NO ESTA EXP

1 dd4 199

1

REYES & REYES
ABOGADOS

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERC
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 04-108760- -00014-0000
Fecha 2010-04-22 09 02 48 Dep 2020 DIR NUEVASCR
Tra 11 PATENTEIYII Eve 379 FASENACIONALII
Act 329 CTOINFORMACION Folios 4

REF: **EXPEDIENTE 04-108-760**

TÍTULO SOLICITADO: **"Formulación de dosis altas de Ibandronato"**

PUBLICACIÓN: **Gaceta 562 de 31-03-2006, número de publicación 1359**

PRIORIDAD : **EP 02028745.4 de Diciembre 20 de 2002**

SOLICITANTE: **F. HOFFMANN-LA ROCHE AG**

APODERADO: **ALICIA LLOREDA RICAURTE**

TRÁMITE: **COMPLEMENTO DE INFORMACION**

JOSÉ LUIS REYES VILLAMIZAR, mayor y vecino de Bogotá, identificado como aparece al pie de la firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.,** dando alcance a la oposición presentada el 04/07/2006, y en atención a la respuesta dada a dicha oposición por el solicitante el 18/01/2007, así como a los argumentos planteados en la respuesta al requerimiento de información del 3/07/2008, me permito insistir en que las formulaciones farmacéuticas con dosis altas de Ibandronato y el proceso para obtenerlas, revelados en la solicitud **04 108.760,** a pesar de las modificaciones introducidas por el solicitante, persisten en carecer de novedad y nivel inventivo, a la luz de los siguientes argumentos:

I. COMPLEMENTO DE INFORMACION

Sea lo primero señalar que las modificaciones hechas por el solicitante al capítulo reivindicatorio no cumplen con el requerimiento hecho por el señor

examinador, en cuanto a la claridad de algunos términos en las reivindicaciones, dado que expresiones como "grano de comprimido" y "material granulado rociado" se mantienen en el capítulo modificado, tal como se aprecia en las reivindicaciones 2, 3 y 8 de éste.

En un segundo aspecto, y dado el énfasis que le da el solicitante a la manera como se disponen los excipientes dentro de la formulación farmacéutica, cualquier persona medianamente versada en la formulación de productos farmacéuticos debe reconocer que un mismo principio activo se puede presentar en diferentes formas, por ejemplo, como comprimido, cápsula dura, cápsula blanda o solución acuosa para administración parenteral, y que a su vez se pueden formular utilizando diferentes excipientes, bajo una previa decisión ajustada a las necesidades técnicas o ventajas existentes entre una forma de dosificación u otra.

Así mismo dicha persona medianamente versada en la materia debe reconocer que **la estabilidad**, la seguridad, la eficacia y la eficiencia no son opcionales, sino que hacen parte de los requisitos de todo medicamento, y por lo general, es lo primero a tener en cuenta por una persona medianamente versada en la formulación de productos farmacéuticos, así como las técnicas de formulación y el conjunto de compuestos que se pueden utilizar para desarrollar dichos productos farmacéuticos viables en sus diferentes formas, y por lo tanto no es inventivo el hecho de involucrar un principio activo en una u otra formulación farmacéutica, eligiendo dentro de los excipientes reconocidos así mismo dentro del estado de la técnica para ese tipo de comulaciones y/o cambiando los porcentajes o disposición dentro de dicha formulación, ya que este procedimiento se resume a aplicar los correspondientes ensayos de preformulación y formulación rutinarios, que aseguran la calidad, eficacia, efectividad, seguridad y estabilidad de toda formulación que se quiera utilizar como medicamento.

En otras palabras, escoger excipientes tales como aglutinantes (llamados "enlazantes" en la solicitud colombiana), diluyentes (llamados "relleno" en la solicitud colombiana), desintegrantes, lubricantes, materiales de recubrimiento y/o modificadores de flujo para obtener una tableta recubierta estable, hacen parte de las capacidades que toda persona medianamente versada en la formulación de productos farmacéuticos debe poseer y determinar para asegurar la calidad de dicho medicamento.

El solicitante especifica, además, que las ventajas sorprendentemente adquiridas (no presentar agrietamiento después de cierto tiempo especifico bajo ciertas condiciones de temperatura y humedad) son consecuencia de que la cantidad de aglutinante (enlazante) sea mayor (en relación con las anterioridades citadas por el examinador) y a que el desintegrante se incluye dentro del núcleo a recubrir mezclado con el principio activo. Una persona medianamente versada en la materia puede intuir fácilmente que al aumentar la cantidad de la crospovidona (aglutinante) y al llevar la mayor parte de crospovidona (desintegrante) que tiene una gran afinidad por el agua al centro de la tableta, el resultado de dicha modificación se verá reflejado en la estabilidad, puesto que es lógico que si alejo de la superficie uno de los excipientes que tiene mayor afinidad por el agua y consigo una mejor aglomeración de las partículas en el núcleo de la tableta, la humedad tardará mas tiempo en acceder a la tableta y causar el agrietamiento.

