are many factors which could explain these differences but one which the authors did not explore was formulation. Unfortunately, no details on the drug formulation were given but it would seem most likely that crushed tablets were used to administer the dose to younger age groups. Using an inappropriate formulation leading to inaccurate dosing could have been a factor in these patients requiring more blood tests (potentially traumatic finger/heel pricks) and failing to reach target INR values as quickly. This example highlights the potential problem encountered when narrow therapeutic index drugs are not available in liquid formulation showing that in such situations, dosing accuracy is a problem.

Why Have Formulation Issues Not Been Addressed In the Past?

Drug formulation issues are frequently overlooked in the reports of paediatric clinical trials. One of the core principles in reporting scientific research is to give full details on how the experiment was carried out so that it can be repeated. Clinical trials involving medicines in children routinely fail to do this by omitting information on the drug formulation and how it was administered, impairing the reliability and validity of results and hindering the transferability into clinical practice. In the previous two sections, published trials on nifedipine³⁹ (Blaszak *et al.*, 2001) and warfarin³⁸ (Streif *et al.*, 1999) have been mentioned, neither of which gave full details of the formulation used and how the drug was administered. A study on the use of amlodipine in children with hypertension described how they were administered a weight-specific dose using a powder prepared from crushed tablets (Tallian *et al.*, 1999).⁴⁰ The report did not specify how the powder was administered. It is unlikely that each

dose of powder was individually weighed out and as amlodipine is only sparingly soluble in water, dispersing the dose in water without using a suspending agent will lead to variable dosing. Another study⁴¹ (Flynn *et al.*, 2000) on amlodipine in children recognized this problem by using a suspension formulated in the hospital pharmacy. These studies represent the variability of formulation and administration information provided in published paediatric clinical trials. The problem is not isolated to cardiology medicines (Standing and Wong, 2004).⁴² A review of recent paediatric clinical trials in high impact factor journals⁴² (Standing *et al.*, in press) found adequate formulation information is provided in only 37% of reports. Adequate formulation reporting was classified as providing sufficient information for the study to be repeated (formulation and manufacturer stated, where formulation was a tablet/capsule, an account of whether children were able to swallow the dose whole or how an aliquot of the dose was administered). Especially in the case of 'special' or extemporaneous preparations, it is vital that a reference on the medicine's formulation is given, as unlike licensed products, unlicensed preparations may not be bioequivalent between different manufacturers (or between batches). This result suggests that many authors and journal editors do not consider providing formulation information in paediatric clinical trials to be important, when its potential impact on the amount of drug received may have a profoundly negative effect on the reproducibility (reliability) and to a lesser extent validity of the results. In addition to clinical trials frequently not providing formulation information, therapeutic failure can often have a number of explanations. For example, the failure of amiodarone to control a patient's arrhythmia may be due to a dosing with a proportion of a crushed tablet dispersed in water. Many drugs are sparingly soluble such as amiodarone, nifedipine, in water, in absence of a suspending agent; most of the drug will be in the solid form

at the bottom of the measuring device. Unless the mixture is thoroughly stirred immediately prior to giving the dose, the amount of drug received by the patient is likely to be very erratic³² (Tuleu *et al.*, in press). 'Special' and extemporaneous products have almost never been tested for bioavailability and so patients may be under or over dosed compared with a level expected to be achieved by extrapolation data from licensed formulations in adults. It is therefore possible that therapeutic failure or adverse reactions due to overdose resulting from inappropriate formulations go unrecognized by paediatricians and pharmacists caring for the patient. Another important reason for inadequate formulation availability for children is a commercial one. At present in UK, there is no financial incentive for pharmaceutical companies to license paediatric medicines and develop suitable formulations due to the relatively small market and high cost of developing and producing them.

Proposed Solutions and Recommendation⁴³

Access to age-appropriate drug formulations is critical to provide effective and well-tolerated medications to patients. As discussed here, there continues to be a need for extemporaneous formulations of brand and generic drugs for neonates, infants, and children. Given the multitude of challenges, we recommend a number of potential solutions.

Most-Needed Formulations

A prioritized list of needed formulations should be developed in consultation with physicians, pharmacists, and nurses at the local, regional, and national levels.

Funding of Centers of Excellence and Independent Research

Mechanisms for funding of studies to develop extemporaneous formulations should be established from local, regional, and national sources. The NICHD may consider funding of "Centers of Excellence," which could work

collaboratively to conduct studies for the development of high-priority extemporaneous drug formulations. Individual investigators should also have mechanisms to compete for funding of such studies.

Dissemination of Data

Investigators and pharmacy practitioners involved in the development and use of extemporaneous formulations should share their data and experience with others through presentations at national meetings, publications in peer-reviewed journals, and postings on Web sites. Manufacturers possessing any data on drug stability in extemporaneous formulations should share this information through package information and Web sites. Some drugs (eg, captopril, spironolactone) are available commercially in countries other than the United States; information on preparing these drugs extemporaneously should be shared by the manufacturer.

Monitoring Clinical Effectiveness and Tolerability during Use and Sharing of Experience

Because most extemporaneous drug formulations have not undergone clinical studies, their effectiveness and tolerability should be monitored and studied systematically during clinical usage in patients. This clinical experience should be shared through presentations, publications, and Web sites.⁴³

Do Children Need Access to Modified Release Products?

Nifedipine is unlicensed for use in children but is often prescribed for hypertension secondary to renal failure. In adults, short acting nifedipine is not recommended for use in hypertension due to the rapid drops in blood pressure it causes, leading to complications, such as reflex tachycardia (British National Formulary, 2005). The usual recommendation is to give a modified release (m/r) preparation to obviate large changes in blood pressure. However, the only

available m/r nifedipine preparations are in tablet form, and many children are unable to swallow whole tablets. As a result, children are prescribed short-acting nifedipine preparations, which include withdrawing the dose from soft capsules, crushing m/r tablets and using imported drops which have proved to give variable dosing. There is little evidence for the safety of using short-acting nifedipine in children, but a retrospective review did find it effective in producing large reductions in mean arterial blood pressure, albeit giving little information about how doses below 10mg were extracted from the capsules. Serious adverse effects of large decreases in blood pressure in children can include cerebral ischemia particularly when the patient has long-standing hypertension. This, along with a lack of prospectively collected safety data, is the reason that some paediatricians advise against the use of short acting nifedipine outside the specialist hospital environment. Nifedipine provides a prime example of the disparity which exists between medicines for children and adults. Licensing of nifedipine affords adults the benefit of once daily dosing, decreased risk of adverse effects and formalised post-marketing surveillance. Children, treated with the same drug, have to take the dose three times a day, and are placed at potentially increased risk of adverse effects because no m/r formulation is available. So, in answer to the question: do children need access to modified release products; the answer is yes; the challenge being to develop innovative drug delivery methods that children are able to take. Such strategies may include: m/r small platforms (minitables, minicapsules), trans-dermal delivery (especially for neonates), m/r liquids (nano or microparticles) with suitable polymers.

