

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

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Abogado
JAIME EDUARDO DELGADO VILLEGAS

ASUNTO	Radicación	08-34001
	Trámite	11
	Evento	378
	Actuación	519
	Oficio	112732
	Folios	9

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (Fase Nacional) ☒ Capítulo I ☒ Capítulo II ☐

No. Solicitud Internacional PCT/EP2006/009178
Fecha de Presentación Internacional 21 de septiembre de 2006

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 58 a 84	04/04/2008
	Folios 140 a 160	10/05/2012
Reivindicaciones:	Folios 85 a 92	04/04/2008
	Folios 161 a 165	10/05/2012
Respuesta del solicitante:	Folios 131 a 139	10/05/2012
Prioridad:	DE 102005047561.2	04/10/2005

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "FORMAS DE PRESENTACIÓN FARMACÉUTICA SÓLIDAS DE ADMINISTRACIÓN ORAL QUE CONTIENEN 5-CLORO-N-(((5S)-2-OXO-3-[4-(3-OXO-4-MORFOLINIL)FENIL]-1,3-OXAZOLIDIN-5-IL}METIL)-2-TIOFENOCARBOXAMIDA". (Fl. 138)

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El problema planteado en esta solicitud consiste en la necesidad de composiciones con 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida en forma amorfa o de modificación cristalina termodinámicamente metaestables que es de liberación rápida.

Para resolver este problema técnico la solicitud en estudio proporciona una forma de presentación farmacéutica sólida que puede administrarse oralmente que comprende 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida en forma amorfa o de modificación cristalina termodinámicamente metaestables de rápida liberación

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/5377; A61K9/20.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

El término "forma de presentación" contenido en el preámbulo de las reivindicaciones no es claro ya que no es posible identificar a qué tipo de producto se refiere el solicitante, debido a que esta frase no limita el objeto de la solicitud puesto que existen diversas formas de presentación tales como formas farmacéuticas, kits, dispositivos etc., por lo cual se recomienda al solicitante aclarar el objeto de la reclamación.

La expresión "principio activo (I)" carece de claridad ya que dentro de la reivindicación no se clarifica a qué compuesto corresponde dicha denominación.

La reivindicación 1 y sus dependientes no son concisas ya que no se limita el alcance de la solicitud, debido a que no se establece cuál es la forma de presentación reclamada ni sus elementos técnicos constitutivos. Para el caso de un producto tipo composición, las características técnicas esenciales son el principio activo, los excipientes, las proporciones de los mismos y cualidades de los excipientes. Igualmente, en relación con las reivindicaciones de proceso estas deben caracterizarse como un conjunto de actividades ordenadas por una serie de pasos de manera determinada. Se recomienda ajustar las reivindicaciones según los requisitos.

La reivindicación 1 establece que el principio activo (I) corresponde a una forma amorfa o de modificación cristalina termodinámicamente metaestable. Sin embargo no se divulga cuál es específicamente la forma cristalina de la composición ni cuál o cuáles son las formas termodinámicamente metaestables. Es pertinente aclarar al solicitante que en relación con un cristal debe haber una descripción detallada de al menos un modo de lograr el mismo, es decir, se debe divulgar con suficiente detalle todos los pasos esenciales y las condiciones experimentales, para que se pueda reproducir el polimorfo inventado por medio del proceso que permite su obtención. Adicionalmente, en la descripción se deben divulgar los elementos esenciales del cristal por medio de técnicas que permitan caracterizarlo (DRX monocristal o en polvo y métodos de análisis térmico TGA, DTA y DSC) y que aporten información estructural del compuesto de forma complementaria (espectroscopía Raman e IR o espectroscopía RMN-C13), así como del problema técnico que pretende resolver la invención y de los demás elementos característicos asociados a la red cristalina, tal es el caso de las dimensiones de la unidad de celda y del hábito cristalino que le

permitan a la persona versada en la materia comprender el aporte de la invención al estado de la técnica.

Se considerará que la divulgación no es suficiente si:

- No hay una descripción de los métodos de medida usados para determinar los valores de los parámetros de tipo estructural y cristalino del polimorfo reivindicado.
- Los procesos de preparación divulgados en la solicitud son idénticos a los del estado de la técnica, pero se afirma haber obtenido un polimorfo diferente, ó
- Todos los procesos de preparación divulgados preparan los polimorfos reivindicados usando cristales semilla, pero no se describe el proceso para preparar los cristales semilla.

Para las dos cuestiones: tanto de divulgación suficiente, como de nivel inventivo de una invención relacionada con un polimorfo o las composiciones que lo contienen, se considera el mismo nivel de habilidad de la persona del oficio normalmente versada en la materia.

Por otra parte, la reivindicación 1 caracteriza un producto por su proceso de obtención. Las reivindicaciones de productos definidas en términos de un proceso de fabricación son admisibles, solamente si los productos como tales cumplen los requisitos de patentabilidad, es decir, cuando son nuevos e inventivos, y cuando no se pueden definir por sus características estructurales. En el presente caso el producto reclamado puede definirse por sus características técnicas esenciales que para una composición corresponden al compuesto activo, los excipientes, proporciones y cualidades de los excipientes. En consecuencia, el proceso de obtención del principio activo no se considera una característica técnica del producto, por lo tanto las reivindicación 1 y sus dependientes deben ajustarse en forma adecuada.

Finalmente, una reivindicación que comprenda un cristal o polimorfo se considerará debidamente soportada en la descripción si esta divulga:

- Los parámetros fisicoquímicos del polimorfo reivindicado.
- Las condiciones experimentales relevantes de los métodos de medida usados para determinar las características del polimorfo reivindicado junto con las características del cristal y de su estructura, y
- Los procesos de preparación del polimorfo que se reivindican.

Las reivindicaciones 6, 7 y 10 reclama un procedimiento en el que se divulga un elevado número de compuestos denominados "cargas y aglutinante", sin embargo la descripción carece de información que permita evidenciar la utilidad de todos estos excipientes en la formulación y su efecto en el proceso, por otra parte la expresión "excipientes de formación de comprimidos" es una caracterización funcional y no limita el alcance de la solicitud.

La reivindicación 6 utiliza la expresión "se envasa en forma de saquitos", no es claro cuál tipo de envase describe el solicitante, se recomienda revisar dicha expresión.

La reivindicación 9 es dependiente de la 8 pero se refieren a objetos diferentes por lo cual se sugiere eliminar dicha dependencia.

5. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: 4 de octubre de 2005 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D2	US2003153610	Substituted oxazolidinones and their in the field of blood coagulation	14/08/2003
D3	European journal of pharmaceutics and Biopharmaceutics. Vol 54 Issue 2 (2002), pp. 107-117	Melt extrusión: from process to drug delivery technology	23/Enero/2000
D4	Jens T. Cartensen, Editorial Marcel Dekker, Inc. NY, 2001	Advanced pharmaceutical solids	2001

El documento D2¹ enseña una composición sólida en forma de tableta, píldora o granulos, (párrafo 0367), que comprende un compuesto activo derivado de la fórmula (I), específicamente el compuesto 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida (párrafo 0012)

Por su parte, el documento D3 es un artículo de revisión en relación con la metodología de fusión por extrusión, siendo la misma una técnica ampliamente conocida en el arte. (documento completo).

El documento D4 divulga los diversos procesos para la preparación de formas farmacéuticas entre las que se encuentran las cápsulas y tabletas (capítulos 22 y 23)

6. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

En el presente caso, los productos reclamados en la solicitud no tienen nivel inventivo, teniendo en cuenta que la reivindicación 1 se refiere a: *“Forma de presentación farmacéutica sólida que puede administrarse oralmente que comprende 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida y que es de liberación rápida”* (Fl. 161).

La tabla siguiente presenta la comparación entre las características técnicas esenciales de la solicitud estudiada, mencionadas en la reivindicación 1, y las reveladas en el documento D1, que representa el estado de la técnica:

Tabla 1

Características esenciales	D2	D3
Forma de presentación farmacéutica sólida que puede administrarse oralmente que comprende 5-	Discute composiciones solidas en forma de tabletas, píldoras o gránulos (párrafo 0367), la	Enseña las técnicas y resultados de la metodología de fusión por extrusión. (documento completo)

1. http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=20030814&CC=US&NR=2003153610A1&KC=A1
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cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida y que es de liberación rápida caracterizada porque	composición comprende el compuesto activo 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida (párrafo 0012)	
Comprende principio activo (I) en forma amorfa o de modificación cristalina termodinámicamente metaestable, y en la que el principio activo(I) se amorfiza o se convierte en una modificación cristalina termodinámicamente metaestable, mediante un procedimiento de disolución en el que se usa ácido acético como disolvente y se añade polivinilpirrolidona, y el principio activo (I) está presente en la mezcla resultante del procedimiento de disolución a una concentración del 0.1 al 30%, o	El cristal amorfo o termodinámicamente estable es obtenido por disolución debido al paso final de mezcla o disolución del compuesto en el proceso de preparación (párrafos 0571 y 0572). El agente activo está presente en un rango de 0.1-95%, 05-90% y 1 a 85% (párrafo 0367)	No lo divulga, sin embargo el proceso de obtención de la forma amorfa o del cristal termodinámicamente estable no se considera una característica técnica de producto.
En la que el principio activo (I) se amorfiza o se convierte en una modificación cristalina termodinámicamente metaestable mediante un procedimiento de fusión, usándose en el procedimiento de fusión polietilenglicoles o mezclas de polietilenglicoles, y el principio activo (I) está presente en la mezcla resultante o después del proceso de fusión a una concentración de 0.1 al 30%, o	No lo divulga, sin embargo el proceso de obtención de la forma amorfa o del cristal termodinámicamente estable no se considera una característica técnica de producto.	No lo divulga, sin embargo el proceso de obtención de la forma amorfa o del cristal termodinámicamente estable no se considera una característica técnica de producto.
en la que el principio activo (I) se amorfiza o se convierte en una modificación cristalina termodinámicamente metaestable mediante extrusión en estado fundido hidroxipropilcelulosa (HPC) o polivinilpirrolidona (PVP), siendo la proporción de polímero en el extrusionado fundido de al menos el 40% y estando presente el principio activo (I) en el extrusionado fundido a una concentración del 0.1 al 20%.	No lo divulga, sin embargo el proceso de obtención de la forma amorfa o del cristal termodinámicamente estable no se considera una característica técnica de producto.	Este artículo revisa la tecnología de proceso de fusión por extrusión con respecto a la puesta en marcha y elementos específicos de la extrusora, así como su aplicación. Los procesos de fusión por extrusión se aplican actualmente en el campo farmacéutico para la fabricación de una variedad de formas de dosificación y formulaciones tales como gránulos, pellets, comprimidos, supositorios, implantes, stents, sistemas transdérmicos e insertos oftálmicos. La fusión por extrusión se considera una tecnología eficiente en este campo con ventajas particulares sobre los procesos solventes como co-precipitación.

Las anterioridades D2 y D3 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1, debido a que el documento D2 discute composiciones solidas en forma de tabletas, píldoras o gránulos (párrafo 0367), la composición comprende el compuesto activo 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-

morfolinil)fenil]-1,3-oxazolidin-5-il}metil)-2-tiofenocarboxamida (párrafo 0012), en donde el cristal amorfo o termodinámicamente estable es obtenido por disolución debido al paso final de mezcla o disolución del compuesto en el proceso de preparación (párrafos 0571 y 0572). Igualmente, la anterioridad enseña que el agente activo está presente entre 0.1 a 95 %, 0.5 a 90% y de 1 a 85% (párrafo 0367), pudiendo ser la cantidad de activo variable dependiendo de las circunstancias (párrafos 0370 y 0372)

La diferencia entre la invención, definida en la reivindicación 1, y las composiciones del documento D2 consiste en que en la anterioridad no se divulga de manera específica que el uso de ácido acético como disolvente y polivinilpirrolidona ni que el rango de activo sea 0.1 al 30%.

Por su parte, el documento D3 divulga la tecnología de proceso de fusión por extrusión con respecto a la puesta en marcha y elementos específicos de la extrusora, así como su aplicación (resumen).

La diferencia entre la invención, definida en la reivindicación 1, y la divulgación del documento D3 consiste en que la anterioridad no divulga de manera específica que el compuesto extruido corresponda a 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il}metil)-2-tiofenocarboxamida.

El efecto técnico que logra esta diferencia no se puede determinar ya que si bien, el solicitante presenta las tablas de liberación de las formulaciones ejemplares frente a las composiciones que contienen el principio activo micronizado, no existe información en la descripción que permita establecer una ventaja de las composiciones reclamadas con relación a las divulgadas por D2 que también comprenden formas metaestables del compuesto 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il}metil)-2-tiofenocarboxamida.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: ¿cómo modificar las composiciones conocidas en D2 seleccionando una cantidad particular de agente activo para proporcionar formas de presentación farmacéutica alternativas que comprenden 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il}metil)-2-tiofenocarboxamida en forma metaestable?

Ahora bien, D3 enseña que la fusión por extrusión se puede aplicar para dispersar las drogas en una matriz hasta el nivel molecular, por ejemplo, para formar una verdadera solución. Es la conveniencia de la tecnología que da una nueva esperanza para el cristal o el enfoque de solución sólida como un sistema de entrega de los medicamentos poco solubles. El uso de masas fundidas con el fin de obtener dispersiones sólidas moleculares o soluciones sólidas, es bien conocido para el experto y la esencial ventaja de un proceso de fusión en este tipo es no se requiere de disolventes formación de estas dispersiones. Teniendo en cuenta que el uso de disolventes representa varios problemas (contaminación del medio ambiente, la explosión de pruebas y residual disolvente orgánico), todas las medidas para contrarrestar estos problemas son deseables. El proceso de extrusión en fusión es capaz de manejar agentes activos de diferentes tamaños de partículas, así como sólidos amorfos u otras formas polimórficas que conduce al mismo producto. Desde 1974, las dispersiones sólidas de fármacos se describen como: "... un campo relativamente nuevo de la farmacéutica técnica y sus principios juegan un papel importante en creciente disolución, absorción y eficacia terapéutica de las drogas" (pág. 111, tecnología para la liberación de fármacos)

Por otra parte, D3 enseña que el avance de la fusión por extrusión fue logrado gracias a la disponibilidad de una gran variedad de sistemas de soporte farmacéuticamente aprobados. Estos sistemas de transporte incluyen PVP o alguno de sus copolímeros, poli (etileno-co-acetato de vinilo), polietileno glicol (PEG), éteres de celulosa y acrilatos. Las propiedades del óxido de polietileno (PEO) como un portador de drogas en la extrusión de masa fundida. Entre las diferentes clases de polímeros biodegradables, los poliésteres termoplásticos alifáticos como la polilactida (PLA), el poliglicólido (PGA), y el copolímero de lactida y glicolida, polilactida-coglicólido (PLGA) se han utilizado en la extrusión. Igualmente, el almidón y sus derivados se han aplicado junto con excipientes de bajo peso molecular tales como azúcares y alcoholes de azúcar y ceras. El requisito básico para el uso en fusión por extrusión es la termoplasticidad de los polímeros o de las formulaciones respectivas (pág. 112, aplicación de la fusión por extracción como tecnología para la entrega de fármacos).

En consecuencia, una persona normalmente versada en la materia, teniendo en cuenta las enseñanzas de D2 y D3 se vería motivada a seleccionar las cantidades del agente activo en su forma cristalina metaestable divulgada previamente en D2, y utilizaría las técnicas de fusión por extrusión de D3 para generar una composición que produzca los resultados deseados. Por otra parte, no existiendo información en la solicitud que permita establecer que la cantidad de activo en el rango seleccionado provea un resultado inusual o inesperado, o que la técnica de fusión por extrusión provea un efecto inesperado, se considera que las formas de presentación farmacéuticas de la presente solicitud carecen de altura inventiva.

En consecuencia, las reivindicaciones 1, 9 y 18 junto con sus dependientes carecen del requisito de inventivo.