En otras palabras, si en el estado de la técnica se reconocen la granulación por aspersión en un secador de lecho fluidizado, y así mismo los mismos excipientes ya se habían utilizado en la elaboración del mismo tipo de formulación farmacéutica conteniendo el mismo principio activo (tal y como sucede en la patente americana US 6294196), queda claro que, siendo la estabilidad una característica obligatoria en todo medicamento, dicha estabilidad ya se había alcanzado con anterioridad en el estado de la técnica a partir de distintos (y hasta de los mismos) excipientes, y la mejora que expone el solicitante es un simple reporte de lo obtenido en el ejercicio y aplicación de los respectivos ensayos de preformulación y formulación rutinarios en todo proceso de elaboración de medicamentos.

Para concluir podemos citar a la Dra. ZAMUDIO, Teodora, profesora de la Universidad de Buenos Aires[1]:

"Se podría diferenciar la combinación de elementos de la simple agregación. La primera es la sinergia de los elementos de forma tal que se genera uno nuevo con propiedades distintas, de tal manera que el nuevo elemento sólo es resultado de

[1] PROCESO 88-IP-2005 Interpretación prejudicial de los artículos 1 y 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena con fundamento en la consulta formulada por el Consejo de Estado de la República de Colombia, Sala de lo Contencioso Administrativo, Sección Primera. Expediente Interno N° 2001-00039 (6787). Actor: ELI LILLY AND COMPANY. Patente: "FORMULACIONES FARMACEUTICAS ADMINISTRABLES DE FORMA ORAL".aparte de lo Publicado en la página www.dpi.bioetica.org/patfondo.htm.

5
202

dicha combinación sin que puedan determinarse los elementos por separado; la segunda se da cuando los elementos se mantienen intactos en cuanto a su efecto fundamental y, por lo tanto, son claramente distinguibles unos de otros, es decir, no hay una sinergia o combinación intrínseca de los elementos."

Podemos concluir entonces que la solicitud colombiana en tramite es una simple agregación de elementos, todos ellos conocidos en el estado de la técnica, elementos dentro de los que se incluyen tanto la formulación farmacéutica tipo tableta recubierta a través de una previa granulación por aspersión en lecho fluidizado, todos los excipientes (convencionalmente reconocidos para las mismas funciones en otras tabletas) que hacen parte de la misma formulación; agregación que resulta en una formulación farmacéutica convencional y reconocida por cualquier persona medianamente versada en la materia, y que se puede llegar a ella aplicando los ensayos básicos de las etapas de preformulación y formulación correspondientes a este tipo de formulaciones, y por lo tanto podemos afirmar que dicha solicitud carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención.

Por lo expuesto respetuosamente llamo la atención sobre el hecho de que la solicitud de la referencia, en todas sus reivindicaciones, no cumple con los requisitos dispuestos en la Decisión 486 de 2000, por tal razón no puede ser objeto de privilegio de patente de invención.

II. ANEXOS

- Copia de la interpretación prejudicial del PROCESO 88-IP-2005 mencionado en el acápite de Complemento de Información.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79'152.473 de Usaquén
T.P.A 44.655 del C.S.J.

6203

PROCESO 88-IP-2005
Interpretación prejudicial de los artículos 1 y 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena con fundamento en la consulta formulada por el Consejo de Estado de la República de Colombia, Sala de lo Contencioso Administrativo, Sección Primera. Expediente Interno Nº 2001-00039 (6787). Actor: ELI LILLY AND COMPANY. Patente: "FORMULACIONES FARMACEUTICAS ADMINISTRABLES DE FORMA ORAL".

EL TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA, en Quito, a los veintisiete días del mes de julio del año dos mil cinco, procede a resolver la solicitud de Interpretación Prejudicial formulada por el Consejo de Estado de la República de Colombia, Sala de los Contencioso Administrativo, Sección Primera.

VISTOS:

Que de la solicitud de interpretación prejudicial y de sus anexos se desprende que los elementos exigidos por el artículo 33 del Tratado de Creación del Tribunal y 125 de su Estatuto fueron cumplidos, por lo que su admisión a trámite fue considerada procedente en el auto emitido el 22 de junio de 2005.

I. ANTECEDENTES.

El Tribunal, con fundamento en la documentación allegada estima procedente destacar como antecedentes del proceso interno que dio lugar a la presente solicitud, lo siguiente:

A. Las partes:

Demandante: ELI LILLY AND COMPANY.
Demandada: NACION COLOMBIANA - SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO.