Will Formulations Improve In the Future?

In September 2004, the European Commission adopted a legislative framework for regulation of medicinal products for paediatric use in order to work towards an ethical, effective and

favourable environment for paediatric research and development (Medicines for Children, 2004). These arrangements are similar to the one established in USA during the late 1990s. The key objectives of the EU proposed regulation are to increase the development and authorization of paediatric medicines while ensuring they are subject to high quality research, but that no unnecessary clinical trials are carried out. The proposal also aims to improve the information available on medicines for children.⁸

Key elements in the proposal are⁸:

- A new expert committee within the European Medicines Agency (EMA) to assess and agree Paediatric Investigation Plans (PIPs) presented by the pharmaceutical industry. A system of free scientific advice will also be provided by the EMA.
- A requirement at the time of marketing authorization application that data is presented on the drug's use in children. A system of waivers and deferrals will ensure the requirements do not delay the authorization for medicines in adults.
- A reward for studying medicines for children of 6 months extension to the supplementary protection certificate; in effect, 6-month patent extension for the product (including adult use). - For off-patent medicines, 8 plus 2 years of data exclusivity on paediatric use of the product for new studies awarded via a Paediatric Use Marketing Authorization (PUMA). These incentives are very similar to those in USA but the EU proposal is more robust as it requires the sponsor to market the paediatric medicine for the approved indication within 12 months, speeding up the availability for patients. It does not distinguish between studies required (with claimed benefit to children) and those requested (with potential benefit to children) as in USA.

- Increased safety monitoring for children's medicines (pharmacovigilance).
- A compulsory submission by industry of existing studies in children, an inventory of the EU therapeutic needs of children and an EU network of investigators and trial centers to conduct studies required. The EU proposes a transparent approach to negative outcomes of the trials in children as any results (positive or negative) will be included in a database of ongoing or terminated studies; the results will also be incorporated on the drug label, regardless of whether the indication is approved or not. This awaited legislation is likely to become effective late 2006 and it is hoped that all future medicines for children will have been investigated in children and, where there is an appropriate indication, a licensed paediatric formulation will be produced.

However, delays are anticipated as the Medicines Investigation for the Children in Europe (MICE) fund, equivalent to the National Institute of Health and FDA set up to support old and commercially disregarded drugs in USA, has not yet been sourced. This is a real issue as generics manufacturers do not have substantial resources for research and development beyond equivalence studies. In the meantime, extemporaneous preparation, be it at the bedside, by pharmacists or 'special' manufacturers will continue to be a major route by which paediatric oral medicines are prepared. As a result of strong national concern in UK (Safer and Better medicines for children, 2004; National Service Framework (Standard 10), 2004), the first edition of the British National Formulary for Children (BNF-C) is due to be published (British National Formulary for children, 2005). It will provide a practical, relevant, authoritative information source and guide prescribing, dispensing and administration of medicines to children up to 18 years of age. By reflecting current evidence on efficacy and safety of drugs

within the limits of available clinical trial data, BNF-C will provide practical guidance on the 'off label' use of medicines.

In addition to legislative and formulary developments,, innovations in pharmaceutical formulations should improve the ease in which children can access medicines. Innovative m/r preparations have previously been mentioned, and the following areas are also ripe for future developments and research:

- New routes of administration such as oraltransmusosal (buccal strips), intra-nasal and transdermal (for neonates mainly).
- More research into alternative safe excipients for children such as natural polymers (e.g. cyclodextrin to mask taste of drugs, improve solubility or protect drugs/patient).
- Children's ability to swallow and their preferences need to be investigated. This will direct future formulation research towards (mini) tablets, chewable tablets, dispersible tablets or more oral liquids.

Although new and innovative formulations are urgently needed, work on extemporaneous formulation should not be disregarded. Those findings reflect on numerous problems associated with the lack of suitable formulations for children. This emphasized the difficulty in prescribing and administering cardiovascular drugs as a proof of concept, which can be extended to many other therapeutic areas. In an era of evidence-based medicine, it is unacceptable that drug formulations given to children are not better designed to provide accurate and reproducible dosing. With the expected new European regulations and the obligation of clinical testing on the paediatric population, it will be important that a strategy for paediatric formulation research is put in place. The future of paediatric drug formulations seems bright, but legislation must be supported by innovative research on new and existing delivery methods.⁸

Preparation of an Extemporaneous Preparation-A Guide

- Consider an alternative drug.
- Consider an alternative method, for example, tablet dispersion or oral administration of the injection.
- Consult the latest information data-bases and publications. Prepare a formulation according to a published study and follow the conditions of this study as closely as possible. Modifications to published formulations are only appropriate if there are no detrimental effects on stability. A maximum expiry date of one month from preparation is recommended and liquids without antimicrobial preservative should be given a shorter expiry date. If there are no data from a published study consult pharmaceutical manufacturers, other paediatric hospitals and research centers. It may be possible to adapt existing information from drug stability texts (e.g. solubility, stability profile) or from the formulation details of the injection or oral liquid available elsewhere. Monitor use of the product and observe for any signs of physical instability such as colour change or difficulty in re-suspension. Provide information to caregivers to ensure correct use of the product (e.g. storage conditions, use of an oral syringe, shaking before administration). Ensure that formulations details are available to all practitioners involved in the patients care to ensure that the product is consistent in appearance and quality. Prescriptions could contain full details of the formula and hospital pharmacists could provide details to their community colleagues.⁴⁴

CONCLUSIONS

The present article was described a many complex issues that have been described and to highlight some of the factors for pharmacists and paediatricians to consider in order to optimize drug therapy. Information sources such as specialized formularies, drug stability texts and the advice of pharmaceutical companies are invaluable. Most pharmaceutical companies will attempt to provide stability information and can sometimes recommend a specific formulation. Practitioners must continue to lobby for the development and availability of more paediatric oral liquids and paediatric strength tablets some of which may be obtainable in other countries. In order to make information more accessible investigators of clinical drug use should describe the formulation details of the preparation used in their research. This information is often omitted from the publication and can be extremely difficult to source especially when required rapidly. Investigators engaged in stability studies should aim to make the results of their research universally acceptable by designing simple formulations and avoiding the use of unnecessary or difficult to use ingredients. Valid protocol design for the stability study is essential and ideally the study should be carried out on formulations prepared from pure drug as well as tablets and the pure drug formulation used in practice whenever possible. Finally, sharing information on extemporaneous preparation and research collaboration should be further encouraged especially between major paediatric hospitals and research centers to ensure that our patients receive the highest quality drug therapy.

