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Señor

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

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REF: Expediente No. **14 134.651**- solicitud de patente de invención a favor de **SIGNAL PHARMACEUTICALS, LLC**. Título: **COMPOSICIONES FARMACÉUTICAS DE 7-(6-(2-HIDROXIPROPAN-2-IL)PIRIDIN-3-IL)-1-((TRANS)-4-METOXICICLOHEXIL)-3,4-DIHIDROPIRAZINO[2,3-B]PIRAZIN-2(1H)-ONA, UNA FORMA SÓLIDA DE LAS MISMAS Y MÉTODOS DE SU USO.**

RESPUESTA A EXAMEN DE FONDO

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante me permito dar respuesta al Oficio No. 6813 relacionado con la patentabilidad de la presente invención y notificado por fijación en lista el 23 de Junio de 2015.

De manera atenta nos permitimos remitir a su Despacho un nuevo pliego reivindicatorio que consta de veinte (20) reivindicaciones, las cuales mantienen pleno sustento en las divulgaciones del capítulo descriptivo y no exceden de ninguna manera el alcance de la invención previamente reclamada.

En este sentido, es preciso mencionar que dicho nuevo pliego reivindicatorio resulta de una serie de modificaciones llevadas a cabo de acuerdo con las sugerencias y comentarios del señor Examinador a fin de solucionar todas y cada una de sus objeciones. Tales modificaciones se resumen a continuación:

- El objeto de las reivindicaciones 23 a 26 fue completamente eliminado, razón por la que afirmamos que la presente divulgación ya no comprende ninguna materia exceptuada de patentabilidad.
- Las expresiones *"o una sal, isotópologo, metabolito o forma sólida del mismo farmacéuticamente aceptable"*, *"una cantidad efectiva"* y *"alrededor de"* fueron retiradas de todas las reivindicaciones que la contenían, evitando de este modo hacer referencia a expresiones generales o imprecisas.
- Las expresiones *"AVICEL PH 102®"* y *"AC-DI-SOL®"* fueron reemplazadas por los nombres químicos *"celulosa microcristalina"* y *"croscarmelosa de sodio"* respectivamente, con lo cual se evita hacer referencia a marcas o nombres comerciales. Dichas modificaciones se encuentran soportadas por los párrafos [00265], [00266] y [00267] de la correspondiente solicitud PCT/US2012/067172.
- Adicionalmente, la nueva reivindicación 7 caracteriza tal celulosa microcristalina mediante su tamaño de partícula (*"la celulosa microcristalina tiene un tamaño de partícula nominal alrededor de 100 µm"*), en concordancia con las características inherentes de la mencionada marca AVICEL PH 102®.
- La nueva reivindicación 19 (antigua reivindicación 21) incluye la expresión *"y la película es Opadry rosa, Opadry amarillo u Opadry beige"* en referencia a la composición de la película de recubrimiento, inclusión que se encuentra soportada de manera pertinente por el capítulo descriptivo, más específicamente por el párrafo [00342] de la correspondiente solicitud PCT/US2012/067172.

- Las antiguas reivindicaciones 12, 16 y 27 a 32 fueron completamente eliminadas, de manera tal que el actual pliego reivindicatorio ya no se mencionan formas cristalinas de los compuestos relacionados con la presente solicitud, ni se incluyen caracterizaciones relativas a las mismas.

Con base en dichas modificaciones, solicitamos respetuosamente sean retiradas todas y cada una de las objeciones que cuestionan la claridad y concisión de la presente divulgación puesto que las mismas han sido pertinentemente resueltas.

De la mano con lo anterior, solicitamos sea reconocido que, tras la eliminación de las reivindicaciones 16 y 27 a 32, el nuevo pliego reivindicatorio se encuentra dirigido a un único concepto técnico inventivo, razón por la cual la objeción de unidad de invención manifestada por el señor Examinador carece ahora de todo fundamento.

En vista de esta restricción, y con el objetivo de alcanzar una apropiada protección de la materia descrita por la presente solicitud, remitimos a su Despacho un nuevo pliego reivindicatorio conformado por siete (7) reivindicaciones –dirigidas específicamente a la materia de las comentadas reivindicaciones 16 y 27 a 32–, a partir del cual solicitamos se dé lugar al trámite de una solicitud divisional.

Dado que dicho nuevo pliego reivindicatorio divisional se acoge a todos los lineamientos establecidos por su Despacho, es decir, no excede el alcance de la divulgación inicial ni se solapa en contenidos con la solicitud inicial, solicitamos respetuosamente éste sea admitido a trámite.

Así pues, damos por superadas todas las objeciones relacionadas con las antiguas reivindicaciones 16 y 27 a 32 ya que las mismas han sido eliminadas del nuevo pliego reivindicatorio relacionado con esta solicitud, resolviendo de esta manera los problemas de unidad de invención y novedad señalados por el señor Examinador en su oficio técnico.

Ahora bien, en lo que respecta al requisito de nivel inventivo, consideramos oportuno manifestar que, en nuestro concepto, los documentos D1 (*"mTOR kinase inhibitors for oncology indications and diseases associated with the mTOR/PI3K/AKT pathway"*, US2010216781) y D3 (*Handbook of Pharmaceutical Excipients*, Raymond C Rowe, Pharmaceutical press. 2009) fallan completamente en anticipar o sugerir el desarrollo de la presente invención, hecho que procedemos a demostrar.

Partiendo del análisis de dicho arte previo, encontramos que el documento D1 da a conocer composiciones que comprenden el compuesto 7-(6-(2-hidroxiopropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona formulado en un vehículo que comprende ácido esteárico y lactosa como excipientes de elección.

Comparando el objeto de la presente solicitud frente a dicho documento D1, solicitamos sea considerado que la invención aquí descrita representa una composición que combina los siguientes elementos esenciales:

- (i) una cantidad efectiva de 7-(6-(2-hidroxiopropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona;
- (ii) ácido esteárico; y
- (iii) monohidrato de lactosa.

De acuerdo con esto, resulta evidente que las divulgaciones del documento D1 y de la presente solicitud no son equivalentes, diferenciándose principalmente en la utilización de **monohidrato de lactosa** en lugar de lactosa, como describe la anterioridad.

Teniendo en cuenta entonces que las enseñanzas del arte previo difieren sustancialmente del objeto de la presente invención, el señor Examinador cita un segundo documento, documento D3, argumentando que este pone a disposición del versado en la materia toda la información necesaria para que este pueda alcanzar la materia aquí reivindicada sin tener que acudir a la aplicación de su propia habilidad inventiva.

En contraste con esto, es nuestra intención mencionar que el documento D3, en lugar que aportar información valiosa al versado en la material, constituye un texto de referencia general y de consulta habitual en el campo técnico dedicado a la mera descripción y caracterización de diversos excipientes de uso farmacéutico.

Por tanto, consideramos que el documento D3 no representa una referencia válida del estado de la técnica pues no divulga información relacionada con el desarrollo específico de una composición que comprende el fármaco 7-(6-(2-hidroxiopropan-2-il)piridin-3-il)-1-((*trans*)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-*b*]pirazin-2(1*H*)-ona, y que por tanto este falla en aproximar al versado en la materia al objeto de la presente invención.

En este sentido, afirmamos que si bien es posible que el versado en la materia acuda a dicho documento D3 como parte de sus prácticas habituales en el campo de la investigación y desarrollo farmacéutica, éste no encontraría en dicho texto una instrucción o motivación concreta que derive en el desarrollo puntual de la presente invención.

Dicho de otro modo, el documento D3 falla completamente en motivar o favorecer la elección concreta de **monohidrato de lactosa** como aglutinante, diluyente o agente de relleno, razón por la que el versado en la materia no se vería en ningún momento encaminado al desarrollo de la formulación aquí propuesta.

De hecho, llamamos la atención sobre el hecho de que precisamente el documento D3 da a conocer una gran variedad de excipientes que pueden ser incorporados en una composición como aglutinantes, diluyentes o agentes de relleno, hecho que demuestra con claridad que, al momento de desarrollar la presente invención, el versado en la materia enfrentaba un sinnúmero de posibilidades que, gracias a su propia habilidad inventiva, concluyen en una única composición eficaz y segura.

De la mano con lo anterior, consideramos que en caso de que dicho versado en la materia buscara modificar la composición divulgada en el documento D1 siguiendo los preceptos del documento D3, éste daría lugar al desarrollo de un **número infinito de composiciones** derivadas de la combinación aleatoria de excipientes, hecho que evidentemente se **aleja** del alcance de la presente invención.

Así pues, solicitamos respetuosamente sea reconocida la falta de relevancia que implica el citado documento D3 en el análisis de patentabilidad de la presente invención, la cual cumple satisfactoriamente con el requisito de nivel inventivo a la luz del arte previo en estudio.

De igual manera, solicitamos sea reconocido que, pese a las afirmaciones del señor Examinador, el versado en la materia no contaba con ninguna instrucción concreta que lo incitara a modificar la composición descrita en el documento D1 reemplazando uno de sus excipientes de manera deliberada a fin de alcanzar la materia aquí reivindicada.

Con base en lo ya comentado, concluimos que la objeción del señor Examinador carece totalmente de fundamentos puesto que los documentos D1 y D3 no contienen ninguna información de utilidad para el versado en la materia que le permita **alcanzar** exactamente la composición que aquí se reivindica sin necesidad de aplicar su propia habilidad inventiva.

Aclarado lo anterior, consideramos pertinente mencionar que, como es bien sabido en el campo de la investigación y desarrollo farmacéutico, las actividades de formulación y pre-formulación constituyen una etapa crítica y fundamental en la obtención de una nueva composición farmacéutica, en donde cualquier tipo de cambio, por más sutil que éste sea, puede tener un impacto radical sobre el comportamiento final de la formulación en desarrollo.

En conexión con este hecho, es de notar que las modificaciones llevadas a cabo a nivel de una formulación, o más específicamente de sus excipientes, constituyen un acto completamente impredecible puesto que es imposible prever el impacto de cualquier modificación sobre el comportamiento farmacotécnico y biofarmacéutico de una nueva composición, tal que no hay garantía de que el uso de un excipiente particular resultará inequívocamente en una formulación estable y con mejores o siquiera iguales propiedades que la formulación inicial.

Así pues, el desarrollo de una nueva composición farmacéutica se ve acompañado de un análisis exhaustivo de la interacción que surge entre excipientes; entre ingredientes activos; y entre excipientes e ingredientes activos, hecho que se relaciona con la naturaleza inherente de cada uno de los componentes, es decir, sus **propiedades físicas y químicas**, las cuales a pesar de conocerse con anterioridad, pueden generar una infinidad de interacciones o comportamientos, tanto favorables como desfavorables, como parte de una formulación. Es justamente este hecho el que da lugar a la incertidumbre que rodea el proceso de formulación, el que le otorga un claro nivel de dificultad a esta actividad en concreto y el que, sin lugar a dudas, requiere de la aplicación de la habilidad inventiva del inventor a fin de lograr una formulación exitosa.

Inclusive, vale la pena mencionar que, como es común en este campo técnico, durante el desarrollo de una nueva composición surgen casos en los que el hecho de modificar uno o varios de los excipientes de una composición concreta da lugar a **problemas de estabilidad y eficacia**, razón por la que insistimos en que el desarrollo de nuevas composiciones no simboliza ninguna actividad obvia o de rutina, sino que constituye un área de constante desafío para el profesional farmacéutico.

Con el fin de sustentar de mejor manera la argumentación precedente, anexamos al presente memorial el estudio llevado a cabo por Bharate *et al.* (Bharate *et al.*, J. Excipients and Food Chem., 1(3):3-26, 2010), el cual concluye que el reemplazo de un excipiente puede afectar de manera significativa la **naturaleza química, estabilidad y biodisponibilidad de los principios activos**, y en consecuencia, su **eficacia terapéutica y seguridad**.

Concretamente, Bharate *et al.* llevan a cabo un estudio que evalúa en profundidad la gran variedad de **incompatibilidades fármaco-excipiente** que tiene lugar durante las etapas de pre-formulación y formulación de una nueva forma farmacéutica, las cuales son completamente impredecibles y son determinadas únicamente al momento de su ocurrencia.