Las reivindicaciones 6, 7, 8 y 10 reclaman procedimientos para la producción de una forma de presentación farmacéutica:

Tabla 2

Características esenciales	D2	D4
Procedimiento de producción de una forma de presentación farmacéutica caracterizado por:	Discute composiciones solidas en forma de tabletas, píldoras o gránulos (párrafo 0367), la composición comprende el compuesto activo 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)metil)-2-tiofenocarboxamida (párrafo 0012)	Describe los diferentes procedimientos para la preparación de formas farmacéuticas
Preparar una mezcla por disolución del principio activo (I) con cargas y aglutinantes. Envasar en forma de saquitos o cápsulas o, se prensa preferentemente por compresión directa dando comprimidos, que finalmente pueden recubrirse.	El compuesto de formula (I) puede estar en forma de tabletas y gránulos los cuales se forman mediante mezcla con excipientes adecuados (párrafos 0367 a 0369)	Proceso para llenado de cápsulas (pág. 376) Proceso para preparación de tabletas a partir de mezclas de polvos. Durante la formación de comprimidos, el polvo en el troquel de la máquina de comprimir se transforma por la influencia de golpes inferior y superior (págs. 387 a 390)

Las anterioridades D2 y D4 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1, debido a que el documento D2 discute composiciones solidas en forma de tabletas, píldoras o gránulos (párrafo 0367), la composición comprende el compuesto activo 5-cloro-N-({[(5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il}metil)-2-tiofenocarboxamida (párrafo 0012), en donde el cristal amorfo o termodinámicamente estable es obtenido por disolución debido al paso final de mezcla o disolución del compuesto en el proceso de preparación (párrafos 0571 y 0572) lo que lleva a la formación de formas metaestables o amorfas de acuerdo con las reivindicaciones 40, 45 y 50. Igualmente, la anterioridad enseña que el agente activo está presente entre 0.1 a 95 %, 0.5 a 90% y de 1 a 85% (párrafo 0367), pudiendo ser la cantidad de activo variable dependiendo de las circunstancias (párrafos 0370 y 0372)

La diferencia entre la invención, definida en la reivindicación 6, los procesos del documento D2 consiste en que en la anterioridad no se divulga el listado de excipientes expuesto en la presente reivindicación.

Por su parte el documento D4 describe los diferentes procedimientos para la preparación de formas farmacéuticas entre los que se encuentran el proceso para llenado de cápsulas (pág. 376) y el proceso para preparación de tabletas a partir de mezclas de polvos. Durante la formación de comprimidos, el polvo en el troquel de la máquina de comprimir se transforma por la influencia de golpes inferior y superior, y dichas tabletas pueden recubrirse (págs. 387 a 390).

Por lo tanto, el problema técnico que se pretende resolver consiste en seleccionar procesos para la elaboración de formas farmacéuticas como las divulgadas en D2.

Dado que no hay evidencia de que se haya logrado algún efecto técnico inesperado por el hecho de mezclar el compuesto (I) con excipientes de carga y aglutinantes para luego envasarlo en forma de cápsulas o formar tabletas, se considera que los procesos reivindicados son obvios para la persona normalmente conocedora de la materia.

En consecuencia, una persona normalmente versada en la materia, teniendo en cuenta las enseñanzas de D2 y D4 se vería motivada a seleccionar entre los procesos divulgados por D4 algunos para la preparación de composiciones que contengan el agente activo que enseña D2, en donde dicho proceso no provee un efecto técnico inesperado o sorprendente. Por lo cual, las reivindicaciones 6, 7, 8, 10 y 15 a 17 no tienen nivel inventivo.

7. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D2	US2003153610	1 a 18	Nivel Inventivo
D3	European journal of pharmaceutics and Biopharmaceutics. Vol 54 Issue 2 (2002), pp. 107-117	1 a 5, 9, 11 a 14 y 18	Nivel Inventivo
D4	Shayne Cox Gad. Wiley- interscience.2008	6, 7, 8, 10 y 15 a 17	Nivel inventivo

8. Respuesta a los argumentos del señor solicitante

El señor solicitante adjunto un nuevo capítulo descriptivo de la solicitud contenido en Expediente 08-34001 2do Art 45

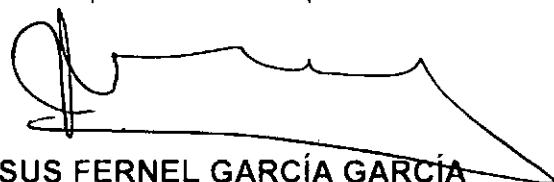
los folios 140 a 160. Al respecto y luego de la revisión de dicho documento, esta Superintendencia encuentra que las modificaciones realizadas no constituyen una ampliación de la materia contenida en la solicitud original y por lo tanto el nuevo capítulo descriptivo es aceptado.

El señor solicitante afirma que la forma cristalina divulgada en los documentos D1 y D2 se define como "modificación cristalina I" y por lo tanto, es diferente a la "modificación cristalina termodinámicamente metaestable" y a la "forma amorfa" abarcadas por las reivindicaciones de la presente solicitud, por lo tanto, la invención es novedosa con relación a los documentos D1 y D2.

En respuesta a los anteriores argumentos esta Oficina encuentra que las anterioridades D1 y D2 no afectan la novedad del nuevo capítulo reivindicatorio allegado por el solicitante. Sin embargo, de acuerdo con el examen de Patentabilidad realizado la solicitud carece de nivel inventivo, toda vez que las formas de presentación farmacéuticas reclamadas y los procesos carecen de efecto técnico sorprendente o inesperado y se derivan de manera evidente del estado de la técnica.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JESUS FERNEL GARCÍA GARCÍA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha
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Review article

Melt extrusion: from process to drug delivery technology

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Abstract

Starting from the plastic industry, today melt extrusion has found its place in the array of pharmaceutical manufacturing operations. This article reviews the process technology with regard to the set up and specific elements of the extruder as well as its application. Melt extrusion processes are currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts. As a specific area the manufacture of solid dispersions, in particular, solid molecular dispersions using the melt extrusion process is reviewed. Melt extrusion is considered to be an efficient technology in this field with particular advantages over solvent processes like co-precipitation. Potential drawbacks like the influence of heat stress and shear forces on the drug active have been overcome in a number of examples with drugs of different chemical structure. Examples of suitable excipients and recent findings like self-emulsifying preparations are presented. The article concludes with a number of published examples of melt extrudates applying the principle of solid molecular dispersions. Improved bioavailability was achieved again demonstrating the value of the technology as a drug delivery tool. © 2002 Published by Elsevier Science B.V.

Keywords: Melt extrusion; Solid dispersion; Solid molecular dispersion; Extruder; Bioavailability; Solubility

1. Introduction

Industrial application of the extrusion process dates back to the 1930's [1]. One can therefore consider the extrusion process as being a well elaborated manufacturing technology with a plethora of different technical solutions already available in other fields. Extrusion is a process of converting a raw material into a product of uniform shape and density by forcing it through die under controlled conditions [2]. Extrusion may be operated as a continuous process, which affords a consistent product flow ideally at relatively high throughput rates.

An extruder consists of two distinct parts: a conveying system which transports the material and sometimes imparts a degree of distributive mixing, and a die system which forms the materials into the required shape. Extrusion may be broadly classified into molten systems under temperature control or semisolid viscous systems. In molten extrusion, heat is applied to the material in order to control its viscosity, to enable it to flow through the die. Semisolid systems are multiphase concentrated dispersions containing a high proportion of solid mixed with a liquid phase [3].

Solid molecular dispersions of drugs in a matrix fit the

molten systems especially as the fusion method in polymeric matrices has been applied to achieve such specific distributions of drugs. Generally, solid dispersions of drugs with poor solubility revealed remarkably higher bioavailability [4,5]. Less drug material may be applied and potentially a lower degree of variability in bioavailability are obvious advantages [6]. With the recent advent of high throughput screening and the growing specificity for given receptors poorly soluble drugs present a frequent and growing challenge to formulation scientists [7,8].

Solid dispersions of drugs therefore fulfill the prerequisites of drug delivery systems being designed to:

- increase the active agent bioavailability,
- reduce side effects,
- increase the duration of the drug action in the body.

At the same time, extrusion represents an efficient manufacturing technology required to disperse drugs in a melt up to a true molecular solution of the active agent in the matrix. It is a striking example of a technology transfer establishing a new technology life cycle curve.

The most relevant technologies for the manufacture of solid dispersions are hot spin mixing [9], embeddings by means of spray drying [10], co-evaporation, co-precipitation [11], freeze-drying [12] and roll-mixing or co-milling [13,14].

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An indication that life cycle management is a key driver for the melt extrusion technology is the remarkable amount of publications in the patent literature.

2. Melt extrusion: the process technology

2.1. General remarks

With regard to pharmaceuticals, most systems extruded today consist of particles dispersed in a matrix. Although consideration is given to the manufacture of pure thermoplastics, the main emphasis is still on paste extrusions [15]. These differ in the fact that a connective matrix is present between solid particles. The relative position of solid and liquid can change during the various stages of the extrusion process, and hence produce effects different from those associated with single-phase systems like a molecular distribution of a drug in a polymeric matrix. In the latter, the matrix acts as a real solvent for the drug. Ideally, such systems are supposed to have a single-phase over a wide range of solubility of the drug in the polymeric matrix.

The various types of extruders have a common feature of forcing the extrudate from a wider cross-section through the restriction of the die. The theoretical approach to understand the system, is therefore, generally associated with dividing the process of flow into four sections:

- feeding of the extruder,
- conveying of mass and entry into the die,
- flow through the die,
- exit from the die and down-stream processing.

These four sections drive considerations of different aspects like flow of powder, shear force, residence time and pressure, cooling rate and shaping.

Generally, the extruder consists of at least one rotating screw inside a stationary cylindrical barrel. The barrel is often manufactured in sections, which are bolted or clamped together. An end-plate die, connected to the end of the barrel, determines the shape of the extruded product (see Fig. 4).

Sometimes as much as 80% of the heat required to melt or fuse the material is supplied by the heat generated by friction as the material is sheared between the rotating screws and the wall of the barrel. Additional heat may be supplied by electric or liquid heaters mounted on the barrel. It is important to realize that residence time and pressure in the die area might have a significant impact on the impurity profile of the product [16].

Most commercial extruders have a modular design, providing a choice of screws or interchangeable sections which alter the configuration of the feed, transition, and metering zones. This makes it possible to modify the process to meet particular requirements, for example, from a standard to a high shear extrusion. Modified screw designs allow the extruder to perform a mixing role in addition to

extrusion, so that the material can be blended into the extrudate or even dissolved (Fig. 1). The various screw and die designs available and practical considerations of thermoplastic extrusion are reviewed by Whelan and Dunning [17].

The extrusion channel is conventionally divided into three sections: feed zone, transition zone, and metering zone (Fig. 4). The starting material is fed from a hopper directly into the feed section, which has deeper flights or flights of greater pitch (Fig 2). This geometry enables the feed material to fall easily into the screw for conveying along the barrel. Pitch and helix angle determine the throughput at constant rotation speed of the screws. The material is transported as a solid plug to the transition zone where it is mixed, compressed, melted, and plasticized. Compression is developed by decreasing the thread pitch but maintaining a constant flight depth or by decreasing flight depth while maintaining a constant thread pitch [18]. Both methods result in increased pressure as the material moves along the barrel. The melt moves by circulation in a helical path by means of transverse flow, drag flow, pressure flow, and leakage; the latter two mechanisms reverse the flow of material along the barrel. The space between screw diameter and width of the barrel is normally in the range of 0.1–0.2 mm.

The material reaches the metering zone in the form of a homogeneous plastic melt suitable for extrusion. For an extrudate of uniform thickness, flow must be consistent and without stagnant zones right up to the die entrance. The function of the metering zone is to reduce pulsating flow and ensure a uniform delivery rate through the die cavity.

The twin-screw extruder has two agitator assemblies mounted on parallel shafts (Fig. 3). These shafts are driven through a splitter/reducer gearbox and rotate together with the same direction of rotation (co-rotating) or in the opposite sense and are often fully intermeshing. In such case, each agitator element wipes both the surface of the corresponding element on the adjacent shaft, and the internal surfaces of the mixing chamber. The agitators are said to be self-wiping, an arrangement that eliminates stagnation areas within the mixing chamber and ensures a narrow and well-defined residence time distribution. If the agitators are chosen not to intermesh, the arrangement comes close to a single-screw set up. In general, co-rotating shafts have better mixing capabilities as the surfaces of the screws move towards each other. This leads to a sharp change in mass flow between the screw surfaces [19]. As the screws rotate, the flight of one screw element wipes the flank of the adjacent screw, causing material to transfer from one screw to the other. In this manner the material is transported along the extruder barrel.

The twin-screw extruder is characterized by the following descriptive features:

Short residence time: The residence time in the twin-screw extruder in a typical extrusion process is of the order of up to 2 min.

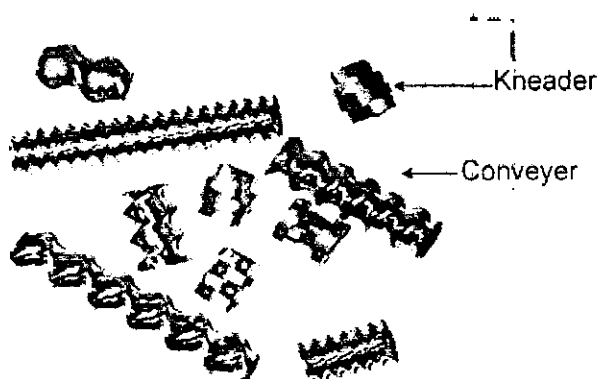


Fig. 1. Screw and kneading elements.

Self wiping screw profile: The self wiping screw profile i.e. the flight of one screw wipes the root of the screw on the shaft next to it, ensures near complete emptying of the equipment and minimises product wastage on shutdown.

Minimum inventory: Continuous operation of the equipment coupled with the low volume of the mixing chamber load to reduced inventories of work in progress. This is important when processing valuable or potentially hazardous materials.

Versatility: Operating parameters can be changed easily

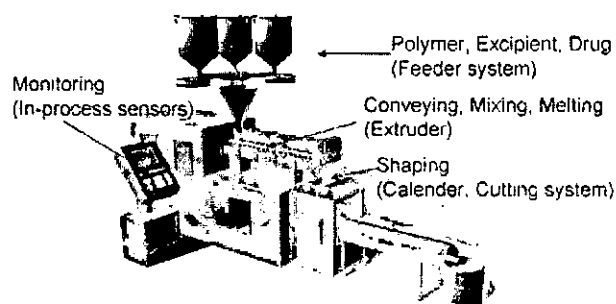


Fig. 3. Schematic presentation of a twin-screw extruder set-up.

and continuously to change extrusion rate or mixing action. The segmented screw elements allow agitator designs to be easily optimized to suit a particular application. Die plates can also be easily exchanged to alter the extrudate diameter and hence the spheroid diameter. This allows processing of many different formulations on a single machine, leading to good equipment utilization. Polymers with a wide range of viscoelastic and melt viscosities can be processed and even fine powders can be directly fed into the system (Fig. 3).

