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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Actuación : 444

Referencia : Expediente No. 06049473
Asunto : Solicitud de patente para: "Procedimiento
para la producción de una composición
farmacéutica sólida de administración oral".
Solicitante : BAYER SCHERING PHARMA AG
Fecha de solicitud: 23 de mayo de 2006.

1. Yo, Luz Clemencia de PAÉZ, mayor de edad, domiciliada en Bogotá, D.C., identificada con la Cédula de ciudadanía N° 35.456.344 de Usaquén, obrando como apoderada del solicitante en el asunto antes identificado, me refiero al Oficio No. 18383 notificado por fijación en lista del 25 de Noviembre de 2011.

2. Mediante el Oficio No. 18383 se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la siguiente manera:

3. Nivel inventivo.

Su Despacho concluye que los documentos US 6514529 (D1) y US 2003153610 (D3) afectan el nivel inventivo de la presente solicitud de patente. Con respecto a lo señalado por su Despacho, mi representada desea poner de presente lo siguiente:

De acuerdo con el artículo 18 de la Decisión 486:

"Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado

obvia ni se hubiese derivado de manera evidente del estado de la técnica".

De lo anterior, es claro que para determinar si una invención es inventiva o no, el examinador debe determinar si la misma se deriva de manera obvia a partir del estado de la técnica.

El estado de la técnica es el conjunto de conocimientos técnicos dentro del campo de la invención que hayan sido publicados por cualquier medio, antes de la fecha de solicitud de la invención o de la prioridad reivindicada. A pesar de que esta búsqueda de anterioridades se realiza a posteriori, es decir, tomando como punto de partida la invención y la forma como efectivamente se solucionó el problema técnico, al realizar la evaluación de nivel inventivo el examinador debe ponerse en el lugar del inventor al momento de realizar la invención junto con los conocimientos técnicos existentes al momento de la solicitud con el fin de entender el esfuerzo y análisis que dicho inventor requirió para resolver el problema técnico planteado. Lo anterior, por cuanto si la invención es analizada con los avances tecnológicos hoy conocidos y adicionalmente se toma como punto de partida la forma como efectivamente se solucionó el problema técnico, la invención en todos los casos le resultará obvia y evidente.

Teniendo en cuenta el anterior, podemos concluir que una invención no se considera obvia u evidente y por tanto cumple con el requisito de nivel inventivo cuando la misma haya resultado a través de estudio y experimentación (investigación) y constituya un adelanto tecnológico, **materializado en un resultado inesperado (mejorado)** y además no evidente para alguien del oficio.

Ahora bien, con el fin de demostrar que los argumentos esgrimidos por el Señor Examinador no resultan de recibo en el presente caso, mi representada desea poner de presente lo siguiente:

Nuevamente, se pone de presente que la presente invención busca resolver el problema de proveer una composición farmacéutica sólida, oralmente administrable para el compuesto 5-cloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida (rivaroxaban), la cual conlleva a la biodisponibilidad mejorada de la formulación obtenida (ver página 3, líneas 1 a 7 de la descripción). El objetivo también se relaciona con proveer un proceso para la producción de esta composición farmacéutica.

Este problema fue resuelto por medio de una composición oralmente administrable que contiene rivaroxaban en forma hidrofilizada. Esta composición farmacéutica es producida por granulación húmeda.

La granulación húmeda consiste en un tratamiento especial de la superficie del compuesto activo (rivaroxaban) y el cual permite un comportamiento de absorción mejorado. De modo que el problema técnico objetivo en el cual se basa la presente invención consiste en proporcionar una composición farmacéutica de rivaroxaban con biodisponibilidad mejorada y no solamente una composición con propiedades de liberación in vitro aceptables.

3.1 Con respecto a los documentos D1 y D3.

Ahora bien, tal como se describe en el pliego descriptivo de la presente solicitud, la forma hidrofílica del rivaroxaban se obtiene a partir de un tratamiento especial de la superficie del compuesto activo (I) (rivaroxaban) por medio de granulación húmeda.

Debido a que la hidrofílicación de un ingrediente activo requiere de un tratamiento de la superficie de las partículas del ingrediente activo, es claro que la sola mezcla física de un ingrediente activo con un surfactante o un polímero no logra este efecto. Lo anterior, debido a que las propiedades de la superficie del ingrediente activo no son alteradas por la mezcla física del mismo con un surfactante o un polímero. Esto es evidente, a partir del hecho de que la velocidad de disolución de un ingrediente activo mezclado físicamente con un excipiente no se ve mejorada en comparación con el estado original.

D1 se refiere a otros ingredientes activos formulados en forma hidrofílica y cristalina por medio de granulación húmeda y son convertidos en una formulación farmacéutica con excipientes farmacéuticamente aceptables tales como hidroxipropilmetilcelulosa (HPMC). El examinador afirma que una persona versada en la materia estaría motivado a formular el rivaroxaban de acuerdo con el método descrito en D1 con una expectativa razonable de éxito porque la referencia enseña que las formulaciones allí descritas presentan una biodisponibilidad aumentada. Sin embargo, respetuosamente mi representada desea poner de presente que no comparte la opinión del Señor Examinador.

Como se demostrará a continuación, una persona versada en la materia ubicándose en el momento histórico que se presentó la solicitud de interés, no habría derivado el presente invento a partir de las referencias citadas. En efecto, una persona versada en la materia no tendría en cuenta las enseñanzas de D1 como guía para formular el rivaroxaban.

El Examinador afirma que debido a que D1 se refiere a la formulación de agentes de oxazolidinonas, una persona versada en la materia buscando formular rivaroxaban el cual es un agente de oxazolidinona, tendría en cuenta las enseñanzas de D1 y una expectativa razonable de éxito con la modificación. Sin embargo, es importante resaltar la diferencia significativa entre las solubilidades del compuesto linezolid, que es el compuesto empleado en los ejemplos de D1, y el rivaroxaban.

Para una persona versada en el diseño de formas de dosificación farmacéuticas, las mayores consideraciones en el diseño de las mismas NO incluye similitudes en la estructura química. Por ejemplo, en el texto "Pharmaceutics, The Science of Dosage Form Design" menciona que las mayores consideraciones a este respecto son las siguientes:

- "1. Las propiedades fisicoquímicas de la droga.*
- 2. Consideraciones biofarmacéuticas, tales como la vía de administración de una forma de dosificación afecta a la velocidad y el grado de absorción de drogas en el cuerpo, y*
- 3. Consideraciones terapéuticas del estado de la enfermedad a tratar, que a su vez deciden el tipo de forma de dosificación más adecuado, posibles rutas de administración y la duración más adecuada y frecuencia de dosis para la droga en cuestión".*

Michael E. Aulton (editor), publicó con Elsevier Ltd (2002), textos en los cuales se proporciona una tabla que lista las propiedades de sustancias medicamentosas importantes en el diseño de formas de dosificación. Estas propiedades no incluyen la estructura química (ver Anexo 6.1). Las propiedades son el tamaño de partícula, con el área de superficie; solubilidad; disolución; coeficiente de partición; constante de ionización; propiedades de cristales, incluyendo polimorfismo; estabilidad y organoléptica (ver tabla 1.3, página 7). Adicionalmente, Aulton especifica lo que se entiende por propiedades químicas y físicas de una sustancia medicamentosa y señala: "Estas propiedades, tales como disolución, tamaño del cristal y forma polimórfica, estabilidad del estado sólido y las interacciones entre droga-aditivo, pueden tener efectos profundos en la disponibilidad fisiológica y la estabilidad física y química de la droga" (Ver página 6).

Igualmente, existen otros autores que recalcan la importancia de las propiedades físico químicas y no la estructura química en la formulación de medicamentos. La FDA propone un sistema de clasificación de biofarmacéuticos ("BCS") como una directriz regulatoria de biodisponibilidad-bioequivalencia, que reconoce que la disolución de la droga y la permeabilidad gastrointestinal son los parámetros fundamentales al controlar la velocidad y extensión

de la absorción de la droga (Ver documentos: "Jain et al., "Pharmaceutical product development technologies based on the biopharmaceutical classification system", Pharmazie 64 (2009) 8, pp. 483-490 y "El sistema de clasificación biofarmaceutica" (BCS) de la FDA). De acuerdo con el BCS, las drogas se ubican en una de cuatro clases con base en propiedades fisicoquímicas: clase 1: solubilidad alta-permeabilidad alta; clase 2: solubilidad baja-permeabilidad alta; clase 3: solubilidad alta-baja permeabilidad; y clase 4: baja solubilidad-baja permeabilidad.

Por lo tanto, una persona versada en la materia preparando una nueva forma de dosificación habría identificado las propiedades fisicoquímicas de una droga, tales como solubilidad, al ser uno de los factores de mayor importancia. Las similitudes en la estructura química entre dos compuestos no es una propiedad que estas referencias enseñan como indicador de que las mismas vayan a presentar similitudes en la formulación. De tal manera que, una persona versada en la materia no se vería motivada a usar una formulación para una droga diferente que puede tener un parte del núcleo de la estructura similar pero que tiene una diferencia significativa en la solubilidad, tal como en el caso con linezolid y rivaroxaban.

De modo que, una persona versada en la materia buscando formular rivaroxaban tendría en cuenta la solubilidad. El rivaroxaban es poco soluble en agua, teniendo una solubilidad de únicamente 7 mg/l. En contraste, en D1 donde se divulga principalmente formulaciones de linezolid, que tiene una solubilidad mucho mayor en agua que el rivaroxaban. El linezolid tiene una solubilidad de 3000 mg/l y por tanto es más de 400 veces más soluble que el rivaroxaban.

Asimismo, esta diferencia significativa en solubilidad se ve reflejada en que el linezolid se clasifique en la Farmacopea Británica del 2009 como "ligeramente soluble" mientras que el rivaroxaban se caracteriza como "prácticamente insoluble".

Una persona versada en la materia habría notado esta gran diferencia en la solubilidad entre la droga de D1 y el rivaroxaban y por tanto, no se habría visto motivada a sustituir el rivaroxaban por linezolid. Asimismo, una persona versada en la materia no se vería influenciado a emplear rivaroxaban en lugar de linezolid teniendo en cuenta que ambos compuestos comparten una estructura similar, toda vez que en el campo de la nuevas formas de dosificación se buscan propiedades físico químicas similares, en especial la solubilidad. Así entonces, teniendo en cuenta que las propiedades fisicoquímicas entre estos dos compuestos son tan

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diferentes, una persona versada en la materia no esperaría obtener una sustitución exitosa.

De otro lado, el Examinador señala que D1 esta relacionado con derivados de oxazolidinonas. En efecto, D1 menciona en el resumen de la solicitud que la tableta contiene "oxazolidinona antibacterial" (col 1, líneas 27-31). Sin embargo, D1 no proporciona ninguna enseñanza directa de oxazolidinonas diferentes a aquellas formulaciones sugeridas para linezolid. De hecho, D1 no proporciona datos que demuestren el efecto de las formulaciones allí descritas y que las mismas son efectivas para la actividad reivindicada (no se presenta ningún dato de biodisponibilidad para las formulaciones).

De otro lado, D1 establece que existe la necesidad de una formulación en forma de tableta que permita una carga alta del fármaco con niveles de sangre similares a la administración IV (col.1, líneas 24 a 35), mas sin embargo, no proporciona dato alguno aparte de las afirmaciones generales realizadas que demuestren que dicho efecto fue obtenido. Una persona versada en la materia se basaría en datos existentes y no en afirmaciones generales de los efectos deseados antes de tener una expectativa razonable de éxito con una formulación determinada.

Igualmente, D1 no enseña o sugiere suspender el linezolid en un granulado líquido o emplear granulación húmeda de lecho fluidizado. En contraste, la formulación de linezolid de D1 es granulada usando un mezclador de alta cizalladura, tal como se muestra en la columna 10, línea 10 y que se incluye un secador de lecho fluido en lugar de la granulación húmeda (ver columna 10, líneas 4-14 y col 8, líneas 27 a 40). En la columna 5, líneas 52 a 67 y 55-57 se refiere a la etapa de granulación, mas in embargo, se mencionada que la granulación se lleva a cabo con un mezclador de alta cizalladura en lugar de un lecho fluidizado.

Con respecto al documento US2003153610 (D3), vale la pena resaltar que la tableta A y la tableta B NO son obtenidas a partir de gránulos de principios activos hidrofílicos. En la tableta A el ingrediente activo no es hidrofílico. En la tableta A el ingrediente activo y el excipiente/aglutinante son físicamente mezclados lo cual no da a lugar a un ingrediente activo hidrofílico. La tableta B es obtenida por granulación de lecho fluidizado y esta tableta contiene un ingrediente activo hidrofílico.

El problema técnico de la presente invención, cómo se mencionó anteriormente, es la necesidad de proporcionar una composición farmacéutica sólida de rivaroxaban, administrable por vía oral con

biodisponibilidad mejorada. Este problema es resuelto por el hecho que la composición farmacéutica contiene rivaroxaban en su forma hidrofílica. Por lo tanto, la composición de la presente invención tiene la ventaja técnica que presenta una biodisponibilidad mejorada.

La forma hidrofílica del Rivaroxaban no se podría derivar de manera obvia u evidente a partir de D3 por cuanto, en dicho documento no se enseña o sugiere que el ingrediente activo en su forma hidrofílica se proporcionaría una dosificación sólida con biodisponibilidad mejorada. De la misma forma, el conocimiento general en el campo de interés alejaría a emplear granulación húmeda de un ingrediente activo en el cual se busca mejorar su biodisponibilidad.

Ahora bien, una persona versada en la materia sabría que la granulación húmeda puede llevar a reducir la velocidad de liberación. Sin embargo, se piensa que una de las razones que permite esto es que la granulación húmeda favorece la formación de hidratos de los ingredientes activos particulares.

El hecho que los hidratos en comparación con el anhidrato del ingrediente activo generalmente presenta una solubilidad reducida y en consecuencia, reduce la liberación, puede tener un efecto duradero en la biodisponibilidad. No obstante, aunque no se conoce una explicación concreta para un peor rendimiento de la disolución de ingredientes activos debido a la granulación húmeda, este fenómeno como tal es bastante familiar para una persona versada en la materia y es descrito en una multiplicidad de documentos. Como prueba de lo anterior, se presentan documentos de *Liebermann* que demuestran lo anterior (ver anexos 6.3, 6.4 y 6.5). En dichos textos, en la página 150 del anexo 6.3 se menciona que "Se puede disminuir la disolución de las drogas a partir de los gránulos del interior luego de la desintegración de la tableta si no es formulada y procesada correctamente" y asimismo, en el anexo 6.4, en la página 202 aparece bajo el título de disolución que "la disolución de los gránulos de la droga puede ser un problema". En el anexo 6.5, se menciona de forma general la producción de formulaciones farmacéuticas. Además de la granulación en húmedo, otros métodos de formulación son descritos, tales como granulación en seco, compactación directa, etc. De modo que, la granulación húmeda corresponde a uno de varios métodos usados en la tecnología farmacéutica y en dicho documento, no se hace un énfasis especial en el proceso de granulación en húmedo como particularmente adecuado. De hecho, en la página 115 de este anexo se menciona que "la mayor desventaja de la granulación en húmedo es el costo. Es un proceso costoso debido a la mano de obra, tiempo, equipos, energía, y espacio requeridos".

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En el desarrollo de composiciones, una persona versada en la materia no comenzaría a emplear el método más caro y laborioso. Incluso, si el proceso de granulación húmeda proporcionara velocidades mejoradas de disolución: "La velocidad de disolución de una droga hidrofóbica puede mejorarse con la elección correcta de solvente y aglutinante" (ver página 115, líneas 1 y 2 del anexo 6.5). En efecto, una persona versada en la materia no se vería motivada a usar rivaroxoban en forma hidrofilizada en la búsqueda de una composición farmacéutica de rivaroxaban con biodisponibilidad alta, ya que esto implica sin duda un riesgo de fracaso".

Adicionalmente, las velocidades altas de liberación de composiciones farmacéuticas no son cruciales para obtener una biodisponibilidad alta, tal como se señala en el anexo 6.5 "la droga en la tableta debe ser biodisponible. Esta propiedad es monitoreada en dos pruebas, la prueba de desintegración y la prueba de disolución. Sin embargo, la biodisponibilidad de la droga de una tableta u otra forma de dosificación es un problema bastante complejo, y los resultados de estas dos pruebas en sí mismas no proporcionan un indicador de biodisponibilidad" (ver página 11 de anexo 6.5).

Este elemento es confirmado por los ejemplos de la presente invención. Las tabletas A y B presentan velocidades de liberación similares in vitro pero biodisponibilidades distintas (Ver páginas 10 y 11 de la solicitud internacional).

El documento D3 no proporciona enseñanza o sugerencia alguna que sea crucial para resolver el problema relacionado con que el rivaroxaban se encuentra presente en su forma hidrofilizada. De modo que, la materia de invención de la presente solicitud, no se derivaría de manera obvia u evidente de las enseñanzas de dicho documento.

Adicionalmente, mi representada desea presentar una prueba sencilla realizada para ilustrar el proceso de la hidrofilización. Para este propósito, en el ensayo se siguieron las instrucciones del ejemplo 5 de la presente solicitud para preparar tabletas conteniendo rivaroxoban bien sea por tableteado directo sin granulación (tableta A) o lecho fluidizado (tableta B). En adición a los componentes especificados en la solicitud, cada una de las formulaciones contenía un tinte de color verde brillante incluido en la mezcla física del polvo y en el granulado líquido respectivamente. Una imagen de las dos tabletas obtenidas se anexa al presente memorial (ver anexo 6.6: tableta A a la izquierda y tableta B a la derecha).

A partir de la comparación visual de ambas tabletas se puede observar que ha sucedido lo siguiente: (i) La tableta A presenta un color ligeramente gris con inclusiones irregulares de color y (ii) la tableta B, en contraste, presenta un color pálido uniforme azul/turquesa. La granulación húmeda de la tableta B ha tenido el efecto que el tinte se haya dividido adecuadamente y se ubique en la superficie de las partículas del ingrediente activo. No obstante, en el caso del tableteo directo, una proporción significativa del tinte es dividida y por lo tanto no se observa en la superficie de la tableta. La tableta tiene un color grisáceo no uniforme.

Los diferentes efectos de partición de la tinta en el ensayo de tableteo directo vs granulación húmeda son explicados por las diferencias en el comportamiento del aglutinante en estos procesos. La mezcla íntima del tinte y el ingrediente activo que permite envolver las partículas del ingrediente activo con el aglutinante se logra con la granulación húmeda pero no por la mera mezcla de estos componentes en el tableteo directo. Por lo tanto, es claro que el envolvimiento del ingrediente activo permite la humectabilidad deseada de las partículas del ingrediente activo, i.e. el efecto de hidrofiliación del ingrediente activo.

Así entonces, el problema de proveer una composición con una liberación *in vitro* aceptable sería resuelto con la fabricación de tabletas de rivaroxavan sin granulación previa. Tal como demuestran las tabletas A y B de la descripción, se provee una liberación *in vitro* similar. La tableta es obtenida de manera directa, pero el rivaroxavan no está presente en forma hidrofiliada y es precisamente esta forma una característica técnica de la invención, la cual contribuye a resolver el problema que muestran los resultados de las tabletas A y B. La biodisponibilidad de la tableta B es incrementada en un 35%.

Por todo lo anterior, consideramos que ninguno de los documentos D1, D3 resultan anterioridades capaces de afectar el nivel inventivo de la presente invención y que la objeción en este sentido se ve superada.

4. Modificación de una solicitud en trámite.

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, se presenta un nuevo capítulo reivindicatorio constituido por 17 reivindicaciones como sustituto del anteriormente presentado. Lo anterior, con el fin de hacer claridad sobre la materia que se solicita proteger y

sobre el alcance de la misma. En particular, se ha redactado nuevamente la reivindicación 1, incluyendo en la misma la característica técnica revelada en la reivindicación 2 y esta última no ha sido incluida en el nuevo pliego reivindicatorio.

5. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

6. Anexos:

6.1 Michael E. Auton (editor), publicado por Elsevir Ltd (2002).

6.2 Jain et al., "Pharmaceuticall product development technologies based on the biopharmaceuticall classification system", Pharmazie 64 (2009), pp483-490.

6.3 "Pharmaceuticall Dosage Forms", Herbert A. Lieberman et al., Segunda Edición, Vol. 1, p.149/150.

6.4 "Pharmaceuticall Dosage Forms", Herbert A. Lieberman et al., Segunda Edición, Vol. 1, p.202/203.