Dentro de los casos de incompatibilidades expuestos a lo largo de este anexo más relevantes para la argumentación aquí presentada, destacamos los siguientes:

(i) **Lactosa:**

A pesar de ser uno de los excipientes de mayor uso en cualquier cantidad de formas farmacéuticas de administración oral, es conocido que la lactosa es un **disacárido reductor** que dada tal naturaleza, tiende a reaccionar con fármacos provistos de grupos amino, dando lugar a una **adición aldehído-amina** que sigue la secuencia descrita por la reacción de Maillard, la cual deriva en la **glicosilación del compuesto activo** como ilustra el siguiente esquema:

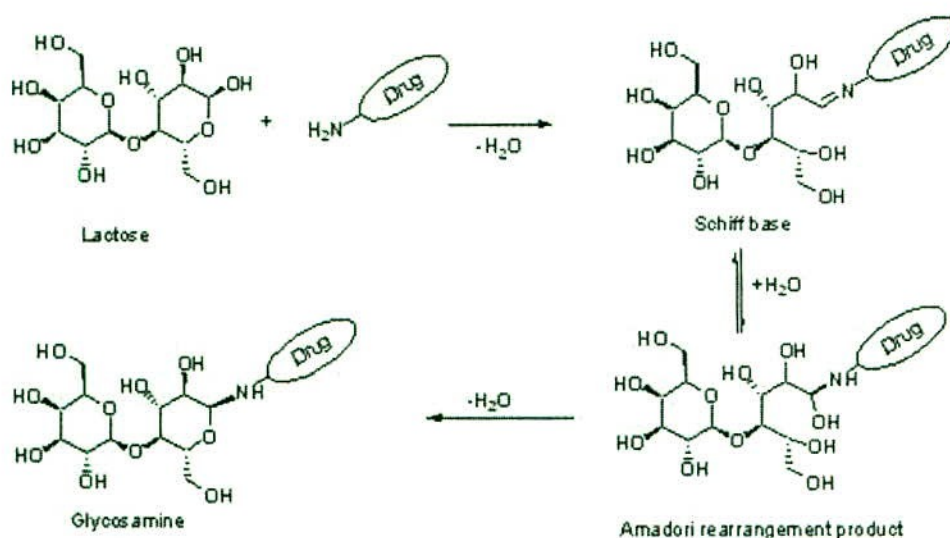


Figura 1. Típica reacción de Maillard entre un fármaco que contiene grupos amino y lactosa.

Adaptada de Anexo 1 – Bharate *et al.*

Tal y como describe el anterior esquema, la reacción de Maillard que tiene lugar entre la lactosa y el fármaco portador de un grupo amino primario inicia con la formación de una base de Schiff, la cual da lugar a la apertura del heterociclo pirano

de dicho excipiente. Posteriormente, la base de Schiff formada sufre un rearreglo de Amadori que concluye en la obtención de un **derivado de glucosamina** producto de la re-ciclación del anillo pirano.

De acuerdo con ello, presentamos dos ejemplos puntuales en donde se observa dicha interacción indeseable entre la lactosa y principios activos cuya estructura incluye grupos amina primarios:

- El fármaco Seproxetina, un inhibidor selectivo de la recaptación de serotonina, consiste en un análogo del conocido fármaco antidepresivo Fluoxetina que cuenta con un **grupo amino primario** como se ilustra a continuación:

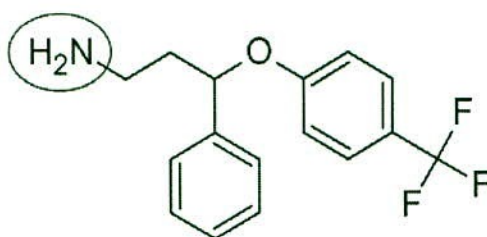


Figura 2. Fórmula estructural del fármaco Seproxetina.

Se encontró que el maleato hemihidratado de Seproxetina demostró una incompatibilidad con lactosa y almidón, formulación empleada en la elaboración de cápsulas de gelatina de este fármaco, correspondiente a la formación del **producto de adición 1-4** entre el fármaco y el ácido maleico facilitada por la humedad libre relacionada con el almidón.

La formación del producto de adición 1-4 fue determinada aún en la presencia de almidón pregelatinizado, a su vez que se identificó la formación del producto de la reacción de Maillard por la interacción del fármaco con la lactosa.

- Amlodipino es un fármaco perteneciente al grupo de las dihidropiridinas que se emplea actualmente en terapéutica como bloqueador de los canales de calcio útil en el tratamiento de la hipertensión arterial. Este fármaco cuenta con un grupo amino primario como se indica a continuación:

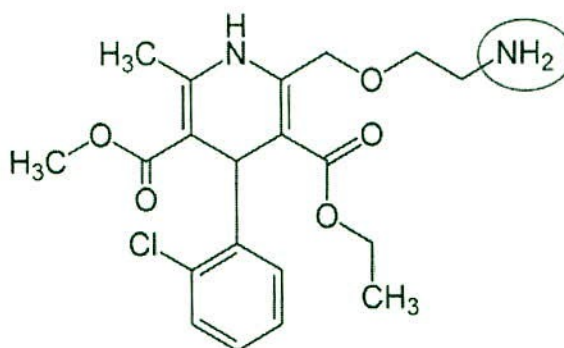


Figura 3. Fórmula estructural del fármaco Amlodipino.

Se encontró que debido a la presencia de este grupo amino primario, el fármaco Amlodipino es inestable al ser incorporado en un vehículo multicomponente que comprende lactosa, estearato de magnesio y agua, lo cual podría ser fácilmente una composición habitual en el desarrollo farmacéutico. En concreto, el producto de degradación mayoritario fue el **glicósido de besilato de amlodipino**, el cual corresponde a un producto formado mediante la reacción de Maillard entre dicho fármaco y la lactosa.

Con base en estos ejemplos, los cuales son apenas una muestra del sinnúmero de posibles interacciones indeseadas que pueden tener lugar entre un fármaco y la lactosa, afirmamos que el proceso de pre-formulación y formulación no corresponde a una simple selección y combinación de excipientes sino a un proceso inventivo *per se* toda vez que requiere de un análisis cuidadoso de los posibles inconvenientes que puedan presentarse, como en este caso la **formación de derivados de glucosamina**.

(ii) **Monohidrato de lactosa:**

A pesar de representar una de las formas hidratadas de la lactosa, y de presuntamente presentar menos reactividad por tal razón, este excipiente también interactúa de manera negativa con fármacos sensibles a la humedad, **perjudicando la estabilidad** de la forma farmacéutica general. Es de notar que, similar al caso anteriormente expuesto, el monohidrato de lactosa promueve la formación de **derivados de glucosamina** mediante la reacción de Maillard; sin embargo, este excipiente es capaz de reaccionar con aminas primarias,

secundarias y terciarias, abarcando entonces un **mayor rango de posibles incompatibilidades**.

Dos de los ejemplos de incompatibilidad entre el monohidrato de lactosa y un ingrediente activo más relevantes corresponden a los siguientes:

- El fármaco Ranitidina se emplea ampliamente en su forma clorhidrato como parte del tratamiento farmacológico de la úlcera gástrica, una condición que actualmente afecta a una gran población. Este fármaco cuenta con una **amina secundaria** como se muestra a continuación:

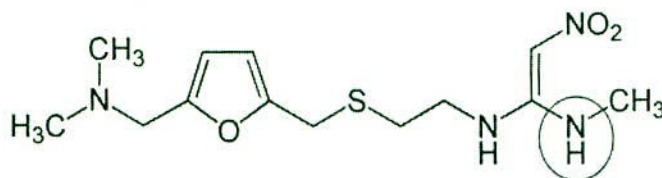


Figura 4. Fórmula estructural del fármaco Ranitidina.

Para determinar la incidencia de posibles interacciones entre este fármaco y el excipiente monohidrato de lactosa, se llevó a cabo un análisis calorimétrico diferencial de barrido (DSC) comparando el comportamiento del excipiente de manera individual versus el comportamiento de una mezcla binaria 1:1 de Ranitidina y el mismo.

El termograma obtenido para el análisis del excipiente reveló un pico de deshidratación a 150°C, seguido de un pico de fusión endotérmica a 222°C. En contraste con ello, el termograma correspondiente al análisis de dicha mezcla binaria mostró un pico mucho más amplio a 150°C, mientras que el pico de fusión a 222°C esperado desapareció completamente.

Este comportamiento confirma la existencia de interacciones entre Ranitidina y monohidrato de lactosa, las cuales evidentemente ponen en riesgo la **estabilidad** de una posible formulación en desarrollo.

- La sal de clorhidrato de Prometazina es conocida por sus efectos antiemético, antihistamínico y sedativo. A diferencia de los casos ya comentados, este fármaco cuenta con una **amina terciaria** como indicamos en la siguiente figura:

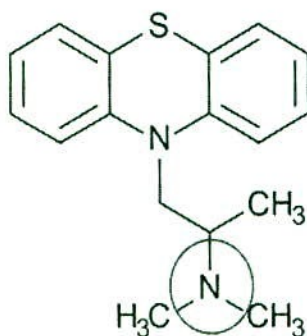


Figura 5. Fórmula estructural del fármaco Prometazina.

A pesar de que las aminas terciarias tienden a ser menos reactivas que las aminas primarias y secundarias –en base a lo cual se esperaría que estas presentaran mayor estabilidad–, los estudios han demostrado que las mismas también sufren degradación en presencia de monohidrato de lactosa.

Más específicamente, el análisis de una mezcla binaria sometida a condiciones de estrés (almacenamiento a 55°C durante un periodo de tres semanas) evidenció la incompatibilidad del monohidrato de lactosa con el fármaco Prometazina a través de manifestaciones como **cambios de color**.

En vista de estos ejemplos, es nuestra intención demostrar que contrario a lo afirmado por el señor Examinador, la elección de monohidrato de lactosa como excipiente a incorporar en la composición de la presente invención no constituye ninguna modificación obvia a partir de las anterioridades disponibles en el estado de la técnica ya que no hay manera de garantizar el éxito del uso de este excipiente, el cual también da lugar a **problemas de inestabilidad e incompatibilidad con una amplia variedad de principios activos**.

(iii) **Ácido esteárico:**

El ácido esteárico es un ácido graso comúnmente empleado como lubricante en la industria farmacéutica. Pese a esto, se han reportado **problemas de incompatibilidad** con sustancias básicas en general, hidróxidos metálicos, agentes oxidantes, y agentes reductores.

El ejemplo más común de incompatibilidad entre el ácido esteárico e ingredientes farmacéuticamente activos corresponde a la interacción que surge entre el mismo y el fármaco Doxilamina, el cual es un antihistamínico H1 conocido por su utilidad como agente sedativo.

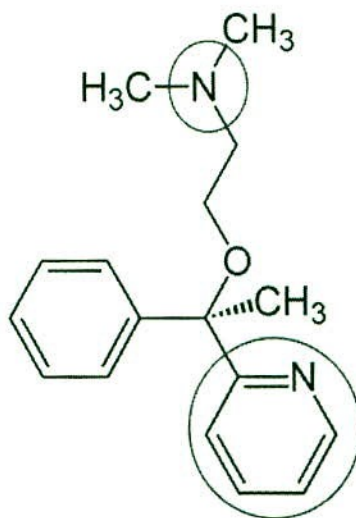


Figura 6. Fórmula estructural del fármaco Doxilamina.

Tal y como se puede apreciar, dicho fármaco tiene una naturaleza básica derivada de la presencia de los grupos amino terciario y piridina, la cual además de ocasionar **incompatibilidades con el ácido esteárico**, da lugar igualmente a problemas de inestabilidad y alteraciones fisicoquímicas en combinación con estearato de magnesio, povidona (PVP) y lactosa.

A la luz de estos ejemplos, los cuales fueron seleccionados específicamente por su pertinencia y relevancia en relación con la materia aquí reivindicada, es nuestra intención reiterar que, contrario a lo afirmado por el señor Examinador, el versado en la materia no contaba con ninguna instrucción que lo indujera a seleccionar un vehículo compuesto por monohidrato de lactosa y ácido esteárico como

excipientes de elección, más aun considerando los **problemas de incompatibilidad e inestabilidad fisicoquímica reportados para dichos excipientes**.