Typical twin-screw laboratory scale machines have a diameter of 16–18 mm and a length of four to ten times

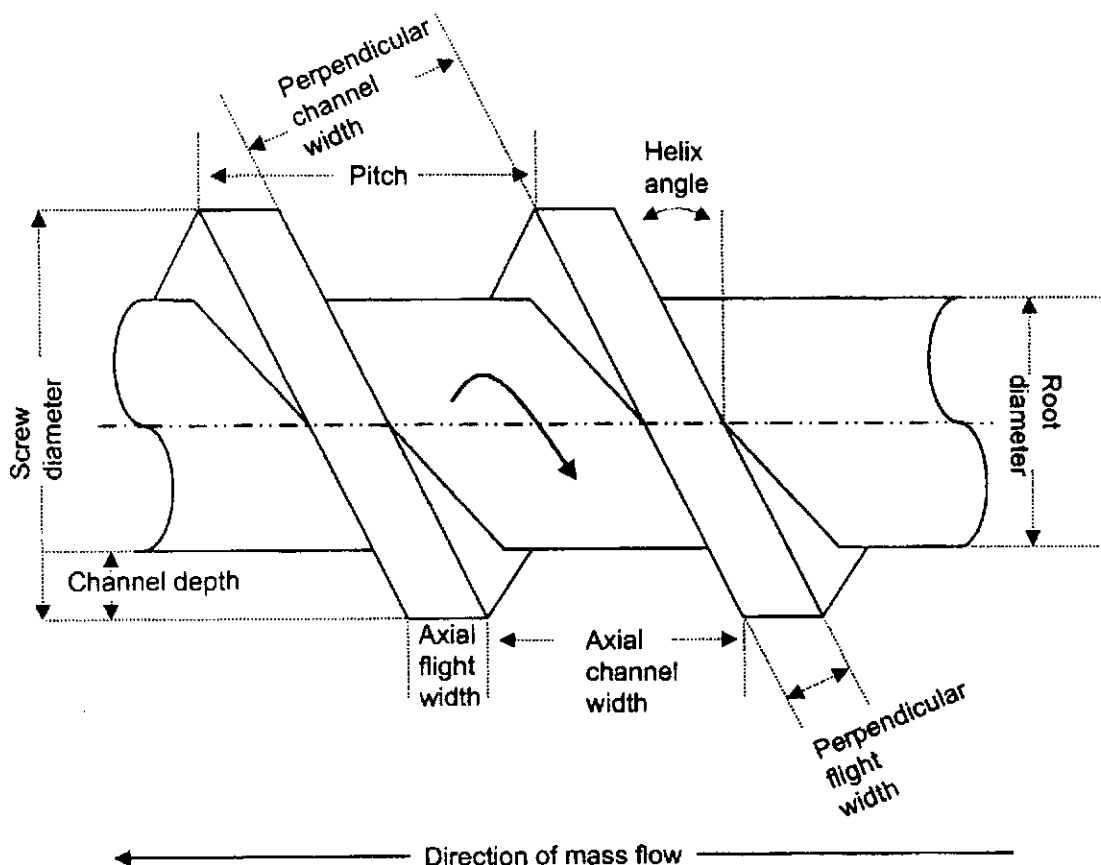


Fig. 2. Extrusion screw geometry.

the diameter. A typical throughput for such type of equipment is 0.5–3 kg/h.

As the residence time in the extruder is rather short and the temperature of all the barrels are independent and can be accurately controlled from low temperatures (30°C) to high temperatures (250°C) degradation by heat can be minimized. In addition oxygen and moisture may be excluded almost completely – an advantage for components sensitive towards oxidation and hydrolysis.

Extrusion processing requires close monitoring and understanding of the various parameters: viscosity, variation of viscosity with shear rate and temperature, elasticity, extensional flow, and slippage of the material over hot metal surfaces. Today extruders allow in process monitoring and control of parameters, such as the temperature in the extruder, head and die as well as pressures in extruder and die (Fig. 4) [20].

In particular, the molecular weight of polymeric matrices, their respective glass transition temperature and the sensitivity of the matrix or the drug towards heat and shear force create a basic set of data that qualify materials for the extrusion process. Additionally, miscibility can experimentally be determined with differential scanning calorimetry (DSC) and hot stage microscopy (HSM). In order to determine the miscibility of drug and excipient to predict if glass solutions are likely to form when drug and excipient are melt extruded, estimation of drug/excipient miscibility has been investigated. Melt extrusion of miscible components resulted in solid solution formation, whereas extrusion of an 'immiscible' component led to amorphous drug dispersed in crystalline excipient. In conclusion, combining calculation of solubility parameters with thermal analysis of drug/excipient miscibility has been successfully applied to predict formation of glass solutions with melt extrusion [21]. The challenge to determine the solubility of a drug in a polymeric matrix still needs to be addressed more adequately. A screening system based on a dimeric moiety

of polyvinylpyrrolidone (PVP) has been presented which is capable of comparing the solubility in the liquid to that in the solid, in this case the polymer [22].

2.2. Industrial applications

2.2.1. General

Extrusion technology is extensively applied in the plastic and rubber industries, where it is one of the most important fabrication processes. Examples of products made from extruded polymers include pipes, hoses, insulated wires and cables, plastic and rubber sheeting, and polystyrene tiles. Plastics that are commonly processed by extrusion include acrylics (polymethacrylates, polyacrylates) and copolymers of acrylonitrile, cellulose (cellulose acetate, propionate, and acetate butyrate), polyethylene (low and high density), polypropylene, polystyrene, vinyl plastics, polycarbonates, and nylons.

The process often is referred to as profile or line extrusion in which the shape of the extrudate like a tube is determined by the die. The extruded profile proceeds horizontally to the cutoff equipment, which controls its length. Profiles may be further processed, for example, as in film extrusion, blow molding, or injection molding [23].

In film extrusion, the polymer melt is extruded through a long slit die onto highly polished cooled rolls which form and wind the finished sheet. This is known as cast film. Plastic packaging film is also formed by blow extrusion, where tubular film is produced by the melt, usually vertically, through an annular-shaped slit die. The extruded tube is inflated by air to form a large cylinder. Blow molding refers to a process where the plastic is heated to a melted or viscous state and a section of molten polymer tubing is extruded usually downward from the die head into an open mold. The mold is closed around it, sealing it at one end. Compressed air is blown into the open end of the tube, expanding the viscous plastic to the walls of the cavity, thus

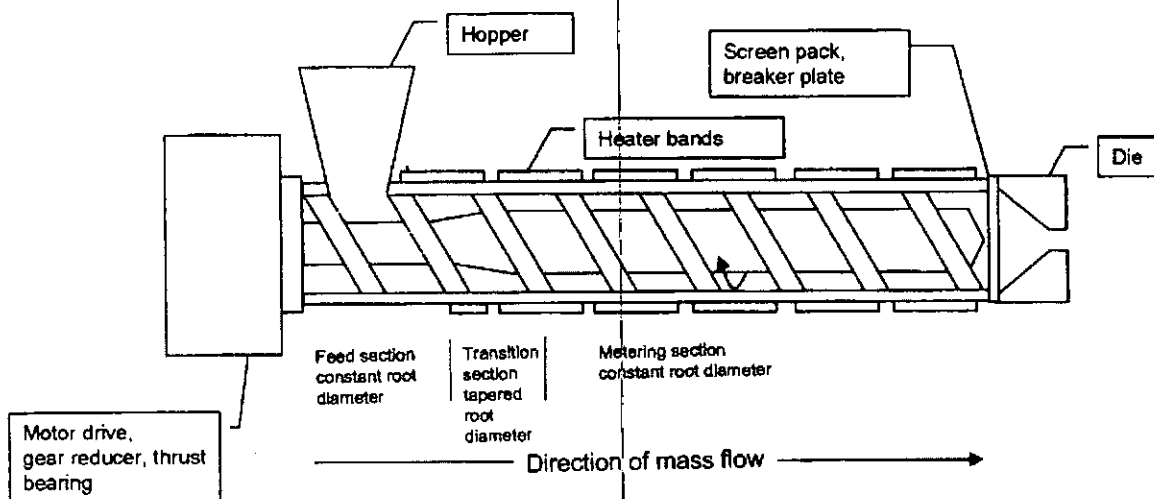


Fig. 4. Component parts of a single-screw extruder.

forming the desired shape of the container. During injection molding the molten plastic is not extruded but rather injected into a cavity mold at high pressure. The material cools in the cavity and solidifies. The mold is then opened and the article is removed.

Injection molding, has been used to manufacture tablets [24] and sustained release preparations [25]. In terms of feasibility, fast drug release, and economics, injection molding was considered suitable for drug solid dispersion or solution manufacture [26]. Injection molding has been exploited for its potential to manufacture sophisticated bi-layer tubular systems for customized release profiles [27].

In the food industry extrusion has been utilized since 1930s for pasta production. A widely used versatile technique combines cooking and extrusion in a so-called extrusion cooker [28].

In the animal feed industry, extrusion is most commonly applied as a means of producing pelletized feeds [29]. The manufacture of implants by extrusion or injection molding is another field of application in the veterinary field.

The need to formulate drugs with poor solubility is not only limited to the pharmaceutical field. Fast dispersing PVP melt extrudates of poorly soluble active agents as molecular dispersions are marketed in the crop protection field [30].

2.2.2. Application in the pharmaceutical industry

The most important application of extrusion in the pharmaceutical industry is in the preparation of granules or pellets of uniform size, shape, and density, containing one or more drugs [31]. The process involves a preliminary stage in which dry powders, drug, and excipients are mixed by conventional blenders, followed by addition of a liquid phase and further mixing to ensure homogeneous distribution. The wet powder mass is extruded through cylindrical dies or perforated screens with circular holes, of typically 0.5–2.0 mm diameter, to form cylindrical extrudates [32]. In the large-scale manufacture of suppositories and pessaries extrusion rather refers to forcing the material through a capillary die [33,34].

Melt extrusion for the manufacture of pellets [35] had revealed the potential for controlled release of polymer-embedded drugs and limitations. Pioneering work in the field employing the melt extrusion process as a manufacturing tool was performed by Doelker [36]. Typically, a co-rotating twin-screw configuration is used in most of the published studies. The equipment for the manufacture of solid dispersions has been described more precisely by Nakamichi [37,38].

The second core element of the integrated technological system is the device to shape on-line the thermoplastic strand leaving the extruder [39]:

(a) Calendering, in which the molten strand is forced between two calender rollers, thus producing films, flakes or sheets which may already contain single tablet cores.

(b) Pellet-forming, which may, for example, be a rotating knife cutting spaghetti-like extruded strands.

2.2.3. Regulatory aspects

Oral pharmaceutical products from the melt extrusion process have been approved in the USA, European and Asian countries. The process technology lends itself to comprehensive documentation, thus satisfying regulatory authorities. It is a major advantage that extrusion is a mature engineering technology. As a process it provides many parameters, such as feeding rate, segmental temperatures and pressure or applied vacuum, which can be monitored on-line with local meters and sensors. Such data contribute to the comprehensive documentation and the quality of production lots and may finally simplify quality control.

3. The drug delivery technology

3.1. Introduction

Melt extrusion may be applied to disperse drugs in a given matrix down to the molecular level, e.g. to form a true solution. It is the convenience of the technology that gives new hope to the glass or solid solution approach as a delivery system for poorly soluble drugs. The use of melts in order to obtain solid molecular dispersions, e.g. glass or solid solutions, is well known to the expert and the essential advantage of a melt process in this domain is its solvent-free formation of such dispersions [40]. Since with solvent processes there are various problems relating to their use (environmental pollution, explosion-proofing and residual organic solvent) and measures to counteract these problems are desirable [41].

The melt extrusion process is capable of handling active agents of different particle sizes as well as amorphous solids or other polymorphic forms leading to the same product. Basically, solid dispersion systems can be divided into six different categories (Fig. 5) [42].

Sekiguchi and Obi were first to report the melting or fusion method [43]. In 1974 solid dispersions of drugs were described as: "... a relatively new field of pharmaceutical technique and its principles play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs" [44].

When we look at the market of pharmaceutical products today solid dispersion systems, in particular, solid molecular dispersions are still found to be neglected. Only a few ever made it to the market including a griseofulvin–polyethyleneglycol-dispersion (Gris-PEG[®] marketed by Wander), Cesamet[®] a nabilone-PVP (polyvinyl pyrrolidone) preparation (marketed by Lilly) [45] as well as a formulation of troglitazone (Rezulin[®]) marketed by Parke-Davis which had to be withdrawn from market for toxicology related issues of the drug. Several implants containing

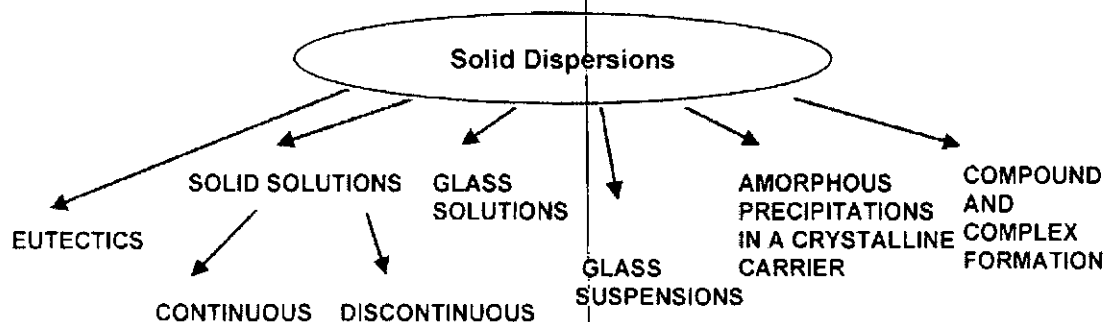


Fig. 5. Categories of solid dispersions.

LHRH agonists for parenteral use have become commercially available, such as goserelin (Zoladex®) or buserelin (Depot-Profact®) embeddings in poly(lactide-co-glycolide) (PLGA) [46].

The troglitazone formulation in PVP was actually manufactured by melt extrusion [47]. Melt extrusion technology has proven to be a suitable method for the production of controlled release reservoir systems consisting of polyethylene vinylacetate (EVA) co-polymers. Based on this technology, two controlled release systems Implanon® and NuvaRing®, have been developed [48].

Problems limiting the commercial application of solid dispersions involve mainly the method of preparation, reproducibility of physicochemical properties, formulation into dosage forms, the scale up of manufacturing processes, and the physical and chemical stability of drug and vehicle [49].

A matter of uncertainty rarely addressed is the analytical differentiation of amorphous embeddings in crystalline carriers compared to a true solid solution, where the drug is molecularly dispersed in the carrier. The same holds true for the amorphous embedding in a glassy carrier compared to a glass solution. The term solid molecular dispersion differentiates from amorphous embeddings [50]. Solid molecular dispersion summarizes solid and glass solution irrespective of the nature, e.g. the molecular weight, of the solvent or solute.

Two major factors that stabilize solid molecular dispersions are intermolecular interactions [51–53] between the drug and the carrier and the viscosity of the carrier [54]. Glass transition temperature has long been seen as the predominant factor governing the physical stability of solid dispersions. However, this concept only holds for true solid molecular dispersions above their saturation limit. Within solid amorphous dispersions, the mobility of the active molecule is already given in the amorphous phase of the active itself possibly leading to recrystallization processes [55]. In the meantime investigations have shown that direct linear correlations between glass transition temperature and recrystallization tendency are rarely given. The solubilizing and stabilizing effects of the carrier systems' intermolecular interactions are often of far greater importance for physicochemical stability [56–59].

The mechanisms of drug release from solid dispersions in water-soluble polymers has been reviewed recently [60]. Because of surface activity of carriers used, complete dissolution of drug from melt extruded solid dispersions can be obtained without the need for further pulverization, sieving and mixing with excipients [61]. The effect of the molecular weight of the matrix polymers on the dissolution profile has been described with special respect to solid dispersions and solid molecular dispersions [62].

These findings contribute to the field of melt extrusion as the molecular weight and other characteristics of a polymeric carrier such as crystallinity and hydrogen bonding, vice versa pre-determine the manufacturing conditions in the extrusion process.

3.2. Application of melt extrusion as drug delivery technology

The breakthrough was achieved by the availability of a great variety of pharmaceutically approved carrier systems [63]. Such carrier systems include PVP [64] or its co-polymers [65], poly(ethylene-co-vinylacetate) [66], polyethylene glycol (PEG) [67], cellulose-ethers [68], and acrylates [69]. The properties of polyethylene oxide (PEO) as a drug carrier in melt extrusion with the aim to obtain chlorpheniramine maleate matrix tablets was examined by McGinity [70]. Amongst the different classes of biodegradable polymers, the thermoplastic aliphatic poly(esters) like poly(lactide) (PLA), poly(glycolide) (PGA), and the copolymer of lactide and glycolide, poly(lactide-co-glycolide) (PLGA) have been used in extrusion. Starch and starch derivatives have been applied along with [71] low molecular weight excipients like sugars and sugar alcohols and waxes [72]. The basic prerequisite for the use in melt extrusion is the thermoplasticity of the polymers or that of the respective formulations.