6.5 Pharmaceuticall Dosage Forms: Tablets.

6.6 Experimento de la tableta.

6.7 Nuevo pliego reivindicatorio conformado por diecisiete reivindicaciones.

6.8 Formulario de modificaciones.

6.9 Recibo por concepto de 7 reivindicaciones adicionales a la décima reivindicación.

Señor Director,


LUZ CLEMENCIA DE PAEZ
T.P.A. No. 23.555

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COLO-15846-845-014-9
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No. M-2012-210648\MGM



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FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE:																	
	☐ Corrección de Error Material	☒ Modificación a una solicitud																
2	SOLICITANTE Nombre: BAYER SCHERING PHARMA AG Sociedad constituida y existente bajo las leyes de la República Federal de Alemania. Dirección: Leverkusen- 51368 República Federal de Alemania Domicilio: Leverkusen República Federal de Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____																
3	REPRESENTANTE O APODERADO Nombre: Luz Clemencia de PAEZ Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>35.456.344</u> TP <u>23.555</u>																
4	Número de expediente: <u>06.049.473</u>																	
5	Descripción de la corrección o modificación solicitada: Presento nuevo pliego reivindicatorio compuesto por 17 reivindicaciones y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas. _____ _____																	
6	<table><tr><td>Comprobante de pago No.</td><td><u>12-0013583</u></td><td>Fecha:</td><td><u>10 de febrero de 2012</u></td></tr><tr><td>Comprobante de pago No.</td><td><u>12-0013584</u></td><td>Fecha:</td><td><u>10 de febrero de 2012</u></td></tr><tr><td>Comprobante de pago No.</td><td><u>12-006208</u></td><td>Fecha:</td><td><u>23 de enero de 2012</u></td></tr><tr><td>Comprobante de pago No.</td><td><u>12-0011449</u></td><td>Fecha:</td><td><u>03 de febrero de 2012</u></td></tr></table>		Comprobante de pago No.	<u>12-0013583</u>	Fecha:	<u>10 de febrero de 2012</u>	Comprobante de pago No.	<u>12-0013584</u>	Fecha:	<u>10 de febrero de 2012</u>	Comprobante de pago No.	<u>12-006208</u>	Fecha:	<u>23 de enero de 2012</u>	Comprobante de pago No.	<u>12-0011449</u>	Fecha:	<u>03 de febrero de 2012</u>
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7

Anexos

- ☐ Comprobante de pago de la tasa por \$120.000, por concepto de modificaciones.
- ☒ Comprobante de pago por 7 reivindicaciones adicionales después de la décima reivindicación por \$210.000.oo.
- ☐ Poderes, si fuere el caso
- ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.
- ☐ Copia auténtica de la sustitución que del poder otorgado por la Sociedad Solicitante hizo el Doctor EMILIO FERRERO a mi favor, y para lo cual solicito me sea reconocida personería para continuar con el trámite del asunto de la referencia.

8

NOMBRE: LUZ CLEMENCIA DE PAEZ FIRMA:

Luz Clemencia De Paez

C.C. 35.456.344 de Usaquén T.P.A. 23.555

MGM

REIVINDICACIONES

1. Un procedimiento para la producción de una composición farmacéutica sólida de administración oral que contiene 5-cloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)-fenil]-1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida (I) en forma hidrofilizada, caracterizado porque

(a) en primer lugar se produce, mediante granulación húmeda, un granulado que contenga el principio activo (I) en forma hidrofilizada

(b) y luego, el granulado, dado el caso con adición de aditivos farmacéuticos adecuados, se transforma en la composición farmacéutica.

Un procedimiento según la reivindicación 1, caracterizado porque para el procedimiento para la granulación húmeda se utiliza la granulación en lecho fluidizado.

En donde, para el procedimiento de granulación húmeda se utiliza la granulación de lecho fluidizado.

2. Un procedimiento según la reivindicación 1, caracterizado porque el principio activo (I) se utiliza en forma cristalina.

3. Un procedimiento según la reivindicación 2, caracterizado porque el principio activo (I) se utiliza en forma micronizada.

4. Un procedimiento según una de las reivindicaciones de la 1 a la 3, caracterizado porque el principio activo (I) se incorpora en la granulación húmeda suspendido en el líquido de granulación.

5. Un procedimiento según una de las reivindicaciones de la 1 a la 4, caracterizado porque la composición farmacéutica es un comprimido de liberación rápida del principio activo (I).

6. Una composición farmacéutica sólida de administración oral que se produce mediante el procedimiento de acuerdo con la reivindicación 1.

7. Una composición farmacéutica sólida de administración oral que contiene 5-cloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)-fenil]-1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida (I) en forma hidrofilizada que se obtiene mediante el procedimiento de acuerdo con la reivindicación 1.

8. Una composición farmacéutica según la reivindicación 7, que contiene el principio activo (I) en forma cristalina.

9. Una composición farmacéutica según la reivindicación 8, que contiene el principio activo (I) en forma micronizada.

10. Una composición farmacéutica según una de las reivindicaciones de la 6 a la 9, caracterizada porque el principio activo (I) está presente en una concentración del 1 al 60%, referida a la masa total de la formulación.

11. Una composición farmacéutica según una de las reivindicaciones de la 6 a la 10, que contiene laurilsulfato de sodio como humectante.

12. Una composición farmacéutica según la reivindicación 11, que contiene laurilsulfato de sodio en una concentración del 0,1 al 5%, referida a la masa total.

13. Una composición farmacéutica, según una de las reivindicaciones de la 6 a la 12, que contiene hidroxipropilmetil celulosa como aglutinante hidrófilo.

14. Una composición farmacéutica según la reivindicación 13, que contiene hidroxipropilmetil celulosa en una concentración del 1 al 15%, referida a la masa total.

15. Una composición farmacéutica según una de las reivindicaciones de la 6 a la 14, en forma de comprimido.

16. Una composición farmacéutica según la reivindicación 15, en forma de comprimido de liberación rápida.

17. Una composición farmacéutica según la reivindicación 15 ó 16, caracterizada porque la pastilla está recubierta con un esmalte.

Pharmaceutics

The Science of Dosage Form Design

Edited by

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SECOND EDITION

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Contents

What is 'Pharmaceutics'? xiii

1. The design of dosage forms 1
Peter York

PART ONE

Scientific principles of dosage form design 13

2. Dissolution and solubility 15
Michael Aulton
3. Properties of solutions 33
Michael Aulton
4. Rheology 41
Chris Marriott
5. Surface and interfacial phenomena 59
John Fell
6. Disperse systems 70
David Attwood
7. Kinetics and product stability 101
John Pugh
8. Pharmaceutical preformulation 113
James Wells

PART TWO

Particle science and powder technology 139

9. Solid-state properties 141
Graham Buckton
10. Particle-size analysis 152
John Staniforth
11. Particle-size reduction 166
John Staniforth
12. Particle-size separation 174
John Staniforth

13. Mixing 181

Andrew Twitchell

14. Powder flow 197

John Staniforth

PART THREE

Biopharmaceutical principles of drug delivery 211

15. Introduction to biopharmaceutics 213
Marianne Ashford
16. The gastrointestinal tract – physiology and drug absorption 217
Marianne Ashford
17. Bioavailability – physicochemical and dosage form factors 234
Marianne Ashford
18. Assessment of biopharmaceutical properties 253
Marianne Ashford
19. Dosage regimens 275
Stuart Proudfoot, (updated by John Collett)
20. Modified-release peroral dosage form 289
John Collett, Chris Moreton

PART FOUR

Dosage form design and manufacture 307

21. Solutions 309
Michael Billany
22. Clarification 323
Andrew Twitchell
23. Suspensions and emulsions 334
Michael Billany

What is 'Pharmaceutics'?

One of the earliest impressions that many new pharmacy and pharmaceutical science students have of their chosen subject is the large number of long and sometimes unusual-sounding names that are used to describe the various subject areas within pharmacy. The aim of this section is to explain to the reader what is meant by the term 'pharmaceutics', how it has been interpreted for the purpose of this book, and how pharmaceutics fits into the overall scheme of pharmaceutical science. It will also lead the reader through the organization of this book and explain why an understanding of the material contained in its chapters is important in the design of modern drug delivery systems.

The word pharmaceutics is used in pharmacy and pharmaceutical science to encompass many subject areas, which are all associated with the steps to which a drug is subjected towards the end of its development – i.e. it is the stages that follow its discovery or synthesis, its isolation and purification, and testing for advantageous pharmacological effects and the absence of serious toxicological problems. Put at its most simplistic, pharmaceutics converts a drug into a medicine. Pharmaceutics, and therefore this book, is concerned with the scientific and technological aspects of the design and manufacture of dosage forms.

Pharmaceutics is arguably the most diverse of all the subject areas in pharmaceutical science and encompasses:

- an understanding of the basic physical chemistry necessary for the efficient design of dosage forms (physical pharmaceutics)
- the design and formulation of medicines (dosage form design),
- the manufacture of these medicines on both a small (compounding) and a large (pharmaceutical technology) scale;
- the cultivation, avoidance and elimination of microorganisms in medicines (microbiology).

Medicines are drug delivery systems. That is, they are a means of administering drugs to the body in a safe, efficient, reproducible and convenient manner. The first chapter in the book introduces, in a general way, the considerations that must be made so that this conversion of drug to medicine can take place. It emphasizes the fact that medicines are rarely drugs alone, but require additives to make them into dosage forms and this in turn introduces the concept of formulation. The chapter explains that there are three major considerations in the design of dosage forms:

1. The physicochemical properties of the drug itself,
2. Biopharmaceutical considerations, such as how the route of administration of a dosage form affects the rate and extent of drug absorption into the body, and
3. Therapeutic considerations of the disease state to be treated, which in turn decide the most suitable type of dosage form, possible routes of administration and the most suitable duration of action and dose frequency for the drug in question.

This first chapter is an excellent introduction to the book as a whole and the perfect justification for the need to understand the subject matter of this text. New readers are encouraged to read this chapter thoroughly and carefully so they can grasp the basics before delving into the later, more detailed information.

Part 1 of this book describes some of the more important physicochemical knowledge that it is necessary to have in order to study and understand the design and preparation of dosage forms. The chapters have been designed to give the reader an insight into those scientific and physicochemical principles that are important to the formulation scientist. They are not intended as a substitute for a thorough

antifungals, anti-inflammatory agents, as well as skin emollients for protective effects.

Pharmaceutical topical formulations – ointments, creams and pastes – are composed of drug in a suitable semisolid base which is either hydrophobic or hydrophilic in character. The bases play an important role in determining the character of drug release from the formulation. Ointments are hydrophobic, oleaginous-based dosage forms, whereas creams are semisolid emulsions. Pastes contain more solids than ointments and thus are stiffer in consistency. For topical application in liquid form other than solution, lotions – suspensions of solids in aqueous solution – or emulsions are used. More recently, interest in transdermal electrotransport systems has grown. Here a low electrical potential maintained across the skin can improve drug transport.

The application of drugs to other topical surfaces, such as the eye, ear and nose, is common and ointments, creams, suspensions and solutions are utilized. Ophthalmic preparations are required, among other features, to be sterile. Nasal dosage forms include solutions or suspensions delivered by drops or fine aerosol from a spray. Ear formulations in general are viscous to prolong contact with affected areas.

Respiratory route

The lungs provide an excellent surface for absorption when the drug is delivered in gaseous, aerosol mist or ultrafine solid particle form. For drug presented in an aerosol or solid form, particle size largely determines the extent to which they penetrate the alveolar region, the zone of rapid absorption. Particles in the region 0.5–1 μm diameter reach the alveolar sacs. Particles outside this range are either exhaled or deposited upon larger bronchial airways. This delivery route has been found particularly useful for the treatment of asthmatic problems, using both powder aerosols (e.g. sodium cromoglycate) and metered aerosols containing the drug in liquefied inert propellant (e.g. salbutamol sulphate aerosol). Importantly, this delivery route is being increasingly recognized as a means of administering the therapeutic agents emerging from biotechnology, such as peptides and proteins.

DRUG FACTORS IN DOSAGE FORM DESIGN

Each type of dosage form requires careful study of the physical and chemical properties of drug sub-

stances to achieve a stable, effective product. These properties, such as dissolution, crystal size and polymorphic form, solid-state stability and drug – additive interactions, can have profound effects on the physiological availability and physical and chemical stability of the drug. By combining such data with those from pharmacological and biochemical studies, the most suitable drug form and additives can be selected for the formulation of chosen dosage forms. Although comprehensive property evaluation will not be required for all types of formulations, those properties that are recognized as important in dosage form design and processing are listed in Table 1.3, together with the stresses to which the formulation might be exposed during processing and manipulation into dosage forms, as well as the procedures involved. Variations in physicochemical properties, occurring for example between batches of the same material or resulting from alternative treatment procedures, can modify formulation requirements as well as processing and dosage form performance. For instance, the fine milling of poorly soluble drug substances can modify their wetting and dissolution characteristics, properties that are important during granulation and product performance, respectively. Careful evaluation of these properties and understanding of the effects of these stresses upon these parameters is therefore important in dosage form design and processing, as well as in product performance.

Particle size and surface area

Particle size reduction results in an increase in the specific surface (i.e. surface area per unit weight) of powders. Drug dissolution rate, absorption rate, dosage form content uniformity and stability are all dependent to varying degrees on particle size, size distribution and interactions of solid surfaces. In many cases, for both drugs and additives particle size reduction is required to achieve the desired physicochemical characteristics.

It is now generally recognized that poorly aqueous-soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided form with larger surface than as a coarse material. Examples include griseofulvin, tolbutamide, indomethacin, spironolactone and nifedipine. The fine material, often in micrometre or submicrometre (nanometre) form with large specific surface, dissolves at a faster rate, which can lead to improved drug absorption by passive diffusion. On the other hand, with formulated nitrofurantoin preparations an

Properties	Processing stresses	Manufacturing procedures
Particle size, surface area	Pressure	Precipitation
Solubility	Mechanical	Filtration
Dissolution	Radiation	Emulsification
Partition coefficient	Exposure to liquids	Milling
Ionization constant	Exposure to gases and liquid vapours	Mixing
Crystal properties, polymorphism	Temperature	Granulation
Stability		Drying
Organoleptic		Compression
(Other properties)		Autoclaving
		Crystallization
		Handling
		Storage
		Transport

Rates of drug dissolution can be adversely affected, however, by unsuitable choice of formulation additives, even though solids of appropriate particle size are used. Tableting lubricant powders, for example, can impart hydrophobicity to a formulation and inhibit drug dissolution. Fine powders can also increase air adsorption or static charge, leading to wetting or agglomeration problems. Micronizing drug powders can lead to polymorphic and surface energy changes which cause reduced chemical stability. Drug particle size also influences content uniformity in solid dosage forms, particularly for low-dose formulations. It is important in such cases to have as many particles as possible per dose to minimize potency variation between dosage units. Other dosage forms are also affected by particle size, including suspensions (for controlling flow properties and particle interactions), inhalation aerosols (for optimal penetration of drug particles to absorbing mucosa) and topical formulations (for freedom from grittiness).

pounds can exhibit erratic or incomplete absorption, and it might be appropriate to use more soluble salt or other chemical derivatives. Alternatively, micronizing, complexation or solid dispersion techniques might be employed. Solubility, and especially degree of saturation in the vehicle, can also be important in the absorption of drugs already in solution in liquid dosage forms, as precipitation in the gastrointestinal tract can occur and bioavailability be modified.

The solubilities of acidic or basic compounds are pH dependent and can be altered by forming salt forms with different salts exhibiting different equilibrium solubilities. However, the solubility of a salt of a strong acid is less affected by changes in pH than is the solubility of a salt of a weak acid. In the latter case, when pH is lower the salt hydrolyses to an extent dependent on pH and pK_a , resulting in decreased solubility. Reduced solubility can also occur for slightly soluble salts of drugs through the common ion effect. If one of the ions involved is added as a different, more water-soluble salt, the solubility product can be exceeded and a portion of the drug precipitates.

All drugs, by whatever route they are administered, must exhibit at least limited aqueous solubility for therapeutic efficiency. Thus relatively insoluble com-

As mentioned above, for a drug to be absorbed it must first be dissolved in the fluid at the site of absorption. For example, an orally administered drug in tablet form is not absorbed until drug particles are

dissolved or solubilized by the fluids at some point along the gastrointestinal tract, depending on the pH-solubility profile of the drug substance. Dissolution describes the process by which the drug particles dissolve.

During dissolution, the drug molecules in the surface layer dissolve, leading to a saturated solution around the particles that forms the diffusion layer. Dissolved drug molecules then pass throughout the dissolving fluid to contact absorbing mucosa, and are absorbed. Replenishment of diffusing drug molecules in the diffusion layer is achieved by further drug dissolution, and the absorption process continues. If dissolution is fast, or the drug is delivered and remains in solution form, the rate of absorption is primarily dependent upon its ability to transverse the absorbing membrane. If, however, drug dissolution is slow owing to its physicochemical properties or formulation factors, then dissolution may be the rate-limiting step in absorption and influence drug bioavailability. The dissolution of a drug is described in a simplified manner by the Noyes-Whitney equation:

$$\frac{dm}{dt} = kA(C_s - C)$$

where $\frac{dm}{dt}$ is the dissolution rate, k is the dissolution rate constant, A is the surface area of dissolving solid, and C_s is the concentration of drug in the dissolution medium at time t . The equation reveals that dissolution rate can be raised by increasing the surface area (reducing particle size) of the drug, by increasing the solubility of the drug in the diffusing layer and by increasing k , which incorporates the drug diffusion coefficient and diffusion layer thickness. During the early phases of dissolution $C_s > C$, and if the surface area A and experimental conditions are kept constant, then k can be determined for compacts containing drug alone. The constant k is now termed the intrinsic dissolution rate constant, and is a characteristic of each solid drug compound in a given solvent under fixed hydrodynamic conditions.

Drugs with k values below $0.1 \text{ mg}^{-1} \text{ cm}^{-2}$ usually exhibit dissolution rate-limiting absorption. Particulate dissolution can also be examined where an effort is made to control A , and formulation effects can be studied.

Dissolution rate data, when combined with solubility, partition coefficient and pK_a , provide an insight to the formulator into the potential in vivo absorption characteristics of a drug. However, in vitro tests only have significance when they are related to in vivo results. Once such a relationship has been established, in vitro dissolution tests can be used as a predictor of in vivo behaviour. The impor-

tance of dissolution testing has been widely recognized by official compendia, as well as drug registration authorities, with the inclusion of dissolution specifications using standardized testing procedures for a range of preparations.

Partition coefficient and pK_a

As pointed out above, for relatively insoluble compounds the dissolution rate is often the rate-determining step in the overall absorption process. Alternatively, for soluble compounds the rate of permeation across biological membranes is the rate-determining step. Whereas dissolution rate can be changed by modifying the physicochemical properties of the drug and/or by altering the formulation composition, the permeation rate is dependent upon the size, relative aqueous and lipid solubility and ionic charge of drug molecules, factors that can be altered through molecular modifications. The absorbing membrane acts as a lipophilic barrier to the passage of drugs which is related to the lipophilic nature of the drug molecule. The partition coefficient, for example between oil and water, is a measure of lipophilic character.

The majority of drugs are weak acids or bases and, depending on their pH, exist in an ionized or unionized form. Membranes of absorbing mucosa are more permeable to unionized forms of drugs than to ionized species, because of the greater lipid solubility of the unionized forms and the highly charged nature of the cell membrane, which results in the binding or repelling of the ionized drug, thereby decreasing penetration. Therefore, the dominating factors that influence the absorption of weak acids and bases are the pH at the site of absorption and the lipid solubility of the unionized species. These factors, together with the Henderson-Hasselbalch equations for calculating the proportions of ionized and unionized species at a particular pH, constitute the pH-partition theory for drug absorption. However, these factors do not describe completely the process of absorption, as certain compounds with low partition coefficients and/or which are highly ionized over the entire physiological pH range show good bioavailability, and therefore other factors are clearly involved.

Crystal properties: polymorphism

Practically all drug substances are handled in powder form at some stage during manufacture into dosage forms. However, for those substances composed of, or containing, powders or compressed

powders in the finished product, the crystal properties and solid-state form of the drug must be carefully considered. It is well recognized that drug substances can be amorphous (i.e. without regular molecular lattice arrangements), crystalline, anhydrous, at various degrees of hydration or solvated with other entrapped solvent molecules, as well as varying in crystal hardness, shape and size. In addition, many drug substances can exist in more than one form, with different molecular packing arrangements in the crystal lattice. This property is termed polymorphism, and different polymorphs may be prepared by manipulating the conditions of particle formation during crystallization, such as solvent, temperature and rate of cooling. It is known that only one form of a pure drug substance is stable at a given temperature and pressure, with the other forms, termed metastable, converting at different rates of the stable crystalline form. The different polymorphs vary in physical properties such as dissolution and solid-state stability, as well as processing behaviour in terms of powder flow and compaction during tableting in some cases.

These different crystalline forms can be of considerable importance in relation to the ease or difficulty of formulation and as regards stability and biological activity. As might be expected, higher dissolution rates are obtained for metastable polymorphic forms; for example, the metastable form of chlorthalidone hydrochloride exhibits improved rate and extent of bioavailability. In some cases, amorphous forms are more active than crystalline forms.

The polypeptide hormone insulin, widely used in the regulation of carbohydrate, fat and protein metabolism, also demonstrates how differing degrees of activity can result from the use of different crystalline forms of the same agent. In the presence of acetate buffer, zinc combines with insulin to form an extremely insoluble complex of the proteinaceous hormone. This complex is an amorphous precipitate or crystalline product, depending on environmental pH. The amorphous form, containing particles of no uniform shape and smaller than 2 μm , is absorbed following i.m. or s.c. injection and has a short duration of action, whereas the crystalline product, consisting of 10–40 micrometre-sized rhombohedral crystals, is more slowly absorbed and has a longer duration of action. Insulin preparations that are intermediate in duration of action are prepared by taking physical mixtures of these two products.