Por esta razón, insistimos en que las enseñanzas del estado de la técnica no sugieren el desarrollo de la presente invención pues las **mismas no podrían garantizar el éxito de una composición farmacéutica particular**, hecho que es completamente evidente para la persona normalmente versada en las ciencias farmacéuticas y que solicitamos sea debidamente reconocido por su Despacho.

En conclusión, luego de llevar a cabo un exhaustivo análisis abarcando muchos más ejemplos similares a los citados anteriormente con respecto a los excipientes (i) lactosa, (ii) monohidrato de lactosa y (iii) ácido esteárico, Bharate *et al.* afirman que:

- El análisis de compatibilidad entre el fármaco y el excipiente representa una etapa importante de la etapa de pre-formulación, la cual tiene lugar durante el desarrollo de cualquier tipo de forma de dosificación; y
- Los excipientes incluidos en una formulación pueden originar una serie de efectos accidentales o involuntarios, entre ellos **degradación del fármaco**.

En complemento de esto, consideramos pertinente resaltar que en nuestro concepto, los ejemplos anteriormente expuestos demuestran de manera convincente que la elección de un sistema de excipientes determinado como vehículo para una nueva composición no representa de ninguna manera una actividad obvia o rutinaria, razón por la cual solicitamos sea reconocido que la modificación de excipientes no constituye en ningún momento una actividad obvia puesto que la misma puede desencadenar en una composición menos eficaz o inclusive perjudicial para el consumo humano.

Consecuentemente, solicitamos sea retirada la objeción que cuestiona el nivel inventivo de la presente invención pues, como hemos demostrado, su desarrollo constituye un proceso auténtico que involucra de manera necesaria la aplicación de las habilidades inventivas del versado en la materia.

Asimismo, reiteramos que en ausencia de una instrucción puntual que motive el reemplazo del excipiente lactosa por monohidrato de lactosa derivada del arte previo citado, el versado en la materia no contaba con ninguna expectativa de éxito asociada al desarrollo de la presente invención, hecho que solicitamos sea reconocido como muestra contundente de la patentabilidad de la misma.

Así las cosas, llamamos nuevamente la atención sobre el hecho de que en el contexto de la modificación de una formulación farmacéutica, cualquier cambio a nivel de los excipientes, bien sea adición, sustracción o reemplazo de los mismos, representa un cambio apreciable en cuanto al comportamiento farmacotécnico y biofarmacéutico que manifestará tal formulación para eventualmente ejercer un efecto farmacológico.

Debido a esto, consideramos que es completamente inapropiado calificar de obvia la selección del excipiente monohidrato de lactosa que incorpora la presente invención y que la hace diferente del estado de la técnica, ya que como bien sabrá el versado en la materia, la inclusión de un excipiente monohidratado –comparado frente a la lactosa descrita en el documento D1– se relaciona con cambios a nivel físico y químico que, sin lugar a dudas, tienen un impacto valioso sobre el comportamiento y estabilidad de la presente invención.

Por tanto, solicitamos respetuosamente sea reconocido que el proceso de desarrollo que rodea a la presente invención constituye en esencia un proceso en el cual es necesaria la intervención y la aplicación de la habilidad inventiva enfocada en la obtención de una composición estable, segura y eficaz; y que consecuentemente sea retirada la objeción de nivel inventivo que cuestiona la patentabilidad de la misma.

En complemento de la argumentación precedente, nos permitimos destacar que más allá de satisfacer el requisito de nivel inventivo, la presente invención exhibe un efecto técnico inesperado y sorprendente, el cual procedemos a comentar brevemente.

Como parte del desarrollo de la composición reivindicada, se dio lugar a la elaboración de una serie de Formulaciones I a VIII combinando diferentes excipientes a fin de caracterizar el comportamiento farmacotécnico de las mismas. Tras comparar los resultados obtenidos se concluyó lo siguiente:

"Se observó picado cuando se comprimen las formulaciones I a IV. La adición de ácido esteárico en las formulaciones V a VIII mejoró la lubricación sin desintegración por impacto y comprimibilidad. (...) El monohidrato de lactosa, NF (Fast Flo 316) se utilizó como un diluyente alterno y se prefirió sobre la lactosa anhidra (Formulación III) por sus propiedades capacidad de flujo."

Adaptado del capítulo descriptivo de la presente solicitud

Tal y como describe el anterior fragmento, las formulaciones I a IV (las cuales carecían de ácido esteárico) presentaron **picado**, resultando entonces en composiciones que **no cumplían con parámetros de calidad**. En contraste, las formulaciones V a VIII, que sí incluían ácido esteárico, manifestaron un mejor comportamiento en cuanto a **lubricación**, siendo igualmente **resistentes a la desintegración por impacto y comprimibilidad**.

Ahora bien, con relación a la inclusión de monohidrato de lactosa, los ensayos practicados revelaron que las composiciones de acuerdo con la presente invención manifiestan **mejor capacidad de flujo** en comparación con la formulación III, la cual incluía lactosa anhidra en su lugar.

Teniendo en cuenta que dicha formulación III es representativa del arte previo definido por el documento D1, es decir, composiciones que comprenden lactosa como excipiente de elección, concluimos que los anteriores resultados demuestran de manera contundente que la presente invención es **farmacotécnicamente superior** a los desarrollos existentes en el estado de la técnica, y por tanto, constituye una **mejora** a los mismos.

Dicho esto, solicitamos sea tenido en cuenta que esta **ventaja o superioridad** asociada a la formulación aquí reclamada representa un indicio de nivel inventivo que, como tal, respalda la patentabilidad de la presente invención pues demuestra que la misma constituye un claro **aporte** al campo técnico y su desarrollo no representa un proceso obvio para el versado en la materia.

En vista de lo anteriormente expuesto, respetuosamente solicitamos el retiro de las objeciones de la presente solicitud, ya que en opinión del solicitante cumple con todos los requisitos establecidos en la Decisión 486.

Atentamente,



JUAN PABLO CADENA SARMIENTO

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

C.C. 80.410.337 de Usaquén

Calle 70 A No. 4 - 41

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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*** Soporte del Pago ***

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CONSIGNACION	BANCO DE BOGOTA	062754387	669317994	16/03/2015	32.370.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
10 50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	32.000.00	320.000.00
			\$320.000.00

SON: **TRESCIENTOS VEINTE MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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REIVINDICACIONES

1. Una composición farmacéutica caracterizada porque comprende 7-(6-(2-hidroxiopropan-2-il)piridin-3-il)-1-((*trans*)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-*b*]pirazin-2(1*H*)-ona, ácido esteárico y monohidrato de lactosa.
2. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque comprende de 0.1-5% en peso de ácido esteárico.
3. La composición farmacéutica de conformidad con la reivindicación 2, caracterizada porque comprende de 0.4% en peso de ácido esteárico.
4. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque comprende de 40-60% en peso de monohidrato de lactosa.
5. La composición farmacéutica de conformidad con la reivindicación 4, caracterizada porque comprende de 49.2% en peso de monohidrato de lactosa.
6. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada además porque comprende celulosa microcristalina.
7. La composición farmacéutica de conformidad con la reivindicación 6, caracterizada porque la celulosa microcristalina tiene un tamaño de partícula nominal alrededor de 100 μm .
8. La composición farmacéutica de conformidad con la reivindicación 6, caracterizada porque comprende alrededor de 20-40% en peso de celulosa microcristalina.

9. La composición farmacéutica de conformidad con la reivindicación 6, caracterizada porque comprende alrededor de 31% en peso de celulosa microcristalina.

10. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque además comprende un desintegrante.

11. La composición farmacéutica de conformidad con la reivindicación 10, caracterizada porque el desintegrante es croscarmelosa de sodio.

12. La composición farmacéutica de conformidad con la reivindicación 11, caracterizada porque la composición farmacéutica comprende de 1-5% en peso de croscarmelosa de sodio.

13. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición farmacéutica comprende de 40-60% en peso de 7-(6-(2-hidroxiopropan-2-il)piridin-3-il)-1-((*trans*)-4-metoxyciclohexil)-3,4-dihidropirazino[2,3-*b*]pirazin-2(1*H*)-ona.

14. La composición farmacéutica de conformidad con la reivindicación 13, caracterizada porque la composición farmacéutica comprende de 15% en peso de 7-(6-(2-hidroxiopropan-2-il)piridin-3-il)-1-((*trans*)-4-metoxyciclohexil)-3,4-dihidropirazino[2,3-*b*]pirazin-2(1*H*)-ona.

15. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque además comprende estearato de magnesio.

16. La composición farmacéutica de conformidad con la reivindicación 15, caracterizada porque la composición farmacéutica comprende de 0.5-3% en peso de estearato de magnesio.

17. La composición farmacéutica de conformidad con la reivindicación 16, caracterizada porque la composición farmacéutica comprende de 1% en peso de estearato de magnesio.

18. La composición farmacéutica de cualquiera de la reivindicación 1, caracterizada porque la composición farmacéutica está formulada como una tableta.

19. La composición farmacéutica de conformidad con la reivindicación 18, caracterizada porque la tableta está revestida de película, y la película es Opadry rosa, Opadry amarillo u Opadry beige.

20. La composición farmacéutica de conformidad con la reivindicación 19, caracterizada porque el revestimiento de película es de 4% en peso de la tableta.

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Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review.

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ABSTRACT

Studies of active drug/excipient compatibility represent an important phase in the preformulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drugs and, consequently, their therapeutic efficacy and safety. The present review covers the literature reports of interaction and incompatibilities of commonly used pharmaceutical excipients with different active pharmaceutical ingredients in solid dosage forms. Examples of active drug/excipient interactions, such as transacylation, the Maillard browning reaction, acid base reactions and physical changes are discussed for different active pharmaceutical ingredients belonging to different therapeutic categories *viz* antiviral, anti-inflammatory, antidiabetic, antihypertensive, anti-convulsant, antibiotic, bronchodilator, antimalarial, antiemetic, antiamebic, antipsychotic, antidepressant, anti-cancer, anticoagulant and sedative/hypnotic drugs and vitamins. Once the solid-state reactions of a pharmaceutical system are understood, the necessary steps can be taken to avoid reactivity and improve the stability of drug substances and products.

KEY WORDS: Incompatibility, interaction, active pharmaceutical ingredient, excipients, lactose, magnesium stearate

INTRODUCTION

Preformulation is the first step in the rational formulation of an active pharmaceutical ingredient (API). It is an investigation of the physical-chemical properties of the drug substance, alone and in combination with

excipients. Assessment of possible incompatibilities between the drug and different excipients is an important part of preformulation. The formulation of a drug substance frequently involves it being blended with different excipients to improve manufacturability, and to maximize the product's ability to administer the drug dose effectively. Excipients are known to facilitate administration and modulate release of the active component. They can also stabilize it against degradation from the environment.

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Most excipients have no direct pharmacological action but they can impart useful properties to the formulation. However, they can also give rise to inadvertent and/or unintended effects such as increased degradation of the drug. Physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drug products, and consequently, their therapeutic efficacy and safety (1).

There have been several approaches proposed that satisfy the requirements of a drug-excipient chemical compatibility screen. The most resource sparing of these approaches is computational, where drug-excipient chemical compatibility can be predicted. This requires a comprehensive database of reactive functional groups for both drugs and excipients, combined with an in-depth knowledge of excipients and their potential impurities. Such an approach provides a rapid analysis and requires no bulk substance. However, there are inherent risks with using this computational approach as the sole source of information.

Binary mixture compatibility testing is another commonly used method. In this approach, binary (1:1 or customized) mixtures of the drug and excipient, with or without, added water and sometimes compacted or prepared as slurries, are stored under stressed conditions (also known as isothermal stress testing (IST)) and analyzed using a stability-indicating method, e.g. high performance liquid chromatography (HPLC). The water slurry approach allows the pH of the drug-excipient blend and the role of moisture to be investigated. Alternatively, binary mixtures can be screened using other thermal methods, such as differential scanning calorimetry (DSC) (2, 3). DSC is currently the leading technique in this field (4). The main benefit of DSC, rather than stressed storage methods, is its ability to quickly screen potential excipients for incompatibilities derived from the appearance, shifts or disappearances of peaks and/or variations in the corresponding ΔH (enthalpy of transition) (5). Other features such as low sample consumption also makes it

an attractive method. Although DSC is unquestionably a valuable technique, interpretation of the data may not be straightforward. In this method, the sample is exposed to high temperatures (up to 300°C or more), which in reality is not experienced by the dosage form. Thus, DSC results should be interpreted carefully, as the conclusions based on DSC results alone can be often misleading and inconclusive. Therefore results obtained with DSC should always be confirmed with IST.