Table 1: Examples of medications not available in a suitable dosage form (eg, a liquid formulation) for infants and young children.⁷

Acetazolamide	Albendazole	Amiodarone	Amitriptyline	Arginine
Biotin	Bupropion	Busulfan	Captopril	Carbenicillin
Cholestyramine	Clindamycin	Clobazam	Clonazepam	Clonidine

Dantrolene	Dexamethasone	Enalapril	Ethambutol	Ethionamide
Famciclovir	Glutamine	Hydroxyurea	Irbesarta	Lansoprazole
Leucovorin	Lisinopril	Lomustine	Mefloquine	Methimazole
Methotrexate	Methylphenidate	Minoxidil	Neomycin	Nicardipine
Nimodipine	Olanzapine	Pancrelipase	Paromomycin	Phenobarbital
Prazosin	Primidone	Probenecid	Procarbazine	Propafenone
Pyridoxine	Riboflavin	Saquinavir	Scopolamine	Sertraline
Sildenafil	Sotalol	Testosterone	Tiagabine	Topiramate
Ursodiol	Verapamil	Vigabatrin	Warfarin	Zinc sulfate

Table 2: Commonly used cardiovascular drugs for which no licensed liquid is available in UK.³⁴

Drug	Paediatric License	Remarks
Amiodarone	No	Drug sparingly soluble in water. Special only has 1 month self life. Extemporaneous preparation can be made (suspension from tablets).
Amlodipine	No	Drug sparingly soluble in water. Special only has 1 month shelf life. Crushed tablets suspended in water often used.
Aspirin	No	Very water soluble drugs – use dispersible tablets.
Bosentan	No	Crushed tablets suspended in water, very expensive.
Captopril	No	Solution- must be refrigerated, only 1 month shelf life. Licensed solution in Australia, packed under nitrogen with only one month shelf life once opened. Easy dispersible low strength tablets crushed and mixed in water (these have recently been withdrawn from the market).
Carvedilol	No	Drugs sparingly soluble in water. Special only has one month shelf life. Crushed tablets suspended in water often used.
Clonidine	No	Dilution in water of the injection is often used, must be refrigerated. Special has 1 month shelf life.
Enalapril	No	Drug sparingly soluble in water. Crushed tablets suspended in water often used.
Hydralazine	No	Soluble tablets available. The injection can be diluted and used orally and kept 24 h at room temperature.
Nadolol	No	Drug sparingly soluble in water. Special only has 1 month shelf life. Crushed tablets suspended in water often used. Low strength tablets recently withdrawn in UK.
Nifedipine	No	Drops in macrogol 200 can be imported – Crushed modified release tablets or removal of nifedipine liquid from soft capsules used.

Pravastatin	No	Drugs freely soluble in water, crushed tablets often dissolved in water. Special has 1 month shelf life.
Prazosin	Yes	Manipulated solid oral dosage forms suspended in water.
Ramipril	No	Drug sparingly soluble in water. Crushed tablets suspended in water often used. Special only has 1 month shelf life.
Sildenafil	No	Crushed tablets suspended in water – expensive
Spironolactone	No	Large range of strength available.
Warfarin	No	Drug freely soluble in water, crushed tablets often dissolve in water. Special only has 1 month shelf life

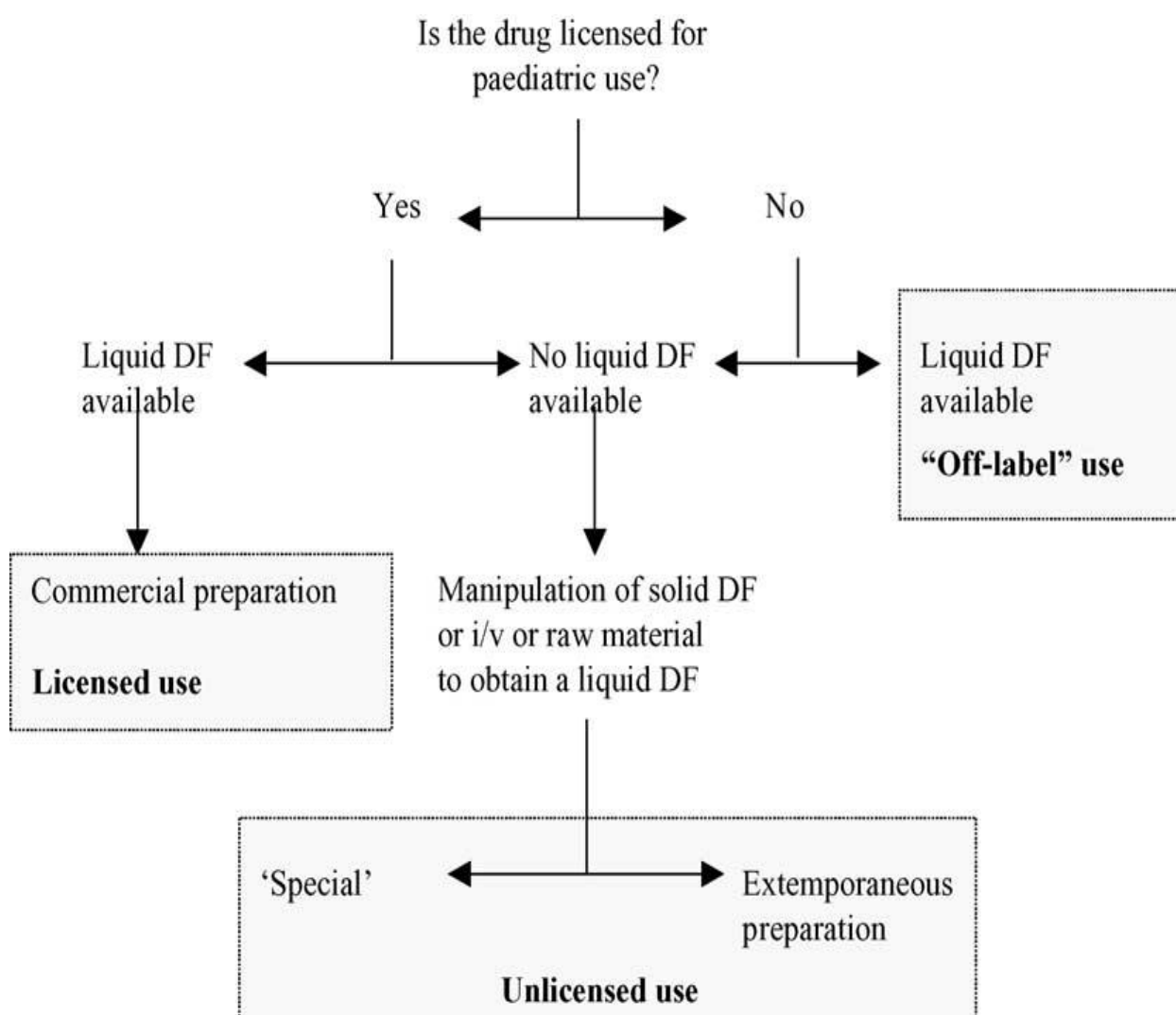


Figure1: Decision pathway for providing oral doses to children for whom whole tablets/capsules are unsuitable (DF: dosage form; i/v: intravenous).⁸