Polymorphic transitions can also occur during milling, granulating, drying and compressing operations (e.g. transitions during milling for digoxin and amlodipine). Granulation can result in solvate

formation or, during drying, a solvated or hydrated molecule may be lost to form an anhydrous material. Consequently, the formulator must be aware of these potential transformations, which can result in undesirable modified product performance even though routine chemical analyses may not reveal any changes. Reversion from metastable forms, if used, to the stable form may also occur during the lifetime of the product. In suspensions this may be accompanied by changes in the consistency of the preparation which affect its shelf life and stability. Such changes can often be prevented by the inclusion of additives, such as hydrocolloids and surface-active agents.

Stability

The chemical aspects of formulation generally centre around the chemical stability of the drug and its compatibility with the other formulation ingredients. In addition it should be emphasised that the packaging of the dosage form is an important contributing factor to product stability and must be an integral part of stability testing programmes. Only a brief summary is given at this point. It has been mentioned previously that one of the principles of dosage form design is to ensure that the chemical integrity of drug substances is maintained during the usable life of the product. At the same time, chemical changes involving additive and any physical modifications to the product must be carefully monitored to optimize formulation stability.

In general, drug substances decompose as a result of the effects of heat, oxygen, light and moisture. For example, esters such as aspirin and procaine are susceptible to solvolytic breakdown, whereas oxidative decomposition occurs for substances such as ascorbic acid. Drugs can be classified according to their sensitivity to breakdown:

1. Stable under all conditions (e.g. kaolin)
2. Stable if handled correctly (e.g. aspirin)
3. Moderately stable even with special handling (e.g. vitamins)
4. Very unstable (e.g. certain antibiotics in solution form).

Although the mechanisms of solid-state degradation are complex and often difficult to analyse, a full understanding is not a prerequisite in the design of a suitable formulation containing solids. For example, in cases where drug substances are sensitive to hydrolysis, precautions such as minimum exposure to moisture during preparation, low moisture content specifications in the final product, and moisture resistant packaging can be used. For oxygen-

2. If $B-B \gg A-A$, the solvent will not be able to break the binding forces between solute molecules and disperse them. This situation would apply if you tried to dissolve sodium chloride in benzene. The sodium chloride crystal is held together by strong electrovalent forces which cannot be broken by benzene. A conducting solvent, such as water, would be required to overcome the attraction between solute molecules.
3. If $A-B > A-A$ or $B-B$, or the three forces are of the same order, the solute will disperse and form a solution.

The above is a simplified overview of the situation. The rest of this chapter will attempt to explain the basic physicochemical properties of solutions that lead to such observations.

Physicochemical prediction of solubility

Similar types of intermolecular force may contribute to solute-solvent, solute-solute and solvent-solvent interactions. The attractive forces exerted between polar molecules are much stronger, however, than those that exist between polar and non-polar molecules, or between non-polar molecules themselves. Consequently, a polar solute will dissolve to a greater extent in a polar solvent, where the strength of the solute-solvent interaction will be comparable to that between solute molecules, than in a non-polar solvent, where the solute-solvent interaction will be relatively weak. In addition, the forces of attraction between the molecules of a polar solvent will be too great to facilitate the separation of these molecules by the insertion of a non-polar solute between them, because the solute-solvent forces will again be relatively weak. Thus, solvents for non-polar solutes tend to be restricted to non-polar liquids.

The above considerations are often expressed very generally as 'like dissolves like', i.e. a polar substance will dissolve in a polar solvent and a non-polar substance will dissolve in a non-polar solvent. Such a generalization should be treated with caution, because the intermolecular forces involved in the process of dissolution are influenced by factors that are not obvious from a consideration of the overall polarity of a molecule. For example, the possibility of intermolecular hydrogen-bond formation between solute and solvent may be more significant than polarity.

Solubility parameter Attempts have been made to define a parameter that indicates the ability of a liquid to act as a solvent. The most satisfactory approach is based on the concept that the solvent power of a liquid is influenced by its intermolecular cohesive forces and

that the strength of these forces can be expressed in terms of a solubility parameter. The initially introduced parameters, which are concerned with the behaviour of non-polar, non-interacting liquids, are referred to as Hildebrand solubility parameters. Although these provide good quantitative predictions of the behaviour of a small number of hydrocarbons, they only provide a broad qualitative description of the behaviours of most liquids because of the influence of factors such as hydrogen-bond formation and ionization. The concept has been extended, however, by the introduction of partial solubility parameters, e.g. Hansen parameters and interaction parameters, that have improved the quantitative treatment of systems in which polar effects and interactions occur.

Solubility parameters, in conjunction with the electrostatic properties of liquids, e.g. dielectric constant and dipole moment, have often been linked by empirical or semiempirical relationships either to these parameters or to solvent properties. Studies on solubility parameters are sometimes reported in the pharmaceutical literature. The use of dielectric constants as indicators of solvent power has also received attention, but deviations from the behaviour predicted by such methods may occur.

Mixtures of liquids are often used as solvents. If the two liquids have similar chemical structures, e.g. benzene and toluene, then neither tends to associate in the presence of the other, and the solvent properties of a 50:50 mixture would be a mean of those of each pure liquid. If the liquids have dissimilar structures, e.g. water and propanol, then the molecules of one of them tend to associate with each other and so form regions of high concentration within the mixture. The solvent properties of this type of system are not so simply related to its composition as in the previous case.

Solubility of solids in liquids

Solutions of solids in liquids are the most common type encountered in pharmaceutical practice. The pharmacist should therefore be aware of the general method of determining the solubility of a solid in a liquid and the various precautions that should be taken during such determinations.

Determination of the solubility of a solid in a liquid

The following points should be observed in all solubility determinations:

1. The solvent and the solute must be pure.

2. A saturated solution must be obtained before any solution is removed for analysis.
3. The method of separating a sample of saturated solution from undissolved solute must be satisfactory.
4. The method of analysing the solution must be reliable.
5. Temperature must be adequately controlled.

A saturated solution is obtained either by stirring excess powdered solute with solvent for several hours at the required temperature until equilibrium has been attained, or by warming the solvent with an excess of the solute and allowing the mixture to cool to the required temperature. It is essential that some undissolved solid should be present at the completion of this stage in order to ensure that the solution is saturated.

A sample of the saturated solution is obtained for analysis by separating it from the undissolved solid. Filtration is usually used, but precautions should be taken to ensure that:

1. it is carried out at the temperature of the solubility determination, in order to prevent any change in the equilibrium between dissolved and undissolved solute; and
2. loss of a volatile component does not occur.

The filtration process has been simplified by the introduction of membrane filters that can be used in conjunction with conventional syringes fitted with suitable inline adapters.

The amount of solute contained in the sample of saturated solution may be determined by a variety of methods, e.g. gravimetric or volumetric analysis, electrical conductivity measurements, ultraviolet (UV) spectrophotometry and chromatographic methods. The selection of an appropriate method is affected by the natures of the solute and the solvent and by the concentration of the solution.

Factors affecting the solubility of solids in liquids

Knowledge of these factors, which are discussed below together with their practical applications, is an important aspect of the pharmacist's expertise. Additional information, which shows how some of these factors may be used to improve the solubilities and bioavailabilities of drugs, is given in Chapters 21 and 17, respectively.

Temperature Earlier discussion centred on Eqn 2.2 shows that the free energy change (ΔG) that accompanies dissolution is dependent on the value and sign of the change in enthalpy (ΔH). The addi-

tional comments that referred to Eqn 2.3 indicate that when ΔH is positive the dissolution process is usually an endothermic one, i.e. heat is normally absorbed when dissolution occurs. If this type of system is heated it will tend to react in a way that will nullify the constraint imposed upon it, e.g. the rise in temperature. This tendency is an example of Le Chatelier's principle. Thus, a rise in temperature will lead to an increase in the solubility of a solid with a positive heat of solution. Conversely, in the case of the less commonly occurring systems that exhibit exothermic dissolution, an increase in temperature will give rise to a decrease in solubility.

Plots of solubility versus temperature, which are referred to as *solubility curves*, are often used to describe the effect of temperature on a given system. Some examples are shown in Figure 2.3. Most of the curves are continuous; however, abrupt changes in slope may be observed with some systems if a change in the nature of the dissolving solid occurs at a specific transition temperature. For example, sodium sulphate exist as the decahydrate $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ up to 32.5°C , and its dissolution in water is an endothermic process. Its solubility therefore increases with rise in temperature until 32.5°C is reached. Above this temperature the solid is converted into the anhydrous form Na_2SO_4 , and the dissolution of this compound is an exothermic process. The solubility therefore exhibits a change from a positive to a negative slope as the temperature exceeds the transition value.

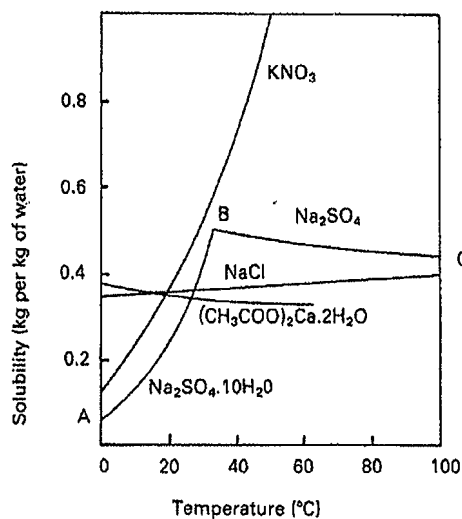


Fig. 2.3 Solubility curves for various substances in water

Molecular structure of solute It should be appreciated from the previous comments on the prediction of solubility that the natures of the solute and the solvent will be of paramount importance in determining the solubility of a solid in a liquid. It should also be realized that even a small change in the molecular structure of a compound can have a marked effect on its solubility in a given liquid. For example, the introduction of a hydrophilic hydroxyl group can produce a large improvement in water solubility, as evidenced by the more than 100-fold difference in the solubilities of phenol and benzene.

In addition, the conversion of a weak acid to its sodium salt leads to a much greater degree of ionic dissociation of the compound when it dissolves in water. The overall interaction between solute and solvent is markedly increased and the solubility consequently rises. A specific example of this effect is provided by a comparison of the aqueous solubilities of salicylic acid and its sodium salt, which are 1:550 and 1:1, respectively.

The reduction in aqueous solubility of a parent drug by its esterification may also be cited as an example of the effects of changes in the chemical structure of the solute. Such a reduction in solubility may provide a suitable method for:

1. masking the taste of a parent drug, e.g. chloramphenicol palmitate is used in paediatric suspensions rather than the more soluble and very bitter chloramphenicol base;
2. protecting the parent drug from excessive degradation in the gut, e.g. erythromycin propionate is less soluble and consequently less readily degraded than erythromycin;
3. increasing the ease of absorption of drugs from the gastrointestinal tract, e.g. erythromycin propionate is also more readily absorbed than erythromycin.

Nature of solvent: cosolvents The importance of the nature of the solvent has already been discussed in terms of the statement 'like dissolves like', and in relation to solubility parameters. In addition, the point has been made that mixtures of solvents may be employed. Such mixtures are often used in pharmaceutical practice to obtain aqueous-based systems that contain solutes in excess of their solubilities in pure water. This is achieved by using cosolvents such as ethanol or propylene glycol, which are miscible with water and which act as better solvents for the solute in question. For example, the aqueous solubility of metronidazole is about 100 mg in 10 mL. Chien (1984) has shown, however, that the solubility of this drug can be increased exponentially by the

incorporation of one or more water-miscible cosolvents, so that a solution containing 500 mg in 10 mL and suitable for parenteral administration in the treatment of anaerobic infection, can be obtained.

Crystal characteristics: polymorphism and solvation The value of the term ΔH_c in Eqn 2.3 is determined by the strength of the interactions between adjacent molecules (or ions) in a crystal lattice. These interactions will depend on the relative positions and orientations of the molecules in the crystal. When the conditions under which crystallization is allowed to occur are varied, some substances produce crystals in which the constituent molecules are aligned in different ways with respect to one another in the lattice structure. These different crystalline forms of the same substance, which are known as **polymorphs**, consequently possess different lattice energies, and this difference is reflected by changes in other properties; for example, the polymorphic form with the lowest free energy will be the most stable and possess the highest melting point. Other less stable (or metastable) forms will tend to transform into the most stable one at rates that depend on the energy differences between the metastable and the stable forms. Polymorphs are explained more fully in Chapter 9.

The effect of polymorphism on solubility is particularly important from a pharmaceutical point of view, because it provides a means of increasing the solubility of a crystalline material and hence its rate of dissolution by using a metastable polymorph.

Although the more soluble polymorphs are metastable and will convert to the stable form the rate of such conversion is often slow enough for the metastable form to be regarded as being sufficiently stable from a pharmaceutical point of view. The degree of conversion should obviously be monitored during storage of the drug product to ensure that its efficacy is not altered significantly. In addition, conversion to the less soluble and most stable polymorph may contribute to the growth of crystals in suspension formulations.

Many drugs exhibit polymorphism, e.g. steroids, barbiturates and sulphonamides. Examples of the importance of polymorphism with respect to the bioavailabilities of drugs and to the occurrence of crystal growth in suspensions are given in Chapters 17 and 23, respectively.

The absence of crystalline structure that is usually associated with a so-called **amorphous** powder (see Chapter 9) may also lead to an increase in the solubility of a drug compared to that of its crystalline form.

In addition to the effect of polymorphism the lattice structures of crystalline materials may be altered by

the incorporation of molecules of the solvent from which crystallization occurred. The resultant solids are called *solvates*; the phenomenon is referred to correctly as *solvation* and sometimes incorrectly and confusingly as *pseudopolymorphism*. The alteration in crystal structure that accompanies solvation will affect ΔH_c so that the solubilities of solvated and unsolvated crystals will differ.

If water is the solvating molecule, i.e. if a *hydrate* is formed, then the interaction between the substance and water that occurs in the crystal phase reduces the amount of energy liberated when the solid hydrate dissolves in water. Consequently, hydrated crystals tend to exhibit a lower aqueous solubility than their unhydrated forms. This decrease in solubility can lead to precipitation of drugs from solutions.

In contrast to the effect of hydrate formation, the aqueous solubilities of other, i.e. non-aqueous, solvates are often greater than those of the unsolvated forms. Examples of the effects of solvation and the attendant changes in solubilities of drugs on their bioavailabilities are given in Chapter 17.

Particle size of the solid The changes in interfacial free energy that accompany the dissolution of particles of varying sizes cause the solubility of a substance to increase with decreasing particle size, as indicated by Eqn 2.10:

$$\log \frac{S}{S_0} = \frac{2\gamma M}{2.303RT\rho r} \quad (2.10)$$

where S is the solubility of small particles of radius r , S_0 is the normal solubility (i.e. of a solid consisting of fairly large particles), γ is the interfacial energy, M is the molecular weight of the solid, ρ is the density of the bulk solid, R is the gas constant and T is the thermodynamic temperature.

This effect may be significant in the storage of pharmaceutical suspensions, as the smaller particles in such a suspension will be more soluble than the larger ones. As the small particles disappear, the overall solubility of the suspended drug will decrease and the larger particles will grow. The occurrence of crystal growth by this mechanism is of particular importance in the storage of suspensions intended for injection (Winfield and Richards, 1998).

The increase in solubility with decrease in particle size ceases when the particles have a very small radius, and any further decrease in size causes a decrease in solubility. It has been postulated that this change arises from the presence of an electrical charge on the particles and that the effect of this charge becomes more important as the size of the particles decreases.

pH If the pH of a solution of either a weakly acidic drug or a salt of such a drug is reduced then the proportion of unionized acid molecules in the solution increases. Precipitation may therefore occur because the solubility of the unionized species is less than that of the ionized form. Conversely, in the case of solutions of weakly basic drugs or their salts precipitation is favoured by an increase in pH. Such precipitation is an example of one type of chemical incompatibility that may be encountered in the formulation of liquid medicines.

This relationship between pH and the solubility of ionized solutes is extremely important with respect to the ionization of weakly acidic and basic drugs as they pass through the gastrointestinal tract and experience pH changes between about 1 and 8. This will affect the degree of ionization of the drug molecules, which in turn influences their solubility and their ability to be absorbed. This aspect is discussed in some detail, elsewhere in this book and the reader is referred to Chapters 3 and 17 in particular.

The relationship between pH and the solubility and pK_a value of an acidic drug is given by Eqn 2.11, which is a modification of the Henderson-Hasselbalch equation (Eqn 3.12):

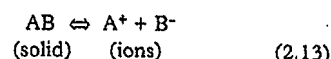
$$pH = pK_a + \log \frac{S - S_u}{S_0} \quad (2.11)$$

where S is the overall solubility of the drug and S_u is the solubility of its unionized form, i.e. $S = S_0 +$ solubility of ionized form (S_i). If the pH of the solution is known then Eqn 2.11 may be used to calculate the solubility of an acidic drug at that pH. Alternatively, the equation allows determination of the minimum pH that must be maintained in order to prevent precipitation from a solution of known concentration.

In the case of basic drugs the corresponding relationship is given by Eqn 2.12:

$$pH = pK_a + \log \frac{S_u}{S - S_u} \quad (2.12)$$

Common ion effect The equilibrium in a saturated solution of a sparingly soluble salt in contact with undissolved solid may be represented by:



From the Law of Mass Action the equilibrium constant K for this reversible reaction is given by Eqn 2.14:

$$K = \frac{[\text{A}^+][\text{B}^-]}{[\text{AB}]} \quad (2.14)$$

8

Pharmaceutical preformulation: the physicochemical properties of drug substances

James Wells

CHAPTER CONTENTS

The concept of preformulation 114

Spectroscopy 114

Solubility 115

Aqueous solubility 115

Intrinsic solubility (C_0) 115

pK_a from solubility data 116

Salts 116

Solvents 118

Partition coefficient (K_o) 119

Solvent solubility 119

Methodology and structure-activity

prediction 119

Choice of non-aqueous solvent (oil) 119

Structure-activity relationships 120

Dissolution 122

Intrinsic dissolution rate 122

Measurement of intrinsic dissolution rate 123

Common ion effect 123

Melting point 124

Techniques 124

Capillary melting 124

Hot-stage microscopy 124

Differential scanning calorimetry and thermal

analysis 124

Polymorphism 124

Pseudopolymorphism (solvates) 125

True polymorphism 126

Crystal purity 126

Solubility 126

Assay development 127

UV spectroscopy 128

Molecular weight 128

pK_a 128

Thin-layer chromatography 128

High-performance liquid chromatography

(HPLC) 128

Normal-phase HPLC 129

Reverse-phase HPLC 129

Drug and product stability 129

Temperature 130

Order of reaction 130

Hydrolysis 130

The influence of pH 130

Solvolysis 131

Oxidation 131

Chelating agents 131

Photolysis 131

Solid-state stability 132

Hygroscopicity 132

Stability assessment 132

Microscopy 132

Crystal morphology 133

Particle size analysis 133

Powder flow properties 133

Bulk density 133

Angle of repose 134

Compression properties 134

Plastic material 134

Fragmentation 135

Elastic material 135

Punch filming (sticking) 136

Excipient compatibility 136

Method 136

Interpretation 136

Conclusions 138

References 138

Bibliography 138

THE CONCEPT OF PREFORMULATION

Almost all new drugs are marketed as tablets, capsules or both (Table 8.1). Although only a few are marketed as an injection (25% of those marketed as tablets) the intravenous route is always required during early toxicity, metabolic, bioavailability and clinical studies to provide a precise drug and dose deposition. Other dosage forms may be required (Table 8.1) but these are drug specific and depend to a large extent on the successful development of tablets, capsules and injections.

Prior to the development of these three major dosage forms, it is essential that certain *fundamental* physical and chemical properties of the drug molecule and other *derived* properties of the drug powder are determined. This information dictates many of the subsequent events and approaches in formulation development. This first learning phase is known as *preformulation*.

A recommended list of the information required in preformulation is shown in Table 8.2. This is assembled, recognizing the relative importance and probable existence of only limited quantities of new bulk drug (mg rather than g). Investigators must be pragmatic and generate data of immediate relevance, especially if the likely dosage forms are known.

Two fundamental properties are mandatory for a new compound:

- 1. Intrinsic solubility (C_0),
- 2. Dissociation constant (pK_a).

Table 8.1 Frequency distribution of dosage form types manufactured in the UK	
Dosage form	Frequency (%)
Tablets	46
Liquid oral	16
Capsules	15
Injections	13
Suppositories and pessaries	3
Topicals	3
Eye preparations	2
Aerosols (inhalation)	1
Others	1

Independent of this pharmaceutical profiling (Table 8.2), analysts will generate data (Table 8.3) to confirm structure and purity, and this should be used to complement and confirm pharmaceutical data. Their greater training and knowledge in analysis will assist in the identification of suitable stability-indicating assays by high-performance liquid chromatography (HPLC).