IST involves storage of drug-excipient blends with, or without moisture, at elevated temperatures for a specific period of time (typically 3–4 weeks) to accelerate drug degradation and interaction with excipients. The samples are then visually observed for any changes in color or physical characteristics, and the drug content, along with any degradants, is determined quantitatively (6). Although more useful, the disadvantage with this method is that it is time consuming and requires quantitative analysis using e.g. HPLC. Ideally, both techniques, DSC and IST should be used in combination for the selection of excipients. Similarly, isothermal micro calorimetry is a popular method for detecting changes in the solid state of drug-excipient mixtures through changes in heat flux (7). The results from using thermal techniques can be indicative of whether formulations are stable, but reveal no information concerning the cause or nature of any incompatibility. Techniques such as hot stage microscopy and scanning electron microscopy can be used in conjunction with DSC to determine the nature of an apparent incompatibility (8). These techniques study the morphology of the drug substance and can determine the nature of physical transformations, thus indicating the type of incompatibility that has occurred (4). A more definitive result would be obtained using e.g. HPLC or HPLC-MS/MS. It is well known that the chemical compatibility of an API in a binary mixture may differ from that of a multi-component prototype formulation. An alternative is to test “prototype” formulations. The amount of API in the blend can be modified

according to the anticipated drug-excipient ratio in the final compression blend (9).

There are several examples of formulation instability resulting from solid-solid interactions (10, 11). Certain classes of compounds are known to be incompatible with particular excipients (12). Therefore knowledge of the chemistry of the drug substance and excipients can often minimize formulation surprises. Heat and water are the primary catalysts for drug-excipient interactions and play a critical role in the degradation of a drug substance (13). The majority of 'small molecule' API instability reactions occur via hydrolysis, oxidation and Maillard reaction. The moisture content of the drug and excipients plays a critical role in their incompatibility. Heat and moisture accelerate most reactions, even if moisture is not involved in the reaction scheme, since moisture brings molecules closer together, and heat always increases the reaction rate. The incompatibility between a drug and an excipient *per se*, and that which occurs between a drug and moisture/water activity due to the ability of the excipient to absorb moisture, represents two different kinds of incompatibilities. Excipients such as starch and povidone may possess a high water content (the equilibrium moisture content of povidone is about 28% at 75% relative humidity), which can increase drug degradation. The moisture level will affect the stability depending on how strongly it is bound and whether it can come into contact with the drug (14). It is generally recognized that aspirin is incompatible with magnesium salts. Higher moisture contents and humidity accelerate the degradation even further (14). Many different moisture mediated degradation mechanisms exist, but those mediated by surface moisture appear to be the most common (15). Consequently it is important that stress methods incorporate water to encourage the formation of all possible impurities. The way in which water facilitates degradation is not fully understood, but work carried out by Kontny *et al.* (15) has confirmed its importance. Degradation problems can, therefore, be difficult to avoid because water often cannot be entirely

excluded from drug product formulations. Many excipients are hygroscopic, (16, 17) and absorb water during manufacturing, for example during wet granulation. Depending on the degree of hydrolytic susceptibility, different approaches to tablet granulation can be used to minimize hydrolysis. For compounds such as acetylsalicylic acid that are readily hydrolysable, direct compression or dry granulation is preferable, to wet granulation. However drug-excipient incompatibility may still occur.

Chemical interaction between the drug and excipients may lead to increased decomposition. Stearate salts (e.g. magnesium stearate, sodium stearate) should be avoided as tablet lubricants if the API is subject to hydrolysis via ion-catalyzed degradation. Excipients generally contain more free moisture than the drug substance (16), and in an attempt to obtain the most thermodynamically stable state, water is able to equilibrate between the various components (18). Formulation can, therefore, potentially expose the drug substance to higher levels of moisture than normal, which greatly increases the possibility of even stable compounds degrading. In selecting excipients, it is probably best to avoid hygroscopic excipients when formulating hydrolytically labile compounds, although examples exist where the drug is deliberately formulated with over-dried hygroscopic excipients (e.g. Starch 1500) which act as a moisture scavenger to prevent the drug from coming into contact with water.

One of the most effective ways to stabilize a pH sensitive drug is through the adjustment of the microscopic pH of the formulation. Excipients with high pH stability and buffering agents are recommended. Humidity is another major determinant of product stability in solid dosage forms. Elevation of relative humidity usually decreases the stability, particularly for drugs that are highly sensitive to hydrolysis. For example, nitrazepam in the solid state showed a linear relationship between the logarithm of the rate constant for the decomposition of the drug at different relative humidities (19). In addition, increased humidity can also accelerate the

degradation process by facilitating interaction with excipients (20, 21). Molecular mobility is also responsible for solid-solid reactions (22-24). Systems with enhanced mobility have more reactivity. Mechanical stress is also expected to accelerate such reactions by creating a larger surface area, increasing the number of defects, and increasing the amount of amorphous material (10).

Oxidation reactions are complex and it can be difficult to understand the reaction mechanism. The best approach is to avoid excipients containing oxidative reactants such as peroxides and fumed metal oxides like fumed silica and fumed titanium dioxide. Excipients such as povidone and polyethylene glycols (PEGs) may contain organic peroxides as synthetic by-products which are typically more reactive than hydrogen peroxide. Although most compendial excipients have limits on metals, free ethylene oxide or other oxidizing agents via the peroxide or iodine value there are still some instances of oxidative degradation of drug due to presence of reactive peroxides in excipients such as povidone. For example, Hartauer *et al.* (2000) reported oxidative degradation of Raloxifene H.L. occurring via peroxide impurities in povidone (25). Thus, it is important to understand the purity and composition of the excipient prior to formulation.

Aldehyde-amine addition is another important type of reaction, which is responsible for incompatibility between excipients comprising reducing sugars (e.g. lactose, dextrose) and amine-containing drugs. Aldehyde-amine addition leads to the formation of a Schiff base, which further cyclizes to form a glycosamine followed by an Amadori rearrangement (26, 27). This sequence of reactions is called the Maillard reaction, and is responsible for a large number of incompatibilities between APIs and excipients.

Monkhouse (28) listed common solid-state incompatibilities as shown in Table 1.

Table 1 List of common solid-state incompatibilities

Functional Group (Example of API)	Incompatible with	Type of Reaction	Reference
Primary amine (e.g. Acyclovir)	Mono and disaccharides (e.g. lactose)	Maillard reaction	(26, 29)
Esters (e.g. Moexipril)	Basic components (e.g. magnesium hydroxide)	Ester hydrolysis	(30)
Lactone (e.g. Irinotecan HCl)	Basic components (e.g. magnesium hydroxide)	Ring opening (hydrolysis)	(31)
Carboxyl	Bases	Salt formation	(28, 32)
Alcohol (e.g. Morphine)	Oxygen	Oxidation to aldehydes and ketones	(33, 34)
Sulphydryl (e.g. Captopril)	Oxygen	Dimerization	(33, 34)
Phenol	Metals, polypladone	Complexation	(28, 32)
Gelatin	Cationic surfactants	Denaturation	(28, 32)

This present review discusses incompatibilities of 'small molecule' API's associated with different pharmaceutical excipients as summarized in Table 2. Incompatibilities of APIs with different pharmaceutical excipients are discussed below in subsequent sections relating to excipient types as follows: Saccharides, Stearates, Polyvinylpyrrolidone, Dicalcium phosphate dihydrate, Eudragit polymers, Celluloses, Polyethylene glycol, Polysorbate 80, Sodium lauryl sulfate, Chitosan, Magnesium oxide, Silicon dioxide, Carbonates, and Miscellaneous.

Saccharides

Lactose is perhaps one of the most commonly used excipients in pharmaceutical oral dosage forms (tablets) and, is in its crystalline form, generally considered to be least reactive. Blaug and Huang (99) reported that, crystalline lactose, rather than, amorphous lactose caused a problem in interaction of dextroamphetamine sulfate with spray dried lactose. Lactose is a reducing disaccharide and reactions between it and drugs containing amino groups have been reported. This interaction is shown in Figure 1. This sequence of such reaction is referred to as the Maillard reaction (26).

Table 2 A list of excipients and their incompatibilities with API's belonging to different therapeutic classes

Excipient	API and its Therapeutic Class
Saccharides	
(A) Lactose	Acyclovir (29) - Antiviral; Aceclofenac (35) and Ketoprofen (36-38) - Anti-inflammatory; Metformin (29)- Antidiabetic; Amlodipine (39), Ceronapril (40), Lisinopril (41) and Oxprenolol (42) - Antihypertensive; Fluconazole (43) - Antifungal; Primaquine (44) - Antimalarial; Promethazine (45) - Antiemetic; Fluoxetine (46) and Seproxetine Maleate (47) - Antidepressant; Picotamide (48) - Anticoagulant; Elamylate (43) - Antihemorrhagic; Aminophylline (49) and Clenbuterol (50) - Bronchodilator; Baclofen (51)- CNS Drug; Ranitidine (52) - GI Agent; Doxylamine (53) - Antihistaminic; Thiaminechloride HCL (54) - Vitamin; Pefloxacin (55) - Antibiotic
(B) Lactose/meglumine/ Tris Buffer Blend	Glipizide (56) - Antidiabetic
(C) Mannitol, Pearlitol (80% Mannitol +20 % Maize Starch)	Quinapril (9)- Antihypertensive; Primaquine (44)- Antimalarial; R-omeprazole (57) - GI Agent; Promethazine (45) - Antiemetic
(D) Starch	Seproxetine Maleate (47) - Antidepressant; Clenbuterol (50) - Bronchodilator
(E) Sodium Starch Glicollate	Clenbuterol (50) - Bronchodilator
(F) Dextrose	Pefloxacin (55) - Antibiotic
Stearates	
(A) Magnesium Stearate	Acyclovir (58) - Antiviral; Aspirin (59-62), Ibuprofen (8), Indomethacin (63, 64) and Ketoprofen (36-38)- Anti-inflammatory; Glipizide (56), Chlorpropamide (65), Glimepiride (66) and Glibenclamide (67) - Antidiabetic; Captopril (68, 69), Fosinopril (40), Moexipril (10, 30, 70), Oxprenolol (42) and Quinapril (9) - Antihypertensive; Cephalexin (71), Erythromycin (72), Nalidixic Acid (73), Oxacillin (74) and Penicillin G (74) - Antibiotic; Primaquine (44)- Antimalarial; Promethazine (45)- Antiemetic; Albendazole (75) - Antiamoebic; β -lapachone (76)- Anticancer; Clopidogrel (77)- Anticoagulant; Doxylamine (53) - Antihistaminic; Temazepam (42) - Hypnotic
(B) Stearic Acid	Doxylamine (53)- Antihistaminic
Polyvinyl Pyrrolidone (PVP)	Indomethacin (63, 64), Ibuprofen (8) and Ketoprofen (36-38) - Anti-inflammatory; Atenolol (63) and Oxprenolol (42)- Antihypertensive; Sulfathiazole (78) - Antibiotic; Haloperidol (79)- Antipsychotic; Ranitidine (52)- GI Agent; Doxylamine (53)- Antihistaminic; Temazepam (42)- Hypnotic; Clenbuterol (50) - Bronchodilator
Dicalcium Phosphate Dihydrate (DCPD)	Ceronapril (40), Oxprenolol (42) and Quinapril (9)- Antihypertensive; Metronidazole (80) - Antiamoebic; β -lapachone (76) and Parthenolide (81)- Anticancer; Famotidine (82)- GI Agent; Temazepam (42) - Hypnotic
Eudragit Polymers	
(A) Eudragit RS and RI	Diffunisal (83, 84), Flurbiprofen (83, 84) and Piroxicam (83, 84) - Anti-inflammatory
(B) Eudragit RL100	Ibuprofen (85) (86)- Anti-inflammatory
(C) Eudragit E100	Ranitidine (52) - GI Agent
Celluloses	
(A) Microcrystalline Cellulose (MCC), Avicel PH 101	Enalapril (87, 88) - Antihypertensive; Isosorbide Mononitrate (6) - Antiangina; Clenbuterol (50) - Bronchodilator
(B) Cellulose Acetate	Isosorbide Mononitrate (6)- Antiangina
(C) Hypromellose Acetate Succinate (HPMCAS)	Dyphylline (89) - Bronchodilator
(D) Hydroxypropyl Cellulose	Trichlormethiazide (90) - Diuretic
PEG	Ibuprofen (91), Ibuprofen (8) and Ketoprofen (36-38)- Anti-inflammatory; Phosphomycin (92) - Antibiotic; Clopidogrel (77)- Anticoagulant
Polysorbate 80	Ibuprofen (91) - Anti-inflammatory
Sodium Lauryl Sulfate	Chlorpropamide (65) - Antidiabetic; Clopidogrel (77)- Anticoagulant; Chlordiazepoxide (11, 93) - Hypnotic
Chitosan	Diclofenac (11, 94) and Piroxicam (95)- Anti-inflammatory
Magnesium Oxide	Ibuprofen (96) - Anti-inflammatory
Silicon Dioxide	Enalapril (87, 88) - Antihypertensive
Carbonates	
(A) Sodium Carbonate	Adefovir Dipivoxil (97) - Antiviral
(B) Sodium Bicarbonate	Ibuprofen (96) - Anti-inflammatory
Miscellaneous	
(A) Plasdone	Glimepiride (66) - antidiabetic
(B) Ascorbic acid	Atenolol (63) - antihypertensive
(C) Citric acid	Atenolol (63)- antihypertensive
(D) Butylated hydroxyanisole	Atenolol (63)- antihypertensive
(E) Succinic acid	Phosphomycin (92)- antibiotic
(F) Na dioctylsulfocuccinate	Phosphomycin (92) - antibiotic
(G) Ca and Mg salts	Tetracyclins (98) - Antibiotic
(H) Talc	Seproxetine maleate (47) - antidepressant
(i). Precirol ATO 5	Temazepam (42)- hypnotic