B. Hechos Relevantes.

1. Los hechos.

Entre los hechos principales relatados en la demanda, se encuentran los siguientes:

a. El 27 de julio de 1994, la sociedad ELI LILLY AND COMPANY presentó ante la División de Nuevas Creaciones de la Superintendencia de Industria y Comercio solicitud de Patente de Invención para "FORMULACIONES FARMACÉUTICAS ADMINISTRABLES DE FORMA ORAL".

b. El Superintendente de Industria y Comercio, mediante Resolución 04752 del 29 de febrero de 2000, negó el privilegio de patente de invención solicitado.

c. Mediante la Resolución 18634 del 31 de julio de 2000, se resolvió el recurso de reposición presentado por la sociedad ELI LILLY AND COMPANY, confirmando la Resolución 04752 del 29 de febrero de 2000.

C. La demanda.

La Sociedad ELI LILLY AND COMPANY, en ejercicio de la acción de nulidad y restablecimiento del derecho, presentó demanda en relación con los actos administrativos mencionados

anteriormente. Los argumentos en que se fundamentó son los siguientes:

Se violó el artículo 1 de la Decisión 344 de la Comisión del Acuerdo de Cartagena, por cuanto la demandada negó el privilegio de patente para el objeto de la solicitud 94-032.770, aún cuando se cumplió con el requisito de novedad, altura inventiva y aplicación industrial.

Igualmente se desconoció el artículo 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena, ya que no se reconoció el nivel inventivo de una creación que no resultaba obvia ni derivada de manera evidente del estado de la técnica para una persona versada en la materia.

Los conceptos técnicos que se tuvieron en cuenta para la expedición de los actos administrativos acusados no reflejan un correcto análisis del nivel inventivo y, además, no se tomó en consideración la posición de la persona versada en la materia en el momento de la creación de la invención, sino que se hicieron análisis posteriores a la misma; de esta manera se restó mérito a los efectos sorprendentes obtenidos con el invento, que superan los problemas técnicos observados en las formulaciones conocidas en el estado de la técnica.

Las formulaciones anteriores tenían un problema técnico que debía ser superado; consistía en que el principio activo de las mismas presentaba una biodisponibilidad limitada. Dicho problema fue superado por la solicitud denegada, por cuanto suministró *"una formulación sólida administrable que consiste de clorhidrato de raloxifeno en combinación con un tensoactivo, polivinilpirrolidona y un diluyente soluble en agua, en la cual: el tensoactivo es un éster de ácido graso de sorbitán o un éster de ácido graso de polioxietileno de sorbitán; y el diluyente soluble en agua es un poliol o azúcar".*

En el objeto de la solicitud denegada queda claro que ni el clorhidrato de raloxifeno, ni el tensoactivo, ni el diluyente soluble en agua, ni el ligante hidrófilo son novedosos e inventivos por sí solos, sino que es la combinación de dichos elementos lo que le proporciona una formulación novedosa e inventiva. No obstante lo anterior, los examinadores hacen un análisis con criterios generales, de donde concluyen que como lo excipientes de la lista de la anterioridad son solamente algunos de los que se usan comúnmente y no importa cuál de ellos se elija, la composición formulada no tendría nivel inventivo.

La novedad y el nivel inventivo del objeto de la solicitud denegada ha sido reconocida por varias oficinas de patentes alrededor del mundo, tales como la Oficina de Patentes de los Estados Unidos de América y la Oficina de Patentes Europea.

D. La contestación a la demanda.

La Superintendencia de Industria y Comercio contestó de la demanda con los siguientes argumentos:

La característica principal de la tableta reivindicada es el raloxifeno, el cual carece de novedad como se demuestra en la patente US 44418068 en la cual se establece que este principio activo ya se había formulado en una tableta con los mismos aditivos.

Si se compara la composición reivindicada con las contenidas en los documentos encontrados como anterioridades, se concluye que si bien no son idénticas, en lo único que se diferencian es que la reivindicada contiene un éster ácido graso de sorbitán o un éster ácido graso de polioxietilensorbitán (pe), polisorbato 80 como tensoactivo.

Para una persona normalmente conocedora de la materia, sería obvio el cambiar los agentes

8 205

tensoactivos de las anterioridades para obtener finalmente la composición reivindicada. En este sentido, las composiciones encontradas no tienen carácter inventivo porque la formulación no va más allá del progreso normal de la tecnología y no implica el ejercicio de una habilidad más allá de la esperada por personas conocedoras de la materia.

II. COMPETENCIA DEL TRIBUNAL:

El Tribunal de Justicia de la Comunidad Andina es competente para interpretar por la vía prejudicial las normas que conforman el Ordenamiento Jurídico de la Comunidad Andina, con el fin de asegurar su aplicación uniforme en el territorio de los Países Miembros.