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CHAPTER

1

LIQUID DOSAGE FORMS

1. INTRODUCTION

Compared to conventional tablets and capsules, oral liquid dosage forms including solutions, syrups, suspensions, elixirs, and concentrates offer unique advantages to many patients. For example, liquids may provide better patient compliance for those with swallowing difficulties and better dosage control versus a fixed tablet dose. However, there are also a number of “challenges” surrounding the formulation and development of these forms. Hence, liquid dosage forms are generally formulated for use in geriatric and pediatric patients. But, this section of patients have been regarded as a small fraction of the overall population, pharmaceutical companies often develop oral liquid formulations out of necessity rather than responding to a patient need. However, there are potential advantages of oral liquid dosage forms, such as no dissolution time and rapid absorption from the stomach/intestines compared to tablets, which may be an important factor for pain-relieving drugs. Inherent in this benefit is the risk of reaching peak plasma levels too fast, which could be harmful. Finally, as the excipient technology advances, a controlled release profile in liquid dosage forms will likely become readily available.

Oral liquid dosage – forms include solutions, syrups, suspensions, elixirs, and concentrates that offer better patient compliance for those with swallowing difficulties and better dosage control versus a fixed tablet dose. However, there are also a number of “challenges” in the formulation and development of these dosage forms.

It is the effective use of excipients, which allows formulators overcome these challenges.

2. FORMULATIONS OF LIQUIDS¹

Oral liquids are formulated as solutions, suspensions and emulsions depending on the nature of the active ingredient particularly solubility and stability. They are also designed as ready to use liquids and powders for reconstitution into liquid orals like syrups, solutions, suspensions and emulsions. Liquid formulation needs various excipients including

Pharmaceutically, Oral liquids are formulated as solutions, suspensions and emulsions depending on the nature of the active ingredient particularly solubility and stability.

vehicle, solubilizer, stabilizer, and viscosity builder, preservative and off course sweeteners, colour and flavour. The selection of these excipients is of major concern to design stable, effective and palatable oral liquid formulation.

Selection of Excipients

Characteristics of active drug are of major concern in developing an oral liquid dosage formulation. The major challenges in developing oral liquid dosage forms are

- (i) The stability of a drug in solution,
- (ii) The solubility of a drug at the required level, and
- (iii) An acceptable taste.

It is the effective use of excipients, which allows formulators overcome these challenges. Additionally, an excipient's compatibility with a drug in the solid state cannot infer the same compatibility in solution. However, if the mechanism of degradation of the drug is understood, the process of selecting suitable excipients to use in a solution will be much easier. Finally, some knowledge of the drug's physical and chemical characteristics such as the solubility, pH stability, and pKa value (s) of reactive functional groups is essential in order to choose the proper excipients, effectively.

Ideally, the pH at which the drug is most stable would also be close enough to the solubility for delivering the desired dose in a tea spoon (approximately 5 mL). Requiring patients to take more than two tea spoon full at a time may not be advisable because of lower patient compliance. In such conditions, a simple oral solution or syrup formulation may be developed. However, if the pH at which the drug is most stable is not one at which there is enough solubility, a suspension formulation may be required.

A quick means to identify whether or not a drug may be more suitable for solution or suspension is to overlap the pH-stability profile with the pH-solubility profile.

A quick means to identify whether or not a drug may be more suitable for solution or suspension is to overlap the pH-stability profile with the pH-solubility profile. This overlap creates a window, which may suggest which dosage form might be most desirable and subsequently the type of excipients needed. The overlapped figures below demonstrate for aspirin (which is a weak acid) that the pH of greatest stability is also the pH at which there is low solubility (Figure 1.1).

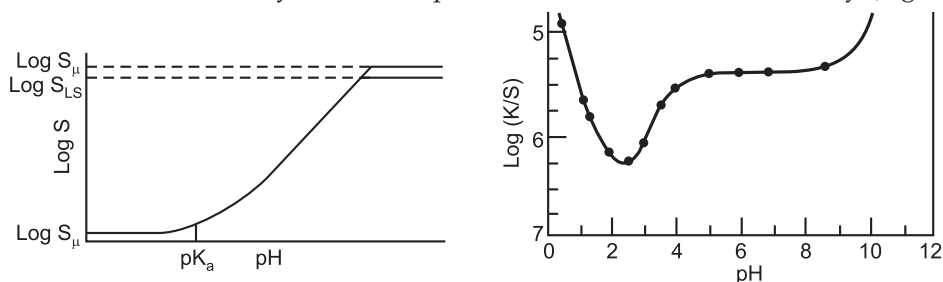


Fig. 1.1. pH, Solubility and Stability Relationship

The decision to develop a solution, syrup or a suspension of a drug is influenced by many factors like solubility and the desired release profile of the drug and properties of the base vehicle like surface tension, viscosity, boiling point, and specific heat of solution, all of which may be affected in various ways. In case of clear liquids, lack of solubility of the drug in the base vehicle may demand the need for miscible co-solvents. Similarly, a miscible solvent may be needed to decrease the solubility of the drug in a primary vehicle in formulating a suspension. Another approach to increasing the solubility of a drug in solution is to use a complexing agent such as a cyclodextrin. Currently in the United States, only hydroxypropyl- β -cyclodextrin has been used in an oral liquid formulation. However, many other cyclodextrins are widely used outside the United States in both oral and parenteral formulations. Surfactants are also used to increase aqueous solubility of the drugs.

Excipients for Oral Liquid Formulations²

Oral liquid formulation needs a meticulous blend of ingredients to perform various functions like wetting and solubilisation, stabilization and to impart suitable colour, taste and viscosity. The blend should be compatible, non reactive and stable. The common excipients generally required for any liquid formulation are vehicles (base), viscosity builders, stabilizers, preservatives, colours and flavours. In addition, solubilizers are required in case of clear liquids, suspending agents are needed for suspensions and emulsifying agents for emulsions.