SPECTROSCOPY

The first step in preformulation is to establish a simple analytical method. Most drugs absorb light in the ultraviolet wavelengths (190–390 nm) as they are

Table 8.2 Preformulation drug characterization	
Test	Method/function/characterization
Spectroscopy	Simple UV assay
Solubility	Phase solubility, purity
aqueous	Intrinsic solubility, pH effects
pK_a	Solubility control, salt formation
salts	Solubility, hygroscopicity, stability
solvents	Vehicles, extraction
partition coeff K_w	Lipophilicity, structure activity
dissolution	Biopharmacy
Melting point	DSC – polymorphism, hydrates, solvates
Assay development	UV, TLC, HPLC
Stability (in solution and solid state)	Thermal, hydrolysis, oxidation, photolysis, metal ions, pH.
Microscopy	Morphology, particle size
Powder flow	Tablet and capsule formulation
bulk density	
angle of repose	
Compression properties	Tablet and capsule formation
Excipient compatibility	Excipient choice

Tablet
Injection
Purity
Assay
Quality

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CONCLUSIONS

Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical paths in both liquid and solid dosage form technology (Fig. 8.8). The need for adequate drug solubility cannot be overemphasized. The availability of good solubility data should allow the selection of the most appropriate salt for development. Stability studies in solution will indicate the feasibility of parenteral or other liquid dosage forms, and can identify methods of stabilization. In parallel, solid-state stability by DSC, TLC and HPLC, and in the presence of tablet and capsule excipients, will indicate the most acceptable vehicles for solid dosage forms.

By comparing the physicochemical properties of each drug candidate within a therapeutic group (using C_s , pK_a , melting point, K_{ow}) the preformulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response, and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

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CRYSTALLIZATION

Materials in the solid state can be crystalline or amorphous (or a combination of both). Crystalline materials are those in which the molecules are packed in a defined order, and this same order repeats over and over again throughout the particle. In Figure 9.1(a) an ordered packing of a molecule is shown, here the shape of the molecule is represented by a 'hockey-stick' style image, illustrating a planar structure with a functional group pointing up at the end. (This is not a real molecule: it has been drawn to provide an easy representation of a possible crystal packing arrangement.) A characteristic property of a crystal is that it has a melting point. This is the temperature at which the crystal lattice breaks down, owing to the molecules having gained sufficient energy from the heating process to overcome the attractive forces that hold the crystal together. It follows that crystals with weak forces holding the molecules together (such as paraffins, which only have van der Waals interactions) have low melting points, whereas crystals with strong lattices (i.e. those held together with strong attractive forces, such as extensive hydrogen bonding) have high melting points.

Crystals are produced by inducing a change from the liquid to the solid state. There are two options: one is to cool a molten sample to below its melting point. Pharmaceutical examples of crystallizing through cooling include the formation of suppositories, creams and semisolid matrix oral dosage forms. The other method of crystallization is to have a solu-

tion of the material and to change the system so that the solid is formed. At a given temperature and pressure, any solute (where the solute is the material that has been dissolved and the liquid is the solvent) has a certain maximum amount that can be dissolved in any liquid (called a saturated solution). If crystals are to be formed from a solution, it is necessary to have more solute present than can be dissolved at that temperature; this will eventually result in the formation of a solid in equilibrium with a saturated solution. In order to make a solid precipitate out of solution one can either:

- remove the liquid by evaporation (this is the way sea salt is prepared)
- cool the solution, as most materials become less soluble as the temperature is decreased
- add another liquid which will mix with the solution, but in which the solute has a low solubility. This second liquid is often called an antisolvent.

Many drugs are crystallized by adding water as an antisolvent to a solution of the drug in an organic liquid. For example, if a drug is almost insoluble in water but freely soluble in ethanol, the drug could be crystallized by adding water to a near-saturated solution of the drug in ethanol.

The processes by which a crystal forms are called **nucleation** and **growth**. Nucleation is the formation of a small mass on to which a crystal can grow. Growth is the addition of more solute molecules to the nucleation site. In order to achieve nucleation and growth, it is necessary to have a supersaturated solution, i.e. one where the amount of solute dissolved in the liquid is greater than the true solubility. Supersaturated solutions are not thermodynamically stable; in these circumstances the system will adjust in order to move back to the true solubility, and to do this the excess solute will precipitate. However, in some circumstances the process of nucleation can be slow. Most students will at some stage have a supersaturated solution which has not crystallized; then, simply by scratching the side of the beaker with a glass rod, crystallization can be induced. The scratching action produces a small amount of rough surface or glass spicule that acts as a nucleation site and causes the supersaturated solute to precipitate rapidly.

POLYMORPHISM

If the crystallization conditions are changed in any way, it is possible that the molecules may start to

form crystals that were used for different purposes. Impurities alternate occurred both the repeating these we

By loc 9.1 it can be spaced (two crystals the same different volume in physics (b), as the structure have a known mill the easily, as cally or have an

This conclusion (tableting summary: the same forms, characteristics

Many excipients form known one polymorph stable different material stable less common. Consider polymorphism, the point as metastable a period chance of Different times or stable for which the

In general melting point

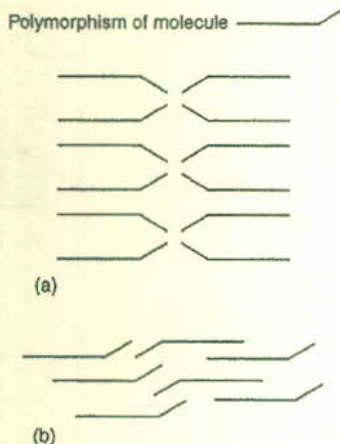


Fig. 9.1 Representation of two polymorphic forms of a crystal consisting of a molecule represented by a 'hockey-stick' shape.

form crystals with a different packing pattern from that which occurred when the original conditions were used. The change in conditions could be a different solvent, or a change in the stirring, or different impurities being present. Figure 9.1(b) shows an alternative packing arrangement from that which occurred for the same molecule in Figure 9.1(a). As both the packing arrangements in Figure 9.1 are repeating ordered systems, they are both crystals; these would be called polymorphic forms.

By looking at the packing arrangements in Figure 9.1 it can be seen that the molecules in (a) are more spaced out than those in (b), which means that the two crystal forms would have different densities (i.e. the same mass of material would be housed in different volumes). It looks as though it would be easier to physically pull a molecule off structure (a) than off (b), as the molecules in (b) are more interwoven into the structure. If this were the case then (a) would have a lower melting point than (b) and might dissolve more easily. Also, if an attempt were made to mill the two crystals, it appears that (a) would break easily, as there are natural break lines (either vertically or horizontally), whereas (b) does not seem to have an obvious weak line to allow easy breakage. This could mean that the milling and compaction (tableting) properties of the two forms will differ. In summary, a change in the packing arrangement of the same molecule, giving two different crystal forms, could result in significant changes in the properties of the solid.

Many organic molecules, including drugs and excipients, exhibit polymorphism. Usually this is of a form known as monotropic, which means that only one polymorphic form is stable and any other polymorph that is formed will eventually convert to the stable form. However, some materials exhibit enantropic polymorphism, which means that under different conditions (temperature and pressure) the material can reversibly transform between alternative stable forms; however, this type of behaviour is less common and will not be considered further. Considering the more usual monotropic polymorphism, the true stable form has the highest melting point and all other forms are described as metastable. This means that the other forms exist for a period of time and thus appear stable, but given a chance they will convert to the true stable form. Different metastable forms can exist for very short times or for many months before they convert to the stable form, depending upon the conditions under which they are stored.

In general there will be a correlation between the melting point of the different polymorphs and the

rate of dissolution, because the one with the lowest melting point will most easily give up molecules to dissolve, whereas the most stable form (highest melting point) will not give up molecules to the solvent.

High melting point = strong lattice = hard to remove a molecule = low dissolution rate (and vice versa).

It is relatively easy to understand that changes in polymorphic form can cause changes in the rate at which a drug will dissolve. However, it is less easy to understand why this can lead to a change in the apparent solubility. None the less, it is true that when a metastable polymorphic form is dissolved it can give a greater amount of material in solution than the saturated solubility. In other words, metastable forms can dissolve to give supersaturated solutions. These supersaturated solutions will eventually return to the equilibrium solubility, owing to the stable crystal form precipitating from solution, but this process may not be instantaneous. In fact, the supersaturated solution can often exist long enough to cause an increase in bioavailability of a poorly soluble drug. Figure 9.2 shows the solubility of two different polymorphs of sulphamethoxydiazine. It can be seen that Form III has a higher solubility than Form II, and that this lasts throughout

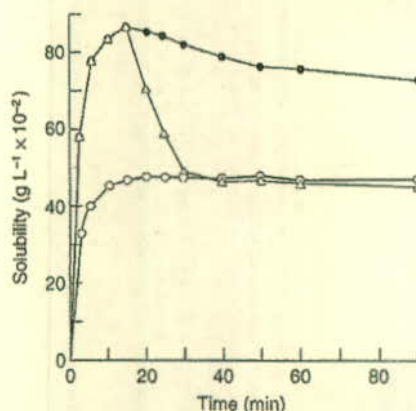


Fig. 9.2 The solubility time relationship for sulphamethoxydiazine. O, solubility of polymorphic Form III, which rises to the drug's equilibrium solubility and plateaus. ●, solubility of polymorphic Form II, which dissolves to twice the extent of Form III and then shows a gradual decline with time, as the stable form crystallizes from solution. △, the effect of adding crystals of Form III to the solution of Form II at the peak of solubility. It can be seen that the amount dissolved falls rapidly from the supersaturated level to the true equilibrium solubility because the added crystals of Form II act as nucleation sites. (Reproduced from Ebien et al 1973, with permission.)

the 90-minute experiment. However, if crystals of Form II are added to the solution of Form III, then the solubility reverts rapidly to that of Form II because the excess solute in the supersaturated solution will have seed crystals of Form II on which to precipitate.

Polymorphism and bioavailability

Many drugs are hydrophobic and have very limited solubility in water. Owing to the limited aqueous solubility of such drugs the rate at which they dissolve (slow dissolution rate) can result in only a small percentage of the administered drug actually being available to the patient (low bioavailability). A classic example of the importance of polymorphism on bioavailability is that of chloramphenicol palmitate suspensions. In Figure 9.3 the blood serum level is plotted as a function of time after dosing. It can be seen that the stable α -polymorph produces low serum levels, whereas the metastable β -polymorph yields much higher serum levels when the same dose is administered.

For drugs that are freely soluble in water the bioavailability is not likely to be limited by the dissolution, so it would be surprising for polymorphism to influence bioavailability in this way. However, for drugs with low aqueous solubility the polymorphic form must be well controlled to ensure that the bioavailability is the same each time the product is made, and throughout the shelf-life of the product. It would be risky to deliberately make a product using

anything other than the stable form of a drug, as other polymorphic forms could convert to the stable form during the shelf-life of the product, which could result in a reduction in bioavailability and hence the therapeutic effect of the product.

In conclusion, the stable polymorphic form will have the slowest dissolution rate, and so there may be occasions when it would be desirable to speed the dissolution by using a metastable form. However, the risk associated with using the metastable form is that it will convert back to the stable form during the product's life, and give a consequent change in properties. As polymorphism can have such serious consequences for the bioavailability of drugs with low aqueous solubility, it is essential that manufacturers check for the existence of polymorphism and ensure that they use the same appropriate polymorphic form every time they make a product.

As mentioned above, many properties other than rate of solution can change when a material is in a different polymorphic form. For example, paracetamol is a high-dose drug with poor compression properties, which can make it difficult to form into tablets. Consequently, researchers have tried to use different polymorphic forms of paracetamol to find one that is more compressible.

HYDRATES AND SOLVATES

It is possible for materials to crystallize and in so doing to trap molecules of the solvent within the lattice. If the solvent used is water, the material will be described as a hydrate. This entrapment is often in an exact molar ratio with the crystallizing material: for example, a monohydrate will have one molecule of water for each molecule of the crystallizing material. It is possible to have many different levels of hydrate: for example, some drugs can exist as a monohydrate, a dihydrate and a trihydrate (respectively one, two and three molecules of water to each molecule of drug). Morris (1999) notes that about 11% (over 16000 compounds) of all structures recorded on the Cambridge Structural Database exist as hydrates. Of the classes of hydrate materials that were similar to drugs, about 50% were monohydrates (one water molecule for each one of host), over 20% were dihydrates (two water molecules to one of host), 8% were trihydrates (three water molecules to one host) and 8% were hemihydrates (one water molecule to two of host); other hydrate levels (up to 10 water to one host) became progressively less common.

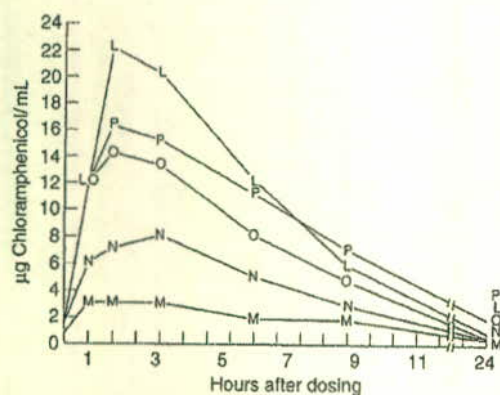


Fig. 9.3 Comparison of mean blood serum levels after the administration of chloramphenicol palmitate suspensions using varying ratios of the stable (α) and the metastable (β) polymorphs. M, 100% α polymorph; N, 25:75 β : α ; O, 50:50 β : α ; P, 75:25 β : α ; L, 100% β polymorph. (Reproduced from Aguiar et al 1976, with permission.)

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Assessment of biopharmaceutical properties

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CHAPTER CONTENTS

Introduction	253
Measurement of key biopharmaceutical properties	254
Release of drug from its dosage form into solution	254
Stability in physiological fluids	255
Permeability	256
Partition coefficients	256
Cell culture techniques	257
Tissue techniques	259
Perfusion studies	260
Assessment of permeability in humans	261
Intestinal perfusion studies	261
Non-invasive approaches	262
Presystemic metabolism	262
Assessment of bioavailability	262
Plasma concentration-time profiles	262
Minimum effective (or therapeutic) plasma concentration	263
Maximum safe concentration	263
Therapeutic range or window	264
Onset	264
Duration	264
Peak concentration	264
Time of peak concentration	264
Area under the plasma concentration-time curve	264
The use of plasma concentration-time curves in bioavailability studies	264
Cumulative urinary drug excretion curves	265
The use of urinary drug excretion curves in bioavailability studies	266
Absolute and relative bioavailability	267
Absolute bioavailability	267
Relative bioavailability	269
Bioequivalence	270
Assessment of site of release in vivo	271
The Biopharmaceutical Classification Scheme	273
Class I drugs	273
Class II drugs	273
Class III drugs	273
Class IV drugs	273
Summary	273
References	273

INTRODUCTION

Biopharmaceutics is involved with factors that influence the rate and extent of drug absorption. As discussed in Chapters 16 and 17, the factors that affect the release of a drug from its dosage form, its dissolution into physiological fluids, its stability within those fluids, its permeability across the relevant biological membranes and its presystemic metabolism will all influence its rate and extent of absorption (Fig. 18.1). Once the drug is absorbed into the systemic circulation, its distribution within the body tissues (including to its site of action), its metabolism and elimination are described by the pharmacokinetics of the compound. The pharmacokinetics of the compound influence the length and magnitude of the therapeutic effect or the response of the compound, i.e. its pharmacodynamics (see Chapter 15).

The key biopharmaceutical properties that can be quantified and therefore give an insight into the absorption of a drug are its:

- release from its dosage form into solution at the absorption site;
- stability in physiological fluids;
- permeability;
- susceptibility to presystemic clearance.

As most drugs are delivered via the mouth, these properties will be discussed with respect to the peroral route. The bioavailability of a compound is an overall measure of its availability in the systemic circulation, and so the assessment of bioavailability will also be discussed. Other methods of assessing the performance of dosage forms in vivo will also be briefly mentioned. The Biopharmaceutical Classification Scheme, which classifies drugs according to two of their key biopharmaceutical properties, solubility and permeability, is outlined.

THE BIOPHARMACEUTICAL CLASSIFICATION SCHEME

A biopharmaceutical classification scheme has been proposed which classifies drugs into four classes according to their solubility across the gastrointestinal pH range and their permeability across the gastrointestinal mucosa (Amidon et al 1995). Two of the four potential barriers to absorption are thus addressed by the scheme (see Fig. 18.1).

The scheme was originally proposed for the identification of immediate-release solid oral products for which in vivo bioequivalence tests may not be necessary, but it is also useful to classify drugs and predict bioavailability issues that may arise during the various stages of the development process. The four classes are:

- Class I: high solubility/low permeability
- Class II: low solubility/high permeability
- Class III: high solubility/low permeability
- Class IV: low solubility/low permeability.

A drug is considered to be highly soluble where the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range 1–8. The volume is derived from the minimum volume anticipated in the stomach when a dosage form is taken in the fasted state with a glass of water. If the volume of aqueous media taken to dissolve the drug in pH conditions ranging from 1 to 8 is greater than 250 mL then the drug is considered to have low solubility. The classification therefore takes into account the dose of the drug as well as its solubility. A drug is considered to be highly permeable when the extent of absorption in humans is expected to be greater than 90% of the administered dose. Permeability can be assessed using one of the methods discussed earlier which has been calibrated with known standard compounds or by pharmacokinetic studies.

Class I drugs Class I drugs will dissolve rapidly when presented in immediate-release dosage forms, and are also rapidly transported across the gut wall. Therefore, unless they form insoluble complexes, are unstable in gastric fluids or undergo presystemic clearance, it is expected that such drugs will be rapidly absorbed and thus show good bioavailability. Examples of class I drugs are the β -blockers propranolol and metoprolol.

Class II drugs In contrast, for drugs in class II the dissolution rate is liable to be the rate-limiting step in oral absorption. For class II drugs, therefore, it should be possible to generate a strong correlation between in vitro dissolution and in vivo

absorption (see earlier). Examples of class II drugs are the non-steroidal anti-inflammatory drug ketoprofen and the antiepileptic carbamazepine. This class of drug should be amenable to formulation approaches to improve the dissolution rate and hence oral bioavailability.

Class III drugs Class III drugs are those that dissolve rapidly but which are poorly permeable; examples are the H_2 -antagonist ranitidine and the β -blocker atenolol. It is important that dosage forms containing class III drugs release them rapidly, in order to maximize the amount of time these drugs, which are slow to permeate the gastrointestinal epithelium, are in contact with it.

Class IV drugs Class IV drugs are those that are classed as poorly soluble and poorly permeable. These drugs are liable to have poor oral bioavailability, or the oral absorption may be so low that they cannot be given by the oral route. The diuretics hydrochlorothiazide and frusemide are examples of class IV drugs. Forming prodrugs of class IV compounds or finding an alternative route of delivery are approaches that have to be adopted to significantly improve their absorption into the systemic circulation.

SUMMARY

This chapter discusses the range of current approaches to assessing the biopharmaceutical properties of drugs that are intended for oral administration. Methods of measuring and interpreting bioavailability data are described. The concepts of bioequivalence and the biopharmaceutical classification of drugs are introduced. It is imperative that the biopharmaceutical properties of drugs are fully understood, both in the selection of candidate drugs during the discovery process and in the design and development of efficacious immediate- and controlled-release dosage forms.

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Pharmaceutical product development technologies based on the biopharmaceutical classification system

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Poor solubility and poor permeability account for many pharmacokinetic failures and about thirty percent of drug molecules are rejected due to pharmacokinetic failures. When poor pharmaceutical properties are discovered in development, the cost of bringing a potent, but poorly absorbable molecule to the product stage by formulation can become very high. Fast and reliable *in vitro* prediction strategies are needed to filter out problematic molecules at the earliest stage of discovery. This communication will consider recent developments in physiochemical profiles used to identify molecules with physical properties related to good oral absorption. FDA's biopharmaceutical classification system (BCS) is an attempt to rationalize the critical components related to oral absorption and utilization of these principles for selection of a suitable technology to serve the interests of the early stages of drug discovery.

1. Introduction

The biopharmaceutics classification system (BCS) proposed by the FDA as a Bioavailability-Bioequivalence (BA/BE) regulatory guideline allows the estimation of three major factors: dissolution, solubility and intestinal permeability. The biopharmaceutical classification system is used for correlating *in vitro* drug dissolution and *in vivo* bioavailability recognizing that drug dissolution and gastro intestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. The core idea in BCS is an *in vitro* transport model, centrally embracing permeability and solubility, with qualifications related to pH and dissolution. In principle the framework of the BCS could serve the interests of the early stages of discovery research. The BCS can be rationalized by considering Fick's first law, applied to membranes. When molecules are introduced on one side of a lipid membrane barrier and no such molecules are on the other side, passive diffusion will drive the molecules across the membrane. When a certain simplifying assumption is made, the flux equation in Fick's law reduces simply to a product of permeability and solubility. Many other measurable properties are closely related to permeability and solubility. Permeability is a kinetic parameter related to lipophilicity (as indicated by partition and distribution coefficient, log P and log D) relation of lipophilic molecules by the membrane (which is related to lipophilicity and may predict pharmacokinetic volumes of distribution) influence the characterization of permeability. The unstirred water on both sides of the membrane barrier can impose limits on permeability. Solubility is a thermodynamic property, and is closely related to dissolution (Dressman et al. 2001; Löbenberg and Amidon 2000). The

analysis uses a transport model and human permeability results for estimating *in vivo* drug absorption to illustrate the primary importance of solubility and permeability on drug absorption.