III. NORMAS DEL ORDENAMIENTO JURIDICO COMUNITARIO A SER INTERPRETADAS:

Es procedente realizar la interpretación de los artículos solicitados por el consultante, estos son: 1 y 4 de la Decisión 344 de la Comisión del Acuerdo de Cartagena, vigente para la fecha de presentación de la solicitud de patente.

A continuación se inserta el texto de las normas a ser interpretadas:

DESICION 344

Artículo 1

"Los Países Miembros otorgarán patentes para las invenciones sean de productos o de procedimientos en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."

(...)

Artículo 4

"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."

IV. Consideraciones.

Procede el Tribunal a realizar la interpretación prejudicial solicitada, para lo cual analizará aspectos relacionados con: los requisitos de patentabilidad (La novedad, el nivel inventivo y la susceptibilidad de aplicación industrial), y con el examen del nivel inventivo en la combinación de elementos conocidos.

A. DE LOS REQUISITOS DE LA PATENTABILIDAD:

Los requisitos que deben ser cumplidos para la obtención de una patente de invención se encuentran fijados por el artículo 1 de la Decisión 344, y desarrollados por los artículos 2 al 5 de dicho cuerpo legislativo.

Según lo dispuesto por el artículo 1 de esa Decisión, son tres los requisitos para que un invento sea considerado patentable: ser novedoso, tener nivel inventivo y ser susceptible de

9
206

aplicación industrial.

1. De la novedad de la invención:

El artículo 2 de la Decisión 344 dice: *"Una invención es nueva cuando no se encuentra comprendida en el estado de la técnica"*; en el ordenamiento andino, la novedad que se predica de los inventos debe ser absoluta o universal, esto es, que comprende el estado de la técnica a nivel mundial.

A la pregunta qué se entiende por invención, el Tribunal de Justicia de la Comunidad Andina ha sostenido lo siguiente:

> *"el concepto de invención, a efectos de ser objeto de una concesión de patentes, comprende todos aquellos nuevos productos o procedimientos que, como consecuencia de la actividad creativa del hombre, impliquen un avance tecnológico -y por tanto no se deriven de manera evidente del 'estado de la técnica'- y, además, sean susceptibles de ser producidos o utilizados en cualquier tipo de industria"* **[1]**; *lo mismo que se simplifica en la conceptualización recogida por el artículo 1 de la Decisión 344, la que la define como aquellos productos o procedimientos en todos los campos de la tecnología, que posean novedad, nivel inventivo, y sean susceptibles de aplicación industrial."* [2]

Ahora, para que una invención sea novedosa se requiere que no esté comprendida en el estado de la técnica; es decir, que antes de la fecha de presentación de la solicitud de patente o de la prioridad reconocida, tanto la innovación como los conocimientos técnicos que de ella se desprenden no hayan sido accesibles al público, entendiendo que la difusión de la información que se menciona debe ser minuciosa, detallada y suficiente para que una persona versada en la materia pueda utilizar esa información para explotar la invención.

En este punto resulta menester precisar que la información debe resultar útil no para el común de la población sino para destinatarios calificados en un preciso campo, el relacionado con la materia objeto de la información.

Sobre el requisito de la novedad ha señalado la doctrina:

> *"Un invento es novedoso cuando la relación causa efecto entre el medio empleado y el resultado obtenido no era conocido."* [3]

El Tribunal de Justicia de la Comunidad Andina, recogiendo los siguientes criterios expuestos por la doctrina, con la finalidad de delimitar el concepto de novedad ha concluido:

> *"Guillermo Cabanellas indica que las características del concepto de novedad son las siguientes:*
>
> *a) "Objetividad. La novedad de la tecnología a ser patentada no se determina en relación con personas determinadas ni con el pretendido inventor, sino en relación con el estado objetivo de la técnica en un momento determinado."*
>
> *b) "Irreversibilidad de la pérdida de novedad." "...una vez que una tecnología pierde su carácter novedoso, por haber pasado a integrar el estado de la técnica, esa pérdida de novedad se hace irreversible."*

(0
207

c) "Carácter Universal de la Novedad" "... la novedad de la invención se determina en relación con los conocimientos existentes en el país o en el extranjero."

"... no puede pretenderse una patente respecto de una tecnología ya conocida en el extranjero, aunque fuera novedosa en el país."

d) "Carácter público de la novedad." "...la invención patentada pasará a ser conocida a partir de su publicación implícita en su patentamiento, y posteriormente entrará en el dominio público al expirar la patente.[4]". (Proceso 07-IP-2004. Interpretación prejudicial del 17 de marzo de 2004).