Long residence time and high glass transition temperature (T_g) resulting in high process temperatures have often been described as potential drawbacks of the melt extrusion process. The comparison of the influence of two different implant manufacturing techniques, extrusion and injection molding, on the in vitro degradation of the polymeric matrix

of polylactic acid (PLA) was studied. Both kinds of implants were loaded with a somatostatin analogue. It was shown that both molecular weight and polydispersity decreased after extrusion or injection molding. This decrease was more pronounced with the latter technique possibly due to an increased residence time [73]. Repka et al. showed that a thermally labile drug, hydrocortisone, could be successfully incorporated into hydroxypropylcellulose (HPC) films produced by melt extrusion [74].

Apart from distinct dosage forms or tailored release profiles melt extrusion offers the chance to circumvent the problem of polymorphic forms with different solubilities, the possibility to start from different particle sizes and a possible reduction of tablet size. Examples have shown that more favorable polymorphic forms may be stabilized on incorporation into PVP [75,76]. Melt extrusion with pharmaceutical actives having a low melting point has also been described. Under such conditions the extrusion process may serve as an agglomeration step [77]. An example for a change in morphology, continuously introduced in the melt extrusion process, applied to alter the release characteristics has been presented by Gurny et al. [78]. In order to influence the release of an extrudate a 200 μm thick layer on the extrudate surface was introduced while extruding.

In addition, implants [79,80], stents [81], oral dosage forms [82], bioadhesive ophthalmic inserts [83], topical films [84], and effervescent tablets [85] have been developed using the melt extrusion process.

3.3. Solid dispersions with melt extrusion technology

Melt extrusion is a significant step forward to cover the technology related issues and makes the solid molecular dispersion approach a viable option. The viability of melt extrusion technology for the production of thin, flexible, acrylic films for topical drug delivery has been investigated by Aitken-Nichol et al. ([86]). Lidocaine HCl was able to plasticize the acrylic polymer and the drug was completely dispersed at the molecular level in the extruded films. Solubilized drug molecules were shown to plasticize the polymer by increasing the average polymer chain spacing [86].

A contraceptive vaginal ring containing etonogestrel and ethinyl estradiol has been prepared by melt extrusion. Coaxial fibers have been produced with varying steroid concentrations in the polymer and the release has been studied. The powder mixtures were blended in a twin-screw extruder. The polymer melted and the steroids completely dissolved in the polymer. After leaving the extruder, the strands were cooled to room temperature and granulated using a strand granulator. For the preparation of the coaxial fibers, a co-extrusion installation was used. The installation consisted of two single-screw extruders that are connected to a spinning block. The two extruders were used to melt the core and membrane polymer at temperatures above 110°C. The molten polymers were delivered to two gear pumps, which assure an accurate flow of both polymers to the spin-

neret. Subsequently, the membrane and core polymers were combined in a spinneret, thereby forming the coaxial fiber [87].

A floating sustained release dosage form composed of nicardipine hydrochloride and hydroxypropylmethylcellulose acetate succinate was prepared using a twin-screw extruder. By adjusting the position of the high-pressure screw elements in the immediate vicinity of the die outlet, and by controlling the barrel temperature, a puffed dosage form with very small and uniform pores were obtained. It was shown that the puffed dosage form, consisting of enteric polymer prepared using the twin-screw extruder, was very useful as a floating dosage form that was retained for a long period in the stomach [88].

Sustained release formulations of isosorbide nitrates with polyvinylacetate have been developed using melt extrusion as manufacturing process. The *in vitro* release profiles indicate that even at low amounts (w/w) of the polymer the sustaining action of the polymer is sufficient to delay the release [89]. Formulations and dosage forms for poorly soluble drugs applying melt extrusion technology have been evaluated in a number of cases.

Underlining the economic importance of the melt extrusion process Ghebre-Sellassie[90] examined the use of different polymers revealing that hydroxypropyl cellulose may be a better water-soluble polymer compared to PVP for poorly soluble drugs. X-ray powder diffraction studies suggested that the drug substance mostly existed in the crystalline state truly representing a crystalline solid dispersion. Extrusion as a way of manufacture is mentioned and a variety of examples using melt processes are given[90].

A number of glass solutions of poorly soluble drugs have been developed using the melt extrusion process with a drug load ranging from 30 to 60% with real time stability up to 9 years. During this time period no crystallization could be detected by means of X-ray powder diffraction or differential scanning calorimetry [91]. It seems obvious, that stability of solid molecular dispersions is achieved when the solubility of a given drug in the carrier is not exceeded. By definition such systems are thermodynamically stable as their stability is related to the solubility of the active and not to the viscosity of the matrix as in supersaturated systems which are kinetically stabilized.

Glass solutions of a lipophilic drug substance by melt extrusion technology which on dissolution forms nanoparticles and thereby increases the dissolution kinetics have been presented recently [92]. PVP or a vinylpyrrolidone–vinylacetate copolymer have been studied together with different surfactants.

17-Estradiol hemihydrate as a poorly water-soluble drug was improved with respect to its solubility and dissolution rate by melt extrusion. Different compositions of excipients such as PEG 6000, PVP or a vinylpyrrolidone–vinylacetate-copolymer were used as polymers and Sucroester®WE15 or Gelucire® 44/14 as additives. The solid dispersions resulted in a significant increase in dissolution rate when compared

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to the pure drug or to the physical mixtures. A 30-fold increase in dissolution rate was obtained for a formulation containing 10% 17-Estradiol, 50% PVP and 40% GelucireTM 44/14. The solid dispersions were then processed into tablets. The improvement in the dissolution behavior was also maintained with the tablets [93].

Amorphous polysaccharide matrices determining the release rate of melt extruded dispersions have been examined by Rein et al. [94]. Carbohydrate based glassy matrices which are stable in the glassy state at ambient temperatures may be prepared by the use of aqueous plasticizers with melt extrusion. Such glassy matrices are useful for the encapsulation of drugs and flavoring agents [95].

Foster et al. melt extruded indomethacin, lacidipine and tolbutamide with PVP. Indomethacin samples remained amorphous on storage as demonstrated by X-ray powder diffraction (XRPD) and temperature modulated differential scanning calorimetry (TMDSC). For lacidipine and tolbutamide low crystallinity levels were detected which, at estimated 7% crystallinity, decreased the dissolution rate significantly. The presence of significant hydrogen bonding (as indicated by the deviation of the experimental from the theoretical glass T_g values) may decrease uptake of moisture and restrict plasticization of the matrix. However, lacidipine recrystallized even when T_g was well above the storage temperature [96].

Along with literature describing the in vitro performance of solid dispersions a number of melt extruded solid dispersions have been examined in humans.

The antiretroviral agent loviride has been melt extruded to a solid molecular dispersion in HPMC and showed remarkably lower food-effect compared to capsules [97].

Further, the extrusion process has been applied in order to combine a sparingly water-soluble drug compound, a cyclodextrin, and a physiologically tolerable water-soluble organic polymer [98].

Antifungal compositions of itraconazole were prepared as solid dispersions from the melt extrusion process. In a limited number of volunteers the melt extruded tablet gave an area under the curve (AUC) of itraconazole in the fasted state that was 2.3 times the area under the curve of the marketed reference capsule [99].

Melt extruded dispersions of ibuprofen were compared to the lysinate salt of ibuprofen in healthy volunteers. Bioequivalence was demonstrated with the relevant parameters AUC and C_{max} . Also, the t_{max} as a measure for onset proved to be equivalent with 0.5 h for test and reference [100].

4. Conclusions and outlook

Melt extrusion technology today represents an efficient pathway for the manufacture of drug delivery systems. Resulting products are mainly found amongst semi-solid and solid preparations. The potential of the technology is reflected in the wide scope of different dosage forms cover-

ing oral, parenteral and topical applications. In addition, the physical state of the drug in the melt extruded formulations reaches from simple crystalline embeddings, mainly in the field of sustained release applications, to amorphous or molecularly dissolved stages. Compared to solvent processes aiming at solid molecular dispersions melt extrusion offers a promising alternative. The possible use of a broad selection of excipients from high molecular weight polymers to low molecular weight additives like sugar alcohols, waxes or surfactants opens a field of numerous combinations for formulation research.

Drawbacks of the technology are often related to high energy input mainly related to shear forces and temperature. This is where process engineering comes into play. The design of screw assemblies and extruder dies are two major areas, which have significant impact on the degradation of drugs and excipients. As the residence time is rather short compared to conventional processes like sterilization, even drugs known to be sensitive to elevated temperatures have been processed successfully. In addition the exposure to oxygen in the extrusion channel is limited.

Work in the field is increasing and the literature published reveals interesting new aspects like in-situ salt formation, fast dispersing systems with foam like structures, complex formation in the melt, and nanoparticles released from molecular dispersions manufactured by melt extrusion.

Unlike other delivery systems, most of which consist of a random dispersion of a drug in a matrix, extrusion technology may be used to place exact amounts of active drug in well-defined layers of micrometer range thickness. In addition, the processing of the polymer determines not only the design of the device but it influences its morphology, namely its microporous structure, polymeric chain orientation and crystallinity to a high degree.

Further, it remains to be seen whether the intense interaction in the melt can be used to form complexes with rather sensitive molecules like peptides and proteins in order to stabilize such structures.

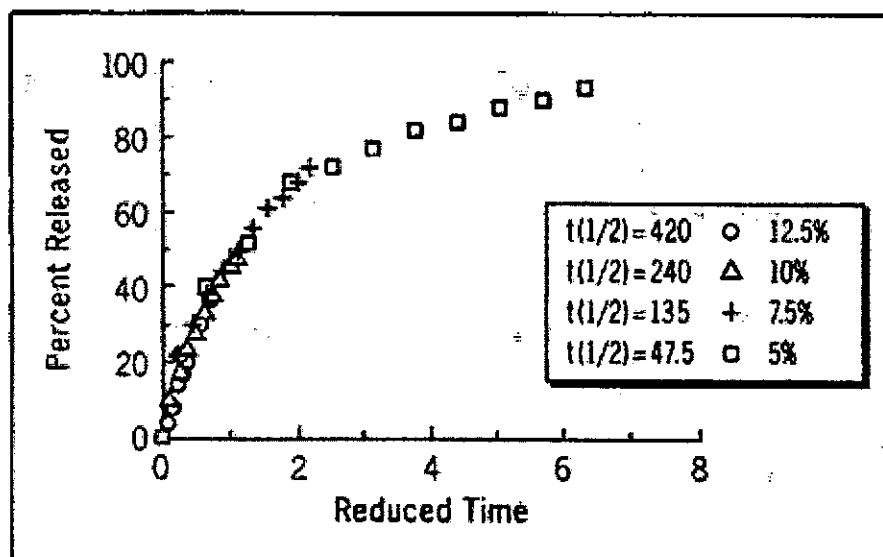
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Advanced Pharmaceutical Solids



Jens T. Carstensen

Hard-Shell Capsules

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Hard-shell capsules are a dosage form that is resorted to when a drug substance is poorly compressible in the desired dosage strength and is moisture-sensitive. It also, at times, results from decisions early in product development, during which original clinical trials were performed in capsules, because of convenience, and the trials went ahead too rapidly to economically change the dosage form. The time lapse between conception of a drug and its introduction into the market place is of importance, and even though hard-shell capsules may be more expensive and cause other problems not encountered in other solid-dosage forms, the development of the dosage form is easier and, in some aspects, more foolproof than direct compression- or wet granulation-based tablets (if those are possible with the drug substance). An example of a drug substance that was introduced into the market place as a capsule because the development got too far ahead of itself is chlorthalidone HCl (Librium Hydrochloride) capsules. Four years later, when the tablet, Libritabs, was introduced, the public was used to a capsule, and the tablets were never a success.

22.1. THE TWO-RING HARD-SHELL-FILLING MACHINE

The commonly used hard-shell capsules are made of gelatin, formed into shapes that allow filling them with particulate matter. The mostly used shapes and sizes are shown in Fig. 22.1.

Before discussing the required powder requirements for hard-shell operations, it is useful, first, to *sketchily* describe the basic principles of the original hard-shell machine. Although it is not used much in actual production today, it is frequently used in early product development (e.g., phase I clinical batches). It is a convenient method for making small batches. For larger batches it is too slow and labor-intensive to retain the popularity it once had.

Figure 22.2 shows the basic principle on which the capsule separation operation is based. The basics of the machine is a set of two rings that fit together, and that have holes which in the upper ring correspond in diameter to that of the top of the capsule, and in the lower ring correspond in diameter to that of the body of the capsule (see Fig. 22.2a and b). Capsules, placed in a hopper, are fed down a so-called raceway with a rectifier bar that aligns the capsules so that they feed into the rings in the position shown in Fig. 22.2c. Vacuum is applied, and the two rings are separated (see Fig. 22.2d), so that all the bodies are now in the bottom ring, and all the tops are in the top ring.

The bottom ring is now transferred to a filling station (Fig. 22.3) where a movable hopper, containing the powder to be filled, is drawn over the ring, and powder fills into the body capsules. After one rotation the hopper is drawn back. The once empty bodies of the capsules are now filled with powder.

The ring with the now-filled bodies of the capsules is placed together with the top ring with the empty tops, and aligned so that the holes line up, they are placed against a plate (Fig. 22.4a). A peg-board is placed in alignment with them (see Fig. 22.4a) and then pushed in (see Fig. 22.4b) so that the bodies are forced into the tops, and the support plate is then removed (see Fig. 22.4c), the peg-board pushes all the way into the rings, so that the capsules can be ejected.

The rings may have one, two, or three circles of holes. One is shown in Fig. 24.4, and two are shown in Fig. 22.5. The hopper has an auger (see Fig. 22.5) which

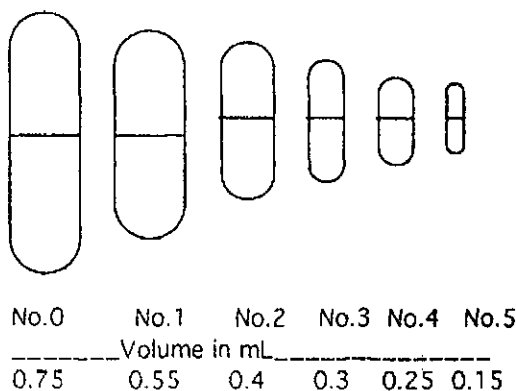


Fig. 22.1 Common shapes and sizes of hard-shell capsules. The volumes may depend on empty shell manufacturer, and other sizes have been reported in the literature: namely, 0: 0.68; 1: 0.50; 2: 0.37; 3: 0.30; 4: 0.21; 5: 0.13 mL.

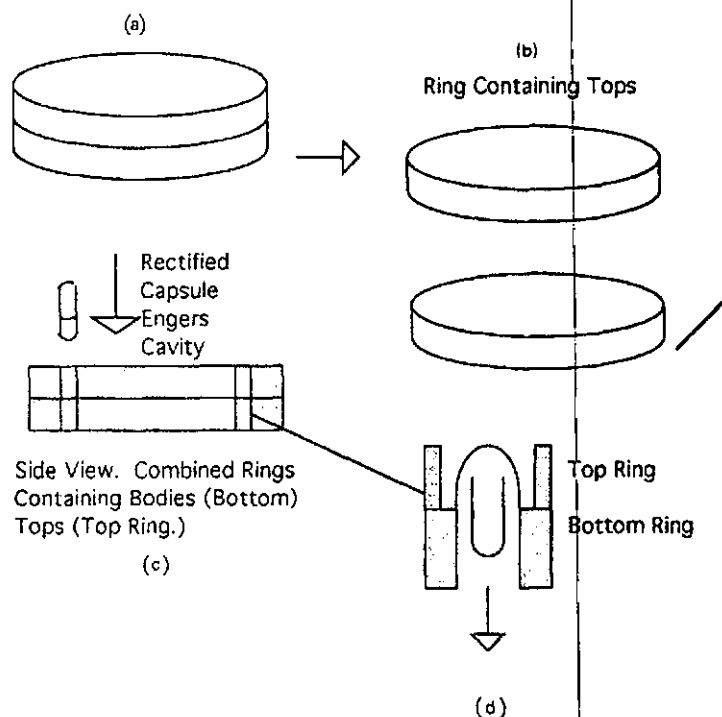


Fig. 22.2 Principle of a two-ring hard-shell machine.

may, or may not, be engaged. If it is engaged, then it helps push powder into the shells, if it is not engaged, then powder fills in simply by gravity.