Oral liquid formulation – needs a meticulous blend of ingredients to perform various functions like wetting and solubilisation, stabilization and to impart suitable colour, taste and viscosity.

2.1 Vehicles

Vehicles, in pharmaceutical formulations, are the liquid bases that carry drugs and other excipients in dissolved or dispersed state. Pharmaceutical vehicles can be classified as under;

Aqueous vehicles: Water, hydro-alcoholic, polyhydric alcohols and buffers. These may be thin liquids, thick syrupy liquids, mucillages or hydrocolloidal bases.

Oily vehicles: Vegetable oils, mineral oils, organic oily bases or emulsified bases.

Vehicles – in pharmaceutical formulations, are the liquid bases that carry drugs and other excipients in dissolved or dispersed state.

Aqueous Vehicles

Water

Natural water contains large number of dissolved and suspended impurities. The dissolved impurities include inorganic impurities like salts of sodium, potassium, calcium, magnesium and iron as chlorides, sulfates and bicarbonates. Organic impurities present in purified water are either in soluble or insoluble state. Micro-organisms are the other impurities and the load of micro-organism in natural substances including water is called as bio-burden. Drinking water, termed as potable water in many texts, contains less than 0.1% of total solid and in United States; they should meet the requirements of U.S. Public health services

Water – is the best vehicle for liquid dosage forms but Organic impurities present in purified water either in soluble or insoluble state and Micro-organisms need purification by distillation, ion exchange treatment or reverse osmosis.

regulations with respect to bacteriologic purity (Bio-burden). In general, acceptable drinking water should be clear, odourless, colourless and neutral with slight deviation in pH (due to dissolved solids and gasses). However, drinking water is not usable in pharmaceutical formulation, obviously due to the possible incompatibility of formulation components with dissolved impurities in water.

Purified water USP is allowed for usage as vehicle or as a component of vehicle for aqueous liquid formulations except for those intended for parenteral administration (injections). It is obtained by distillation, ion exchange treatment, reverse osmosis or any other suitable process from water complying with the Federal Environmental Protection Agency with respect to drinking water. USP criteria for purified water (PW) compared with USP Water for Injection (WFI) as condensed and/or excerpted from section 643 and 645 of United States Pharmacopoeia (USP), 25th edition is presented in Table 1.1.

**Table 1.1. USP Purified Water (PW) and Water for Injection (WFI) Criteria
Selected Criteria**

<i>Parameter</i>	<i>PW</i>	<i>WFI</i>
pH	5.0-7.0	5.0-7.0
TOC (Total organic carbon)	< 500 ppb	<500 ppb
Total bacteria count	10 colony forming units (cfu) /mL, pathogen free	10 colony forming units (cfu) / 100 mL, pathogen free
Endotoxin	Not specified	0.25 EU/mL
Feed water	Potable water	Not specified, but Health. Canada regulations demand that PW be used

Conductivity/Resistivity: USP defines the quality of water in terms of conductivity. Conductivity criteria for PW and WFI are the same. It is measured in three stages. If the Stage 1 Criteria are not met, a Stage 2 should be conducted, and then if necessary (Stage 2 failure) a Stage 3 test may be conducted. The conductivity criteria measured in-line, uncompensated for temperature, is listed in Table 1.2 and are referred to as Stage 1 Criteria.

Table 1.2. Stage 1 Criteria

<i>Temperature (°C)</i>	<i>Conductivity (S/cm)</i>	<i>Resistivity (M_Ω-cm)</i>	<i>Temperature (°C)</i>	<i>Conductivity (S/cm)</i>	<i>Resistivity (M_Ω-cm)</i>
0	0.6	1.67	45	1.8	0.56
5	0.8	1.25	50	1.9	0.53
10	0.9	1.11	55	2.1	0.48
15	1.0	1.00	60	2.2	0.45

Contd...

20	1.1	0.91	65	2.4	0.42
25	1.3	0.77	70	2.5	0.40
30	1.4	0.71	75-90	2.7	0.37
35	1.5	0.67	95	2.9	0.34
40	1.7	0.59	100	3.1	0.32

Alcohol (Ethyl Alcohol)

Next to water, alcohol is the most useful solvent in pharmacy. It is invariably used as hydro-alcoholic mixture that dissolves both water soluble and alcohol soluble drugs and excipients. Diluted alcohol NF, prepared by mixing equal volumes of Alcohol USP and purified water USP is a useful solvent in various pharmaceutical processes and formulations.

Next to water, alcohol is the most useful solvent that is invariably used as hydro-alcoholic mixture that dissolves both water soluble and alcohol soluble drugs and excipients.

Glycerol

Glycerol (or Glycerin) is a clear, colorless liquid, with thick, syrupy consistence, oily to the touch, odourless, very sweet and slightly warm to the taste. When exposed to the air, it slowly abstracts moisture. Glycerol is obtained by the decomposition of vegetable or animal fats or fixed oils and containing not less than 95 percent of absolute Glycerin. It is soluble in all proportions, in Water or Alcohol; also soluble in a mixture of 3 parts of Alcohol and 1 part of Ether, but insoluble in Ether, Chloroform, Carbon Disulphide, Benzin, Benzol, and fixed or volatile oils. Glycerin is used as vehicle in various pharmaceutical products like Elixir of Phosphoric acid, Solution of Ferric Ammonium Acetate, Mucilage of Tragacanthae, Glycerin of boric acid, Glycerin of tannic acid, and in many Extracts, Fluid Extracts, Syrups and Tinctures.

Glycerin – is used as vehicle in various pharmaceutical products like Elixirs. In addition its use as a co-solvent, It has acceptable taste and increased viscosity of the base.

As glycerin is an excellent solvent for numerous substances, such as iodine, bromine, alkalies, tannic acid, many neutral salts, alkaloids, salicin, etc., it is a good vehicle for applying these substances to the skin and to sores. It does not evaporate nor turn rancid, and is powerfully hygroscopic. As glycerin is sweet, it is an excellent flavouring agent. It is demulcent, and is used as a vehicle for applying substances, such as tannic acid, to the throat. It is rarely given by the mouth for any medicinal virtue. It has been administered for dyspepsia, for diabetes, and as a nutritive agent, but in each case without any good result.

In oral liquid formulations, glycerin is used as co-solvent to increase solubility of drugs that show low solubility in water. It is also used to improve viscosity, taste and flavor. In external applications it is used as humectants.

Propylene Glycol is another important ingredient due to its activity as solvent, wetting agent, emulsifier and humectant.