Concretando aún más el concepto de novedad como requisito de las invenciones, este Tribunal ha precisado el concepto de novedad absoluta como requisito esencial para la concesión de una patente, de la siguiente manera:

"El concepto de novedad absoluta respecto de una invención implica que para que un invento sea nuevo y no se encuentre en el estado de la técnica, no puede haber sido conocido ni dentro del territorio en el que se solicita la patente, ni en ningún otro país. Es lo que se conoce como el alcance universal de la novedad, pues no basta que un invento sea nuevo y no esté en el estado de la técnica de un territorio dado, sino que tampoco lo esté en el resto del mundo, salvo el año de prioridad a que se refiere el artículo 12 de la Decisión 344. La novedad absoluta, como criterio para determinar la patentabilidad de una invención, se ha venido abriendo camino en el ámbito internacional. Así en el Reino Unido a partir de 1977 (Patents Act inglesa). En la República Federal Alemana se empezó a exigir la novedad absoluta a partir de la Ley de 16 de diciembre de 1980. En la actualidad, en los Estados Miembros de las Comunidades Europeas se ha impuesto la exigencia de la novedad absoluta como una de las consecuencias de las patentes europeas, según Tratado de Munich de 5 de Octubre de 1963. (Bercovitz, Alberto, "PROTECCIÓN DE LA TECNOLOGÍA", en Revista del Derecho Industrial Nº 35, Depalma 1990, pág. 321)." (Proceso Nº 1-AI-1996. Sentencia de 30 de octubre de 1996, publicada en Gaceta Oficial del Acuerdo de Cartagena Nº 234 de 21 de abril de 1997).

Una vez delimitado el concepto de novedad, es pertinente destacar que el Tribunal ha definido algunas reglas con el objetivo de determinar la novedad del invento:

"a) Concretar cual es la regla técnica aplicable a la solicitud de la patente, para lo cual el examinador técnico deberá valerse de las reivindicaciones, que en últimas determinarán este aspecto.

b) Precisar la fecha con base en la cual deba efectuarse la comparación entre la invención y el Estado de la Técnica, la cual puede consistir en la fecha de la solicitud o la de la prioridad reconocida.

c) Determinar cúal es el contenido del Estado de la Técnica (anterioridades) en la fecha de prioridad.

d) Finalmente deberá compararse la invención con la regla técnica."[5]

2. Del nivel inventivo:

El artículo 4 de la Decisión 344 desarrolla el requisito de nivel inventivo al establecer que la

11
208

invención goza de dicho nivel al no derivar de manera evidente del estado de la técnica, ni que hubiese resultado obvia para una persona entendida o versada en la materia. Este requisito ofrece al examinador la posibilidad de determinar si con los conocimientos técnicos que existían al momento de la invención, se hubiese podido llegar de manera evidente a la misma, o si el resultado hubiese sido obvio para un experto medio en la materia de que se trate, es decir, para una persona del oficio y normalmente versada en la materia técnica correspondiente.

Con respecto a lo anterior, el Tribunal de Justicia de la Comunidad Andina ha manifestado lo siguiente:

> *"Con el requisito del nivel inventivo, lo que se pretende es dotar al examinador técnico de un elemento que le permita afirmar o no si a la invención objeto de estudio no se habría podido llegar a partir de los conocimientos técnicos que existían en ese momento dentro del estado de la técnica... En este punto conviene advertir que uno es el examen que realiza el técnico medio respecto de la novedad y otro el que se efectúa con respecto al nivel inventivo; si bien en uno y otro se utiliza como parámetro de referencia el 'estado de la técnica', en el primero, se coteja la invención con las 'anterioridades' existentes dentro de aquella, cada uno (sic) por separado, mientras que en el segundo (nivel inventivo) se exige que el técnico medio que realiza el examen debe partir del conocimiento general que él tiene sobre el estado de la técnica y realizar el cotejo comparativo con su apreciación de conjunto, determinando si con tales conocimientos técnicos existentes ha podido o no producirse tal invención".* [6]

Ahora bien, a los efectos del artículo 4 de la Decisión 344 resulta pertinente definir que se entiende por "obvio" y por "evidente" a fin de, consecuencialmente, determinar qué se debe entender por nivel inventivo.

Lo obvio es *"aquello que salta a la vista de manera clara y directa; lo que se encuentra o pone delante de los ojos o que no tiene dificultad"*. Mientras que lo evidente *"es algo tan cierto y claro que nadie puede dudar racionalmente de ello; se presenta de manera tan perceptible y manifiesta que muestra certeza y claridad"*[7]. Como se podrá ver, la diferencia radica en lo "tan", de forma que algo que resulte obvio no es necesariamente evidente; empero lo que es evidente, es también obvio.

En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no sea consecuencia clara y directa de dicho estado.

3. De la susceptibilidad de aplicación industrial:

Igualmente, para que un invento pueda ser protegido a través de una patente debe ser susceptible de aplicación industrial, es decir, que pueda ser producido o utilizado en cualquier actividad productiva o de servicios, como lo manifiesta el artículo 5 de la norma comunitaria que se interpreta.