2. Need for BCS

The most widely applied dissolution test methods for products are based on the USP's apparatus I (basket) or II (paddle) at agitation rates of 100 and 50 rpm, respectively. Typically 900 ml of aqueous dissolution media are used. Historical data suggests that *in vitro* dissolution methods are generally sensitive to formulation factors that affect drug dissolution process and often it is observed that two products that exhibit some dissolution differences, *in vitro*, may provide similar drug concentration time profiles in blood. These observations suggest that for many products, dissolution *in vivo* may not be the rate-limiting process. The observed variability in blood level profiles may be due to variability in the physiological processes and not due to minor dissolution differences in products being tested (Waterbeemd 1998). Possible causes for such differences may include; 1) inappropriate specification (dissolution test conditions, primarily media composition, and acceptance criteria), (2) presence of an excipient that may alter drug absorption. Experience gained through development of traditional *in vitro* – *in vivo* correlations (e.g., level A, B, or C correlations) for IR products containing poorly soluble drugs and for extended release products suggests a significant degree of formulation dependency or specificity associated with such correlations. Therefore, for products that are likely to exhibit slow *in vivo* dissolu-

tion, *in vitro* – *in vivo* correlations need to be established and their predictive performance verified through experimentation. Future research in this area should address how to *a priori* identify dissolution test conditions that yield robust *in vitro* – *in vivo* correlations that are applicable to a wide range of formulations (Dressman et al. 2000). If the regulatory utility of dissolution tests for immediate release products are to be expanded, their reliability must be improved by considering the mechanistic relationships between drug dissolution, physicochemical characteristics of drugs, gastrointestinal physiology and absorption or permeation processes. To this effect BCS provides, with minimal reliance on *in vivo* pharmacokinetic data, a rational mechanistic frame work for developing reliable dissolution tests for assessing bioequivalence. The BCS also provides a means for identifying when dissolution *in vivo* is likely or not likely to be rate-limiting and allows for managing risks associated with reliance on *in vitro* dissolution for bioequivalence assessment.

3. Biopharmaceutical drug classes

- 1. Class 1: High solubility-high permeability drugs
- 2. Class 2: Low solubility-high permeability drugs
- 3. Class 3: High solubility-low permeability drugs
- 4. Class 4: Low solubility-low permeability drugs

Based on this classification (Table 1), suggestions are made for setting standards for *in vitro* drug dissolution testing methodology which will correlate with the *in vivo* process. This methodology must be based on the physiological and physicochemical properties controlling drug absorption. The analysis points out conditions that will have no IVIV correlation (Table 2). The fundamental starting point for analysis is

$$J_w = P_w C_w \tag{Eq. 1}$$

where

$J_w (X_1 Y_1 Z_1 t)$ is the flux (mass/area/time) through the intestinal wall at any position and time,
 $P_w (X_1 Y_1 Z_1 t)$ is the permeability of this (complex) membrane,
 $C_w (X_1 Y_1 Z_1 t)$ is the drug concentration at the membrane (intestinal) surface.

Table 1: Biopharmaceutical classification system

	High solubility	Low solubility
High permeability	Class-1 (Amphiphilic)	Class-2 (Lipophilic)
	Diltiazem	Flurbiprofen
	Labetolol	Naproxen
	Captopril	Diclofenac
	Enalapril	Piroxicam
	Metoprolol	Carbamazepine
	Proranolol	Phenytoin
	Phenylalanine	Verapamil
	Antipyrin 1	Ketoprofen 2
	Glucose	Desipramine
Low permeability	L-Dopa	Itraconazole
	Class-3 (Hydrophilic)	Class-4
	Famotidine	Terfenadine
	Cimetidine	Furosemide
	Ranitidine	Cyclosporine
	Hydrochlorothiazide	
	Atenolol	
	Acyclovir 3	4
	Nadolol	

Table 2: *In vitro-in vivo* correlation (IVIVC) expectation for immediate release products based on biopharmaceutical class

Class	Solubility	Permeability	IVIVC Expectation
I	High	High	IVIV correlation if dissolution rate is lower than the gastric emptying rate, otherwise limited or no correlation.
II	Low	High	IVIV correlation expected if the <i>in vitro</i> dissolution rate is similar to the <i>in vivo</i> dissolution rate, unless the dose is very high.
III	High	Low	Absorption (permeability) is rate determining and limiting
IV	Low	Low	Limited or no IVIV correlation expected

This is the Fick’s law applied to membrane and applied to each point along the membrane. It is assumed that sink condition (drug concentration equals zero) exists for the drug inside this complex membrane and that P_w is an effective permeability (Shah et al. 1995). Using molecular size and hydrogen bonding, a fresh view can be taken on the BCS, providing a better insight into its physiochemical meaning (Avdeef 2001). High molecular weight and low polar surface area result in poorly soluble and poorly permeable compounds (class-4). Compounds with high polar surface area and high hydrogen bonding capacity are poorly absorbed despite of favorable solubility (class-3). Compounds with a low molecular weight i.e. below 200, are capable by using the para cellular route for absorption. This potentially make them well absorbed (class-1) but exception need to be better understood. Most drugs fall in the group of well absorbed, but often poorly soluble compounds. So for both properties, permeability and solubility, it appears that molecular size and hydrogen bonding play a major role. Thus, these should be considered as the true fundamental properties (Fig. 1).

3.1. Class-1 system

For many drugs, neither solubility nor permeability is limiting within the target regions of the gastrointestinal tract appropriate to the desired input function. Thus the major challenge from a drug delivery perspective for this category of drugs is to achieve the target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile presented in Fig. 2. Clearly the vast majority of currently available and marketed oral controlled release products fall into this classification. Formu-

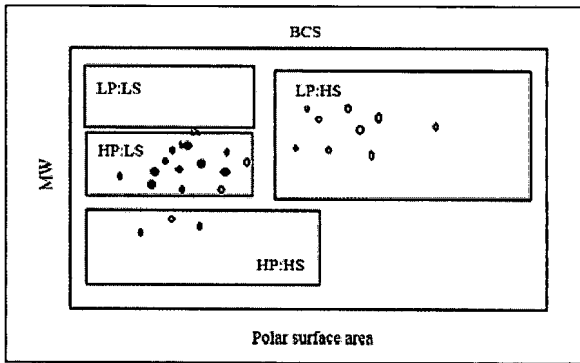


Fig. 1: The BCS projected on a molecular size/H-bonding plot. Tentatively rounded rectangles are drawn to locate the four BCS classes

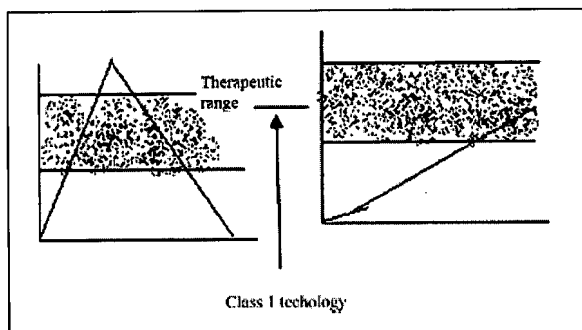


Fig. 2: Solubility and permeability are not limiting for class I drugs, the goal is to change drug exposure

lation approaches include both control of release rate and also certain physicochemical properties of drug, such as dependence of solubility.

Although there are no fundamental solubility or permeability limitations for drugs in this category there are a number of solubility/permeability considerations, particularly in the context of controlled release dosage form development. These considerations include:

- The appropriate choice of *in vitro* dissolution conditions to best match the physicochemical properties of the drug and drug delivery to the technology being employed.
- An understanding of the *in vivo* transit and integrity of the dosage form within the GI tract, including different conditions such as fasted or fed states.
- The regional permeability characteristic and other associated limitation to absorption, such as transporter system (e.g. the P-glycoprotein system) and metabolism system such as cytochrome (Cyt) P-450 system and more particularly the CYP-3A4 system.

3.1.1. Multiunit technologies

Nanotechnology approaches to improve the solubility of hydrophobic drugs

Nanozome Nanocrystal technology (Elan Corporation, Ireland) reduces a drug to extremely small particles (< 400 nm in diameter) using a specialized milling technique. A suspension of the insoluble drug in a stabilizing solution, consisting of GRAS stabilizers and other excipients, is used for the milling process to prevent aggregation of the resulting nanoparticles and also serves to increase the dissolution rate of the nanoparticles by acting as a

surfactant within the GI tract. Additionally, Nano-Crystal technology serves as a platform for targeting drugs to specific anatomical sites or to control delivery over time. Once the nanocrystal form of the insoluble drug has been transformed into a physically more stable form, it can be incorporated into other drug delivery systems such as oral controlled-release or highly concentrated parenteral solutions. Recently, Elan obtained marketing approval from FDA for a tablet form of American Home Products Corporation's drug Rapamune, which represents the first approval for a drug presentation containing Nanocrystal technology. Rapamune is indicated for the prevention of organ rejection in kidney transplant patients, and the new tablet provides easier administration and storage than the currently marketed Rapamune oral solution (Verma et al. 2001).

Nanoparticulate technologies

NanoCrystal (Elan, US): NanoCrystal drug particles (< 1,000 nm) produced by wet-milling and stabilised against agglomeration through surface adsorption of stabilisers; applied to NMEs eg aprepitant/reformulation of existing drugs eg sirolimus.

Biorise (Eurand, Dayton): Nanocrystals/amorphous drug produced by physical breakdown of the crystal lattice and stabilised with biocompatible carriers (swellable microparticles or cyclodextrins).

IDD (SkyePharma, England): Insoluble Drug Delivery: micro-nm particulate/droplet water-insoluble drug core stabilised by phospholipids; formulations are produced by high shear cavitation or impaction.

CAP (BioSante, Illinois): Calcium Phosphate-based nanoparticles: for improved oral bioavailability of hormones/proteins such as insulin; also as vaccine adjuvants.

NAB (American Bioscience, US): Nanoparticle Albumin-Bound technology: injectable suspension of biocompatible protein with drug improves solubility/removes need for toxic solvents; e.g. paclitaxel-albumin nanoparticles.

Nanoedge (Baxter, US): Nanoedge technology: drug particle size reduction to nanorange by platforms including direct homogenisation, microprecipitation, lipid emulsions and other dispersed-phase technology.

Nanostructuring technologies

BioSilicon (pSivida, UK): Drug particles are structured within the nano-width pores of biocompatible BioSilicon microparticles, membranes or fibres; gives controlled release/improves solubility of hydrophobic drugs.

NanoGate (iMEDD Burlingame): Silicon membrane with nano-width pores (10–100 nm) used as part of an implantable system for drug delivery and biofiltration.

NLC8 (PharmaSol, Easton, MA): Nanostructured Lipid Carriers: nanostructured lipid particle dispersions with solid contents produced by high-pressure homogenisation; lipid-drug conjugate nanoparticles provide high-loading capacity for hydrophilic drugs for oral delivery (Saffie-Siebert et al. 2005).

Beodas or Bioerodable Enhanced Oral Drug Absorption System (Elan Corporation, Ireland) is an oral microparticulate drug delivery technology designed for the delivery of macromolecules and is based on the entrapment of ac-

Table 3: Technologies for class I drugs

Technology	Description	Size range
Multi unit		
NANOZOMS	Micron/submicron particles	0.5–5 µm
BEODAS	Small microparticles	5.0–10 µm
PHARMAZOME	Microparticles	10–500 µm
SODAS	Coated beads in a capsule	0.5–2 µm
IPDAS	Compressed coated beads in a rapidly disintegrating tablet	0.5–2 µm
PRODAS	Miniature tablets in a capsule	2–4 mm
Single monolithic		
MXDAS	Erodible matrix tablet	6–30 mm
DUREDAS	Erodible multilayer tablet	6–30 mm
MODAS	Non disintegrating coated	6–30 mm

tive pharmaceutical entities in a range of submicron sizes within biodegradable polymer matrices. Further modifications to the BEODAS platform technology have the potential for targeted delivery and enhanced absorption of pharmaceutical entities that normally are not amenable to oral administration (Verma and Garg 2001).

Pharmzomes or Microparticulate Drug Delivery Technology (Elan Corporation, Ireland) consists of combinations of polymers and drugs in the size range of 5 to 125 μm . Each microparticle is a micromatrix of drug embedded uniformly throughout an insoluble polymer and is produced by either a spray drying or emulsion technique. By varying the amount and nature of the polymer used to form the micro particle, this technology allows controlled- and/or delayed-release of drug from the formulation. In addition, this technology also can be used for taste masking because it acts as a means of physically preventing a drug from going into solution in the mouth and coming into direct contact with taste receptors. For the purpose of palatability, 125 mm is set as the upper limit for Pharmazomes because these particles have a gritty feeling that may be unacceptable to consumers. Pharmazomes can be subsequently incorporated into a variety of delivery systems like chewable tablets, effervescent tablets, and oral ready-made aqueous and non-aqueous suspensions, reconstituable powders, and unitdose sachet or sprinkle systems. Products using Pharmazome technology are currently approved in Japan, Europe, and Central and South America and include twice-daily theophylline.

Sodas or Spheroidal Oral Drug Absorption System (Elan Corporation, Ireland) is a multiparticulate drug-delivery technology and consists of controlled-release beads that can be produced in the range from 1 to 2 mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores within the outer membrane. Fluid then enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the *in vivo* dissolution and absorption phases. The immediate environment of the drug within the seed core can be manipulated by use of excipients to ensure optimal stability and solubility. These controlled-release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form. Products utilizing SODAS technology are approved and marketed throughout Europe, the US, and Japan and include once-daily diltiazem and once-daily verapamil.

Benefits of SODAS: The maintenance of angina control was assessed in a multicenter (three sites), randomized, double-blind, parallel-group study. Patients with stable angina pectoris receiving twice-daily sustained-release (SR) diltiazem were switched to equivalent doses of once-daily controlled-delivery (CD) diltiazem or to diltiazem SR. Patients who were switched from diltiazem SR to diltiazem CD ($n = 28$) experienced a 5% increase in time to termination ($p = 0.0004$) on the exercise tolerance test (ETT), as well as an 8% improvement in time to onset of angina ($p < 0.0001$) on the ETT. A similar trend was observed in patients randomized to diltiazem SR ($n = 7$), which suggested a training effect, and, therefore, equal efficacy between diltiazem SR and diltiazem CD. During exercise

testing in the diltiazem SR baseline phase, 77% of the patients did not experience angina, whereas 60% of the patients did not experience ST-segment depression. Following transfer to diltiazem CD, 79 and 61% of patients, respectively, remained angina- and ST-segment depression free. No significant changes in the number of angina attacks, nitroglycerin use, or any hemodynamic-related parameters were observed following transfer to diltiazem CD. Eleven percent of the patients receiving diltiazem CD experienced treatment-related adverse events, which were limited to headache and abdominal pain; these adverse events did not lead to discontinuation of treatment. These findings suggest that patients whose angina is controlled with twice-daily diltiazem SR can be safely and effectively switched to an equivalent daily dose of the once-daily diltiazem CD (Savard et al. 1995).

IPDAS or Intestinal Protective Drug Absorption System (Elan Corporation, Ireland) is a multiparticulate tablet technology that has been developed to enhance the gastrointestinal tolerability of potentially irritant or ulcerogenic drugs. Unlike other tablet formulations, IPDAS is composed of numerous high-density controlled release beads. Each bead is manufactured by a two-step process that involves the initial production of a micromatrix of drug embedded in polymer and the subsequent coating of this micromatrix with time-release coatings that are transformed into a rate-limiting semipermeable membrane *in vivo*. After ingestion, the tablet rapidly disintegrates and beads are dispersed into the stomach and subsequently pass into the duodenum and along the GI tract in a controlled and gradual manner, independent of the feeding state. Drug release from each bead occurs by a diffusion process through the micromatrix and subsequently through the pores in the rate controlling semipermeable membrane. The intestinal protection of IPDAS is by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the GI tract. The controlled-release characteristics of the individual bead avoid the high concentrations of drug being released locally and absorbed systemically.

An immediate-release granulate also can be included in the tablet and may be required for a fast onset of action. IPDAS products are approved worldwide, and Elan's Naprelan product (once-daily naproxen sodium) is sold in the US market (Gaston. 1996).

Benefits of Elan's IPDAS® Technology:

- High density multiparticulate formulation,
- Intestinal protection from irritant drugs (eg NSAIDs),
- Advantages of multiparticulate in a tablet form,
- Controlled Release through process of diffusion,
- Fast onset if required.

IPDAS®, Intestinal Protective Drug Absorption System, was initially developed as part of the development process for Elan's proprietary naproxen formulation, Naprelan®. The objective was to develop a once daily controlled release system that would have a fast onset of action and reduced gastric irritancy. IPDAS® delivery system can also be employed to confer the advantages of multiparticulate technology, in a tablet dosage form. The IPDAS® technology is composed of numerous high density controlled release beads, which are compressed into a tablet form.

Once an IPDAS® tablet is ingested, it rapidly disintegrates and disperses beads containing a drug in the stomach, which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual

manner, independent of the feeding state. Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and/or the micromatrix of polymer/active ingredient formed in the extruded/spheronized multiparticulates. The intestinal protection of IPDAS® technology is by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract.

Naprelan®, which is marketed in the United States and Canada, employs the IPDAS® technology. This innovative formulation of naproxen sodium is a unique controlled release formulation indicated both for acute and chronic pain (Elan Corporation).

PRODAS®, Programmable Oral Drug Absorption System is a multiparticulate technology, which is unique in that it combines the benefits of tableting technology within a capsule. PRODAS is presented as a number of minitabets combined in a hard gelatin capsule. PRODAS is a very flexible technology, which can be used to pre-program the release rate of a drug. It is possible to incorporate many different minitabets, each one formulated individually and programmed to release drug at different sites within the gastro-intestinal tract. It is also possible to incorporate minitabets of different sizes so that high drug loading is possible. In its most basic form, PRODAS involves direct compression of an immediate release granulate to produce individual minitabets. These minitabets are subsequently packaged into hard gelatin capsules, which represent the final dosage form. A more beneficial use of the technology, however, is in the production of controlled release formulations. In this case the incorporation of various polymer combinations within the granulate delays the release rate of drug from each of the individual minitabets. These minitabets may subsequently be coated with controlled release polymer solutions to provide additional delayed release properties. PRODAS technology can achieve equivalent bioavailability to reference multiple dose product in a once daily formulation, show minimum peak to trough ratio at steady state, show minimal food impact and facilitate pulsed/programmed release to different sites in the GI tract. Additionally, PRODAS technology, by incorporating minitabets with different release rates, can display the characteristics of a number of different conventional dosage forms namely (i) immediate release component will mimic the conventional formulation ensuring that the once daily formulation is as fast acting; (ii) delayed release can provide site/regional release and food resistance and (iii) sustained release component provides additional controlled release/protection. A case study is reported to highlight the attributes of PRODAS technology:

In collaboration with a multi-national pharmaceutical firm Elan employed PRODAS technology to orchestrate precise control of an agent, which is conventionally dosed four times daily, to facilitate once daily dosing. Elan developed the controlled release dosage form despite a number of significant technical challenges, and a full dossier for regulatory submission was prepared. Typical equipment involved multi-tip tableting, tablet coating and multi-station capsule filling. PRODAS is an advanced technology with full scale-up and manufacturing capability available at Elan's Athlone site. However, due to the emergence of significant clinical implications with the drug itself, the commercial viability of the product was suddenly reduced, and the PRODAS formulation was not submitted for regu-

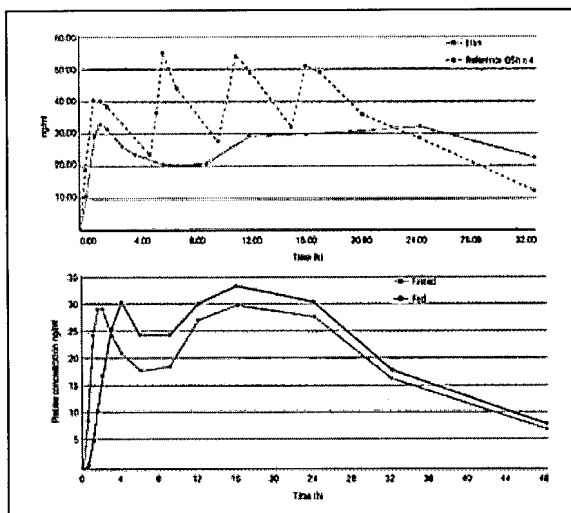


Fig. 3: PRODAS Technology, Sustained plasma profile, 3b. PRODAS Technology, Effect of food, Fed vs. Fasted state

latory approval. A number of biostudies were carried out over the course of the development work, which clearly illustrates the attributes of the PRODAS dosage form as evidenced from Figs. 3a and 3b that clearly demonstrate smooth sustained plasma levels, minimal effect of food on the plasma profile and predictability and reliability of the dosage form (Elan drug technology news). PRODAS is not affected by the presence of food in the GI tract. This is a patient friendly dosage form, leading to increased compliance as the dose can be administered irrespective of the fed or fasting state.

CODAS™ technology. In certain cases immediate release of drug is undesirable. A delay of drug action may be required for a variety of reasons. Chronotherapy is an example of when drug release may be programmed to occur after a prolonged interval following administration. Elan's drug delivery technology can be tailored to release drug after a predetermined delay. The CODAS drug delivery system enables a delayed onset of drug release, resulting in a drug release profile that more accurately compliments circadian patterns.