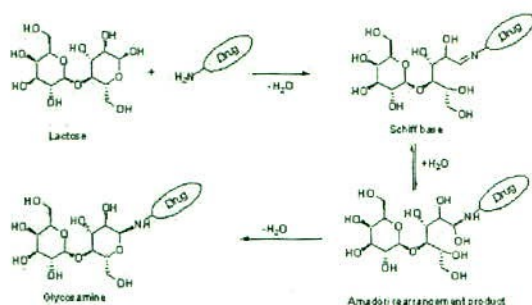


Figure 1 A general Maillard reaction between lactose and an amine group-containing API

There are a number of reports of the incompatibility of lactose with amine-containing APIs. DSC and FT-IR studies showed that aminophylline, a bronchodilator drug consisting of a purine ring system coupled with an ethylenediamine moiety was incompatible with lactose. Brown discoloration appeared in samples containing 1:5 (w/w) mixtures of aminophylline and lactose following three weeks of storage at 60°C (100). Another group of researchers also reported similar findings from stability experiments using aminophylline combined with four tablet excipients (cellulose starch, glucose (dextrose) and lactose) stored at 5°C, room temperature ($27 \pm 3^\circ\text{C}$), 45°C and in direct sunlight for 30 days. Degradation of the drug increased with increase in temperature and on exposure to sunlight. The degradation was particularly intense in the presence of glucose and lactose and a change in color from white to yellow occurred in such mixtures. At 45°C and in sunlight both pure drug and its mixtures changed color during the storage period (49).

Seroxetine, a selective serotonin re-uptake inhibitor, is a primary amine and an active metabolite of fluoxetine. Its maleate hemihydrate salt demonstrated an incompatibility with lactose and starch in a gelatin capsule dosage form. Analogous to a Michael addition, there is a formation of 1-4 addition product between the drug and the maleic acid facilitated by the free moisture associated with the starch. Formation of the 1,4-addition product was noticed in the presence of pregelatinized starch while a Maillard reaction product was formed

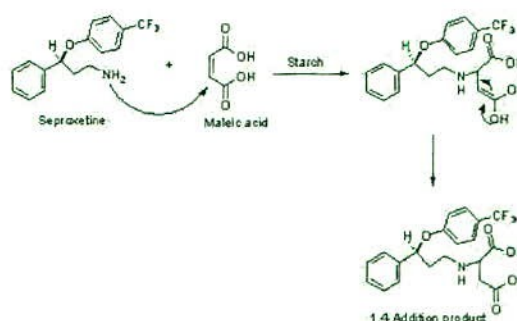


Figure 2 Interaction between Seroxetine and maleic acid in the presence of starch (47).

by interaction of the drug with lactose as shown in Figure 1 (47). The schematic of the interaction between seroxetine and maleic acid in the presence of starch is shown in Figure 2. An ACE inhibitor, ceronapril containing a primary amine function, also exhibited incompatibility with lactose due to a Maillard reaction. HPLC studies of mixtures of ceronapril with lactose after 3 weeks storage at 50°C showed that the ceronapril had degraded by 8.4% (40).

Amlodipine is a dihydropyridine calcium channel blocker containing a primary amine group. It was found to be unstable in a multi-component mixture with lactose, magnesium stearate and water. Amlodipine besylate glycosyl was identified as a major reason for degradation due to a Maillard reaction between the drug and lactose (39). Metformin is a biguanide class of antidiabetic drug also containing a primary amine group. Binary mixtures of metformin with starch and lactose showed interaction upon heating, changing the melting temperature of metformin and the accompanying enthalpy. A change in the melting temperature of metformin was observed for all mixtures tested i.e. metformin: starch ratios of 2:8; 3:7; 1:1; 7:3 and 8:2. The melting peak for metformin was not visible in the presence of lactose suggesting an interaction between them. Displacement of the melting temperature of metformin, for all the metformin–starch mixtures tested, confirmed the interaction between the two materials. One possible reason for this interaction can be a Maillard reaction between

the lactose carbonyl that can react with an amine group of metformin (101). Acyclovir is a purine class of antiviral drug, again, containing a primary amine group. Results of DSC studies of physical mixtures of the drug with lactose suggested an incompatibility, confirmed by liquid chromatography coupled with mass spectrometry (LC-MS) which identified the formation of a Maillard reaction as shown in Figure 1 (29).

Baclofen is a primary amine used in treatment of spastic movement disorders. Using LC-MS studies showed that it was incompatible with lactose as indicated by the formation of a Maillard reaction product. Fourier transform infrared spectroscopic analysis (FTIR) showed the formation of the imine bond, which indicated that baclofen, undergoes a Maillard-type reaction with lactose (51).

Lactose monohydrate also interacted with moisture sensitive drugs and affected the stability of the drug (102). A mixture of thiamine hydrochloride and lactose underwent the Maillard reaction forming the N-glycosylamine, which was further converted to the amino ketone via an Amadori rearrangement. The configuration of an α -(spray-dried) lactose and β -anhydrous lactose was not relevant for the Maillard reaction because the reaction of lactose is believed to occur through an open-chain form. Spray dried lactose also contains amorphous lactose which is important for reactivity (99). Similar changes in spectra were noticed for binary mixtures of both forms of lactose with thiamine hydrochloride. A change of tablet color due to the degradation of drug under accelerated conditions was observed (54).

Although primary amines are the most commonly reported substrates for the Maillard reaction, there are also reports of Maillard reactions with secondary amines. Oxprenolol hydrochloride (42), fluoxetine hydrochloride (46), etamsylate (43), ranitidine (52) and aceclofenac (35) are examples. Etamsylate is 2,5-dihydroxybenzene sulfonic acid containing an N-ethylethanamine group. The DSC thermograms

of the mixtures of etamsylate and lactose showed additional peaks, in addition to those recorded for the individual components. In the case of the etamsylate-lactose mixture an additional prominent endotherm appeared at 118.5°C. The main peak at 136.7°C in the original etamsylate thermogram shifted to a lower temperature of 131.4°C. This was probably due to solid solubility of lactose in etamsylate (43).

Ranitidine HCl is a drug used for the treatment of gastric ulcer. The drug is a secondary amine. An incompatibility was reported in a 1:1 binary mixture of the drug and lactose. The DSC thermogram of lactose monohydrate showed a dehydration peak at 150°C followed by an endothermic melting peak at 222°C. However, the thermogram of the binary mixture showed a broader peak at 150°C and the disappearance of the melting peak of lactose at 222°C, indicating a possible interaction between ranitidine and lactose (52). Aceclofenac is a Non-Steroidal Anti-inflammatory drug (NSAID) with a secondary amine group. It showed an incompatibility with spray-dried lactose (SDL). In the binary mixture of aceclofenac and SDL (7:3), an IR peak at 1848.6 cm^{-1} using pure aceclofenac was observed. This peak disappeared and another peak at 1771.5 cm^{-1} shifted to 1762.8 cm^{-1} . In the mixture of aceclofenac and SDL at a ratio of 6:4, peaks at 1848.6 and 1771.5 cm^{-1} disappeared completely using pure aceclofenac. A further increase in the SDL concentration gave similar results (35).

There are also some reports of lactose interaction with drugs not having a primary or secondary amine group such as Fluconazole and Pefloxacin. The mixture of fluconazole and lactose showed additional peaks by DSC at 86.1°C and 136.4°C respectively, in addition to the peak corresponding to the melting of pure drug at 140.2°C. This indicates an interaction between the drug and the excipient (43).

The antibacterial drug pefloxacin mesylate also does not contain a primary or secondary amine

group but is reported to interact with anhydrous dextrose, Pearlitol® (mannitol), Lactopress SD (directly compressible lactose), Lactochem FP [Natural L (+) Lactic Acid], and Lycatab® (starch/calcium carbonate), as indicated by the loss of the characteristic melting endothermic peak of perfloxacin mesylate in the DSC thermogram. The enthalpy changes in admixtures were within a 10% limit of the calculated enthalpy. However, the results of isothermal stability studies did not support the conclusions from the DSC results (55). Since elevated temperatures in DSC study are not necessarily relevant to ambient conditions, isothermal stress results are more reliable. Further, additional stability studies of prototype formulation at accelerated conditions can be carried out to discover any potential incompatibility. Another tertiary amine drug, promethazine hydrochloride used as an antiemetic, antihistamine and sedative, resulted in a brown color in stressed binary mixture studies (stored at 55°C for 3 weeks) indicating a potential interaction with lactose monohydrate (45).

Meglumine is an amino sugar derived from sorbitol. The incompatibility of the antidiabetic drug glipizide with the blend of meglumine/TRIS buffer has been reported. An interaction was observed between meglumine and glipizide but the mechanism has not been established. A yellow coloration caused by the interaction of the amine group of meglumine/TRIS buffer and lactose was observed. Because the solubility modifier (meglumine/TRIS buffer) was required to increase the solubility of glipizide in the formulation, the presence of lactose in the formulation was considered detrimental to long-term stability. In addition, a melting endothermic peak of glipizide was found to be missing in a glipizide–lactose mixture, which suggested an interaction between the two components. A sharp endothermic peak at 130.32°C was observed in the DSC thermogram of meglumine, which broadened and shifted to lower temperature (122.81°C) for a glipizide and meglumine mixture. The drug peak was completely absent in the DSC trace of

the mixture, which suggested a possible interaction.

The DSC trace of TRIS buffer showed two endothermic peaks at 139.14°C (probably due to evaporation of adsorbed moisture) and 172.73°C (melting point of TRIS buffer), followed by an endotherm at 300°C, probably due to the decomposition of TRIS buffer. In the thermogram of glipizide and TRIS buffer mixture, the TRIS buffer peak at 139.14°C shifted to a lower temperature (135.60°C). In addition, the drug peak was missing and a broad endothermic peak was observed at 296.16°C (56). The DSC results were indicative of an interaction between glipizide and TRIS buffer. However, the IR spectrum of glipizide–TRIS buffer mixture showed the presence of characteristic bands corresponding to glipizide. There was no appearance of new bands. Hence, there was strong evidence of unchanged drug structure and lack of chemical interaction between the two. Thus, it was concluded that there was no chemical incompatibility between glipizide and TRIS buffer.