In the former case, there is a forced consolidation of the powder, in the latter, there is none. The latter procedure is often used when sustained-release beadlets are filled, because the auger might crush the sustaining film. For this, as shall be discussed shortly, there is no internal pressure on the capsule, and to avoid separation of the halves in shipping, the capsules may be banded. By this procedure, a thin gelatin film is placed around the separation line between the halves and, aside from holding the halves together, this also tamper-proofs the product.

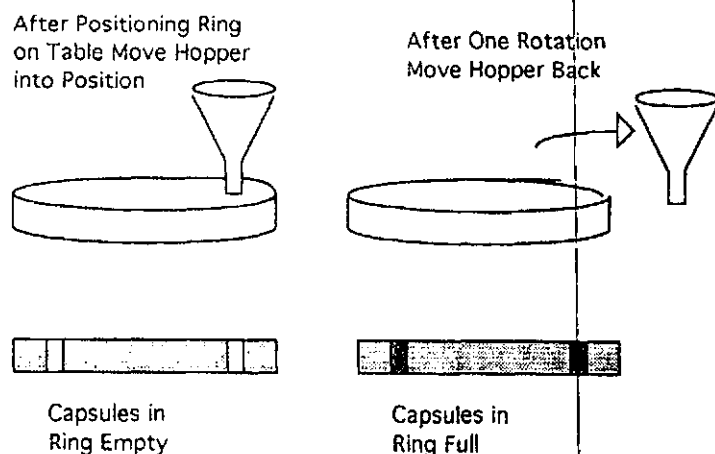


Fig. 22.3 Principle of filling the empty capsules in the bottom ring.

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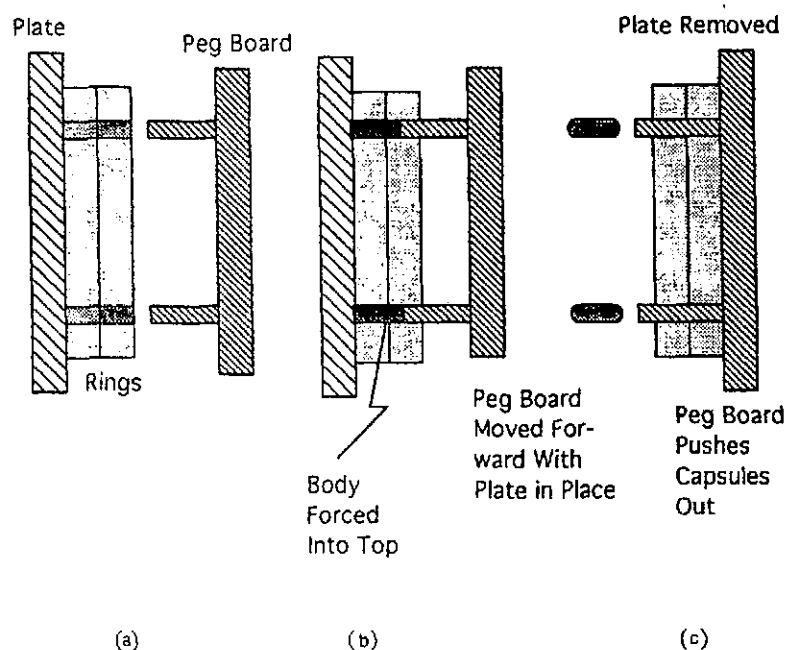


Fig. 22.4 Principle of ejection of capsules in a two-ring machine.

There will be an effect of flow rate both in free-flow fill, and in auger-forced fill. The "dwell time" τ (i.e., the length of time the body in the lower ring is in contact with the powder in the hopper) is the longer the length a of the hopper throat, and the shorter the rotational speed Ω rotations per second (rps), of the die table. If the flow rate, forced or not, is W g/s, then in τ s, $W\tau$ grams will flow into the capsule. The dwell time τ is given by the fact that the linear speed v of the hole under the hopper is

$$v = \Omega 2\pi R \quad (22.1)$$

so that the contact time is

$$\tau = a / (\Omega 2\pi R) \quad (22.2)$$

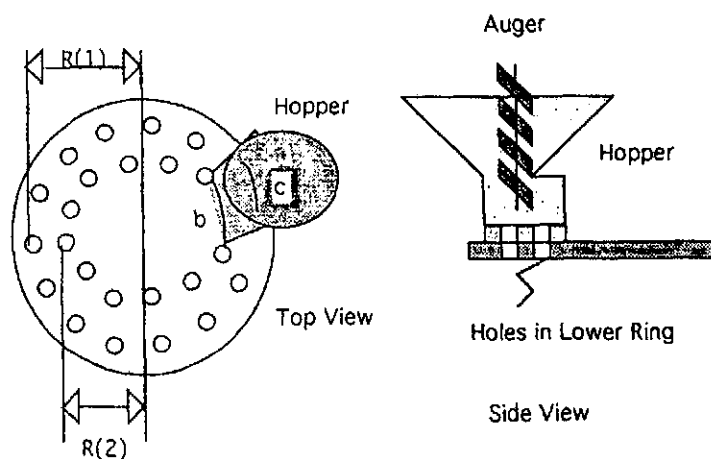


Fig. 22.5 Filling process on a two-ring machine.

where R is the radius of the circle of rings. If the fill dose is D g, then the amount that flows into the die must be D or more, that is, in the limit

$$D = W\tau = Wa/(\Omega 2\pi R) \quad (22.3)$$

For more than one row, the distance a differs from inner to middle to outer row (for three rows of rings) and from inner to outer row [for two rows of rings, i.e., R differs, $R(1)$ being larger than $R(2)$ in Fig. 22.5]. This is compensated by the protrusion on the hopper, making the distance b in Fig. 22.5 different from the distance c . Much of the fill weight variation experienced with multiple-ring filling is due to the different speeds of the hole circles, giving different contact times, in spite of the b and c features of the hopper construction.

From the foregoing, the minimum flow rate, forced or not as the situation may be, would be

$$W = D(\Omega 2\pi R)/a \quad (22.4)$$

Note that D is a function of Ω . The machine can be run at different speeds, so that the fill weight can be adjusted by way of adjustment of the rps.

22.2. OTHER FILLING PRINCIPLES THAN THE TWO-RING MACHINE

High-speed-filling machines usually depend on a dosator principle, which is outlined in Fig. 22.6.

The dosator is set at a given level, to assure a certain free volume. The filling principle is then that the powder is stomped into the dosator by the downward movement of it. (In some machines vacuum is employed in the void section to obtain the fill.) The dosator is then moved out of the bed.

The empty capsules are separated and the body of the capsule is made to coincide with the dosator, and downward movement of the pin, or simply gravity (or application of compressed air), ejects the powder. For precision this should have the nature of a plug.

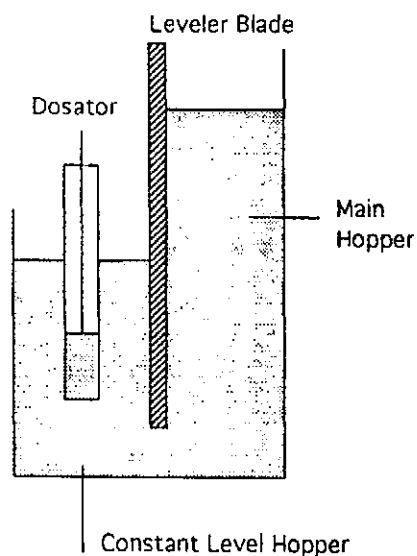


Fig. 22.6 Dosator principle.

The amount filled into the cavity of the dosator (hence, the fill weight) is a function of the apparent density, the compressibility (and indirectly of the particle size distribution).

Flow rate of the powder is important, because (see Fig. 22.6) the powder must flow in a controlled fashion from the main hopper into the constant level hopper. Control of this is accomplished, within limits, by the leveler blade.

It is obvious that the powder must be, to some degree, cohesive because a type of plug has to form. On the other hand it cannot be too cohesive, for flow then is impaired, making a constant level of powder difficult to achieve. The constant level is important, because the stroke of the dosator, and the amount of powder it encounters governs both the fill weight and the precision of fill.

After the body is filled, it is made to coincide with the top, and an insertion mechanism causes joining of top and body.

There are several brands of high-speed hard-shell capsule-filling machines, Häffliger Karg (HK) machine, the Zanazi, and the mG2 being the most common.

The HK machine has a storage hopper for empty capsules, a rectifier, a bulk powder hopper (as shown in the foregoing), a capsule-transport portion, a closing station, and an ejection station. The number after HK machines signifies the number of capsules that can be handled per minute with optimum operation (e.g., HK Model GKF 2500 will handle 2500 capsules per minute).

The mG2 is a continuous-motion machine, the model G38 operating at 1000 capsules per minute. It consists of (a) a hopper for empty capsules with rectifier, (b) a removal station for the capsule top, (c) a cleaning station, (d) a dosator, (e) a powder hopper, (f) a top holder station, and (g) a closing and ejection station.

The highest output of the Zanazi machines is 150,000/h. The BZ-72 model handles powders, pellets, and tablets. Some models have presorters for empty capsules, recovery system for powder, a sampling station for filled capsule, and a check-weigher system.

22.3. PRINCIPLES OF FILLS AND VOLUMES

To make hard shell capsule products, it is a *mixture* of drug substance and excipient (e.g. lactose and magnesium stearate) that is filled into the body of a hard-shell capsule of a known volume. The principle of manufacturing the dosage form is, as described earlier, to (a) separate the cap and body, (b) "fill" the body, and (c) bring the cap and body section together again. This principle applies to other capsule-filling machinery as well.

To obtain the correct fill in a capsule-dosage form requiring, for example, X mg of drug, the drug substance is mixed with Y mg of excipients. Y is selected so that the mixture has the "correct" volume.

If the *appropriate* apparent density is ρ' , and the volume of the capsule is V , then

$$V = (X + Y)/\rho' \quad (22.5)$$

from which Y can be calculated. The problem, however, lies in the term *appropriate*, because, depending on the machine used, this could be the cascaded or the tapped density, somewhat in-between, or even a larger density.

In general, if adjustments are made (e.g., if a trial of the filled capsule does not give the correct weight, the remedy is to adjust Y , so that it becomes correct). As has been seen in Chap. 16, apparent densities of mixtures depend on the state of subdivision of the two (or more) ingredients, so that some measure of *machine adjustment* must be available to allow for fill-weight variations that will occur from batch to batch of raw material used. If the fill weight is approximately correct, then machine speed, as mentioned, may be used to adjust it.

22.4. COMPACTION DURING HARD-SHELL FILLING

If a solid is compressed below its elastic limit, then it will distort a bit, and then return to its original shape once the stress is released (Fig. 22.7a).

Compaction is actually resorted to, to some degree, in all of the different types of capsule machines. When a powder is "compressed" gently, it will then remain within the elastic limit. Figure 22.7 demonstrates this, and shows that when a capsule is filled, there is a residual stress, which actually helps keeping the capsule halves together.

There are several aspects to this. The consolidating pressure P , will affect the apparent density. Kawakita and Taneya (1967) have shown that the porosity ϵ responds to pressure P in the following fashion:

$$\partial\epsilon/\partial P = c\epsilon^x \quad (22.6)$$

This integrates to

$$\epsilon^{x+1}/(x+1) = cP + Q \quad (22.7)$$

where Q is an integration constant that can be derived from the apparent density at zero consolidation pressure. Kawakita and Ludde (1970/71) have compiled a series

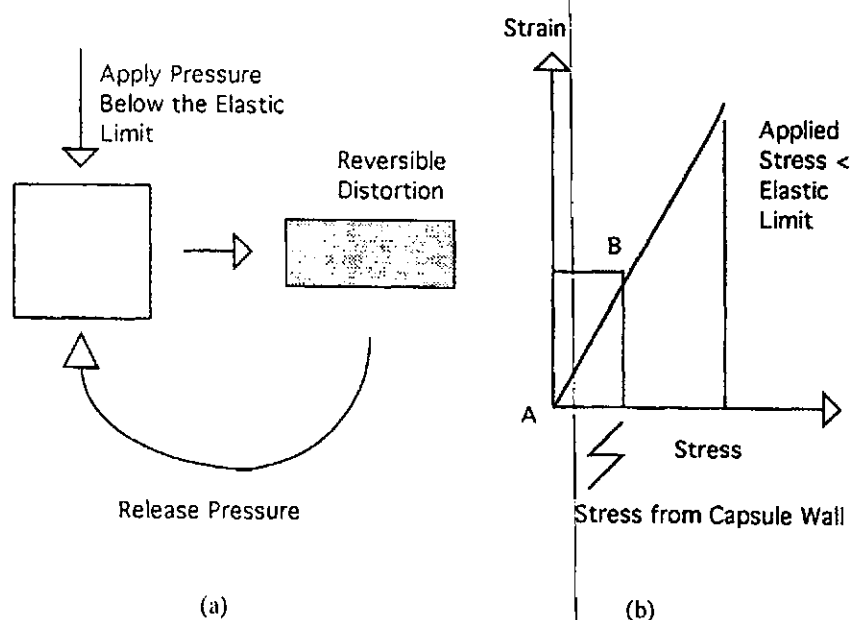


Fig. 22.7 (a) Shapes of a particle under stresses below the elastic limit; (b) Linear stress-strain relation below the elastic limit (Hooke's law).

of consolidation equations. One that has a bearing on compaction equations in Chaps. 23 and 24 is the Cooper equation:

$$\{(V_0 - V)/(V_0 - V')\} = \beta_1 \exp(-\beta_2/P) \quad (22.8)$$

Where V_0 is the volume of the powder at zero pressure, V is the apparent volume at a consolidation pressure of P , and V' is the net volume of the particles. β_1 and β_2 are constants.

22.5. DISSOLUTION AND DISINTEGRATION OF HARD-SHELL CAPSULES

Newton (1972), Newton et al. (1971a,b), and Muhammed et al. (1983) have described the effect of variables in formulation and process on release of drugs in capsule form. The effect of additives and, again, preparation mode on release of active substance from hard-shell capsules has been described (Whitney et al., 1969; Samyn and Jung, 1970; Khalil et al., 1972; Newton et al., 1977, 1980; Stewart et al., 1979).

In fully automated filling machines the powder contents are compressed, so that variables, such as force of compression can affect both dissolution and disintegration. Several authors (Mehta and Augsburger, 1981; Btozolakis et al., 1982, 1984) have investigated the use of disintegrants to improve disintegration and dissolution.

A systematic study of the use of effervescent salt, as compared with conventional disintegrants, in dosator-principle filling machines has been reported by El-Shaboury et al. (1993).

These authors studied effervescent salts as disintegrants as well as conventional disintegrants (Explotab, microcrystalline cellulose). In the former case they found improvement (decrease in disintegration time and t_{50}), when the compression pressure was increased. When their data are plotted as $\ln[M/M_0]$ versus time the plots are not nearly as good (as judged by correlation coefficients) as when a cube-root relation is used (Fig. 22.8). Denoting by M the amount of drug not dissolved, and by M_0 the initial amount, then:

$$1 - [M/M_0]^{1/3} = K(t - t_i) \quad (22.9)$$

where t is time, t_i is lag time, and K is the cube-root dissolution rate constant. This may be recast as

$$[M/M_0]^{1/3} = 1 + Kt_i - (Kt) \quad (22.10)$$

The disintegration time can be deduced from these curves: the intercept minus 1, divided by the value of K . For instance, for the data for 10-kg pressure, the disintegration time would be $0.1695/0.015894 = 10.66$ min. When these are plotted versus disintegration times from conventional disintegration tests, then Fig. 22.9 results.