Propylene Glycol USP

Pharmaceutical grade of Propylene Glycol is monopropylene glycol (PG or MPG) with a specified purity greater than 99.8%. PG is an important ingredient for a multitude of uses, including:

- Solvent for aromatics in the flavour-concentrate industry
- Wetting agent for natural gums
- Ingredient in the compounding of citrus and other emulsified flavors
- Solvent in elixirs and pharmaceutical preparations
- Solvent and coupling agent in the formulation lotion, shampoos, creams and other similar products
- Emulsifier in cosmetic and pharmaceutical creams
- Very effective humectants, preservative and stabilizer

Propylene glycol is also a good cosolvent. It also has wetting, emulsifying, humectant and preservative property.

Propylene glycol is an outstanding solvent for many organic compounds. It is colourless and odourless and has a very slight characteristic taste which is not objectionable. These properties make propylene glycol particularly suitable as a solvent for flavourings and dyes in cosmetics, toothpastes, shampoos, and mouthwashes. Propylene glycol is non-allergenic and may be used in cosmetics and other toilet goods specifically formulated for sensitive skin.

Propylene glycol is a general solvent and antimicrobial preservative used in a wide range of pharmaceutical preparations including oral liquid, topical and parenteral preparations. The toxicity of propylene glycol is quite less in comparison to many other cosolvents generally used. As per the Registry of toxic effects of chemical substances published by U.S. Department of Health and Human Services (1986), the LD 50 of propylene glycol is 24 g. kg⁻¹, 8 g. kg⁻¹ and 9.7 g. kg⁻¹ when administered by oral, IV and IP respectively to mouse. However, In addition to risks associated with adulteration, its use in large volumes in children is discouraged, and it has been associated with CNS adverse events, especially in neonates.

Lipid-Based Delivery Vehicles¹

Lipid based delivery – vehicles are suited for liquid formulation of low water soluble drugs coming under class II or IV drugs.

A large number of new drugs being developed show low water solubility and are characterized as either Class II or IV according to the biopharmaceutical classification system. To overcome low solubility and low bioavailability there has been a growing interest in developing novel oral delivery strategies using lipid-based formulations. While oral liquid emulsions have been used for many years, self-emulsifying drug delivery systems, which utilize a lipid/surfactant-based vehicle, are becoming a more widely used approach to solubilize water-insoluble drugs. Benefits of these types of formulations are that lipids that keep a hydrophobic drug in solution may facilitate the dissolution and absorption of the drug as the lipid vehicle is metabolized in the GI tract. The erratic bioavailability of some drugs may be overcome by formulation into a

microemulsion, which includes oil. A detailed discussion of such formulations are dealt elsewhere in this chapter.

2.2 Solubilizers

2.2.1 Wetting Agents and Surfactants

Wetting agents are routinely used in pharmaceutical formulations, especially in liquid dosage forms to create a homogeneous dispersion of solid particles in a liquid vehicle. This process can be challenging due to a layer of adsorbed air on the particle's surface. Hence, even particles with a high density may float on the surface of the liquid until the air phase is displaced completely. The use of a wetting agent allows removal of adsorbed air and easy penetration of the liquid vehicle into pores of the particle in a short period of time. For an aqueous vehicle, alcohol, glycerin, and PG are frequently used to facilitate the removal of adsorbed air from the surface of particles. Whereas for a non-aqueous liquid vehicle, mineral oil is commonly used as a wetting agent.

Typically, hydrophobic API particles are not easily wetted even after the removal of adsorbed air. Hence, it is necessary to reduce the interfacial tension between the particles and the liquid vehicle by using a surface-active agent. Structurally, wetting agents comprise branched hydrophobic chains with central hydrophilic groups or short hydrophobic chains with hydrophilic end groups. For example, sodium lauryl sulfate is one of the most commonly used surface-active agents. Such surfactants, when dissolved in water, lower the contact angle of water and aid in spreadability of water on the particles surface to displace the air layer at the surface and replace it with the liquid phase. Wetting agents have a hydrophilic-lipophilic balance (HLB) value between 7 and 9.

The following properties must be considered in the assessment of wetting agents:

- The minimum surface tension that can be attained, regardless of the amount of agent required.
- The depression of surface tension achieved with a specified concentration of agent.
- The time required for an agent to achieve equilibrium. A good wetting agent permits the depression of surface tension in water by up to 2.5 mN/m in 15 seconds.

Careful consideration must be given to the potential changes in activity and bioavailability of the API and/or excipients when a surfactant is used. Dramatic changes in the bactericidal activity of certain excipients take place when they are solubilized by surfactants, and the stability of excipients against oxidation and hydrolysis may be modified by solubilization. Additionally, many nonionic surfactants (at high

Wetting agents – are used in liquid dosage forms to create a homogenous dispersion of solid particles in a liquid vehicle. Wetting agents are Surfactants (HLB Value 7 to 9) that when dissolved in water, lower the contact angle and aid in spreadability of water on the particles surface to displace the air layer at the surface and help in wetting and solubilization.

Wetting agents – are surfactants like tweens, spans, poloxamers etc., which reduce the interfacial tension between the particles and the liquid vehicle and promotes wetting and solubilization.

concentrations) exhibit a characteristic temperature above which the solution becomes cloudy. This cloudiness is due to the formation of very large lamellar micelles, which results from the dehydration of the polyoxyethylene chains. For these types of surfactants, it is essential to consider the risk of exceeding the cloud point.

The physicochemical characteristics of some typical wetting agents and/or solubilizing agents are listed in Table 1.3.

Table 1.3. Physicochemical Characteristics of Wetting/Solubilizing Agents

<i>Wetting/Solubilizing Agents</i>	<i>Solubility</i>	
	<i>Water</i>	<i>Alcohol</i>
Benzalkonium chloride, NF	VS	VS
Benzethonium chloride	SOL	SOL
Cetylpyridinium chloride, USP	VS	VS
Docusate sodium, USP	SPSOL	FS
Nonoxynol 9 USP	SOL	SOL
Octoxynol	MISC	MISC
Poloxamer NF	FS	FS
Poloxamer 124NF	FS	FS
Poloxamer 188, 237, 338, 407 NF	FS	FS
Polyoxyl 35 castor oil NF	VS	SOL
Polyoxyl 40 hydrogenated castor oil NF	VS	SOL
Polyoxyl 10 oleyl ether, NF	SOL	SOL
Polyoxyl 20 cetylstearyl ether, NF	SOL	SOL
Polyoxyl 40 stearate, NF	SOL	SOL
Polysorbate 20 NF	SOL	SOL
Polysorbate 40 NF	SOL	SOL
Polysorbate 60 NF	SOL	–
Polysorbate 80 NF	VS	SOL
Sodium lauryl sulfate, NF	FS	–
Sorbitan monolaurate NF	INSOL	–
Sorbitan monooleate NF	INSOL	–
Sorbitan monopalmitate NF	INSOL	#
Sorbitan monostearate NF	##	–
Tyloxapol USP	MISC	–

Abbreviations of Solubility: VS, very soluble, FS, freely soluble, SOL, soluble, SPSOL, SLSOL, VSS, very slightly soluble, INSOL, practically insoluble or insoluble, MISC, miscible.