The results confirmed that DSC could be used as a rapid method to evaluate the compatibility between a drug and excipients. However, caution needs to be exercised while interpreting the DSC results alone. Wherever possible, results from other techniques such as IR and quantitative analysis after storage under stressed conditions, should be taken in conjunction with DSC results to reach any definite conclusion. In the present example, the results from the DSC along with IR and/or HPLC were successfully employed to assess the compatibility of glipizide with the excipients used in the development of extended release formulations. Based on the results of IR and/or HPLC analysis, any possible pharmaceutical incompatibility between glipizide and TRIS buffer and magnesium stearate was ruled out. Other APIs which show possible incompatibilities in binary mixtures with lactose include ketoprofen (36, 37), picotamide (48), primaquine (44), clenbuterol (50), sennosides A and B (103) and lisinopril (41).

Mannitol is a sugar alcohol derived from a sugar by reduction and is a commonly used, non-hygroscopic and chemically stable excipient, with good flow properties and high compressibility. As such, it is suitable for use with APIs sensitive to water. It is primarily used as a diluent (10-90%) in tablet formulations. There have, however, been some reports of adverse effects of mannitol on stability of drugs. This has been attributed to continued crystallization of mannitol from a system that is initially only partially crystalline. This can result in an increase in water activity in amorphous regions where the drug is located, with subsequent adverse effects on stability (104). Mannitol was found to be incompatible with omeprazole (57), primaquine (44) and quinapril (9). Mixing mannitol with either of the omeprazole sodium isomers in their racemic forms led to a decrease in the crystallinity of the resulting mixtures. In the case of S- and R,S-omeprazole sodium the crystallinity is lost. Mixing of mannitol and R-omeprazole sodium leads to the decrease in melting temperatures and broadening the melting peaks that can be attributed to the interaction between two different crystalline structures. There was better compression of the S-omeprazole-mannitol mixture resulting in a smoother tablet surface, compared to that of R-omeprazole-mannitol. Significant physical interaction of R-omeprazole with mannitol was observed from localized thermal analysis (LTA) and DSC results (57).

Despite of the well known interaction of lactose with drugs that contain primary and secondary amine groups, it continues to be one of the most widely used diluents. Most of the Maillard reactions may be prevented by reducing the water activity in the formulations and using appropriate packaging. Castello and Mattocks (1962) reported that the Maillard reaction occurs only in the presence of an amine base and not in the presence of the salt. The release of free-base from the amine salt occurs by reaction of the alkaline lubricant, for example magnesium stearate, which removes hydrogen ion with the formation of stearic acid, furnishing an alkaline medium in the adsorbed moisture (105).

Stearates

Magnesium stearate is widely used as a lubricant in the manufacture of pharmaceutical solid dosage forms. Literature shows that there are numerous reports of the incompatibility between stearates and active pharmaceutical ingredients. Chemical incompatibility between aspirin and magnesium stearate results in a number of potentially undesirable products, such as salicylic acid, salicyl salicylic acid and acetyl salicyl salicylic acid (106, 107). Several theories have been suggested to explain the mechanism of this chemical incompatibility. Acetylsalicylic acid is a moisture-sensitive drug (108) hence its degradation is often associated with the presence of water (109) and/or alkaline pH (110). Tablet mixtures containing aspirin and drugs with easily-acetylated groups react to give acetyl compounds and salicylic acid. Troup and Mitchner (111) reported the reaction of phenylephrine hydrochloride with acetylsalicylic acid where an acetyl group is transferred from acetylsalicylic acid to the phenylephrine. For example, mixtures of phenylephrine hydrochloride and aspirin contained 80% of acetylated phenylephrine after 34 days at 70°C. Adding starch and magnesium stearate slowed this reaction to about 1% in 34 days, while adding magnesium stearate alone resulted in complete decomposition in 16 days. In addition some diacetylated product was produced. This reaction may proceed by direct acetylation. Similarly, aspirin tablets containing codeine or acetaminophen yielded acetylated drugs when heated (112, 113). Kornblum and Zoglio (109) found that the rate of decomposition of acetylsalicylic acid in suspensions with lubricants, such as magnesium stearate, was associated with the high solubility of the magnesium salt of acetylsalicylic acid. This formed a buffer with solvated acetylsalicylic acid, creating a pH environment that was detrimental to the stability of the compound. It has also been suggested that the presence of MgO impurities in magnesium stearate catalyze degradation by creating an alkaline pH environment (59). However, the relationship between pH and

decomposition is controversial, with some authors claiming that pH does not play a significant part in the solid state decomposition (106). Other reports suggested that the main mechanism of incompatibility was a reduction in the melting point of acetylsalicylic acid, which would generate a liquid layer on the surface of the magnesium stearate particles, thereby accelerating decomposition. The presence of liquid films around decomposing acetylsalicylic acid particles was demonstrated by microscopic examination. Similarly, Miller and York (60) described the formation of a magnesium stearate surface film around acetylsalicylic acid particles, suggesting that the intimate contact between the two materials may facilitate the lowering of the acetylsalicylic acid melting point (61, 62). Further Gordon *et al.* (85) noticed that in the presence of stearates ibuprofen forms a eutectic which sublimates.

Oxprenolol hydrochloride, a drug used for the treatment of angina pectoris showed an incompatibility in a binary mixture with magnesium stearate. The binary mixture showed two overlapping endothermic peaks with onsets of transition at 85°C and 96°C. The broad melting endotherm at 110°C to 118°C for magnesium stearate was absent in the binary mixture (42). Albendazole, a benzimidazole class of anthelmintic drug showed an incompatibility in a 1:1 binary mixture with magnesium stearate. Exposure of the binary mixture to heat and moisture resulted in degradation confirmed by DSC and HPLC (75). Compatibility studies of the ACE inhibitor fosinopril sodium with different excipients and 20% added water resulted in the formation of degradation product A as shown in Figure 3. However, in the presence of magnesium stearate, formation of product A was accelerated along with the formation of two other degradation products B and C (Figure 3). The structure of degradation product C appears to be incorrectly transcribed in the original paper (additional terminal methyl should not be present) (40). Based on an HPLC investigation, 90% of the drug degraded in 1 week. In a separate study, when a 1:1 mixture of fosinopril

sodium and magnesium stearate was exposed to 75% RH at 50°C, the degradation of fosinopril sodium after 3 weeks was less than 1%. This was because both fosinopril sodium and magnesium stearate were non-hygroscopic, although the interaction between them is mediated by water. This would not be the case in capsules and tablets where other formulation components, such as microcrystalline cellulose, starch, gelatin shell etc., would result in moisture sorption (40).

The antitumor drug, β -lapachone showed an interaction with magnesium stearate based on FTIR studies. The disappearance of different magnesium stearate bands at 1579.5 and 1465.7 cm^{-1} from the FTIR spectra for both, stressed mixtures (samples were stored in an oven at 40°C and 75% relative humidity in closed containers using sodium chloride saturated solutions for a month) and thermally stressed mixtures (the drug, some excipients and its mixtures were subjected to thermal stress by heating up to 160°C at a rate of 10°C min^{-1}) suggested the decomposition of the excipient. Additionally, some changes were observed in the β -lapachone bands at 2978 cm^{-1} and 1568 cm^{-1} assigned to the aromatic C-H and C-C respectively. Heating-cooling DSC (HC-DSC) experiments confirmed the hypothesis of magnesium stearate degradation since the second heating revealed only the melting peak of β -Lapachone, which was observed at a lower

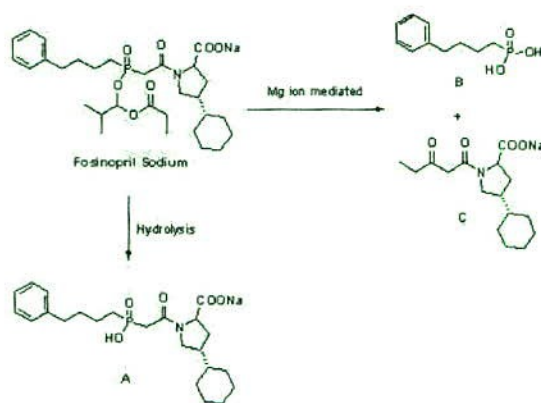


Figure 3 Interaction between Fosinopril sodium and magnesium stearate (40).

temperature and associated enthalpy and none of the magnesium stearate thermal events were observed. Heating to 160°C does not promote changes in the morphology of β -Lapachone or magnesium stearate separately but when heated together the sample becomes black as a result of the degradation of magnesium stearate. This evidence of interaction suggests that magnesium stearate should be avoided in β -lapachone formulations (76).

Captopril is a pyrrolidine carboxylic acid derivative used in the treatment of hypertension. It showed surface interactions with metallic stearates during grinding (5 min at room temperature at 32% or 80% RH). A mixture of captopril and each metallic stearate before and after grinding gave different results in DSC, thermogravimetric (TGA) and FTIR studies. Although there was no interaction between captopril and sodium stearate during grinding, grinding could induce the trans cis isomerization of captopril in a ground mixture of captopril-sodium stearate. There was no evidence of solid-state interaction between captopril and monoaluminum stearate, but grinding appeared to accelerate the solid-state interaction of captopril with magnesium stearate. The solid-state interaction between captopril and magnesium stearate was evidenced by the shifting of the IR spectral peak for the -COOH of the stearate moiety from 1578 cm^{-1} to 1541 cm^{-1} . This was due to the interaction of the -OH group in the carboxylic acid function of captopril with bridging coordination of the -COO⁻ group of magnesium stearate via hydrogen bonding involving water. The interaction between captopril and magnesium stearate was stopped at 60°C due to evaporation of water from the ground mixture (68). Another group of researchers (69) also noticed similar type of results for a captopril and magnesium stearate mixture. The DSC thermogram of the binary mixtures indicated a possible interaction due to the disappearance of the characteristic captopril fusion peak.

Chlorpropamide, a sulfonylurea antidiabetic drug showed a possible solid-solid interaction, but not necessarily a pharmaceutical incompatibility, in a binary mixture of chlorpropamide with magnesium stearate. The DSC curve of the chlorpropamide/magnesium stearate mixture resulted in only one endothermic event at 96.3–108.6°C suggesting a drug-excipient interaction when heated. A substantial decrease in the dissolution rate was observed for chlorpropamide tablets containing magnesium stearate after 6 months of storage at 40°C/75% RH (65). The ACE inhibitor quinapril, a tetrahydroisoquinoline carboxylic acid, was incompatible with magnesium stearate due to the basicity of magnesium stearate, and because the rate of degradation was mediated by the availability of moisture (9). DSC studies showed that the antiviral drug, acyclovir also interacted with magnesium stearate, as shown by the disappearance of the characteristic acyclovir fusion peak in the thermogram of the binary mixture. X-ray powder diffraction (XRPD) did not provide evidence of an incompatibility between acyclovir and magnesium stearate, since the diffraction peaks remained unaltered in the physical mixture. The main difference observed in the FTIR of binary mixtures of acyclovir and stearic acid was the significant decrease in the band attributed to the -OH group, indicating a possible chemical interaction between these compounds (58).

The sedative drug, doxylamine succinate, was incompatible with magnesium stearate, stearic acid, povidone (PVP) and lactose (53). Salt forms of cysteine showed interaction with magnesium stearate and other excipients such as xylitol, sorbitol and two gum bases, Every T Toco and Smily 2 Toco (114). Other APIs which have been found to be incompatible with stearates are glimepiride (66), cephalexin (71), glipizide (56), ibuprofen (8), indomethacin (63, 64), ketoprofen (38), moexipril (10, 30, 70), nalidixic acid (73), primaquine (44), promethazine hydrochloride (45), temazepam (42), glibenclamide (67), penicillin G (74), oxacillin (74), clopidogrel besylate (77) and erythromycin (72). It has been suggested that stearate salts

should be avoided as tablet lubricants if the API is subject to ion-catalyzed degradation. The degradative effect of alkali stearates is inhibited in the presence of malic, hexamic and maleic acid due to competition for the lubricant cation between the drug and additive acid (115). In some cases the interactions may not occur at the typical use level of magnesium stearate (0.25% to 0.5%). An even more important concern is mixing time, which can directly affect the disintegration time and dissolution of the drug from the solid dosage form. This is a detrimental physical interaction.