It is not always, however, that cube-root relations hold best. Data by Tan and Gan (1998) plot better in the semilogarithmic fashion (Fig. 22.10). Cube-root relations may be expected when the capsule contents, once the tablet has disintegrated, presents itself as a particulate powder, whereas plugs or agglomerates will behave in

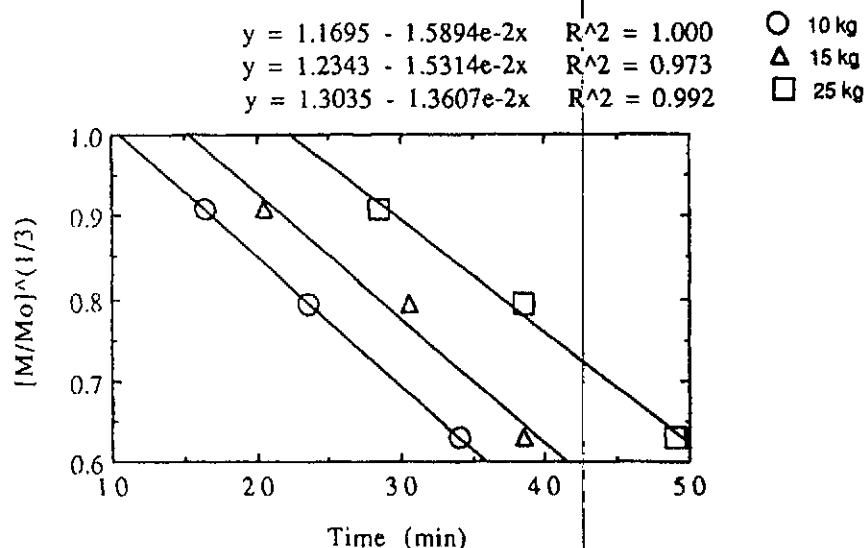


Fig. 22.8 Dissolution of fenopropfen capsules dosator-compacted at different forces. The capsules depicted have no disintegrant or effervescent salt added.

semilogarithmic fashion, because moisture must penetrate the aggregates, dissolve the drug, which then can diffuse out.

In overlubricated powders, disintegration of the shell may occur, but the powder mass will remain intact, and penetration of liquid into a (now hydrophobic) plug gives rise to a slower dissolution. This type of dissolution is likely to follow a square-root law (Higuchi, 1963).

22.6. PELLICULATION

In properly formulated capsules the dissolution steps are (a) rapid dissolution of the shell, followed by (b) dispersion of the powder, followed by (c) dissolution of the drug from distinct drug particles. This type of dissolution curve should simply be a cube-root law, maybe with a slight lag time.

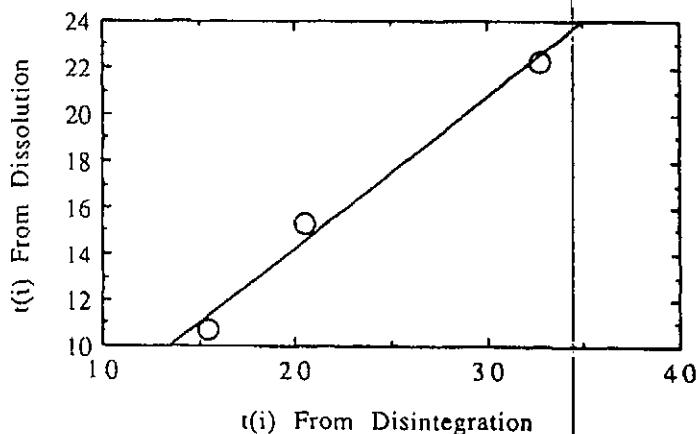


Fig. 22.9 Disintegration values from dissolution plotted versus disintegration from conventional disintegration tests.

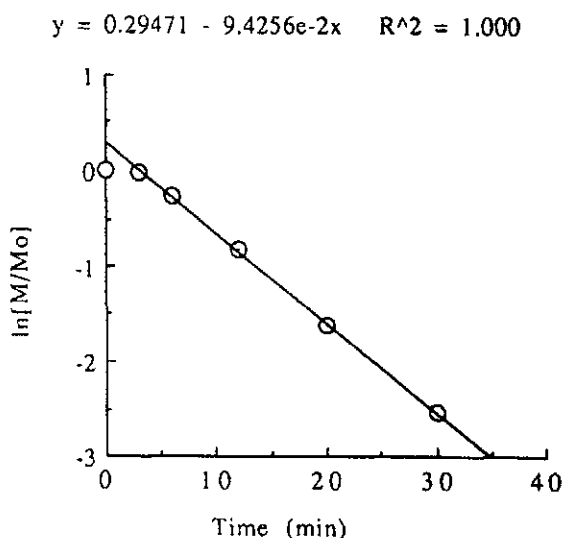
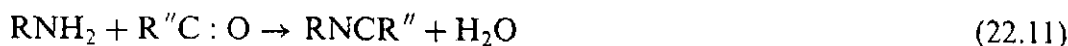


Fig. 22.10 Dissolution of ciprofloxacin HCl capsules. (Data from Tang and Gan, 1998.)

Capsule powders that contain substances with aldehyde or keto groups may experience dissolution rate decrease on storage because of a Maillard-type reaction with the amino groups of the gelatin:



When this occurs, the capsule, when introduced into the dissolution vessel, will form a film (a pellicle or pellicule), which encases the capsule and prevents the drug in it from dissolving.

22.7. SUSTAINED-RELEASE HARD-SHELL CAPSULES

Hard-shell capsules are often used for coated beads and pellet sustained-release dosage forms. The most important aspect of these, owing to their sustained-release nature, is their dissolution pattern.

The common apparatus used is U.S. Pharmacopeia (USP) either method I (basket) or II (paddle). Most common dissolution media are (a) N/10 HCl and (b) water, but some investigators (e.g., Kumar and Pandit, 1997) employ an acid medium at first, and then, at various time periods increasing the pH. For compounds such as ibuprofen, which have higher solubilities at higher pH values, the rate will increase as time (pH) progresses.

Increasing the pH as a function of time in this fashion, the so-called stepped-pH dissolution can be accomplished in different manners (Marty et al., 1997). The pH is usually increased from that of stomach (pH = 1.2) to that of intestine (pH = 7.5).

Two of the methods used to accomplish this involve a total exchange of medium, whereas a third (half-change method) requires exchanging one-half of the liquid with liquid of a higher pH (Brossard and Wouessidjewe, 1990; Münzel, 1960; Ritchel and Orth, 1967). These methods are rather impractical, and there have been other suggested methods for increasing the pH. Marty et al. (1997), Baudy et al. (1989), and Brossard (1976) have used a solid buffer addition to adjust the pH. Sallans et al.

(1988) have suggested a method for which initially one-half of the final volume is used, and liquid addition of buffers then adjusts the pH upward.

SYMBOLS

- a = throat length of hopper
 c = coefficient in pressure/fill equation
 D = fill weight
 K = Hixson-Crowell cube-root constant
 M = mass (weight) of drug not dissolved
 M_0 = initial mass of drug
 P = pressure on fill during filling
 R = radius of die table
 Q = constant in pressure/fill equation
 t = dissolution time
 t_l = lag time
 V_0 = the volume of the powder at zero pressure
 V = (a) apparent powder volume at a consolidation pressure of P ; (b) volume of capsule
 V' = net volume of the particles
 v = linear speed of body of capsule in die
 W = flow rate (g/s)
 X = drug content
 Y = excipient content
 ε = porosity
 β_1 = constant in Cooper-Eaton equation
 β_2 = constant in Cooper-Eaton equation
 τ = dwell time
 Ω = rotations per second (rps) of the die table

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23

Tablet Physics

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As mentioned in the introduction, this text is not geared toward the actual machine and operational details of a solids operation, and only a cursory overview of tablet machines will be given here. This overview is necessary for the further discussion of properties of solids relative to compression.

For further details the reader is referred to the recommended reference texts before the reference list at the end of the chapter for details on tablet machines, methods of instrumentation, and granulation techniques.

23.1. PRINCIPLES OF SINGLE-PUNCH TABLET MACHINES

The *single-punch tablet machine* (or eccentric press) is schematized in Fig. 23.1. In frame A, the hopper is in position over the empty die, bordered below by the bottom punch, and powder flows from the hopper into the die. The amount of powder that flows in is the volume ($V \text{ cm}^3$) times the cascaded apparent density ($\rho' \text{ g/cm}^3$) of the powder, so that the fill weight of the tablet, $U \text{ g}$, is given by:

$$U = V\rho' \quad (23.1)$$

If the fraction of the powder consisting of drug is F , then the dose $D \text{ g}$, is given by

$$D = FV\rho' \quad (23.2)$$

It is obvious that the accuracy and precision of the dose are a function of the accuracy and precision of the fill weight W , and the precision and accuracy of the fraction F . *Content uniformity*, hence, is a function of both these factors.

It is obvious that the fill may be adjusted by the position of the lower punch in the first phase (frame A).

In Fig. 23.1B, the hopper has swung away, and the top punch comes down and compresses the powder into a tablet. The dimensions of the tablet are a function of the longest path this punch takes, and this can be adjusted, so that the *thickness* of the tablet may be adjusted in this way. This also adjusts the *hardness* of the tablet. Hence, in general, in tablets made on a single-punch machine, there is a functional relation between the thickness and the hardness.

Single-punch machines produce, at top speed, about 60 tablets per minute. If the number of tablets per second is denoted N , then the amount of powder flowing into the die per minute is

$$W = NU \text{ g/s} \quad (23.3)$$

W is the required flow rate for the powder. Because most powders have flow rates in excess of 60 g/s there is *generally* no problem with the powder flowing into the die sufficiently rapidly (see Fig. 23.1A). It shall be seen, under rotary presses, that this becomes a problem as the dwell time becomes smaller. The *dwell time* $\tau \text{ s}$ is given by

$$\tau = q/N \quad (23.4)$$

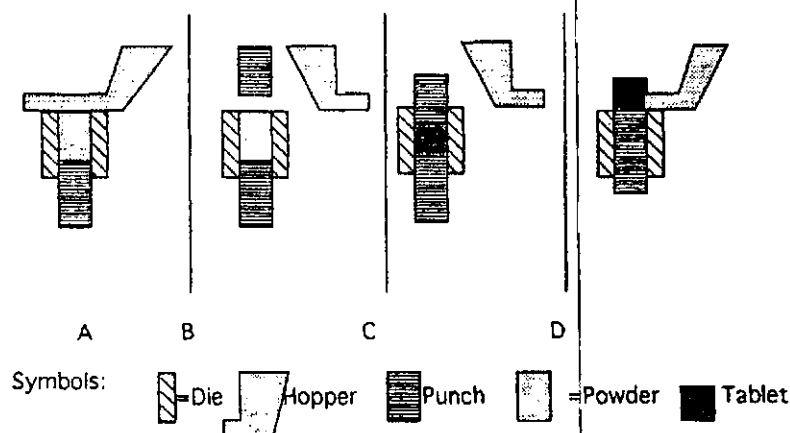


Fig. 23.1 Principle of single-punch tablet machine.

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where q is the fraction of the cycle (see frames A–D) the hopper stays in the position of frame A.

23.2. PRINCIPLES OF ROTARY MACHINES

Single-punch machines are slow and are used mostly in product development and in initial clinical trial batches when raw material (drug substance) is in low quantity.

When larger quantities are required, rotary machines are resorted to, and essentially all manufacturing equipment is of the rotary type.

In a simple setup (Fig. 23.2), a hopper feeds powder into a feed frame, under which dies and lower punches receive the powder (Fig. 23.3). Once outside the feed frame the upper punch descends and its downward movement, in combination with the upward movement of the lower punch, produces the tablet. As opposed to a single-punch machine this is referred to as double-sided compression.

The tablet, ejected from the die by the extreme upward movement of the lower punch is removed from the die table at the end of the circle at the back of the hopper (the knockoff bar), and the cycle repeats.

Many high-speed machines are equipped with two or three hoppers, around the periphery at 120° angles (Fig. 23.4).

Some requirements are apparent from the general setup. It is economically desirable to operate the machine at as high a speed (λ rps; rotations per second) as possible. One of the limiting quantities is the flow rate of the powder.

If the radius of the die table is denoted R , then the linear speed of the dies is $2\pi\lambda R$; hence, the dwell time is

$$\tau = a/2\pi\lambda R \quad (23.5)$$

With a required fill weight of U , it follows that the required flow rate W is given by

$$W = U/\tau = U2\pi\lambda R/a \quad (23.6)$$

or, because the machine operation is adjustable and, for a given powder, W is not (without further manipulation) changeable, the maximum allowable machine speed would be

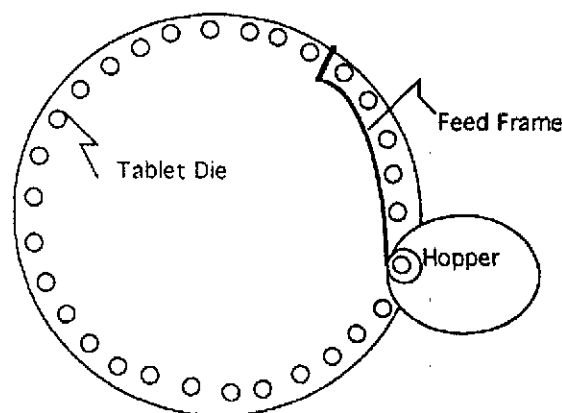


Fig. 23.2 Schematic of rotary machines.

$$\lambda_{\max} = Wa/U2\pi R \quad (23.7)$$

This is *one* of the flow rate requirements of the powder. If there are N stations to be filled under the feed frame, and the flow rate from hopper to feed frame is L g/s then the lag time must be at least

$$\tau = NU/L \quad (23.8)$$

Inserting this in Eq. 23.5 then shows that the maximum machine speed would be:

$$\lambda_{\max} = aL/(U2\pi R) \quad (23.9)$$

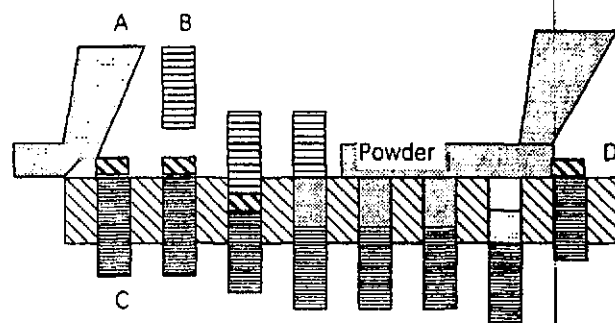
The smaller of the two λ -values in Eqs. (23.6) and (23.8) is the limiting speed at which the machine can be operated and still produce weight-quality product.

Powder flow has been treated in Chap. 18, but it should be mentioned at this point (Carstensen and Laughlin, 1979; Laughlin et al., 1979) that flow rates are dynamic in a sense, in that the powder in the feed frame differs from the static flow rate experienced when a powder flows through an orifice of a stationary hopper.

23.3. MULTIPLE-LAYER AND COMPRESSION-COATED TABLETS

At times, it is necessary to "separate" two components of a solid-dosage form. It could be a case of physical or chemical incompatibility, and a classic example of this is methypylon and caffeine (Carstensen, 1977), for which the two compounds form very low temperature eutectics. An example of chemical incompatibility is aspirin and dialminate.

One manner in which such a separation may be accomplished is by way of either a double-layer tablet or a triple-layer tablet. In the latter, the layout is, as shown in Fig. 23.4, three hoppers are placed at 60° angles to one another, and three granulations, A, B, and C are placed in the appropriate hoppers. A is first filled into dies in a feed frame between A and B, and loosely compacted, granulation B is then filled into the die as it passes hopper B and compressed a bit harder between hoppers B and C, and then finally C is filled into the die as it passes hopper C and the final, desirable pressure is applied. The tablet is then ejected at a knockout bar at the back of hopper A.



Legend: A = Hopper, B = Upper Punch,
C = Lower Punch, D = Tablet

□ = Loose Powder ▨ = Denser Powder

Fig. 23.3 Schematic wrapped-out view of punch positions during the compression on a rotary machine.