In addition to the concentration of surfactant, the location of the API or excipient in the micelle structure can influence its stability. Surrounding the positive surface of the cationic micelle will be a relatively higher concentration of hydroxyl ions from the surrounding solution. If the drug or excipient is more susceptible to base-catalyzed hydrolysis and exposed to the concentrated hydroxyl area near the surface of the micelle, then the result would likely be more degradation (hydrolysis). However, if it is more stable under alkaline conditions, then there may be less degradation (hydrolysis). Therefore, if a correlation between the location of the drug or excipient in the micelle and its pH-dependent stability can be determined, a formulator may be able to optimize the choice of surfactant to prevent degradation.

2.2.2 pH Modifiers and Buffering Agents

The pH of an oral liquid formulation is a key point in many regards. Control of the formulation pH, could prevent large changes during storage. Therefore, most formulations utilize a buffer to control potential changes in the solution pH. The amount of buffer capacity needed is generally between 0.01 and 0.1 M, and a concentration between 0.05 and 0.5 M is usually sufficient. The selection of a suitable buffer should be based on

- (i) Whether the acid-base forms are listed for use in oral liquids,
- (ii) The stability of the drug and excipients in the buffer, and
- (iii) The compatibility between the buffer and container. A combination of buffers can also be used to gain a wider range of pH compared to the individual buffer alone. However, not all buffers are suitable for use in oral liquids. For example, a boric acid buffer may be used for ophthalmic and IV delivery but not in oral liquids because of its toxicity.

Stability of formulation containing non-ionizable API may also depend on pH. For example, a specific functional group or a particular resonance structure that is stabilized in a specific pH range may facilitate a reaction between the excipient and the drug.

However, the buffer may negatively influence the solubility of the drug and other excipients. The effect depends on a combination of the polarity of the solute and of the salt. Non-polar solutes are solubilized (salted in) by less polar organic salts and are desolubilized (salted out) by polar salts. Conversely, polar solutes are salted in by polar salts and salted out by organic salts.

The stabilizing effect of buffers that have multiple charged species in solution could also determine the potential reaction between excipients and API. For example, buffers that use carbonates, citrate, tartrate, and various phosphate salts may precipitate with calcium ions by forming sparingly soluble salts. However, this precipitation is dependent upon the solution pH. The activity of phosphate ions may be lowered due to interactions with other solution components.

There are a number of factors that may also affect the solution pH such as temperature, ionic strength, dilution, and the amount and type

The pH – of an oral liquid formulation is a key point for API stability, solubilization and also to prevent microbial contamination.

Buffers are used to control pH of liquid orals. Combination of buffers can also be used to gain a wider range of pH compared to the individual buffer alone. Buffer selection should be judicious to avoid incompatibility.

of co-solvents present. For example, the pH of acetate buffers is known to increase with temperature, whereas the pH of boric acid buffers decreases with temperature. Finally, the drug in solution may itself act as a buffer. If the drug is a weak electrolyte, such as salicylic acid or ephedrine, the addition of base or acid, respectively, will create a system in which the drug can act as a buffer.

2.2.3 Suspending Agents and Viscosity-modifying Agents³

Suspending agents – impart viscosity, and thus retard particle sedimentation.

The selection of an appropriate suspending agent is crucial in formulating a pharmaceutical suspension.

One of the most crucial factors involved in formulating a pharmaceutical suspension is the selection of an appropriate suspending agent. Suspending agents impart viscosity, and thus retard particle sedimentation. Other factors considered in the selection of the appropriate agent include desired rheological property, suspending ability in the system, chemical compatibility with other excipients, pH stability, length of time to hydrate, batch-to-batch reproducibility, and cost.

Suspending agents can be classified into cellulose derivatives, clays, natural gums, and synthetic gums. In many cases, these excipients are used in combination. Table 1.4 contains a listing of the suspending agents most commonly used in oral liquid formulations and their properties. For each agent, the concentration of use and the respective property such as ionic charge, water dispersibility, pH range, rheological flow behaviour, etc. are listed.

Table 1.4. Stability pH Range and Concentrations of Most Commonly Used Suspending Agents³

<i>Suspending Agents</i>	<i>Stability pH Range</i>	<i>Concentrations Used as Suspending Agent</i>
Sodium alginate	4–10	1 – 5%
Methylcellulose	3–11	1 – 2%
Hydroxyethylcellulose	2–12	1–2%
Hydroxypropylcellulose	6–8	1 – 2%
Hydroxypropylmethylcellulose	3–11	1–2%
CMC	7–9	1–2%
Na-CMC	5–10	0.1–5%
Microcrystalline cellulose	1–11	0.6 – 1.5%
Tragacanth	4–8	1 – 5%
Xanthangum	3–12	0.05–0.5%
Bentonite	pH > 6	0.5 – 5.0%
Carageenan	6–10	0.5 – 1%
Guar gum	4–10.5	1–5%
Colloidal silicon dioxide	0–7.5	2 – 4%

2.2.4 Preservatives

Microbiological contamination presents a significant health hazard in oral liquids. Therefore, the use of preservatives become inevitable to

prevent the growth of microorganisms during the product's manufacture and shelf life, although it may be most desirable to develop a "preservative-free" formulation to address the increasing concerns about the biological activity of these compounds. Most formulations require some kind of preservative to ensure no microbial growth.

The majority of preservatives are bacteriostatic rather than bacteriocidal, and consists of both acid and nonacid types. Among the acidic types are phenol, chloro-cresol, 9-phenyl phenol, alkyl esters of para-hydroxybenzoic acid, benzoic acid, boric acid, and sorbic acid, and their respective salts. Therefore, the pH of solution, and the pKa of the preservative need to be carefully evaluated prior to selecting a preservative for a formulation. Neutral preservatives include chlorobutanol, benzyl alcohol, and beta-phenylethyl alcohol. Under alkaline conditions, it is generally regarded that microbial growth is insignificant and at these pH values, the need for a preservative is not generally recommended.

Many preservatives listed in the FDA inactive ingredient guide for liquid dosage forms. Unfortunately, many of them are not recommended for use in oral liquids and hence the choice of an acceptable preservative for an oral liquid formulation is limited. In addition, the solubility of many preservatives in aqueous system may not be high enough for effective antimicrobial activity. Additionally, it is essential to understand that bacteriostatic agents like para hydroxyl benzoic acids can partition between organic and aqueous phases in a heterogenous liquid formulations in such a way that their activity is significantly reduced. Generally used preservatives in oral liquid formulations are listed in Table 1.5.