Este requisito de la invención encuentra su justificación en el hecho de que la concesión de una patente estimula el desarrollo y crecimiento industrial, procurando beneficios económicos a quienes la exploten, por esto sólo son susceptibles de patentabilidad las

12
209

invenciones que puedan ser llevadas a la práctica.

B. COMBINACION O MEZCLA DE ELEMENTOS CONOCIDOS.

En relación con los requisitos atinentes al nivel inventivo y a la novedad de la invención se presentan algunos casos dudosos que merecen un análisis especial, ya que al aplicar las reglas arriba citadas no es tan fácil determinar su novedad y su altura inventiva.

Uno de esos casos es el que se presenta en relación con la combinación o mezcla de medios o elementos conocidos, que impone que, en primer lugar, el examinador establezca si lo que se trata de patentar es una combinación o una simple agregación de elementos. Al efecto, vale la pena citar que: *"Se podría diferenciar la combinación de elementos de la simple agregación. La primera es la sinergia de los elementos de forma tal que se genera uno nuevo con propiedades distintas, de tal manera que el nuevo elemento sólo es resultado de dicha combinación sin que puedan determinarse los elementos por separado; la segunda se da cuando los elementos se mantienen intactos en cuanto a su efecto fundamental y, por lo tanto, son claramente distinguibles unos de otros, es decir, no hay una sinergia o combinación intrínseca de los elementos".* [8]

Pero dicha distinción no puede llevar a priori una conclusión ya que no se puede predicar instantáneamente falta de nivel inventivo de uno o de otro, ya que en ambos cabe analizar siempre el caso concreto; es el primero el que ofrece una mayor importancia en cuanto al presente asunto y el que podría presentar mayor discusión en cuanto al nivel inventivo.

Daniel R. Zucherino, en su libro "PATENTES DE INVENCIÓN", trata el tema y reconoce la complejidad en determinar un nuevo resultado:

> *"Se reconoce que hay invento cuando se utilizan medios ya conocidos, pero combinados por primera vez en forma tal, que de su combinación deriva un resultado distinto del dado por cada uno de los medios, o por otras combinaciones conocidas.*
>
> *Claro está que en la práctica, resulta a veces difícil determinar si existe un "nuevo resultado", porque éste puede consistir incluso en un resultado mejor que el conocido (por ejemplo, la calidad sonora de un disco compacto con un disco de vinilo). Si el aporte implica un adelanto y se ha hecho alguna contribución novedosa y útil, se considera que hay invento."* [9]

En consideración al tema tratado, no le es dable a las oficinas de patentes de los Países Miembros hacer un análisis apriorístico en contra del invento. Lo que debe hacer la oficina de patentes respectiva, al realizar un análisis del nivel inventivo de agregaciones o de combinaciones o mezclas de elementos, es establecer si con el estado de la técnica actual, dicho producto, así sea por combinación de elementos conocidos, no es obvio ni evidente para un técnico medio en la materia. Es decir, no es acorde con el espíritu de la normativa sobre patentes, que de un simple análisis consistente en que si el producto se genera de elementos conocidos, se concluya per se que no tiene nivel inventivo.

Una combinación de elementos conocidos, dependiendo del caso particular debe ser novedosa, con actividad inventiva y susceptible de aplicación industrial, es decir, debe cumplir los tres requisitos que establece la norma comunitaria, sin que quepa necesariamente hacer dicho análisis en relación con cada componente cuando se trata de patentar este tipo de mezclas o combinaciones.

13
210

El Tribunal de Justicia de la Comunidad Andina sobre el tema, ha sostenido lo siguiente:

> *"La novedad no es un requisito que deban cumplir todos y cada uno de los componentes que conforman la invención, pudiendo incluso ser conocidos individualmente la totalidad de tales elementos, si combinados entre ellos dan lugar a un objeto o a un procedimiento desconocido anteriormente. En efecto, ninguna invención aparece de la nada; por el contrario, toda innovación requiere aplicar conocimientos y objetos previamente creados o descubiertos por la humanidad, los cuales constituirán la «materia prima» para desarrollar un nuevo producto o procedimiento.*
>
> *En este sentido, el invento constituye una derivación del estado de la técnica, pero, para calificar su carácter de patentable, es preciso determinar si dicha derivación no resulta evidente para una persona normalmente versada en la materia técnica. Surge, por consiguiente, un requisito adicional al de la novedad: el nivel inventivo, del cual se desprende que la invención, además de no ser obvia para un experto medio, debe ser siempre el resultado de una actividad creativa del hombre, sin que ello signifique que para alcanzar la regla técnica propuesta, no se puedan utilizar procedimientos o métodos comunes o ya conocidos en el área técnica correspondiente. Específicamente en el área de los inventos químicos y biotecnológicos sucede con frecuencia que aplicando procedimientos conocidos pueden obtenerse resultados inesperados para una persona normalmente versada en la materia. Por ello, el juicio del nivel inventivo no puede ser elaborado con criterios generales, sino que dependerá de las especiales circunstancias de cada caso."* (Proceso 21-IP-2000. Interpretación Prejudicial de 27 de octubre de 2000).