Pressures and speeds are adjusted so that the layer separations are “clean,” particularly if the layers have different colors. The two incompatible compounds, in the foregoing examples, would be in granulations A and C. If the incompatibility is *physical* (e.g., by way of eutectic formation), there may still be interaction in the packed product, if it is simply packed (in random arrangement) in a bottle. In that event, there will be contact point between tablets, and whenever layer A from one tablet touches layer C of another, there may be a “spot” occurring.

Two-layer tablets are employed when the incompatibilities are less pronounced. In that case there will always be interaction in the contact area between the two layers. In two-layer tablet manufacture there are only two (or four) hoppers.

In more pronounced situations of incompatibility, or when special release effects are desired, triple-layer tablets may be resorted to (Fig. 23.4) or, bicoated or tricoated tablets are a solution. It is not used often, primarily because of the complicated nature of the construct, and the associated lower tablet machine speeds. The principle of a bicoated tablet is shown in Fig. 23.5.

Figure 23.5 shows one end of a die table. A die is first half-filled with the outer granulation (A), and a tablet is dropped into it (B), it is then filled to the top with outer granulation (C), and compressed (D).

The process is slow (800 tablets per minute), but for incompatible drugs it may be a last resort. Tablets-within-tablets-within tablets (tricoating) also is possible, and here totally incompatible components can be separated by a neutral layer (see Fig. 23.5).

Thomas et al. (1998) have described how the core material properties affect the compression and the properties of compression-coated tablets made with microcrystalline cellulose as the coating material.

23.4. STRESS AND STRAIN: HOOKE'S LAW; BONDING IN TABLETS

Hiestand states that the mechanical criteria for a successful tablet formulation are good flowability for powders and adequate strength without fracture for compacts. The matter of flow has already been discussed, but further aspects of it will be dealt

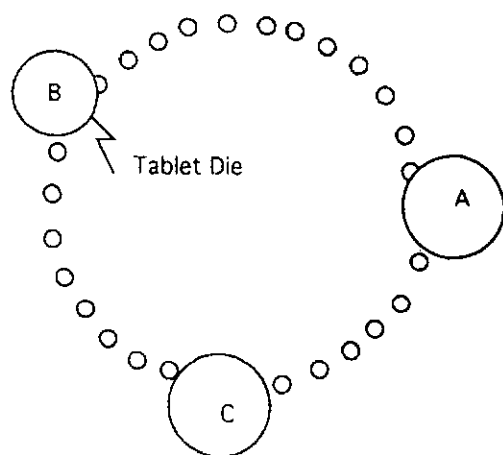


Fig. 23.4 Schematic of triple-layer tablet turret.

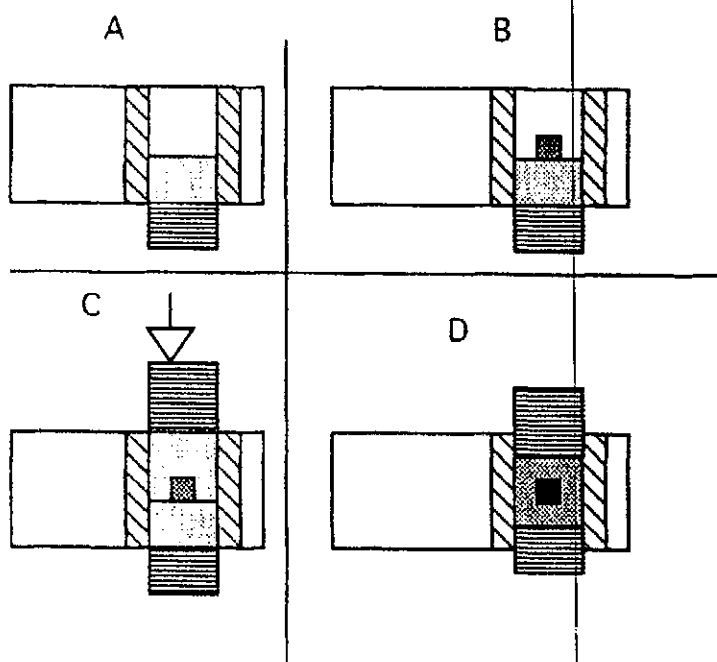


Fig. 23.5 Principle of bicoating (tablet within a tablet).

with in the following. The aspect of strength of materials and of compacts will also be discussed.

It has been seen in previous chapters that efforts are made to make particles "round," and sufficiently large, so that they will flow well, and add binders, so that they will bond when they are compressed. This entails wetting the powder, and then removing the water by drying operations, and as such is energy-inefficient. It is also labor-intensive and, in the 1960s, there was a sustained and successful attempt to accomplish tableting of drug substances by simply mixing them with excipients and compressing them.

Tableting is carried out by applying (compressional) stress to a powder bed. The intent is, by causing close proximity between the molecules in one particle to those in another, to create a "chemical" bond. To this end the surface molecules must be distant by no more than molecular dimension distances. Carstensen (1977, 1981), among others, has shown that the steps, involved in the tableting are (a) elastic deformation, (b) plastic deformation, and (c) fracture (Fig. 23.6). It is one of the two latter steps that is responsible for bond formation.

If, as exemplified in Fig. 23.6 a cubical block is exposed to a pressure P , then it will "give" (i.e., it will become thinner and wider). Up to a certain pressure, $P(1)$, this is reversible (i.e., if the pressure is released then the original form will be regained). The solid, in this range of pressures, is said to exhibit elasticity.

Once $P(1)$ (see Fig. 23.6) is exceeded (point B Fig. 23.7), the deformation becomes irreversible (i.e., if the pressure is lifted, the solid will relax, but it will not return to its original shape). This is denoted the elastic limit or yield value. Beyond this point, further increases in pressure may then result in further deformation (see portion BC in Fig. 23.7). If the pressure is released at any point in this portion, then the block will remain intact, but will be distorted. At a given pressure, $P(3)$ (see point C in Fig. 23.7) breakage will occur, and this is denoted brittle frac-

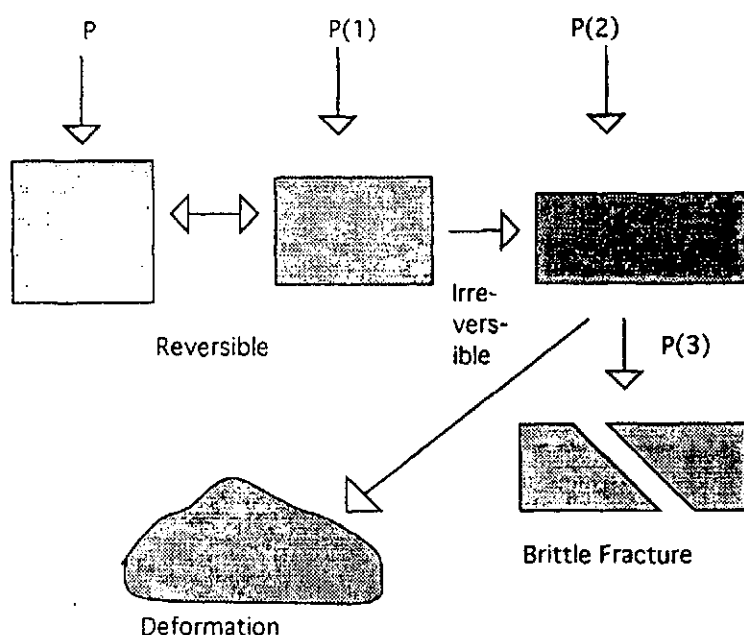


Fig. 23.6 Schematic of yield and fracture of a block.

ture. This is shown, graphically, in Fig. 23.7, which has been shown earlier and is repeated here for convenience.

Often, the portion BC is small, and the bond formation that occurs in this region is insufficient to make a "good" compact, so the pressure has to be brought all the way up to $P(3)$ for good bonding to occur. This situation is denoted bonding by brittle fracture. If, however, adequate bonding between particles occurs in the region BC in Fig. 23.7, then bonding is said to occur by plastic deformation.

The slope of the line AB is denoted the Poisson's ratio, ν . Robers et al. (1994) have determined the Poisson's ratio for microcrystalline cellulose.

23.5. ATHY-HECKEL PLOTS

Up to a certain limit of compression pressure, tablets will become thinner; the higher the compression pressure, the thinner the tablet will become.

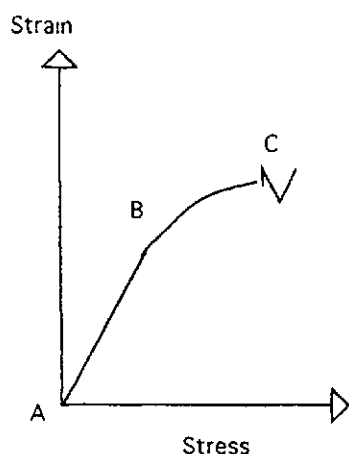


Fig. 23.7 Strain versus stress profile.

The thinner it is, the smaller the porosity (ϵ) and the so-called Athy–Heckel (or simply Heckel) equation states that

$$-\ln[\epsilon] = aP + b \quad (23.10)$$

where a and b are constants (Heckel, 1961).

Table 23.1 and Fig. 23.8 show thickness data of a tablet as a function of compression pressure. The tablet has a cross-sectional area of 1 cm^2 and the true density of the contents is $\rho = 1.5\text{ g/cm}^3$. The fill weight is 900 mg, so that if there were no porosity at all, then the thickness h of the tablet would be given by

$$h = 0.9/1.5 = 0.6\text{ cm} = 6\text{ mm} \quad (23.11)$$

so that, at a thickness of 0.60, all the porosity is gone (i.e., the tablet is simply solid). Knowing the thickness at any given compression pressure, a similar procedure will give the apparent density ρ' , so that the porosity ϵ can be calculated from

$$\epsilon = 1 - \{\rho'/\rho\} \quad (23.12)$$

The thicknesses in Table 23.1 are the experimental value, and the calculated porosities are shown in the third column of the table. The negative of its logarithm is then shown in the fourth column.

The *negative* of the natural logarithm of the porosity is plotted versus applied pressure in Fig. 23.8, and the data linearize. It is strictly an arbitrary convention in literature to plot $-\ln[\epsilon]$ rather than $\ln[\epsilon]$. If the latter were done, then the data would still be linear, but with a positive slope.

Heckel (1961) found, experimentally, that the slopes of such plots are $1/(3\phi)$ where ϕ denotes yield value. The data in Table 23.1 are plotted in Fig. 23.9, and it is seen that $1/3\phi = 0.66$, so that the yield value is calculated to be $\phi 1/(3 \times 0.66) = 0.5\text{ ton/cm}^2$.

23.6. THE COOPER–EATON EQUATION

Linearity in the Athy–Heckel equation is always somewhat lacking. Cooper and Eaton (1962) improved on this by assuming that two processes were at play in the compression. The compression would first, through rupture of particles and their percolation, fill larger void spaces in the powder bed, and once that process was over,

Table 23.1 Example of Porosity as a Function of Applied Pressure

Compression pressure (tons/cm ²)	Thickness (cm)	Porosity	$-\ln[\text{Porosity}]$
2000	2.4	0.4	0.916
2500	1.35	0.5	1.067
4000	0.68	0.118	2.137
5000	0.64	0.062	2.781
6000	0.62	0.032	3.442
7000	0.61	0.016	4.135
(8000)	0.60	0	

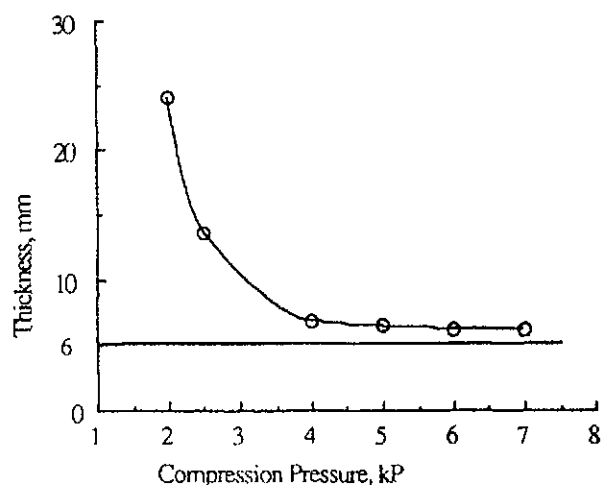


Fig. 23.8 Data in Table 23.1 plotted linearly.

it would repeat, and the now smaller particles would rupture and fill the “smaller” void spaces. This led to a compression profile that was best described by fractional volume compression.

$$(V_0 - V)/(V_0 - V^*) = a \exp(-k_1/P) + b \exp(k_2/P) \quad (23.13)$$

where V_0 is volume before compression, V is volume at a pressure P , and V^* is the volume corresponding to true density; a and k_1 are constants relating to the first fracture and percolation, and b and k_2 are constants relating to the second step. An example of the trace produced by such an equation is shown in Fig. 23.10.

When P tends toward infinity, the exponents tend toward zero, so that the exponential values approach 1.0; hence, the curve in Fig. 23.10 has an asymptote at $(V_0 - V)/(V_0 - V^*) = 0.5 + 0.5 = 1.0$, which is what it should be ($V = V^*$). Chowhan and Chow (1981b), showed that for naproxen and HPMC the equation gave a more rational fit than the Heckel equation (Fig. 23.11).

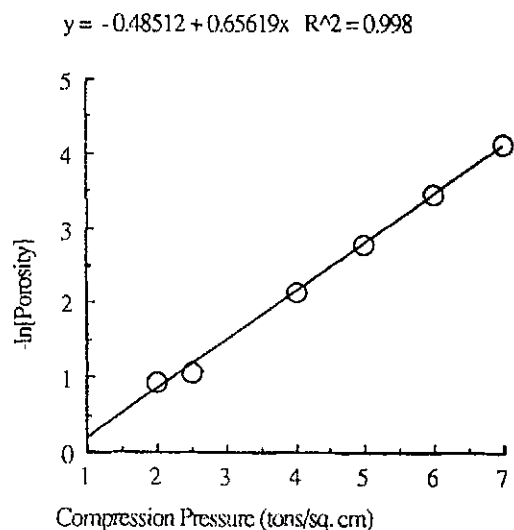


Fig. 23.9 Data in Table 23.1 plotted by the Athy-Heckel equation.

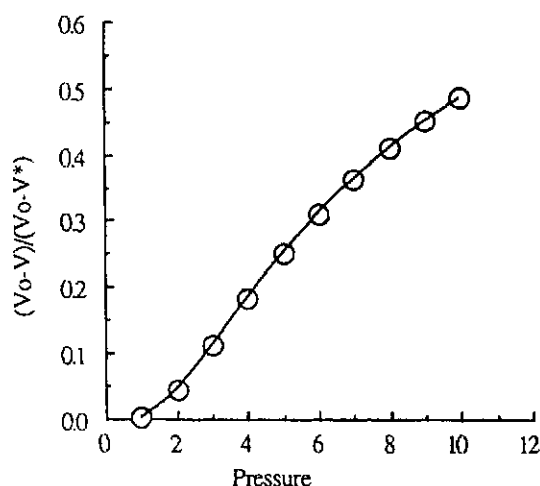


Fig. 23.10 Trace of the equation $(V_0 - V)/(V_0 - V^*) = 0.5 \exp(-5/P) + 0.5 \exp(-10/P)$.

23.7. COMPRESSION CYCLES

If a powder mass is confined in a cylindrical space, and a force is exerted on the top of it, it might, at first sight, seem that the downward force would simply be propagated through the mass, and the reactive force on the bottom of the space would be equal and opposite the force exerted on the top. However, Fig. 23.12 shows, schematically, how some of the force is "diverted" to the walls of the confining space.

In the diagram the hypothetical situation of a "powder mass" of five spheres arranged as two, one, and two is presented. The downward force is A and B, which is then decomposed in EC and DF, toward the wall, and CG and DG toward the center of the sphere in the second layer. This force is propagated along the same center line to the two spheres in the bottom layer GQ and GH, and these are decomposed into wall forces HJ and QK and the downward forces HL and QM.