Elan's Verelan® PM represents a commercialized product using the CODAS technology. The Verelan PM formulation was designed to begin releasing Verapamil approximately four to five hours post ingestion. This delay in release is introduced by the level of release controlling polymer applied to the drug loaded beads. The release controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes in contact with the polymer coat beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug. When taken at bedtime, this controlled onset extended release delivery system enables a maximum plasma concentration of Verapamil in the morning hours, when blood pressure normally rises from its overnight low (Elan Corporation, case study).

The CODAS technology gives rise to attributes that directly benefit individual drugs:

- delivery profile designed to compliment the circadian pattern of blood pressure,

- controlled onset, extended release delivery system,
- rate of release essentially independent of pH, posture and food,
- “Sprinkle” dosing by opening the capsule and sprinkling the contents on food.

3.1.2. Single monolithic technologies

Duredas or Dual Release Drug Absorption System (Elan Corporation, Ireland) utilizes bilayer-tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredas technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate-release and controlled-release combinations of the two drugs are feasible.

Modas or Multiporous Oral Drug Absorption System (Elan Corporation, Ireland) is surrounded by a non-disintegrating, timed-release coating, which after coming in contact with gastrointestinal fluid is transformed into a semi-permeable membrane through which the drug diffuses in a rate-limiting manner (United State Patent: 6,174,873). The tablet consists of a core of active drug plus excipients. This is then coated with a solution of insoluble polymers and soluble excipients. After ingestion, the fluid of the gastrointestinal tract dissolves the soluble excipients in the outer coating leaving just the insoluble polymer, thereby forming a network of tiny, narrow channels connecting fluid from the GI tract to the inner drug core of water-soluble drug. This fluid passes through these channels into the core, dissolves the drug and a resultant solution of drug diffuse out in a controlled manner to the outside. The addition of excipients, such as buffers can help produce a microenvironment within the tablet that facilitates more predictable release rates and absorption. Examples of MODAS products developed by Elan include Bron-12 (a 12 hour multicomponent over-the-counter [OTC] cough and cold product) and once-daily potassium chloride.

Benefits of MODAS: The bioavailability of a new sustained-release potassium chloride (KCl) tablet, designed for once-a-day dosing, was compared to a KCl elixir using urinary excretion data. The study utilized 25 male volunteers dosed in a crossover design in a dietary/activity-controlled environment. The regimens consisted of a total of 80 mEq of potassium in three equally divided doses of elixir every 6 h and a single 80 mEq dose using four 20 mEq sustained-release (SR) tablets. The mean time to maximum rate of potassium urinary excretion was 2.2 h for the first elixir dose and 5.5 h after the SR tablet ($P < 0.01$), thereby supporting the prolonged-release

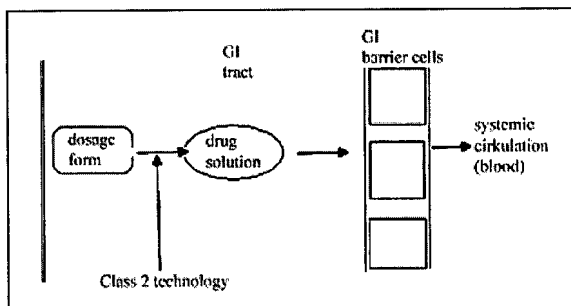


Fig. 4: Solubility/permeability considerations for class 2 drugs

properties of this formulation. After correction for baseline urinary potassium excretion, the mean total 24 h urinary potassium excretion was 42.18 mEq for the elixir and 40.41 mEq for the SR tablet. The results indicated that the absorption pattern from the SR tablet was equal to three doses of KCl elixir dosed 6 h apart (Betlach et al. 1987).

3.2. Class-2 system

This classification relates to the situation in which solubility or dissolution (in general or on a regional basis with in the GIT tract) is limiting and thus significantly affects absorption and bioavailability. Many distinct technology approaches are employed to address class-2 problems for immediate release dosage forms (Fig. 4). These approaches include classical micronisation, stabilization of high energy states (including lyophilized fast melt system) inclusion of surfactants, formulation as emulsion or micro-emulsion systems and use of complexing agents such as cyclodextrins. The problem in the context of extended release dosage forms relates not only to the primary formulation approach required to improve solubility properties but also to the incorporation of this approach in to a final dosage forms that provides for extended release and an associated pharmacokinetic profile. A number of approaches particularly those are not emulsion based, represent the opportunity for solid oral dosage form presentation and potentially manipulation and presentation as an extended release system (if permeability is not limiting).

Indas or Insoluble Drug Absorption System (Elan Corporation, Ireland) addresses the problem of poor solubility by manipulating the physicochemical characteristics of a drug to create a high-energy adsorbate that demonstrates enhanced solubility. This high-energy adsorbate is subsequently combined with Elan's other controlled absorption technologies to deliver the required plasma profile. The drug in question, usually crystalline in nature, is converted into an amorphous form by a combination of energy, excipients, and unique processing procedures. Once the drug is converted into the desirable physical form, an adsorption process utilizing a novel polymer cross-linked tech-

Table 4: Technologies for class 2 drugs

Technology	Description
INDAS	Stabilized, high energy form (crystallization to amorphous)
SODAS	Solid dispersion
EMDAS	Microemulsion
NANODAS	Stabilized, submicron size reduction

nology prevents recrystallization and stabilizes the resulting high-energy complex. The combination of the change in the physical state of the drug coupled with the solubilizing characteristics of the excipients employed ensures that the solubility of the active ingredient is enhanced. Nifelan, a once-daily nifedipine formulation, is based on this technology and is marketed in Europe and Southeast Asia.

Benefits of INDAS – Case study: Nifelan, a sustained-release formulation of nifedipine, is a new antihypertensive agent. However, its effect on peripheral vascular resistance and left ventricular mass is still controversial. The antihypertensive efficacy and safety of nifelan in 20 patients with mild to moderate essential hypertension was evaluated. After 2 weeks of a placebo-qualifying phase, the eligible patients were entered into an 8-week active treatment period in which nifelan was given 10–40 mg once-daily with gradual titration. Seventeen patients (8 men, 9 women; age range 43–72 years, mean 52 years) completed the entire study. The mean sitting systolic and diastolic blood pressures were significantly reduced ($p < 0.0001$) by 13.8 mmHg and 9.6 mmHg, respectively, with a mean nifelan dose of 27.1 ± 2.7 mg per day, while the heart rate remained unchanged (75.9 ± 1.3 vs. 73.6 ± 0.9 beats per minute, $p = \text{NS}$). Four patients (20%) reported side effects necessitating termination of nifelan treatment in 2 patients because of intolerance. One patient was found to be poorly compliant and withdrew prematurely from the study for unknown reasons without complaints of adverse effects. Echocardiographic left ventricular mass index was significantly reduced from 104.2 ± 4.6 g/m² to 96.6 ± 5.2 g/m² ($p < 0.05$), and the left ventricular diastolic function evaluated by E/A ratio showed a trend toward improvement from 0.97 ± 0.06 to 1.10 ± 0.07 ($p = 0.06$). Both forearm hemodynamic parameters showed favorable changes from baseline to the end of the study (forearm blood flow, 3.39 ± 0.28 vs. 4.04 ± 0.31 ml/100 ml/min, $p < 0.05$; forearm vascular resistance, 37.75 ± 4.95 vs. 28.73 ± 3.34 mmHg/ml/100 ml/min, $p < 0.05$). The lipid profiles followed trends toward favorable changes after treatment (high density lipoprotein, 51.8 ± 3.0 vs. 54.4 ± 3.3 mg/dl, $p = \text{NS}$; low density lipoprotein, 146.1 ± 8.8 vs. 139.9 ± 10.6 mg/dl, $p = \text{NS}$). Hematological and biochemical parameters did not change at the end of treatment. It was concluded that once-daily nifelan as monotherapy was safe and effective in Chinese patients with mild to moderate essential hypertension. Regression of left ventricular mass and reversal of unfavorable forearm hemodynamics were observed in these patients after short-term therapy (Chang et al. 1998).

3.3. Class-3 system

The principle barrier in class-3 system is the effective permeability of the GI tract to the target drug. These targets include the transcellular flux of drug, paracellular flux via opening of the tight junctions, promotion of carrier mediated transport via established transport system and/or inhibition of excretory P-glycoprotein mediated efflux system. In addition although it is not a barrier for transport, the presence of degradative enzyme system such as the CYP-3A4 system within the GI tract also represents a significant barrier that may be achieved by manipulating the site or rate of exposure or perhaps by incorporating functional agents in to the dosage form to modify the metabolic activity of these enzyme system. The class-3 system involves emerging technologies that attempt to address the fundamental limitation of absolute

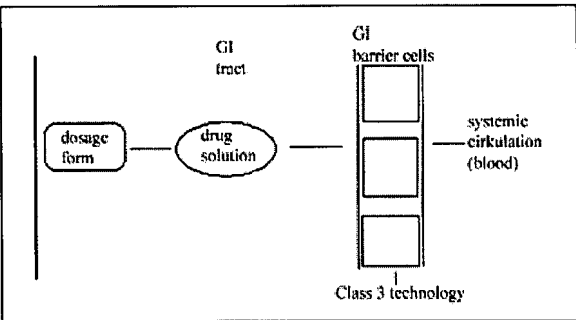


Fig. 5: Solubility/permeability considerations for class 3 drugs

or regional permeability (Fig. 5). Because of the nature of these biological systems the technology in turn represents more fundamental drug delivery approaches in terms of altering the biological system in a transient and specific manner. A broad range of technology is currently under investigation to achieve optimal bioavailability. It is clear that class-1 and/or class-2 technology, alone or combined are not adequate to address these fundamental limitation, so class-3 technologies are being developed. These technologies represent new systems that in many cases involve the development techniques and characterization in addition to the drug delivery aspects.

LOCNAS or Localized Drug Absorption System (Elan Corporation, Ireland) is a novel targeted oral drug delivery technology. This technology utilizes targeting ligands that specifically bind to certain absorption sites located on the apical surface of the epithelium cells of the human GI tract. These ligands are attached to coated microparticles of protein and peptide drugs that serve to protect their contents from the hostile environment of the GI tract. These are subsequently packaged in enteric-coated capsules that deposit the particles at appropriate sites of absorption within the GI tract, example particles for oral delivery of peptides and proteins (Grove 2007).

3.4. Class-4 system

Fortunately, class-4 compounds are the exception and are rarely developed or reach the market. Nonetheless a number of examples of class-4 drugs do exist. Taxol for example, is currently available only in an injectable form, and even then it requires the inclusion of significant solubility enhancing components (such as cremaphor) that have safety implications in the parenteral formulation. Solving class-4 drug delivery requirements will be achieved through a combination of class-2 and class-3 technologies. Class-4 drugs will benefit from the significant progress and improvements that already have been achieved in the other technology categories.

Table 5: Technologies for class 3 drugs

Technology	Description
VACDAS	Oral vaccine system; bio-degradable micron/submicron system; M-cell targeting/adjuvants
LOCNAS	GI receptor targeting and activation; biodegradable submicron particles targeted to GI receptors
PROMDAS	Novel absorption promoters
GRDAS	Gastro retentive system
Smart Pill	Device/dosage form system

4. Conclusion

It is obvious that BCS is a fundamental system in pharmaceutical sciences that gives an idea about solubility characters, which ultimately affect the bioavailability of a particular drug.

Numerous techniques have been developed to increase the solubility of drugs but in formulation of dosage forms, the BCS system is useful. This system proposed by FDA as a Bioavailability-Bioequivalence regulation basically helps to set the standards for *in vitro* drug dissolution testing methodology which ultimately arrows *in vivo* bioavailability and biological action of a drug.

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PHARMACEUTICAL DOSAGE FORMS

Tablets

SECOND EDITION, REVISED AND EXPANDED

In Three Volumes
VOLUME 1

EDITED BY

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Contents

Preface	iii
Contributors	xi
Contents of <i>Pharmaceutical Dosage Forms: Tablets, Second Edition</i> Volumes 2 and 3	xiii
Contents of <i>Pharmaceutical Dosage Forms: Parenteral Medications</i> , Volumes 1 and 2	xv
Contents of <i>Pharmaceutical Dosage Forms: Disperse Systems</i> , Volumes 1 and 2	xxx
 Chapter 1. Preformulation Testing	 1
Deodatt A. Wadke, Abu T. M. Serajuddin, and Harold Jacobson	
I. Introduction	1
II. Organoleptic Properties	2
III. Purity	3
IV. Particle Size, Shape, and Surface Area	5
V. Solubility	12
VI. Dissolution	18
VII. Parameters Affecting Absorption	24
VIII. Crystal Properties and Polymorphism	34
IX. Stability	42
X. Miscellaneous Properties	53
XI. Examples of Preformulation Studies	57
References	69
 Chapter 2. Tablet Formulation and Design	 75
Garnet E. Peck, George J. Baley, Vincent E. McCurdy, and Gilbert S. Banker	
I. Introduction	75
II. Preformulation Studies	77
III. A Systematic and Modern Approach to Tablet Product Design	79
IV. Tablet Components and Additives	88
V. Regulatory Requirements for Excipients in the United States	121
VI. References	128
	vii

Chapter 3. Compressed Tablets by Wet Granulation	131
<i>Fred J. Bandelin</i>	
I. Properties of Tablets	132
II. Formulation of Tablets	133
III. Tablet Manufacture	135
IV. Granulation	148
V. Excipients and Formulation	151
VI. Multilayer Tablets	179
VII. Prolonged Release Tablets	181
VIII. Manufacturing Problems	188
References	190
 Chapter 4. Compressed Tablets by Direct Compression	 195
<i>Ralph F. Shangraw</i>	
I. Introduction and History	195
II. Advantages and Disadvantages of the Wet Granulation Process	197
III. The Direct-Compression Process	198
IV. Direct-Compression Filler Binders	203
V. Factors in Formulation Development	214
VI. Morphology of Direct-Compression Fillers	220
VII. Coprocessed Active Ingredients	225
VIII. Modification and Integration of Direct-Compression and Granulation Processes	227
IX. Future of Direct-Compression Tableting	228
X. Formulations for Direct Compression	229
Glossary of Trade Names and Manufacturers	243
References	245
 Chapter 5. Compression-Coated and Layer Tablets	 247
<i>William C. Gunsel and Robert G. Dusel</i>	
I. Compression Coating	247
II. Formulations (Compression Coating)	260
III. Inlay Tablets	273
IV. Layer Tablets	274
V. Formulations (Layer)	278
References	284
 Chapter 6. Effervescent Tablets	 285
<i>Raymond Mohrle</i>	
I. Introduction	285
II. Raw Materials	286
III. Processing	294
IV. Manufacturing Operations	300
V. Tablet Evaluation	302

It is the oldest and most conventional method of making tablets. Although it is the most labor-intensive and most expensive of the available methods, it persists because of its versatility. The possibility of moistening powders with a variety of liquids, which can also act as carriers for certain ingredients, thereby enhancing the granulation characteristics, has many advantages. Granulation by dry compaction has many limitations. It does not lend itself to all tablet formulations because it depends on the bonding properties of dry powders added as a carrier to the drug thereby increasing the size of the tablet. In wet granulation, the bonding properties of the liquid binders available is usually sufficient to produce bonding with a minimum of additives.

The phenomena of adhesion and cohesion may be defined as follows: adhesion is the bonding of unlike materials, while cohesion is that of like materials. Rumpf [28] identified mechanisms by which mechanical links are formed between particles. The following are involved in the bonding process:

1. Formation of crystalline bridges by binders during drying
2. Structures formed by the hardening of binders in drying
3. Crushing and bonding of particles during compaction

Wet granulation is a versatile process and its application in tablet formulation is unlimited.

B. Advantages of Wet Granulation

1. The cohesiveness and compressibility of powders is improved due to the added binder that coats the individual powder particles, causing them to adhere to each other so they can be formed into agglomerates called granules. By this method, properties of the formulation components are modified to overcome their tableting deficiencies. During the compaction process, granules are fractured exposing fresh powder surfaces, which also improves their compressibility. Lower pressures are therefore needed to compress tablets resulting in improvements in tooling life and decreased machine wear.
2. Drugs having a high dosage and poor flow and/or compressibility must be granulated by the wet method to obtain suitable flow and cohesion for compression. In this case, the proportion of the binder required to impart adequate compressibility and flow is much less than that of the dry binder needed to produce a tablet-by-direct compression.
3. Good distribution and uniform content for soluble, low-dosage drugs and color additives are obtained if these are dissolved in the binder solution. This represents a distinct advantage over direct compression where the content uniformity of drugs and uniform color dispersion can be a problem.
4. A wide variety of powders can be processed together in a single batch and in so doing, their individual physical characteristics are altered to facilitate tableting.
5. Bulky and dusty powders can be handled without producing a great deal of dust and airborne contamination.

6. Wet granulation prevents segregation of components of a homogeneous powder mixture during processing, transferring, and handling. In effect, the composition of each granule becomes fixed and remains the same as that of the powder mixture at the time of the wetting.
7. The dissolution rate of an insoluble drug may be improved by wet granulation with the proper choice of solvent and binder.
8. Controlled release dosage forms can be accomplished by the selection of a suitable binder and solvent.

C. Limitations of Wet Granulation

The greatest disadvantage of wet granulation is its cost because of the space, time, and equipment involved. The process is labor-intensive as indicated by the following.

1. Because of the large number of processing steps, it requires a large area with temperature and humidity control.
2. It requires a number of pieces of expensive equipment.
3. It is time consuming, especially the wetting and drying steps.
4. There is a possibility of material loss during processing due to the transfer of material from one unit operation to another.
5. There is a greater possibility of cross-contamination than with the direct-compression method.
6. It presents material transfer problems involving the processing of sticky masses.
7. It can slow the dissolution of drugs from inside granules after tablet disintegration if not properly formulated and processed.

A recent innovation in wet granulating, which reduces the time and energy requirements by eliminating the drying step, is the melt process. This method relies on the use of solids having a low softening or melting point which, when mixed with a powder formulation and heated, liquefy to act as binders [29,30]. Upon cooling, the mixture forms a solid mass in which the powders are bound together by the binder returning to the solid state. The mass is then broken and reduced to granules and compressed into tablets. Materials used as binders are polyethylene glycol 4000 and polyethylene glycol 6000 [31-33], stearic acid [30], and various waxes [34,35].

The amount of binder required is greater than for conventional liquid binders (i.e., 20 to 30% of the starting material).

Another advantage of the method is that the waxy materials also act as lubricants, although in some cases additional lubricant is required.

A new variation of the granulating process known as "moisture-activated dry granulation" [36] combines the efficiency of dry blending with the advantages of wet granulation. As little as 3% water produces agglomeration. The process requires no drying step because any free water is absorbed by the excipients used. After granulation, disintegrant and lubricant are added and the granulation is ready for compression.