Es conveniente señalar que la normativa andina sobre patentes no estipula nada sobre el tema, como si lo hacen otras legislaciones como la Ley de patentes argentina, artículo 6, inciso f), pero de ello no surge que con base en las normas que regulan la materia, las oficinas de patentes puedan hacer un examen apriorístico de la altura inventiva en casos como el de combinación de elementos conocidos para denegar la patente de invención.

Aún bajo consagraciones legales sobre el tema, lejos de sus problemas sintácticos y de técnica legislativa, es importante tener presente que respecto de los casos dudosos se previene al operador jurídico del supuesto de hecho, es decir, de hacer un análisis simple y apriorístico de la situación presentada y dudosa.

En virtud de lo anteriormente expuesto,

EL TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA,

C O N C L U Y E:

PRIMERO: La novedad, el nivel inventivo y la aplicación industrial constituyen requisitos absolutamente necesarios, insoslayables y de obligatoria observancia para el otorgamiento de una patente de invención, sea de producto o de procedimiento, en todos los campos de la tecnología.

SEGUNDO: La invención, además de no ser obvia para un experto medio, debe ser siempre el resultado de una actividad creativa del hombre, descartando, en efecto, como invención la acción propia de la naturaleza.

10
211

TERCERO: Dentro del Ordenamiento Jurídico Andino no hay norma especial para resolver sobre el nivel inventivo de mezclas y / o combinaciones de elementos conocidos. Sin embargo, lo anterior no implica que el examen de patentabilidad en los casos de combinación de elementos conocidos para generar uno nuevo pueda hacerse a la ligera; por el contrario, se debe partir de que sí pueden llegar a constituir una invención patentable las combinaciones si son novedosas, tienen altura inventiva y aplicación industrial.

De conformidad con el artículo 35 del Tratado de Creación del Tribunal de Justicia de la Comunidad Andina, el Juez Nacional consultante, al emitir el fallo en el proceso interno Nº 2001-00039 (6787), deberá adoptar la presente interpretación. Así mismo deberá dar cumplimiento a las prescripciones contenidas en el párrafo tercero del artículo 128 del Estatuto vigente.

Notifíquese al Juez consultante mediante copia certificada y remítase copia a la Secretaría General de la Comunidad Andina, para su publicación en la Gaceta Oficial del Acuerdo de Cartagena.

Walter Kaune Arteaga
PRESIDENTE (e)

Rubén Herdoíza Mera
MAGISTRADO

Ricardo Vigil Toledo
MAGISTRADO

Olga Inés Navarrete Barrero
MAGISTRADA

Mónica Rosell Medina
SECRETARIA

TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA.- *La sentencia que antecede es fiel copia del original que reposa en el expediente de esta Secretaría. CERTIFICO.-*

Mónica Rosell
SECRETARIA

---

[1] **TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA**. Sentencia de 21 de octubre de 2000. **Proceso N° 21-IP-2000.** Caso: "DERIVADOS DE BILIS HUMANA". Publicada en Gaceta Oficial del Acuerdo de Cartagena N° 631, de 10 de enero de 2001

[2] **TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA**. Sentencia de 14 de abril de 2005. **Proceso N° 07-IP-2005.** Patente de invención; "PROTECTOR DERMATOLOGICO. GEL PARA QUEMADURAS." Publicada en Gaceta Oficial del Acuerdo de Cartagena N° 1203 de 31 de mayo de 2005.

[3] ZUCCHERINO, Daniel R. "MARCAS Y PATENTES EN EL GATT. REGIMEN LEGAL". Editado por Abeledo Perrot. 1997. Pág. 150.

[4] CABANELLAS, Guillermo. "DERECHO DE LAS PATENTES DE INVENCION". Tomo 1.

Editorial Heliasta. Buenos Aires 2001. Págs. 702 a 704.

[5] **TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA**. Sentencia de 20 de mayo de 1998. **Proceso 12-IP-1998.** Patente: "COMPOSICIONES DETERGENTES COMPACTAS CON ALTA ACTIVIDAD CELULOSA". Publicada en Gaceta Oficial del Acuerdo de Cartagena Nº 428 de 16 de abril de 1999.

[6] **TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA. Proceso Nº 12-IP-98.** Doc. Cit.

[7] DICCIONARIO DE LA LENGUA ESPAÑOLA. Vigésima Primera Edición. Madrid – España. 1992. "DEFINICIONES DE EVIDENTE, EVIDENCIA Y OBVIO". Págs. 655 y 1036.