Povidone (PVP, polyvinyl pyrrolidone, copovidone)

PVP is commonly used as a binder in tablet formulations, as a film forming agent, and also for forming amorphous dispersions of drugs. It was found to be incompatible with a wide range of APIs. The antimicrobial drug sulfathiazole interacted with PVP, the rate increasing at higher PVP concentrations (78). In the DSC thermogram of an oxprenolol:PVP mixture, apart from the adsorbed water endotherm, a second broad endotherm, followed by degradation and/or vaporization was seen, while the endotherm characteristic of oxprenolol hydrochloride was absent indicating an interaction (42). Evidence of an interaction between the antihypertensive drug atenolol and PVP showed substantial changes in the DSC thermograms of a drug-excipient binary mixture. This interaction was enhanced or mediated by the free (unbound) water of the PVP. Indications of interaction were greater in the PVP-rich mixture, in the moisture treated mixtures, and in mixtures annealed (at 70°C) in closed containers, where relative humidity would be expected to be higher than in open containers. Temperature conditioning only affected (on the atenolol melting enthalpy) considerably after prolonged annealing in a closed container. This effect was less than that caused by moisture conditioning which, in addition, also appeared to modify the crystalline order of the atenolol (63).

A strong interaction between PVP and haloperidol was observed, favored by mechanical stress and more evident in the 20:80 binary mixture. The melting peak of the haloperidol showed a low temperature shoulder. The onset temperature of this shoulder corresponded to that of the peak present in the 20:80 mixture. The total enthalpy change was about 18% lower than would have been expected if no interaction had occurred between the components (79). PVP also showed an interaction with ibuprofen (8), indomethacin (63, 64), ketoprofen (36-38), clenbuterol (50) and temazepam (42). At 2% to 5% PVP may not prove detrimental to many drugs. However, when used at higher levels for specialized applications such for the formation of amorphous dispersions, then the interactions may be deleterious. Since PVP is produced by free radical polymerization of N-vinylpyrrolidone using hydrogen peroxide as an initiator; a commercial PVP always contains traces of unreacted peroxides which may oxidize APIs. Therefore for drugs where peroxide degradation may be of concern (e.g. Ranitidine HCl), the use of PVP as a binder should be avoided. Hartauer *et al.* (25) reported that the presence of povidone and crospovidone, in the tablet formulation of raloxifene hydrochloride, led to oxidation of the drug. The formation of the N-oxide derivative of the drug substance was confirmed based upon spectroscopic characterization and chromatographic comparison to the synthetic N-oxide. However, the dissolution of Raloxifene HCl could not be achieved without using PVP (116). Same authors also showed that phenolic impurities in tablet binding agents, such as povidone and disintegrants such as crospovidone, can lead to photodegradation of the drug through free radical reactions.

Dicalcium phosphate dihydrate (DCPD, Emcompress®)

DCPD is commonly used as a filler in tablet formulations and as a dental polishing agent in toothpaste that contains sodium monofluorophosphate. It is one of the most common

diluents for tablets, but is susceptible to dehydration at quite low temperatures in the presence of water vapor, thus crucial choosing conditions for processing and storage of the dosage forms. It has been shown to be incompatible with a number of acidic drugs as well as with sodium salts of poorly water soluble drugs due to its alkaline nature (117, 118).

Temazepam is a benzodiazepine hypnotic drug. It is acidic in nature with pKa of 1.61 and therefore when formulated with the basic excipient DCPD, an interaction was observed as indicated by DSC results (42). The combination of the antihypertensive drug oxprenolol hydro-chloride with DCPD showed, apart from the characteristic oxprenolol hydrochloride endo-therm, an extra endotherm with an onset of 136°C indicating an interaction (42). The ACE inhibitor ceronapril, which is incompatible with lactose, was also found to be incompatible with DCPD. HPLC studies of mixtures of ceronapril with DCPD showed that ceronapril degraded by 2.5% after 3 weeks of storage. The degradation product formed in presence of DCPD was identified (Figure 4) using LC-MS and liquid chromatography coupled with mass spectrometry/mass spectrometry (LC-MS-MS). This product was formed through an oxidative process which was not predicted based on initial preformulation testing (40).

The antitumor drug, β -lapachone is sensitive to alkaline pH and when formulated with DCPD was found to be incompatible. The heating-cooling DSC results suggested that lapachone promotes DCPD dehydration at lower temperatures, at the same temperature as the melting range of the drug. The DCPD water of crystallization (20.9% of the DCPD weight) partially dissolves the β -lapachone and the resultant basic environment could decompose the β -lapachone. This was verified by the second heating which showed the broad drug melting peak shifting to a lower temperature with a slight associated enthalpy change, thus a pos-

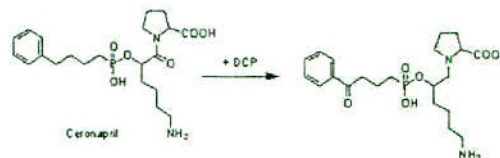


Figure 4 Interaction between Ceronapril with dicalcium phosphate (40).

sible sign of drug degradation. Accentuated changes were also detected in the bands corresponding to the functional groups of the drug, in the thermally stressed mixtures (TSM), which indicated chemical decomposition of β -Lapachone (76).

Parthenolide, a naturally occurring furanone, was found to be incompatible with DCPD. This could be attributed to the alkaline nature of DCPD (81). Other drugs which were found to be incompatible with DCPD include famotidine (82), nalidixic acid (73), quinapril (9) and metronidazole (80).

Eudragit® polymers

Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acid. The physicochemical properties of the different polymers are determined by the types of functional groups. These polymers are available in a range of different physical forms (aqueous dispersion, organic solution granules and powders) and are widely used for targeted and controlled drug delivery. The acidic nature of some Eudragit polymers has resulted in a number of incompatibilities with active ingredients.

Three NSAIDs, diflunisal, flurbiprofen, and piroxicam showed interaction with Eudragit polymers (RS100 and RL100). These researchers showed that, due to the acidic nature of Eudragit RS100 and RL100, except for mechanical dispersion, the drugs interacted with Eudragit matrixes by virtue of electrostatic interactions with the ammonium groups present in the polymer. These interactions were stronger for drugs bearing a carboxylic moiety, thus having lower pK_a values which signi-

ificantly affected the drug release profile from solid dispersions. The progressive disappearance of FT-IR, X-ray, and thermotropic drug signals in solid dispersion was more likely related to the increasing amount of the polymers, which exert a diluting effect on drug signals. DSC of flurbiprofen exhibited a sharp endothermic peak around 115°C, corresponding to its melting point. The dispersion of flurbiprofen in the Eudragit RS and, most often in the Eudragit RL matrix, at both 1:2 and 1:5 weight ratios resulted in a complete suppression of the drug fusion peak, suggesting a homogeneous solution of the drug in the polymer. However, the mere physical dispersion of the drug with Eudragit RS or Eudragit RL also resulted in a modification of the thermotropic profile. At the lower flurbiprofen-polymer ratio a downward shift of the drug fusion peak occurred in 2 partially superimposed peaks (centered at 98°C and 106°C, respectively). In the 1:5 w/w mixture, these peaks were further reduced or even absent, giving a DSC thermogram comparable to that of the corresponding solid dispersion. An XRPD analysis showed clearly that the systems prepared using lower amounts of polymer still showed the typical signals for drug crystals. However, increasing the Eudragit RS ratio progressively weakened their intensity (83, 84).

Ibuprofen (a NSAID) was also incompatible with Eudragit. Physical and chemical interaction with the carboxylic group of ibuprofen occurs because of electrostatic interactions and/or hydrogen bonding with the quaternary ammonium groups in Eudragit RL. This probably inhibits its uniform dispersion in the polymer network and ultimately affects the drug loading and ibuprofen release profile *in vitro* and *in vivo*. Pignatello *et al.* (86) mixed different chemical forms of ibuprofen (free acid, sodium salt, and n-butyl ester) with Eudragit RL100 at increasing weight ratios in order to investigate the role of the carboxylic group in the interaction with the Eudragit RL polymer. As the acid form, ibuprofen crystallized within the polymer network under the experimental conditions when its concentration exceeded the solubility

of the drug in the polymer itself. At lower weight ratios, the drug existed in an amorphous or microcrystalline state, however, thoroughly dispersed in the polymer matrix. The thermal behavior of the solid dispersions and mixtures suggested that the polymer inhibited the melting of the drug crystals. A large endothermic peak is only visible above 140°C, probably due to the beginning of polymer degradation. The systems containing higher polymer ratios (33% of Eudragit RL with acid-free form of the drug (IBU/A) and 33% of Eudragit RL with ibuprofen sodium salt (IBU/S) aqueous solution) showed a melting peak at 146°C and 97.5°C, respectively. These findings from powder X ray diffraction (PXRD) analysis confirmed that, above a certain concentration, the excess of drug was not able to form a homogeneous solid solution with the polymer. IR studies showed that, ibuprofen exhibited a strong peak at 1720 cm⁻¹ for carbonyl group stretching, while for its solid dispersion a broader and weaker signal was visible, at around 1725 cm⁻¹ (86).

A mild interaction between the antiulcer drug ranitidine and Eudragit E100 has been reported. Although there was no alteration in the DSC thermogram of the ranitidine-Eudragit mixture, compared to those of pure compound, careful examination of DRIFTS spectrum (diffuse reflectance infrared Fourier transform spectroscopy) of 1:1 drug-Eudragit E100 mixture revealed a slight shift to a higher wave number of the band associated with the protonated tertiary amine group R₃-NH⁺ of ranitidine HCl at 2560 cm⁻¹. This suggested a mild interaction, such as hydrogen bonding, between protonated tertiary amine group of the drug and a functional group on the polymer (52). The use of acidic film formers Eudragit L 100, hypromellose acetate succinate (HPMCAS-HF), Hypromellose phthalate grade 55 (HP-55), and shellac resulted in instability of the acid-labile proton pump inhibitor omeprazole in solid drug-polymer blends at accelerated storage conditions (40°C/75% RH). HP-55 caused the highest degree of omeprazole degradation, followed by shellac, HPMCAS-

HF, and then Eudragit1 L 100 (119). Despite of the interaction of methacrylic acid co-polymers with most drugs belonging to the proton pump inhibitors group, the polymers are widely used in enteric coat formulations because of their ability to control drug release within a narrow pH range. The incompatibility is avoided by suitably protecting the drug using a barrier coating.

Celluloses

Methylcellulose is widely used in a variety of oral and topical pharmaceutical formulations. It is also extensively used in cosmetics and food products. MCC is used as an inactive filler in tablets and as a thickener and stabilizers in processed foods. Hydroxypropyl methylcellulose (hypromellose) has been used as an excipient in oral tablet and capsule formulations, where, depending on the grade, it functions as a controlled release agent delaying the release of a medicinal compound into the digestive tract. Different grades can also be used as binders or as a component of tablet coatings

It has been reported that the degradation rate of enalapril maleate was accelerated by several orders of magnitude in the presence of MCC. The MCC appeared to reduce the apparent heat of fusion of the enalapril maleate. At a heating rate of 10°C/min, the DSC thermogram for enalapril maleate showed two partially superimposed endothermic events. The first was due to melting and the second due to thermal decomposition. This indicated that decomposition takes place, to some extent, during melting. Moreover, in the DSC thermogram for the enalapril maleate:MCC binary mixture, there is an increase in the degree of overlap of the two events. However, the authors did not attempt to separate the thermal events by decreasing the heating rate (87). Other researchers (88) have also demonstrated an increase in the degradation rate of enalapril maleate in presence of MCC using DTA (differential thermal analysis) studies and accelerated stability testing. Apart from MCC, magnesium stearate, calcium phosphates and

several other common disintegrants (starch, sodium starch glycolate, croscopovidone and croscarmellose sodium) were also shown to contribute to the decomposition of enalapril maleate (120).

Isosorbide mononitrate, a nitrooxy dioxabicyclic compound used for treatment of angina pectoris showed an interaction with cellulose acetate and MCC as evidenced by DSC, IST and HPLC studies. There was also a drastic reduction in the enthalpy value (from 125.32 to 34.10 J/g), which also suggested an incompatibility. When IST samples of an isosorbide mononitrate:cellulose acetate mixture were observed after 3 weeks of storage under stressed conditions, a yellow coloration was observed. The presence of a new peak in the HPLC chromatogram of the stressed samples of isosorbide mononitrate:cellulose acetate mixture further suggested a chemical interaction (6).