The complex nature of wet granulation is still not well understood, which accounts for the continuing interest in research on the process. One significant problem is the degree of wetting or massing of the powders. Wetting plays an exceedingly important roll in the compression characteristics

Anexo 6.4

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Contents

Preface	iii
Contributors	xi
Contents of <i>Pharmaceutical Dosage Forms: Tablets, Second Edition</i> Volumes 2 and 3	xiii
Contents of <i>Pharmaceutical Dosage Forms: Parenteral Medications</i> , Volumes 1 and 2	xv
Contents of <i>Pharmaceutical Dosage Forms: Disperse Systems</i> , Volumes 1 and 2	xxx
 Chapter 1. Preformulation Testing	 1
Deodatt A. Wadke, Abu T. M. Serajuddin, and Harold Jacobson	
I. Introduction	1
II. Organoleptic Properties	2
III. Purity	3
IV. Particle Size, Shape, and Surface Area	5
V. Solubility	12
VI. Dissolution	18
VII. Parameters Affecting Absorption	24
VIII. Crystal Properties and Polymorphism	34
IX. Stability	42
X. Miscellaneous Properties	53
XI. Examples of Preformulation Studies	57
References	69
 Chapter 2. Tablet Formulation and Design	 75
Garnet E. Peck, George J. Baley, Vincent E. McCurdy, and Gilbert S. Banker	
I. Introduction	75
II. Preformulation Studies	77
III. A Systematic and Modern Approach to Tablet Product Design	79
IV. Tablet Components and Additives	88
V. Regulatory Requirements for Excipients in the United States	121
VI. References	128
	vii

Chapter 3. Compressed Tablets by Wet Granulation	131
<i>Fred J. Bandelin</i>	
I. Properties of Tablets	132
II. Formulation of Tablets	133
III. Tablet Manufacture	135
IV. Granulation	148
V. Excipients and Formulation	151
VI. Multilayer Tablets	179
VII. Prolonged Release Tablets	181
VIII. Manufacturing Problems	188
References	190
Chapter 4. Compressed Tablets by Direct Compression	195
<i>Ralph F. Shangraw</i>	
I. Introduction and History	195
II. Advantages and Disadvantages of the Wet Granulation Process	197
III. The Direct-Compression Process	198
IV. Direct-Compression Filler Binders	203
V. Factors in Formulation Development	214
VI. Morphology of Direct-Compression Fillers	220
VII. Coprocessed Active Ingredients	225
VIII. Modification and Integration of Direct-Compression and Granulation Processes	227
IX. Future of Direct-Compression Tableting	228
X. Formulations for Direct Compression	229
Glossary of Trade Names and Manufacturers	243
References	245
Chapter 5. Compression-Coated and Layer Tablets	247
<i>William C. Gunsel and Robert G. Dusel</i>	
I. Compression Coating	247
II. Formulations (Compression Coating)	260
III. Inlay Tablets	273
IV. Layer Tablets	274
V. Formulations (Layer)	278
References	284
Chapter 6. Effervescent Tablets	285
<i>Raymond Mohrle</i>	
I. Introduction	285
II. Raw Materials	286
III. Processing	294
IV. Manufacturing Operations	300
V. Tablet Evaluation	302

Table 1 Comparison of Direct-Compression and Wet Granulation Processes for Making Tablets

Wet granulation	Direct Compression
<u>Compressibility</u>	
Harder tablets for poorly compressible substances	Potential problem for high-dose drugs
<u>Fluidity</u>	
Excellent in most cases	Many formulations may require a glidant Cannot micronize high-dose drugs
<u>Particle Size</u>	
Larger with greater range	Lower with narrower range
<u>Content Uniformity</u>	
Massing and drying induced	Segregation may occur in mass transport, hopper, and feed frame
<u>Mixing</u>	
High or low shear	Low shear with ordered blending
<u>Lubricant</u>	
Less sensitive to lubricant softening and overblending	Minimal blending with magnesium stearate
<u>Disintegration</u>	
Often problems with granules	Lower levels usually necessary
<u>Dissolution</u>	
1. Drug wetted during processing	1. No wetting, may need surface active agent
2. Drug dissolution from granules may be a problem	2. Dissolution may be slower if larger size drug crystals used
3. Generally slower than direct compression	3. Generally faster than wet granulation
<u>Costs</u>	
Increase in equipment, labor, time, process validation, energy	Increase in raw materials and their quality control

Table 1 (Continued)

Wet granulation	Direct compression
<u>Flexibility of Formulation</u>	
Granulation covers raw material flaws	Properties of raw materials must be carefully defined
<u>Stability</u>	
1. Problems with heat or moisture	1. No heat or moisture added
2. Dissolution rate may decrease with time	2. Dissolution rate rarely changes
<u>Attitude of Equipment Suppliers</u>	
Positive	Very negative
<u>Tableting Speed</u>	
May be faster	May require lower speed
<u>Dust</u>	
Less dusty	More dusty
<u>Color</u>	
Deep or pastel (dyes or lakes)	Pastel only (lakes only)

IV. DIRECT-COMPRESSION FILLER BINDERS

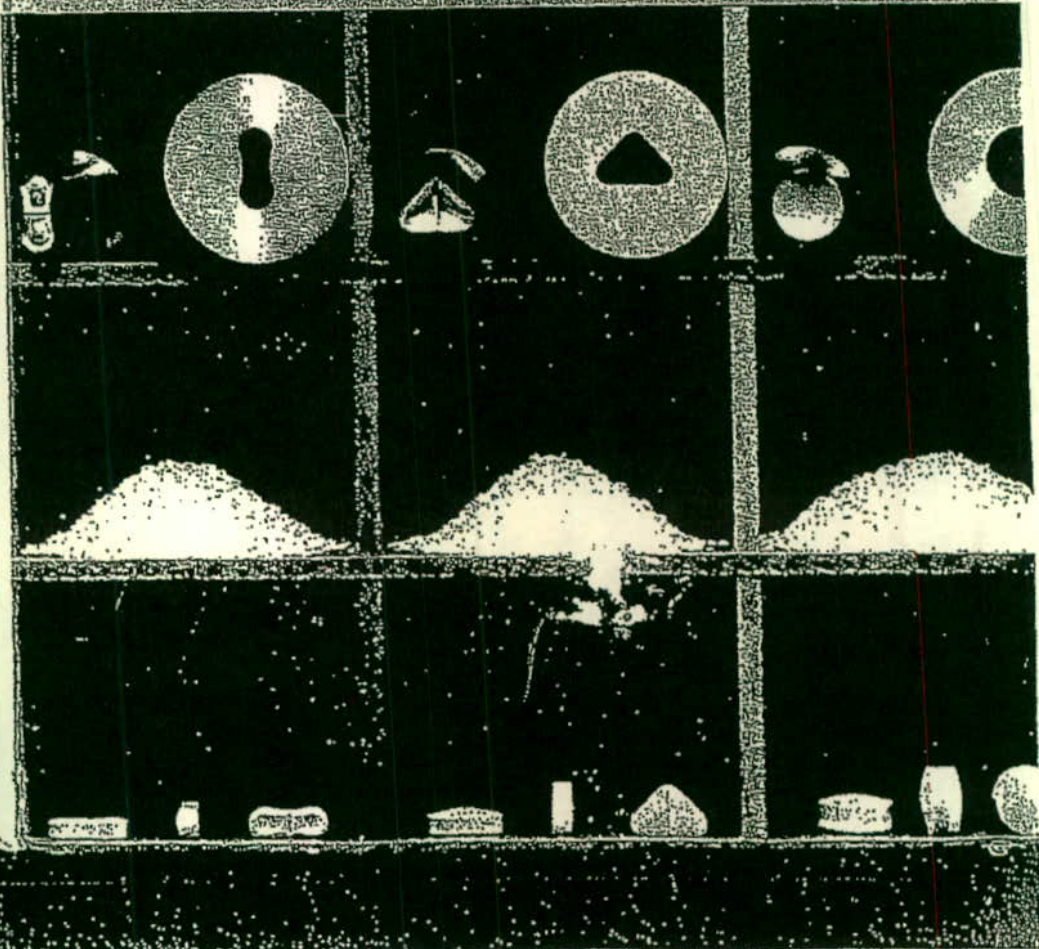
A. General Considerations

Direct-compression excipients, particularly filler-binders, are specialty excipients. In most cases they are common materials that have been modified in the chemical manufacturing process to impart to them greater fluidity and compressibility. The physical and chemical properties of these specialty products are extremely important if they are to perform optimally. It is most important for the direct-compression formulator to understand that there is no chance to cover up flaws in raw materials in direct compression as there is in the wet granulation process.

Many factors influence the choice of the optimum direct-compression filler to be used in a tablet formulation. These factors vary from primary properties of powders (particle size, shape, bulk density, solubility) to characteristics needed for making compacts (flowability and compressibility) to factors affecting stability (moisture), to cost, availability, and governmental acceptability. It is extremely important that raw material specifications be set up that reflect many of these properties if batch-to-batch

Pharmaceutical Dosage Forms: Tablets Volume 1

Edited by Herbert A. Lieberman
and Leon Lachman



PHARMACEUTICAL DOSAGE FORMS

Tablets

In Three Volumes

VOLUME 1

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Contents

Preface	iii
Contributors to Volume 1	ix
Contents of Volume 2	xi
Contents of Volume 3	xiii
1. Preformulation Testing	1
Deodatt A. Wadke and Harold Jacobson	
I. Organoleptic Properties	2
II. Purity	3
III. Particle Size, Shape, and Surface Area	3
IV. Solubility	10
V. Dissolution	14
VI. Parameters Affecting Absorption	18
VII. Crystal Properties and Polymorphism	26
VIII. Stability	34
IX. Miscellaneous Properties	44
X. Examples of Preformulation Studies	46
References	56
2. Tablet Formulation and Design	61
Gilbert S. Banker, Garnet E. Peck, and George Baley	
I. Preformulation Studies	63
II. A Systematic Approach to Tablet Product Design	64
III. Tablet Components and Additives	68
IV. Regulatory Requirements for Excipients in the United States	98
References	105

Compressed Tablets

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Compressed tablets are solid dosage forms prepared by compaction of a formulation containing the drug and certain excipients selected to aid the processing and improve the properties of the product. The term compressed tablet generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression. Tablets can be made in many sizes and shapes, with a variety of properties. Tablets are the most widely used of all pharmaceutical dosage forms for a number of reasons. They are convenient, easy to use, and less expensive to manufacture than other oral dosage forms. They deliver the intended dose with a high degree of accuracy.

A number of different types of tablets have been developed for special application. Buccal tablets are designed to dissolve slowly in the buccal pouch. Sublingual tablets are designed to dissolve rapidly beneath the tongue. Chewable tablets are compressed tablets designed to be chewed rather than swallowed; the widely used antacid tablets and some vitamin tablets are of this type. Effervescent tablets are formulated to dissolve with effervescence due to the reaction of citric acid with sodium bicarbonate, or some other effervescent combination in the formulation, when the tablet is placed in water. Certain tablets are made by multiple compression. These include the layer tablets, generally with two layers, but sometimes with three layers. These tablets are designed to enable the separation of incompatible ingredients, to make sustained-release products, or merely for appearance. A compressed coated tablet is prepared by the compression of a tablet within a tablet. As many as two coats can be compressed around a core. Sugar-coated tablets are compressed tablets with sugar coating applied to the tablet. The coating color

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and thickness can vary. Film-coated tablets are compressed tablets with a film coat applied to the tablet. Film coating is the most desirable approach for preparing coated tablets as it is the most economical and involves minimum exposure of the tablet to heat and solvent. When it is desired to prevent the tablet from disintegrating in the stomach, an enteric-coated tablet is prepared. The coating material in this case is insoluble in the acidic environment of the stomach, but readily dissolves in the intestines. Sustained-release tablets are compressed tablets made of a special formulation designed to release the drug over a long period of time. The technology of making special tablets is an extension of the basic technology of the manufacture of compressed tablets. These various special types of tablets are covered in depth in other chapters of this volume. In the sections that follow, reference to equipment and materials will frequently be made by trade name. The description and sources of materials are listed at the end of the volume.

I. Methods of Manufacture

Tablets are made by compressing a formulation containing a drug or drugs and excipients on a tablet press. The basic functional unit of the tablet press is a set of tooling consisting of a die and an upper and lower punch. The tablet press is designed to have a hopper for holding and feeding the granulation, a feeding mechanism for feeding the granulation to the die cavity, provision for placement of punches in the dies, and cam tracks for guiding the movement of punches. Tablet presses are of two basic types, the single-station or single-punch press and the multistation rotary press. The schematic of the tablet compression process on a single-punch press is shown in Figure 1. The first stage is the filling cycle during which the lower

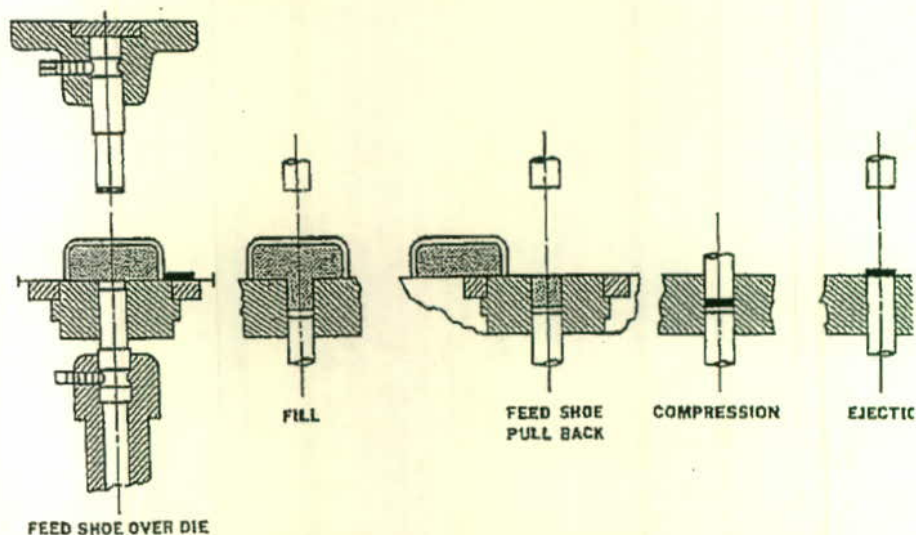


Figure 1. Schematic diagram of the compression process in a single-punch tablet press (Courtesy, Vector Corporation, Hiawatha, Iowa.)

Compressed Tablets

punch is lowered to a preset point to form a cavity in the die to provide a volume corresponding to the correct fill weight for the tablet. Next the feed shoe is pulled out of the way, and the upper punch descends into the die to compress the tablet. Then the lower punch is raised flush with the surface of the die table so that the feed shoe can eject the tablet as it comes over the die for another fill cycle.

Tablet presses operate at production rates ranging from a few to a few thousand tablets per minute. Hence, a tablet formulation must first be prepared in a form suitable for compression on a tablet press. This process is referred to as the preparation of a granulation or, simply, granulation. The resulting product is called the tablet granulation or again, simply, the granulation.

A granulation must have good flow properties for precise volumetric feeding of the material to the die cavity, compressibility to form the compact, and lubricant properties for ejection of the tablet. The methods used for preparing tablet granulations are wet and dry granulation and direct compression. The sequential steps in the manufacture of tablets by each of these processes is shown in Table 1. The first step in each method is to prepare a mixture of the drug and some or all of the excipients, depending upon the method. The wet and dry granulation processes are designed to improve the flow and compressibility of powders that would otherwise be unsuitable for making tablets. When the formulation can be designed to have satisfactory flow and compressibility, the ingredients are mixed and directly compressed into tablets. This latter process is referred to as direct compression.

Each method has its advantages and disadvantages, specific applications, and restrictions. The choice of methods depends upon a number of factors, the most important being the properties and the dose of the drug. Other factors include the choice of available equipment and relevant practical and regulatory concerns. Direct compression is the simplest method and should be evaluated for new products where its use may be feasible. Wet granulation is the most widely used method. The application of the dry granulation method is limited to situations where neither wet granulation nor direct compression can be used.

A Properties of Tablets

Whatever method of manufacture is used, the resulting tablets must have satisfactory properties. The attributes of a good tablet are as follows:

1. The tablet must be sufficiently strong and resistant to abrasion to withstand handling during manufacture, packaging, shipping, and use. This property is measured by two tests, the hardness test and the friability test.
2. The drug in the tablet must be bioavailable. This property is monitored by two tests, the disintegration test and the dissolution test. However, the bioavailability of a drug from a tablet or other dosage form is a very complex problem, and the results of these two tests do not of themselves provide an index of bioavailability.
3. The tablets must be uniform in weight and in the drug content of individual tablets. This is measured by the weight variation test and the content uniformity test.
4. The tablets must be elegant in appearance and must have the characteristic color, shape, and other markings that identify the product. The marking is usually a monogram of the manufacturer. Many tablets also have the National

Table 1
Steps in the Different Methods of Tablet Manufacture

Wet granulation	Dry granulation	Direct compression
1. Milling of drugs and excipients	1. Milling of drugs and excipients	1. Milling of drugs and excipients
2. Mixing of milled powders	2. Mixing of milled powders	2. Mixing of ingredients
3. Preparation of binder solution	3. Compression into large, hard tablets, to make slugs	3. Tablet compression
4. Mixing of binder solution with powder mixture to form wet mass	4. Screening of slugs	
5. Coarse screening of wet mass using 6 to 12 mesh screen	5. Mixing with lubricant and disintegrating agent	
6. Drying of moist granules	6. Tablet compression	
7. Screening of dry granules through 14 to 20 mesh screen		
8. Mixing of screened granules with lubricant and disintegrant		
9. Tablet compression		

Sheth, Bhandari, and Shengraw

Compressed Tablets

- Drug Code number corresponding to the listing of the product in the National Drug Code of the U. S. Food and Drug Administration. Another marking that may appear on some tablets is a score. It is intended to permit the breaking of tablets into two equal parts for the administration of half a tablet; however, it has been shown that substantial variation in drug dose can occur in the administration of tablets manually broken.
5. The tablets must retain all of the functional attributes, which include drug stability and efficacy.

B. Unit Processes

The properties of a tablet are affected by both the formulation and the method of manufacture, and between these two factors there is a high degree of interrelationship. A suitable formulation is critical to the manufacture of satisfactory tablets. However, the formulation must be designed according to the needs, advantages, and limitations of the manufacturing method and equipment used. The major unit processes involved in the manufacture of tablets are: solid-solid mixing, solid-liquid mixing, milling or size reduction, drying, and compaction. The selection of the formulation components and equipment is done to optimize the efficiency of the unit processes involved. Generally, it is necessary to use equipment already available in the manufacturing facility, and the formulation would need to be adapted to the available process and equipment. Certain other general considerations should also be noted. Since tablet manufacture involves the processing of powders, a high degree of control of the temperature and humidity of the work area is necessary. Normal air-conditioning can provide the needed environment in most cases. However, with some drug products, humidity may have to be controlled to lower levels than is feasible with standard air-conditioning equipment. There is also a high potential of cross-contamination between products in the processing of powders. Therefore, both the design of the area as well as the working procedures must be suitably designed for this purpose. Operators working in the area must be protected from the dust of potent drugs and other powders and from solvent vapors.

II. Wet Granulation

The preparation of granulations for tableting by wet granulation is the oldest method and still the most widely used. Before dry compaction became a viable process, wet granulation was—for all practical purposes—the only method available. However, it is laborious, involving considerable material handling; as well as several processing steps, and therefore it is costly. The method nevertheless continues to find extensive application for a number of reasons. One reason is that, because of its universal use in the past, the method persists with established products and with new products where—for one reason or another—it cannot be replaced by direct compression methods. Although a number of these products could now be made by direct compression, to do so would require a change in ingredients or, at a minimum, a change to new forms of previously used excipients. A change of this nature would be considered a major modification requiring a careful review to evaluate the need for additional studies of product stability, safety, and efficacy, as well as the impact of pertinent practical and regulatory considerations. Since

extensive data are likely to have been accumulated on existing products, there is understandable reluctance on the part of the drug industry to undertake such changes unless they are dictated by compelling reasons. A second reason for the use of the method is that some formulators prefer to use wet granulation to assure content uniformity in the resulting tablets. This judgment depends to a great extent upon the personal experience of the formulator in the previous use of different tableting methods. A third reason is that wet granulation is the process of choice to use in tablet formulations of many high-dose drugs where direct compression—because of the necessity to add a considerable amount of filler to facilitate compaction—becomes unfeasible because of the resulting increase in tablet size.

Another advantage of wet granulation is that the drying cycle of the process can be manipulated to produce a dry granulation with a low moisture content. When such low moisture content is not attainable with some direct compression formulations because of the excessive moisture content of the components, the formulation would have to be subjected to a drying cycle, thereby losing much of the benefit of economy of processing.

A. Advantages of Wet Granulation

A comparison of the sequential steps in the manufacture of tablets by different methods is shown in Table 1. It is evident that direct compression would be a much simpler and less expensive process. It is therefore important to understand the advantages of wet granulation in order to appreciate its usefulness. The purpose of granulation is to enlarge the particle size of a powder and obtain uniform particles which will flow readily through the tablet machine hopper and feed frames into the dies. This results in a number of improvements in the properties of the powder with regards to tableting.

1. The cohesiveness and compressibility of powders is improved due to added binder which coats the individual powder particles, causing them to adhere to each other so they can be formed into agglomerates, called granules. Thus by this method, the properties of formulation components are modified to overcome their tableting deficiencies. During the compaction process, granules are fractured exposing fresh, clean powder surfaces, and this also improves compressibility. Lower pressures are therefore needed to compress tablets—resulting in improvements in tooling life and machine wear.

2. High-dosage drugs having poor flow or compressibility properties must be prepared by wet granulation to obtain suitable flow and cohesion for compression. In this case, the proportion of binder required to impart adequate compressibility and flow is much less than the proportion of dry binder needed to produce a tablet by direct compression.

3. Good distribution and uniform content for soluble low dosage drugs and color additives is obtained if these are in the binder solution of a wet granulation. This represents a distinct advantage over direct compression, where content uniformity of drugs and uniform color dispersion can be a problem.

4. Wet granulation prevents segregation of components of a homogeneous powder mix during processing, transferring, and handling. In effect, the composition of each granule becomes fixed and remains the same as—or very nearly that of—the powder mixture at the time of liquid-binder addition.

Compressed Tablets

5. The dissolution rate of a hydrophobic drug may be improved by wet granulation with the proper choice of solvent and binder.

B. Limitations of Wet Granulation

The greatest disadvantage of wet granulation is its cost. It is an expensive process because of the labor, time, equipment, energy, and space requirements. However, a number of improvements have been made in recent years to improve the wet granulation method and reduce its cost. These include:

A solid-liquid twin-shell blender with a dispersion bar to add the binder solution and produce agglomerates, with a heated jacket and vacuum take-off to facilitate and hasten drying. This unit, properly operated, can produce a completed granulation.

A fluidized bed dryer equipped with a spray head to add the binder and other components, granulating and drying simultaneously.

Mixers such as the Lodge and the Diosna, which provide efficient and rapid solid-solid and solid-liquid blending, reducing the time and material handling involved.

Wet granulation of moisture sensitive drugs can usually be overcome by the use of anhydrous solvents with solvent-soluble binders to form the wet mass to produce the granulation. If the solvent presents a health and/or explosion hazard, explosion-proof equipment and adequate air and vapor handling equipment must be used to remove the vapor. The use of soluble dyes in wet granulations often causes migration of the dyes during the drying cycle. As the solvent evaporates, materials soluble in it, including dyes, tend to migrate to the surface of the granules, thus causing unequal distribution of color. Although some redistribution occurs during subsequent mixing and milling, some color mottling of tablets on compression may nevertheless result. This can be overcome by the use of insoluble lake dyes which do not migrate in either aqueous or solvent granulations.