Most liquid formulations require some kind of preservative to ensure no microbial growth. The majority of preservatives are bacteriostatic rather than bacteriocidal.

Table 1.5. Typical Preservatives Used in Oral Liquid Dosage Forms

- | |
|---|
| <ul style="list-style-type: none">• Alcohol• Benzyl alcohol, Bronopol• Chlorbutol, Chlorocresol• Butylparaben, Methylparaben, Propylparaben• Phenol• Phenylethanol Sodium benzoate• Antimicrobial solvents like propylene glycol, chloroform etc. |
|---|

In addition, some formulation ingredients like nonionic surfactants, quaternary ammonium compounds, gelatin, ferric salts, calcium salts and salts of heavy metals, including silver, lead, and mercury prevent microbial growth.

Preservatives often contain reactive functional groups, which are responsible for their antimicrobial activity but lead to unwanted reactions. Therefore, in addition to the excipient's antimicrobial activity, other parameters should be evaluated during the formulation development for its compatibility with the API, other excipients, and the container system. Characteristics of generally used preservatives along with their reported interactions are listed in Table 1.6.

Table 1.6. Characteristics of Generally Used Preservatives and Their Interactions

<i>Preservative</i>	<i>Concentration and Use</i>	<i>pH Range</i>	<i>Interactions</i>	<i>Remarks</i>
Parabens (Methyl and Propyl Parabens)	0.015% to 0.2% w/v Generally used in combination of methyl and propyl paraben.	2 to 6 (unstable at pH 8 or above in solution)	Incompatible with sorbitol, show some discoloration in the presence of iron. Absorption of methyl-paraben by plastics. Certain coloring agents such as yellow iron oxide, ultramarine blue, and aluminum silicate can extensively absorb ethyl paraben and reduce its activity.	Parabens have some antimicrobial activity but are most effective against yeasts and molds. Methyl paraben has the least antimicrobial activity, used with other long-chain parabens. As the chain length of the paraben's alkyl moiety is increased, their antimicrobial activity increases.
Benzyl Alcohol	2%	Not specific	Incompatible with methyl-cellulose. 2% aqueous solution in a polyethylene container. Lose up to 15% of its benzyl alcohol content in 13 weeks. Sorbed by closures composed of natural rubber or neoprene.	Adverse reactions to benzyl alcohol following IV and intrathecal administration and it is not recommended for use in premature infants.
Benzoic Acid		2.5 to 4.4	pH dependent dissociation lead to change in partition coefficient. (To be considered when used in O/W emulsion). Dimmer formation in many non polar solvents.	In suspension, benzoic acid dissociates, with the benzoate anion adsorbing onto the suspended drug particles, thus changing the charge at the surface in turn affect the physical stability of the suspension.
Potassium Sorbate	0.1% to 0.2% antimicrobial and antifungal	<6.0	However, some loss of antimicrobial activity occurs in the presence of nonionic surfactants and some plastics.	Used much more than sorbic acid because of its higher solubility and stability in water.
Glycerin	>20% v/v	Not specific	Iron contaminant in glycerin is responsible for the darkening in color of mixtures containing phenols, salicylates, and tannin.	Glycerin may crystallize if stored at low temperatures, and the crystals do not melt until the temperature is raised to 20°C.
Propylene Glycol	15% to 30%	Not specific	Formulations containing >35% PG can cause hemolysis in humans.	Neonates have a longer PG half-life (16.9 hours) compared with adults (5 hours) and seizures, and respiratory depression has occurred in children who have ingested oral liquid medications containing PG.

2.2.5 Stabilizers

Antioxidants

The oxidation of an API in an oral liquid formulation is difficult to control due to low activation energies (2-12kcal/mol) for oxidation and photolysis compared to solvolysis, dehydration, and polymorphic transformations (10-56kcal/mol). Trace amounts of impurities, which are invariably present in the API or excipient catalyses the oxidation reaction. Most drugs exist in a reduced form, show increased instability when the solution is consistently introduced into an atmosphere of 20% oxygen. The pH of the solution may effect the oxidation of phenolic and sulfhydryl group containing drugs because it is principally the ionized form of these drugs that participate in the oxidation. For example, epinephrine is only slowly oxidized at pH < 4 but rapidly degrades under alkaline pH conditions.

Antioxidants can be compounds that can reduce a drug that has been oxidized, or compounds that are more readily oxidized than the agents they are to protect (oxygen scavengers). Many of the lipid-soluble antioxidants act as scavengers. Antioxidants can also act as chain terminators, reacting with free radicals in solution to stop the free-radical propagation cycle. Mixtures of chelating agents and antioxidants are often used because there appears to be a synergistic effect. This occurs because many of the agents act at differing steps in the oxidative process.

Some substances prone to oxidation include unsaturated oils/fats, compounds with aldehyde or phenolic groups, colours, flavours, sweeteners, plastics and rubbers, the latter being used in containers for products. Oxidation may manifest as products with an unpleasant odour, taste, appearance, precipitation, discoloration or even a slight loss of activity. The term rancidity refers to many typical off-flavors that result from autoxidation of unsaturated fatty acids that are present in oils and fats, and it affects many oils and fats. The distinct rancid odour may result from short-chain, volatile monomers resulting from the cleavage of the longer chain, less volatile oils and fats. Anti-oxidants generally used in liquid formulations are listed in Table 1.7.

Oxidation – may manifest as products with an unpleasant odor, taste, appearance, precipitation, discoloration or even loss of activity.

The oxidation of an API in an oral liquid formulation needs to be prevented using anti-oxidants. Antioxidants act as free radicle scavengers and terminator of chain reaction in auto oxidation.

Table 1.7. List of Anti-oxidants Generally Used in Liquid Formulations

<i>Oil Soluble</i>	<i>Slightly Water Soluble</i>	<i>Water Soluble</i>
α -Tocopherol acetate	Acetone sodium bisulfite	Acetylcysteine
Ascorbic acid	Ascorbyl palmitate	Butylated hydroxyanisole (BHA)
Butylated hydroxytoluene (BHT)	Cysteine	Cysteine hydrochloride
<i>d</i> α -Tocopherol natural	<i>d</i> - α -tocopherol synthetic	Dithiothreitol
Monothioglycerol	Nordihydroguaiaretic acid	Propyl gallate
Sodium bisulfite	Sodium formaldehyde sulfoxylate	Sodium metabisulfite
Sodium sulfite	Sodium thiosulfate	Thiourea