During the compression there will be work exerted, and part of this work will be "lost" to the die wall. This will be touched on further under Sec. 23.8, *Lubrication*. The diagram explains the so-called Uncle equation, that the downward pressure, P_c ,

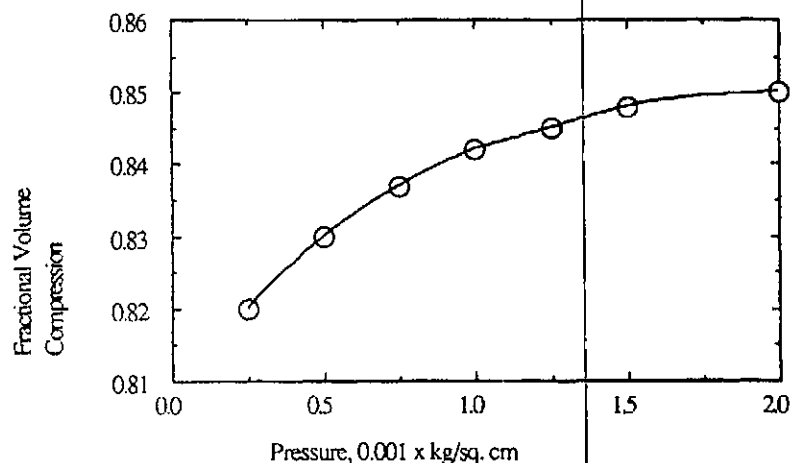


Fig. 23.11 Example of data that would fit the Cooper-Eaton equation. (Data from Chowhan and Chow, 1981.)

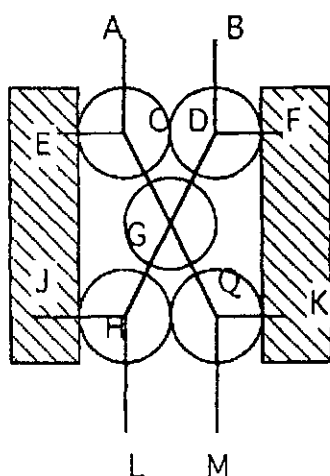


Fig. 23.12 Schematic showing die wall force.

decreases through the compression mass as a function of the distance x , from the surface by the relation:

$$P_x = P_u \exp(-kx) \quad (23.14)$$

Higuchi et al. (1953) were the first to instrument a tablet machine, so that the pressures on the upper and lower punches and on the die wall could be monitored during a compression cycle. This will be shortly dealt with here. A fair amount of older literature on this subject deserves mentioning; namely, that of Long, 1960; Schwartz and Weinstein, 1965; Perelman and Roman, 1971; Schwartz and Holland, 1969; Koerner and McCabe, 1972; Paris et al., 1975; Leigh et al., 1967; and Strijbos et al., 1977.

Applied forces are usually referred to by the symbol P , but in discussion the compression cycle in the following, die wall pressure (stress) will be denoted τ , and applied pressure will be denoted σ . If we refer to the upper portion of Fig. 23.13, the first part of the compression cycle (part A) starts at the point when the punches experience a measurable force from the powder. From this point (line OP) on the die wall stress (or pressure) τ is fairly linear relative to the applied pressure (σ ; as visualized in Fig. 23.13, with a slope equal to the Poisson ratio ν , of the powder), that is,

$$\tau = \nu\sigma \quad (23.15)$$

Marshall (1977) has shown, however, that a more realistic representation is:

$$\text{Line segment OP: } \tau = [\nu/(1 - \nu)]\sigma \quad (23.16)$$

As pharmaceutical examples of Poisson's ratio, Robers et al. (1994) have reported on the ratio for microcrystalline cellulose.

The point P in Fig. 23.13 represents the elastic limit. If this is high, then removal of the load will cause the original line (OP) to be regained, and bonding will not occur.

When forces (or pressures) are applied above point P, then bonding will occur through plastic deformation or brittle fracture. One of these will predominate (Carstensen and Touré, 1980).

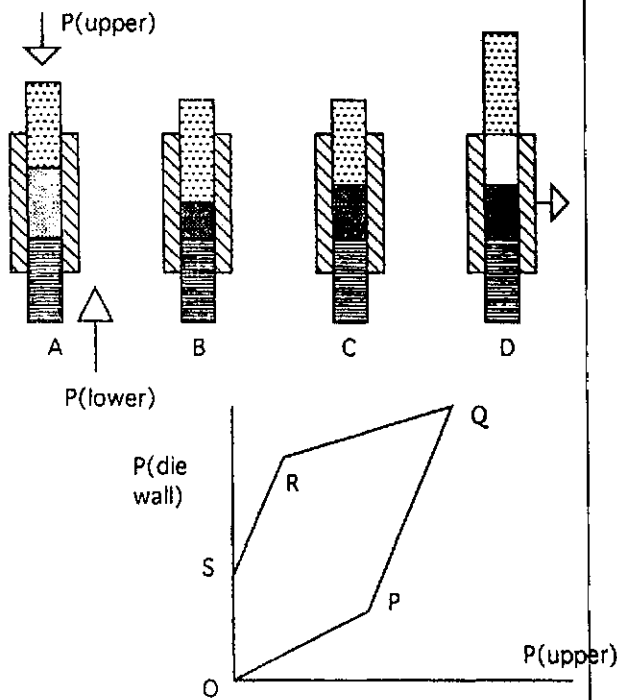


Fig. 23.13 Compression cycle.

If the bonding is by *plastic deformation* (i.e., considering the body viscoelastic), then the solid behaves as a liquid, and if the yield value is denoted ϕ , then the equation for the line segment PQ is:

$$\text{Line Segment PQ: } \tau = \sigma - \phi \quad (23.17)$$

where τ is the stress on the die wall.

Line QR obeys the equation (Parrott, 1990)

$$\text{Line Segment QR: } \tau = (\nu/(1 - \nu))\sigma + \{1 - (\nu/(1 - \nu))\}\sigma_{\max} - \phi \quad (23.18)$$

At point R the die wall stress is greater than the applied stress by a value equal to the yield stress so the equation for line RS is:

$$\text{Line Segment RS: } \tau = \sigma + \phi \quad (23.19)$$

Carstensen and Touré (1980) integrated these equations to find the area (OPQRS) within the compression cycle and found it to be linear with $\tau_{\max}$ (i.e., the “applied compression pressure”).

It is noted that the cycle predicts a *residual die wall stress* of ϕ .

23.7.1 Mohr Bodies

Hiestand (1997) also points out that describing the properties of compacts by linear-elasticity equations has limitations, because compacts (in practice) are porous, and they are nonhomogeneous, viscoelastic Mohr bodies.

A Mohr body is a construction showing τ versus σ and, to some degree applies to a powder bed as well as to a solid body. This is akin to the shear loci discussed in Chap. 17.

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The shear loci depicted in Fig. 17.7 may be presented in the fashion shown in Fig. 23.14. Mase (1970) points out that "frequently... a state of plane stress is represented by a single Mohr's circle... this representation is necessarily incomplete since all three circles are required to show the complete stress picture... A single circle Mohr's diagram is able, however, to display the stress points for all those planes at the point P which include the zero principal stress axis..."

This, notwithstanding, a two-dimensional representation is shown here (as, to my knowledge, it is used in all pharmaceutical publications).

The construct essentially states that when a given normal load is applied to a powder bed, there will then be a plane of maximum stress at an angle of ϕ to the principal stress axis. The tangential component of the stress will be

$$\tau = (\sigma_1 - \sigma_3)/2 \quad (23.20)$$

and the normal component will be

$$\sigma = (\sigma_1 + \sigma_3)/2 \quad (23.21)$$

If total symmetry is assumed, only one Mohr circle then suffices. If the failure is characterized by that of a Mohr body, then the segment OP is still governed by Eq. (23.16).

$$\text{Line Segment OP: } \tau = [\nu/(1 - \nu)]\sigma \quad (23.22)$$

If the stress increases beyond C (see Fig. 23.14), then failure occurs. In the plane of shear, τ , in this situation, equals

$$\sigma/2 - \tau/2 \quad (23.23)$$

The tangential stress in excess of C (see QR - NO in Fig. 23.14) is, hence,

$$(\sigma/2 - \tau/2) - C \quad (23.24)$$

The normal stress in the symmetrical situation equals

$$\sigma/2 + \tau/2 \quad (23.25)$$

and recalling that tangential stress equals friction times normal stress then gives

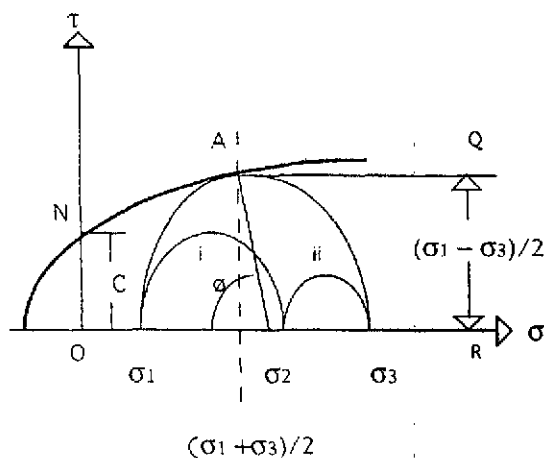


Fig. 23.14 Shear locus and Mohr circles.

$$(\sigma/2 - \tau/2) - C = \mu(\sigma/2 + \tau/2) \quad (23.26)$$

This may be rearranged to express τ as a function of σ , which gives the equation for

$$\text{Line Segment PQ: } \tau = [(1 - \mu)\sigma/(1 + \mu)]\sigma - [(2C)/(1 + \mu)] \quad (23.24)$$

The line segment QR is parallel to line segment OP and passes through the point $(\sigma_{\max}, \tau_{\max})$, where

$$\tau_{\max} = [(1 - \mu)\sigma_{\max} - 2C]/(1 + \mu) \quad (23.25)$$

so that the equation for line segment QR becomes

$$\text{Line Segment QR: } \tau = \{[(1 - \mu)\sigma_{\max} - 2C]/(1 + \mu)\} + \{[\nu(\sigma - \sigma_{\max})]/(1 - \nu)\} \quad (23.26)$$

At one point (point R) the radial stress will exceed the normal stress, and the descent will now be of a Poisson type, with the restriction that it goes through the point where $\sigma = \tau$. The equation for this line is

$$\text{Line Segment RS: } \tau = \{[(1 + \mu)/(1 - \mu)]\sigma - [2C/(1 - \mu)]\} \quad (23.27)$$

It is noted that the residual die wall pressure is obtained by setting $\sigma = 0$; that is, it is

$$\text{Residual die wall pressure: } \{2C/(1 - \mu)\} \quad (23.28)$$

Carstensen and Touré (1980) integrated these equations to find the area within the compression cycle and found it to be proportional to the square of $\tau_{\max}$ (i.e., the "applied compression pressure").

Such plots, hence, give information on whether bonding occurs primarily through plastic deformation or through brittle fracture.

23.8. LUBRICATION

After completion of the cycle there remains a residual die wall pressure, being the residual force $F(d)$, divided by the area of the wall. The definition of frictional coefficient is recalled, and is exemplified in Fig. 23.15.

To eject the tablet, a certain ejection force E is necessary. The residual die wall force, $F(d)$ in Fig. 23.15 is the normal force and E is the tangential force, so that the definition of frictional coefficients gives

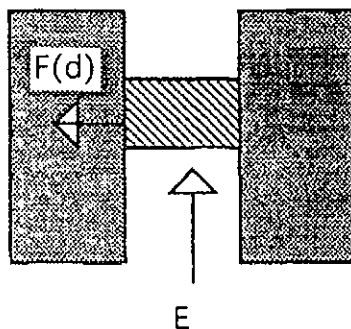


Fig. 23.15 Example of the definition of frictional coefficient.

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$$E = \mu F(d) \quad (23.29)$$

where μ is the frictional coefficient between the die wall and the tablet mass.

There have been attempts in literature to assess the frictional coefficient between a compressed powder mass and adjoining metal (Carstensen et al., 1980).

Higuchi (1954) suggested that the ratio between upper F_u and lower punch pressure F_l , the so-called F-ratio, was an indication of the lubrication efficiency of the formulation; that is, the closer the ratio

$$F_{\text{Higuchi}} = F_l/F_u \quad (23.30)$$

is to unity, the better the formula is lubricated. Guyot et al. (1977) suggested that work on the lower punch divided by the energy input of the upper punch in the compression cycle would be a better index.

If the thickness of the compressional mass is denoted h , then combining Eq. (23.30) with the Unckel equation then yields

$$F_{\text{Higuchi}} = R = (F_u \exp(-kh)/F_u = \exp(-kh) \quad (23.31)$$

23.9. ENERGY CONSIDERATIONS IN COMPRESSION

By means of displacement gauges, it is possible to monitor upper punch, F_u and lower punch, F_l , forces and at the same time measure the depth of the upper punch intrusion (on a single-punch machine). When such traces are obtained, profiles such as shown in Fig. 23.16 result.

During compression a curve, such as OA, will be obtained, and after pressure is released a curve, such as AB, will be obtained. Work equals force times distance, so that the compression work or energy W_c , is given by

$$W_c = \text{area OADO} = \int_0^d f_l(x) dx \quad (23.32)$$

The energy lost (the elastic energy, W_e) after the pressure is released is given by

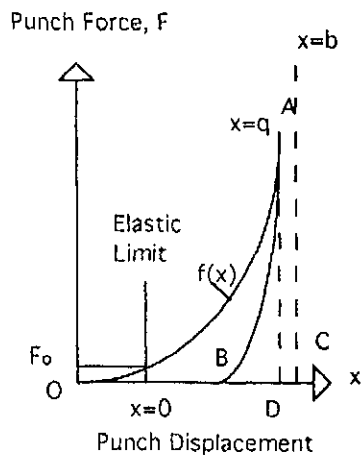


Fig. 23.16 Force-displacement plot.

$$W_e = \text{area BADB} = \int_B^A f_2(x) dx \quad (23.36)$$

so that the total energy or work, W_{total} imparted on the tablet after the cycle is complete is given by

$$W_i = \text{area OADO} = \int_0^A \{f_1(x) - f_2(x)\} dx \quad (23.37)$$

The first part of the compression event is a consolidation below the elastic limit (F_0). The energy consumption in this area is relative small. Beyond this limit, there will be a substantial amount of work needed for further invasion of the upper punch, and brittle fracture or plastic deformation of the particles will take place. The deepest invasion of the upper punch is denoted $x = q$ in Fig. 23.16.

The force displacement profile is denoted $f(x)$ in Fig. 23.16, and Führer (1965) and Parmentier (1974) suggested that $f(x)$ was hyperbolic, asymptoting at $x = b$. Hence, the force equation would be

$$F = F'/(b - x) \quad 0 \leq x < b \quad (23.38)$$

where F' is a characteristic constant. From this it follows that

$$F' = F_0 b \quad (23.39)$$

and, hence,

$$F = F_0 b / (b - x) \quad (23.40)$$

Data treated in the logarithmic form of this (Fessi et al., 1981) are shown in Fig. 23.17. The fit is good, although the slope differs from negative unity.

In Fig. 23.16, the maximum applied force F^* (occurring at $x = q$) is

$$F^* = F_0 b / (b - q) \quad (23.41)$$

Eq. 23.40 may be written:

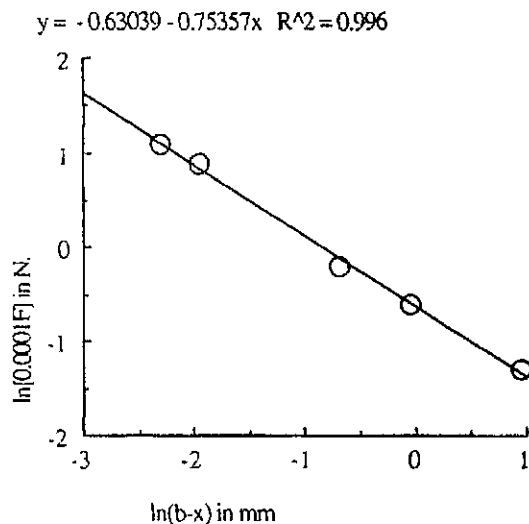


Fig. 23.17 Diphenhydramine hydrochloride tablets containing 50% polyvinyl polymer. (Data from Fessi et al., 1981.)