An inherent limitation of wet granulation is that any incompatibility between formulation components will be aggravated by the granulating solvent bringing them into close contact.

C. Process Parameters in Wet Granulation

The various steps involved in the wet granulation process have a significant effect on the tableting properties of the resulting granulation. It is therefore important to understand these process parameters in terms of their impact on process design and selection of formulation components. Essential to the wet granulation process are the following operations and processes:

- Preparation of the powder mixture with screening and mixing
- Addition of binder solution and mixing with powder to proper wetness
- Drying the solid-liquid blend
- Milling the dry granulation to size
- Addition of lubricant, glidant, and/or other excipients prior to compression

Wet granulation consists of moistening the mixture of active ingredient and diluent with the granulating liquid comprising the binder in solution in water, alcohol, or mixture of these two, or any other acceptable liquid to moisten and bind the powders together by causing the particles to adhere to each other. The wet mass produced by mixing the liquid with the solid should have a doughlike consistency so that a handful can be formed into shape without crumbling. When pressed into a ball with the hands and broken in half, it should give a clean fracture without sticking or crumbling. If the mass has a tendency to stick or not break clean, the granulation is usually too wet. If the mass crumbles or breaks into pieces it is too dry.

The wet mass is then passed through a standard 4, 6, 8, or 12 mesh screen, depending upon the ease with which the wet mass can be forced through the screen. Starting with a 12 mesh screen in an oscillating granulator or a Fitzpatrick mill with the knife edges forward and a Fitzpatrick screen, the smallest opening through which the wet mass will pass should be determined. It is desirable to use the smallest opening possible so that small granules can be obtained, which facilitate drying because of their greater surface area and smaller individual mass.

III. Tablet Excipients

A tablet formulation contains a number of excipients in addition to the active ingredients. Each excipient is selected to meet the needs of processibility and product use. The major types of excipients used are fillers or diluents, binders, disintegrating agents, and lubricants—which are present in nearly all tablet formulations. Other excipients may be needed for specific purposes. Colors are added to a large proportion of tablets to provide a characteristic appearance and also to improve quality assurance by minimizing the chances for product mix-up during in-process stages of manufacture. Glidants and antiadherents are needed in some formulations. Sweeteners and flavors are needed in chewable tablets.

A. Fillers

Fillers or diluents are used to increase the bulk of the tablet so as to enable a formulation to become suitable for compression. It is generally not feasible to make tablets with a weight of less than about 70 mg. In addition to lending bulk to the formulation, fillers are selected to improve the binding and flow properties of the formulation. It is essential that fillers be inert and stable. A list of the more commonly used fillers in wet granulation is shown in Table 2. Fillers used in direct compression are discussed in detail in Section IV.C.

Lactose, also known as milk sugar, is probably the most widely used tablet diluent or filler. The solubility and sweetening power of lactose is lower than that of other sugars. It is obtained by crystallization from whey, a milk by-product of cheese manufacture. The most common form commercially available is α -lactose monohydrate, which is produced by crystallization from supersaturated solutions below 93.5°C. If crystallization occurs above 93.5°C, the β -anhydride is obtained. This form is also commercially available but in lesser quantities. Lactose for tableting purposes is available as crystalline and spray-dried products. The spray-dried form is used largely in direct compression. For the manufacture of tablets by the wet granulation procedure, crystalline lactose is used. It is available as a

Compressed Tablets

Table 2

Fillers Commonly Used in Wet Granulation Formulations

Insoluble fillers	Soluble fillers
Calcium sulfate NF	Lactose
Dibasic calcium phosphate NF	Sucrose
Tribasic calcium sulfate NF	Mannitol
Starch	Sorbitol
Calcium carbonate	
Microcrystalline cellulose	
Modified starches	

fine impalpable powder in two particle size ranges, Impalpable Powder in the particle size range of 200 to 225 mesh and Impalpable C Powder in the size range of 300 to 325 mesh—as compared to spray-dried lactose which is available in the particle size range of 100 to 200 mesh. Lactose tends to crystallize in pure form, leaving impurities behind in the mother liquor. As crystalline lactose, it does not have as great a tendency to turn brown, as occurred with the earlier supplies of spray-dried lactose. Although contaminants are removed during the manufacturing process, the possibility of browning still remains. Lactose has very few incompatibilities and can be used with most drugs. The form most generally used is the Impalpable Powder. The Impalpable C Powder is used for molded tablets.

Sucrose is used generally as a tablet diluent in the form of confectioners sugar, which is a finely ground sucrose containing 3% starch to prevent caking. It is available as 4x and 6x powders representing different degrees of fineness: the 4x has a particle size such that approximately 90% passes through a 200 mesh screen, and approximately 80% of the 6x passes through a 325 mesh screen. Sucrose is used, in some cases, to impart sweetness to chewable tablets. But its more important use in wet granulation is to impart hardness to tablets. Used in the dry state in the tablet, it binds to a moderate hardness, depending upon the amount used and the solubility of the other ingredients. If a mixture of alcohol and water is used to granulate, softer granules are produced than if water alone is used. Sugar should be used in small amounts in tablet formulations since it has the disadvantage of being somewhat hygroscopic. If it is used in sufficient quantities the tablets will harden with time, which would interfere with the dissolution of the drug from the tablet. Sucrose, like lactose, will turn brown if used with alkaline materials. Some of the directly compressible forms of sucrose, such as Di-Pac and Nu Tab, can be used with granulations prepared by the wet process for imparting hardness to the tablet. However, this can be done only with white granulations since the techniques for adding color to this type of formulation have not been developed.

Dextrose has found some use in wet granulation as a diluent as well as a binder. It can be used essentially in the same way as sucrose, but is not available in fine powder form such as confectioners sugar. It is also not as sweet as sucrose,

and tablets containing dextrose tend to increase in hardness with time, especially if the anhydrous form of dextrose is used.

Mannitol is another sugar that is used particularly in chewable tablets. It is a white, odorless, pleasant-tasting crystalline powder which is essentially inert and nonhygroscopic. Mannitol is the preferred tablet diluent for the production of chewable tablets because of its pleasant, slightly sweet taste giving tablets a smooth, melt-down mouth-feel; its negative heat of solution gives it a cool taste. Mannitol may be granulated with a variety of granulating agents. It has been shown that mannitol requires more granulating solution than either sucrose or lactose and approximately the same amount as dextrose. This is shown in Table 3. The moisture content of these granulations after overnight drying at 140 to 150° F for sucrose, dextrose, and mannitol was less than 0.2%, except for the dextrose granulations made with 10% gelatin and 50% glucose, in which the moisture content was 1.15% and 0.26%, respectively. In all of the lactose granulations, the moisture was between 4 and 5%. Mannitol and sucrose were the lowest, having about the same moisture content. However, it was found that mannitol, although it required more granulating solution, generally gave a softer granulation than did sucrose or dextrose. Lactose granulations more closely resembled mannitol.

Table 3

Granulating Solution Required by 3000 g of Diluent

Volume of granulating solution required (ml)	Diluent			
	Sucrose	Lactose	Dextrose	Mannitol
10% Gelatin	200	290	500	560
50% Glucose	300	325	500	585
2% Methocel (400 cps)	290	400	335	570
Water	300	400	660	750
10% Acacia	220	400	685	675
10% Starch paste	285	460	660	810
50% Alcohol	460	700	1000	1000
10% PVP ^a in water	260 ^b	340 ^b	470 ^b	525
10% PVP ^a in alcohol	780 ^b	650 ^b	825 ^b	900
10% Sorbitol in water	280 ^b	440 ^b	750 ^b	655

Source: Taken in part from the Technical Bulletin, Atlas Mannitol, ICI Americas, Inc., Wilmington, Del., 1969.

^a Polyvinylpyrrolidone.

^b Derived by one of the authors (F.J.B.), not from source noted above.

Compressed Tablets

Calcium sulfate is an insoluble, nonhygroscopic, mildly abrasive fine powder. It is an inexpensive filler that can be used as a diluent for acidic, neutral, and basic compounds. It has a high absorption capacity for oils. However, it is essentially nonadsorptive of organic bases, so that drug-excipient interactions due to sorption are minimized with the large majority of drugs. It can be used with a wide range of drugs since it has few incompatibilities. When granulated with polymer solutions, the tablets will generally not harden with time. The use of sugar solutions for granulation should be avoided as the resulting tablets will tend to harden with time.

Example 1: Vitamin B₁₂ Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Vitamin B ₁₂	55 µg ^a	0.55 g ^a
Calcium sulfate	110 mg	1100 g
Sucrose	20 mg	200 g
10% Pregelatinized starch solution	q.s.	q.s.
Sta-Rx starch	10 mg	100 g
Avicel PH 101	12 mg	120 g
Sterotex	0.75 mg	7.5 g

^a Includes 10% manufacturing excess.

Mix the sucrose and calcium sulfate. Dissolve the vitamin B₁₂ (cyanocobalamin) in about 50% of the pregelatinized starch solution to be used, and add it slowly with mixing to the sucrose and calcium sulfate mixture. Allow to mix 15 min. Add sufficient of the remaining starch solution to granulate. Add slowly and allow to mix 30 min. Pass the wet mass through a 14 mesh screen and dry the granules in an oven at 120 to 130° F. When dry, pass through a 20 mesh screen. Mix the Sta-Rx, Avicel, and Sterotex and pass through an 80 mesh screen. Add to the granulation and mix in a tumble mixer for 20 min. Compress to weight with 1/4-in. standard concave punches.

Dicalcium phosphate is an insoluble, neutral, nonhygroscopic, mildly abrasive fine white powder. The unmilled dihydrate form of this material is used extensively in direct compression. Its properties are similar to those of calcium sulfate, but it is more expensive and is used only to a limited extent in wet granulation (Example 2). It should not be used with strong acid salts of weak organic bases. If inorganic acetate salts are present in the formulation, the tablets are likely to develop an acetic acid odor on standing. It can be used with most salts of organic bases, such as antihistamines, and also with water-soluble vitamins, chlorothiazides, barbiturates, and similar drugs.

Tricalcium phosphate is an insoluble, slightly alkaline, nonhygroscopic, abrasive fine white powder. It is used to a limited extent in wet granulation. Its use should be avoided with strong acid salts of weak organic bases and when inorganic acetate salts are present in the formulation. Because of its alkalinity, it should also not be used with water-soluble vitamin B salts or with certain esters such as vitamin E.

Example 2: Sodium Phenobarbital Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Sodium phenobarbital	64.8 mg	648 g
Dicalcium phosphate	60.6 mg	600 g
Starch	12.0 mg	120 g
10% Polyvinylpyrrolidone in 50% alcohol	q.s.	q.s.
Carbowax 6000 (fine powder)	3.5 mg	35 g
Avicel	7.5 mg	75 g

Mix the sodium phenobarbital, dicalcium phosphate, and starch and moisten with the PVP hydroalcoholic solution to proper wetness to granulate. Pass the wet mass through a 14 mesh screen or through a #2B Fitzpatrick Mill perforated plate at medium speed, hammers forward. Dry the granulation on trays in a forced-air oven overnight at 130 to 140° F. Pass the dry granulation through a 20 mesh screen. Mix the Carbowax 6000 with the Avicel and pass the mixture through an 80 mesh screen. Add this to the dried granulation and mix in a tumble mixer for 15 to 20 minutes. Compress to weight with 1/4-in. flat-face punches.

acetate. It can be used with most salts of organic bases, chlorothiazides, and barbiturates. There is more variation in alkalinity and in particle size between various sources of tribasic calcium phosphate than with dibasic calcium phosphate. It is also more difficult to granulate than either calcium sulfate or dibasic calcium phosphate.

Starch is a naturally occurring diluent which is bleached white and can be obtained in varying degrees of whiteness. The material most frequently used is cornstarch. It is a multiple-purpose product in that it can also be used as a disintegrant agent and as a binder in the form of starch paste. It has the disadvantage of having compressibility too poor to make tablet of sufficient hardness. It also tends to expand after compression. Therefore, it is not used to any great extent as a filler in compressed tablets; it is used to a greater extent as a diluent in capsules. Starch is used widely as a disintegrant in the concentration range of 5 to 20%. In this application, starch may be added to the powder prior to wet granulation, or it may be added dry to a granulation prepared by the wet process. Starch has few incompatibilities, but it should not be used as a diluent for strongly acidic compounds since it will partially hydrolyze on drying.

Microcrystalline cellulose is a white, insoluble, neutral, nonreactive, free-flowing, versatile filler. Used in sufficient quantity, usually 10 to 20%, it also serves as a dry binder and disintegrating agent. It is widely used in direct compression. It has an extremely low coefficient of friction, both static and dynamic, so that it has no lubricant requirement itself. However, when more than 20% of drugs and other excipients is added, lubrication is necessary. It has few if any incompatibilities and can be used with other diluents with excellent results. Microcrystalline cellulose is available in two grades, Avicel PH 101, which was the original product, and Avicel PH 102, which is a partially agglomerated product with

Compressed Tablets

large particle size distribution and slightly better fluidity with no significant decrease in compressibility. It has been suggested that both Avicel PH 101 and PH 102 can be used advantageously in wet granulation. A level of 5 to 15% is recommended. When used as a wet-massing adjunct, the wicking action of microcrystalline cellulose promotes rapid, even wetting of the powder mix. Its ability to retain water makes the wet mass less sensitive to overwetting due to excess of granulating fluid. The milling of the wet mass is easier due to less clogging of the screen. This produces a more uniform granulation, which is readily dried with reduced case hardening. This is particularly useful with some materials which, when wetted or overmixed, become a chalky, claylike mass clogging screens during the wet milling process. When dried, these granules often are hard and resist disintegration. A material in which this problem may be encountered is calcium carbonate, as shown in the following examples.

Example 3

Ingredient	Quantity
Calcium carbonate	1000 g
Water	300 ml

Example 4

Ingredient	Quantity
Calcium carbonate	1000 g
Avicel PH 101	100 g
Water	300 ml

The material of Example 3 produces a sticky mass whereas Example 4 produces a nonsticky mass which can be granulated through a 12 mesh screen.

Microcrystalline cellulose may be added dry to a granulation prepared by the wet method to improve bonding and reduce capping and friability.

Example 5

	Quantity per tablet	Quantity per 20,000 tablets
Drug	500 mg	10,000 g
Starch	9.83 mg	197 g
Polyvinylpyrrolidone (PVP-K30, 8% alcohol solution)	18.58 mg	372 g
Avicel PH 101	60 mg	1,200 g
Calcium stearate	4 mg	118 g

Mix the drug and starch; granulate with the alcoholic solution of PVP. Pass the wet mass through a 12 mesh screen and dry at 120 to 130° F. Pass the dry granulation through a 16 mesh screen. Mix with Avicel and calcium stearate previously screened through a 40 mesh screen. Compress using 7/16-in. standard concave tooling.

Because of its low bulk density, tablets with a higher proportion of microcrystalline cellulose tend to have a greater porosity. Other examples in the chapter will also serve to illustrate the use of these fillers in wet granulation formulations.

B. Binders

The appearance, elegance, and ease of compression of tablets are directly related to the granulation from which the tablets are compressed. Granulations in turn are dependent—on the materials used, processing techniques, and equipment—for the quality of the granulation produced. Of these variables, none is more critical than the binder used to form the granulation—for it is largely the binder which is fundamental to the granulation particle size uniformity, and adequate hardness, ease of compression, and general quality of the tablet.

Direct compression, facilitated by techniques such as induced die feeding and by the availability of compressible materials for admixture with medicinal agents, is a streamlined and more economical method of tablet manufacture than the wet granulation approach. However, direct compression cannot completely replace wet granulation in the immediate future. Wet granulation is necessary to produce uniformly colored tablets, tablets containing potent drugs of low dosage level with minimal intertablet variation, chewable tablets where mouth-feel is enhanced by

Table 4
Binders Used in Wet Granuation

Starch	5-10% w/v Aqueous paste
Pregelatinized starch	5-10% Added dry to powder
Gelatin	2-10% Aqueous solution or 2% in starch paste
Polyvinylpyrrolidone	5-20% Aqueous or alcoholic solution
Methylcellulose (various viscosity grades)	2-10% Aqueous solution
Sodium carboxymethylcellulose (low-viscosity grade)	2-10% Aqueous solution
Ethylcellulose (various viscosity grades)	5-10% Alcohol or hydroalcoholic solution
Polyacrylamides (Polymer JR)	2-8% Aqueous solution
Polyvinylloxazolidone (Devlex)	5-10% Aqueous or hydroalcoholic solution
Polyvinyl alcohols	5-20% Aqueous solutions

wet granulation, and special granulations such as sustained-release and compression-coated tablets.

Binders are either sugars or polymeric materials. The latter fall into two classes: (1) natural polymers such as starches and gums, including acacia and tragacanth, and (2) synthetic polymers such as polyvinylpyrrolidone and methylcellulose. Binders of both types may be added dry to the powder mix, and the mixture wetted with water, alcohol, and alcohol-water mixtures—or the binder may be put into solution in the solvent and added. The latter method, using the solution of the binder, requires much less of the binding materials to achieve the same hardness than if added dry. In some cases, it is not possible to get granules of sufficient hardness using the dry method. A list of the binders used in wet granulation is shown in Table 4.

Starch, probably the most commonly used binder in the past, has been starch in the form of starch paste, typically used in concentrations of 5 or 10%. A simple way to make starch paste is to suspend the starch in 1 to 1 1/2 parts of cold water, then add 2 to 4 times as much boiling water with constant stirring. The starch swells almost immediately to make a translucent paste which can then be diluted with cold water to the desired concentration. Starch paste may also be prepared by suspending the starch in cold water and heating to boiling in a steam-jacketed kettle with constant stirring. Starch paste is a versatile binder, yielding granules and tablets which disintegrate readily (Examples 6 and 7). It is also an excellent carrier for dyes which have been dissolved in the cold water used in making the paste. Granulation of the powder mix with colored starch paste produces uniform distribution

Example 6: Phenobarbital Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Phenobarbital	65 mg	650 g
Lactose (fine powder)	40 mg	400 g
Starch (as starch paste)	4 mg	40 g
Starch (dry)	10 mg	100 g
Talc	10 mg	100 g
Mineral oil, 50 cps	4 mg	40 g

Mix the phenobarbital and lactose and moisten with 10% starch paste to proper wetness. Granulate by passing through a 14 mesh screen and dry at 140°F. When dry, pass through a 20 mesh screen; add the dry starch and talc; mix well; and, finally, add the mineral oil, mix again, and compress using 9/32-in. standard cup punches.

of color with little or no tendency for the colors to migrate to the surface of the granules on drying. Starch paste generally forms firm yet soft and cohesive granules. One reason why starch paste is much used is that it is an excellent binder for such common diluents as calcium sulfate, dibasic calcium phosphate, lactose, and starch. It is neutral and nonreactive and can be used with many active ingredients.

Example 7: Thiamine Hydrochloride Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Thiamine hydrochloride	55 mg ^a	550 g ^a
Lactose (fine powder)	200 mg	2000 g
Tartaric acid (fine powder)	5 mg	50 g
Starch (as starch paste)	6 mg	60 g
Sterotex	8 mg	80 g
Alginic acid	10 mg	100 g

^a Includes 10% excess thiamine hydrochloride.

Mix the thiamine hydrochloride, lactose, and tartaric acid and moisten with starch paste. Pass through a 14 mesh screen to granulate. Dry at 120° F and reduce through a 20 mesh screen. Add the alginic acid and Sterotex; mix well, and compress using 3/8-in. standard concave punches.

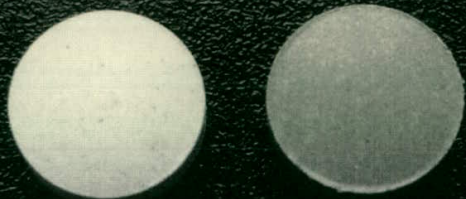
Pregelatinized starch can be used in place of starch as starch paste. Its binding properties are slightly greater than starch paste, and it offers the advantage of being soluble in warm water without boiling. It is available from most of the major starch companies. Pregelatinized starch may also be used as a binder by adding it dry to the powder mix and wetting with water to granulate.

Example 8: Aminophylline Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Aminophylline	100 mg	1.0 kg
Tricalcium phosphate	50 mg	0.5 kg
Pregelatinized starch	15 mg	0.15 kg
Water	q.s.	q.s.
Talc	30 mg	0.3 kg
Mineral oil, light	2 mg	0.02 kg

Mix the aminophylline, tricalcium phosphate, and starch and moisten with water. Pass through a 12 mesh screen and dry at 110° F. Size the dry granules through a 20 mesh screen; add the talc and mix. Add the mineral oil, mix for 10 minutes, and compress using 5/16-in. deep cup punches for enteric coating.

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CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO Vr. CONCEPTO
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			100.000.00 100.000.00 ✓
			\$100.000.00
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Act. 444 RESPUESTAREQUE Folios: 79

Colo:15846-845-014-9.

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*** Conceptos Pagados ***

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				100.000.00 ✓
				\$100.000.00

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*** Conceptos Pagados ***

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TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
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*** Conceptos Pagados ***

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