HPMCAS is a widely used excipient in solid dispersion technology. HPMCAS potentially undergoes hydrolysis to produce succinic acid and acetic acid, the hydrolysis rate being higher at higher temperatures and higher relative humidities. The use of HPMCAS is not recommended for APIs containing hydroxyl group(s) due to the potential of ester formation with succinic acid and/or acetic acid. Dyphylline, a drug used to treat bronchial asthma, consists of a purine skeleton with a 2,3-dihydroxy-side chain. In order to test the potential incompatibility of hydroxy group containing APIs with HPMCAS, Dong and Choi (89) used a dyphylline as a model drug. Dyphylline was stored at 140°C for 5 hours in the following three forms: (a) pure powder, (b) physical mixture with succinic acid (50:50) and (c) physical mixture with HPMCAS with a drug-excipient ratio of 40:60 to mimic a 40% loading HME (hot melt extrusion) composition. The samples were dissolved in a diluent (95% pH 8.25 50 mM phosphate buffer + 5% acetonitrile) to form a 0.1 mg/mL solution of dyphylline for HPLC analysis. Upon heat treatment, three degradants were observed in

the physical mixture of dyphylline and HPMCAS. They were identified as two monoesters and one di-ester of two dyphylline molecules with one succinic acid molecule (Figure 5), suggesting potential drug–excipient incompatibility during formulation development (89).

The diuretic drug, trichlormethiazide was found to be stable in a solid state under humid conditions, but when made into tablets was not stable under the same conditions. Trichlormethiazide degradation was accelerated by the addition of hydroxypropylcellulose. Various factors that could affect the trichlormethiazide stability in tablets were considered, such as, adsorption of water, amount of free water and pH (90).

Polyethylene glycol (PEG)

PEG is widely used as a lubricant and as a cosolvent/dispersant for poorly soluble drugs in pharmaceutical dosage forms. The purity of PEG plays a very important role in the degradation of drugs. High purity grades available from reputable manufacturers are less likely to lead to degradation of drugs. Ibuprofen showed an incompatibility with PEG in tablets stored for three weeks at 70°C/75% RH resulting in the formation of ibuprofen degradation products. One of the identified de-

gradation products was a known toxin 4-isobutylacetophenone (91). Aspirin undergoes pseudo-first order decomposition in combination with several grades of PEGs due in part to trans-esterification to form salicylic acid and acetylated PEG (121). The rate of decomposition was considerably greater when a fatty base, such as cocoa butter, was used (122). Analysis of commercial batches of 100 mg indomethacin-PEG suppositories showed that approximately 2%, 3.5% and 4.5% of the original amount of indomethacin was esterified with PEG 300 after storage of one, two and three years respectively. The formation of polyethylene glycol (PEG) sulfonate/ besylate esters have been reported during hot melt granulation of clopidogrel besylate with PEG 6000, several of which are genotoxic (77). Other APIs which showed interaction with PEG are ibuprofen (8) ketoprofen (38) and calcium phosphomycin (92).

Polysorbate 80

Polysorbate 80, commercially known as Tween® 80, is a nonionic surfactant and emulsifier used in food and pharmaceuticals. Formation of peroxide in neat polysorbate 80 in the presence of air during incubation at elevated temperatures has been reported. This can affect the stability of oxidation-sensitive drugs (123). Ibuprofen showed an incompatibility with polysorbate 80 in tablets stored for three weeks at 70°C/75% RH (91).

Sodium lauryl sulfate (SLS)

SLS is widely used in solid oral formulations as a surfactant/wetting agent to improve the solubility of poorly soluble drugs. Incompatibility between the antidiabetic drug chlorpropamide and SLS has been reported. The DSC thermogram of a chlorpropamide/SLS mixture showed a wide endotherm at 99–120°C with the disappearance of the double melting peak of the drug. A considerable decrease in the dissolution rate of chlorpropamide from tablets containing SLS was observed after 6 months of

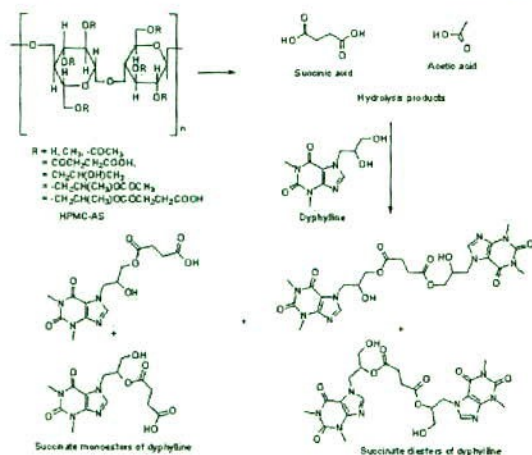


Figure 5 Interaction between hydroxypropyl methylcellulose acetate succinate and dyphylline (89).

storage at 40°C/75% RH which clearly suggested incompatibility between the active drug and excipient. (65). An *in vitro* study found that chlordiazepoxide, which can exist in cationic form, formed an ion pair with the anionic SLS, resulting in decreased membrane permeability (11, 93). The anti-coagulant drug, clopidogrel besylate was also found to be incompatible with SLS (77).

Chitosan

Chitosan has been investigated as an excipient for use in direct tablet compression, as a tablet disintegrant, for the production of controlled release solid dosage forms and for the improvement of drug dissolution (124). Chitosan inhibited the release of the NSAID diclofenac sodium from matrix tablets at low pH, possibly due to the formation of an ionic complex between the diclofenac sodium and the ionized amino groups of the cationic polymer (11, 94). Chitosan also interacted with piroxicam. The solubility of piroxicam and its biological availability increased 10-fold when mixed with chitosan (95).

Magnesium oxide

Magnesium oxide is used in antacids as an active ingredient and may also be used as a pH modifier (e.g. in Levothyroxine sodium pentahydrate tablets) (125). A solid-solid reaction in 1:1 and 2:1 mixtures of ibuprofen/magnesium oxide stored at 55°C has been reported as showed by the disappearance of ibuprofen melting endotherm in DSC curve and changes in the infrared spectrum after reaction. Comparison with authentic samples indicated that Mg(diibuprofen) was the product of the reaction (Figure 6). This reaction is greatly influenced by moisture and the molecular mobility of the reactants. Solid-solid reactions of ibuprofen were also observed with basic oxides (e.g. calcium oxide) and hydroxides (e.g. magnesium hydroxide) (96).

Silicon dioxide (Silica)

In pharmaceuticals, silica (SiO₂) is used as a glidant during tablet manufacturing. Colloidal SiO₂ was found to noticeably decrease the thermal stability of enalapril maleate. The TG/DTG and DSC thermograms of the binary mixtures of enalapril maleate and SiO₂ indicated that SiO₂ results in a decrease of more than 20°C in the onset temperature of degradation of the drug. Therefore, the use of SiO₂ as an excipient should be avoided in formulations containing enalapril maleate, since it may act as a catalyst in the thermal decomposition of the drug even though SiO₂ is usually employed at low concentrations (typically <1% mass/mass) (120).

Carbonates

The addition of aqueous soluble carbonate salts, such as sodium carbonate, compromised the stability of adefovir dipivoxil in the solid state, increasing the hydrolysis of the drug (Figure 7). However, aqueous insoluble carbonates, such as calcium carbonate and magnesium carbonate, enhanced the stability of adefovir dipivoxil as compared to a control formulation. Pivalic acid, a degradation product of adefovir dipivoxil, was shown to accelerate the degradation rate of adefovir dipivoxil in the solid state. The de-stabilizing effect of this acid on adefovir dipivoxil stability was diminished in the presence of magnesium carbonate. Pivalic acid also increased the rate at which adefovir dipivoxil dimers were formed in the presence of formaldehyde vapor. Addition of insoluble carbonates reduced the rate of formaldehyde-catalyzed dimerization of adefovir dipivoxil (97). Solid-solid reactions of ibuprofen with sodium bicarbonate and potassium carbonate were also observed (96).



Figure 6 Acid-base reaction of ibuprofen and magnesium oxide (96).

Miscellaneous

Apart from API-excipient incompatibilities discussed above, several other incompatibilities have been reported as summarized in Table 3.

Table 3. Miscellaneous API-excipient incompatibilities

Excipient (s)	API	Reference
Ascorbic acid, citric acid, butylated hydroxyanisole	Atenolol ^a	(126)
Maize starch, pregelatinized starch, sodium starch glycolate, Avicel [®] PH 101	Clenbuterol	(50)
Plasdone [®]	Glimepiride	(66)
Palmitic acid	Ketoprofen	(38)
Methyl paraben, cetostearyl alcohol, glyceryl monostearate	Lapachol	(127)
Methyl paraben, propyl paraben, butylated hydroxytoluene, acetylated lanolin	Lipoic acid	(128)
Succinic Acid	Na ₂ -Phosphomycin	(92)
Sodium dioctylsulfosuccinate	Ca-Phosphomycin	(92)
Pearlitol [®] SD200 ^c	Promethazine hydrochloride	(45)
Precirol [®] ATO 5 ^d	Temazepam	(42)
Ca and Mg salts	Tetracycline	(98)
Sodium edetate, sodium bisulfite	Hydralazine HCl ^e	(129)
Talc	Saproxetine maleate ^f	(47)
Vitamin E succinate-processed films	Tetrahydrocannabinol	(130)

^a Formation of the degradation products (N-formyl atenolol, carbamic formic anhydride of atenolol, -acetyl atenolol) have been reported

^b Incompatibility was indicated by yellow to brown coloration or white precipitation

^c Pearlitol SD is a spray dried mannitol containing 20% maize starch

^d Precirol Ato 5 is a glyceryl palmitostearate and is used as multipurpose functional excipient (lubricant, sustained release agent and/or a taste masking agent for oral dosage forms

^e A yellow coloration was observed

^f The amide derivative was formed due to interaction of drug with maleic acid in the presence of talc

CONCLUSION

Drug-excipient interactions/incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance. Acid-base interactions and Maillard reactions are probably the most common API-excipient interactions reported. The excipients lactose and magnesium stearate are the most widely used excipients in oral solid dosage forms. Combined with their propensity for reaction with certain functional groups, it is no accident therefore, that they are involved in higher number of incompatibilities and should always be used with caution. Use of lactose as a

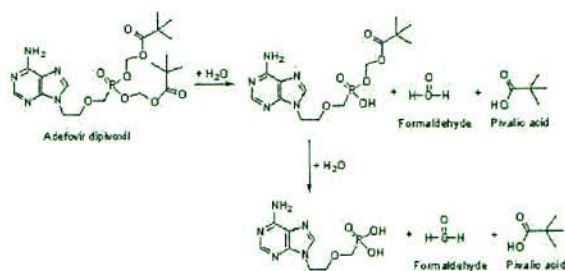


Figure 7 Hydrolysis of adefovir dipivoxil (97).

diluent should be avoided for active pharmaceutical ingredients containing amines due to the possibility of a Maillard reaction. Stearate salts should be avoided as tablet lubricants if the API is subject to hydrolytic ion-catalyzed degradation. Alkaline excipients such as DCPD should not be used in the formulation of acidic drugs. The use of Eudragit RL should be avoided with drugs containing a carboxyl group (e.g. ibuprofen, lower pKa) since these exhibit strong electrostatic interaction with ammonium groups present in Eudragit polymer affecting the release profile of the active ingredient. Care should also be taken when formulating drugs containing hydroxyl groups. The use of HPMCAS should be avoided due to potential ester formation with succinic acid or acetic acid. Although, in many of the examples discussed above, the incompatibility is evident at elevated temperatures or at unrealistically high concentration ratios of excipient to API, and thus they may not be seen at ambient (real) temperatures or at commonly used excipient to API ratios for the duration of the product shelf-life. However, such information is very helpful for analyzing any instability issues with commercial formulations or during the development of new formulations. Once solid-state reactions are understood in a pharmaceutical system, the necessary steps can be taken to avoid the reactivity and improve the storage stability for drug products.

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