[8] Esta distinción la podemos encontrar en los cursos sobre patentes dictados por la Dra. ZAMUDIO, Teodora, profesora de la Universidad de Buenos Aires. Publicado en la página www.dpi.bioetica.org/patfondo.htm.

[9] ZUCCHERINO, Daniel R. "PATENTES DE INVENCION", Gráfica laf s.r.l, Buenos Aires, 1998, Pág. 72.

213

2 0 TH EDITION

Remington: The Science and Practice of Pharmacy

ALFONSO R GENNARO
Chairman of the Editorial Board
and Editor

itor, Daniel Lammot
anaging Editor, Matthew J Hauber
arketing Manager Anne Smith

ppincott Williams & Wilkins

·1 West Camden Street
altimore, Maryland 21201 2436 USA

17 East Washington Square
hiladelphia, PA 19106

rinted in the United States of America

ntered according to Act of Congress, in the year 1885 by Joseph P Remington,
the Office of the Librarian of Congress, at Washington DC

brary of Congress Catalog Card Information is available
BN 0 683 306472

hase additional copies of this book call our customer service department
) 638-3030 or fax orders to (301) 824-7390. International customers
call (301) 714-2324.

02 03 04
2 3 4 5 6 7 8 9 10

213

CHAPTER 45

Oral Solid Dosage Forms

Edward M Rudnic, PhD
Vice President, Pharmaceutical Research and Development
Pharmavene, Inc
Gaithersburg, MD 20878

Joseph D Schwartz, PhD
Burroughs-Wellcome Fund Professor of Pharmaceutics
Director of Industrial Pharmacy Research
Philadelphia College of Pharmacy
University of the Sciences in Philadelphia
Philadelphia, PA 19104

Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules Large-scale production methods used for their preparation, as described later in the chapter, require the presence of other materials in addition to the active ingredients Additives also may be included in the formulations to facilitate handling, enhance the physical appearance, improve stability, and aid in the delivery of the drug to the bloodstream after administration These supposedly inert ingredients, as well as the production methods employed, have been shown in some cases to influence the absorption or bioavailability of the drug substances [1] Therefore, care must be taken in the selection and evaluation of additives and preparation methods to ensure that the drug delivery goals and therapeutic efficacy of the active ingredient will not be diminished

In a limited number of cases it has been shown that the drug substance's solubility and other physicochemical characteristics have influenced its physiological availability from a solid dosage form These characteristics include its particle size, whether it is amorphous or crystalline, whether it is solvated or nonsolvated, and its polymorphic form After clinically effective formulations are obtained, such variations among dosage units of a given batch, as well as batch-to-batch differences, should be reduced to a minimum through proper in-process controls and good manufacturing practices The recognition of the importance of validation for both equipment and processes has enhanced assurance in the reproducibility of formulations greatly It is in these areas that significant progress has been made with the realization that large-scale production of a satisfactory tablet or capsule depends not only on the availability of a clinically effective formulation but also on the raw materials, facilities, personnel, documentation, validated processes and equipment, packaging, and the controls used during and after preparation (Fig 45-1)

TABLETS

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either compression or molding methods They have been in widespread use since the latter part of the 19th century, and their popularity continues The term *compressed tablet* is believed to have been used first by John Wyeth and Brother of Philadelphia During this same period, molded tablets were introduced to be used as *hypodermic* tablets for the extemporaneous preparation of solutions for injection Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste, and ease of administration)

Although the basic mechanical approach for their manufacture has remained the same tablet technology has undergone great improvement Efforts are being made continually to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the drug substance from the dosage form after oral administration Tableting equipment continues to improve in both production speed and the uniformity of tablets compressed Recent advances in tablet technology have been reviewed [2,3]

Although tablets frequently are discoid in shape, they also may be round, oval, oblong, cylindrical, or triangular They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration They are divided into two general classes by whether they are made by compression or molding Compressed tablets usually are prepared by large-scale production methods, while molded tablets generally involve small-scale operations The various tablet types and abbreviations used in referring to them are listed below

COMPRESSED TABLETS (CT)
These tablets are formed by compression and contain no special coating They are made from powdered, crystalline, or granular materials, alone or in combination with binders, disintegrants, controlled-release polymers, lubricants, diluents, and in many cases colorants

Sugar-Coated Tablets (SCT)—These are compressed tablets containing a sugar coating Such coatings may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors and in protecting materials sensitive to oxidation

Film-Coated Tablets (FCT)—These are compressed tablets that are covered with a thin layer or film of a water-soluble material A number of polymeric substances with film-forming properties may be used Film coating imparts the same general characteristics as sugar coating, with the added advantage of a greatly reduced time period required for the coating operation

Enteric-Coated Tablets (ECT)—These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine Enteric coatings can be used for tablets containing drug substances that are inactivated or destroyed in the stomach, for those that irritate the mucosa, or as a means of delayed release of the medication

Multiple Compressed Tablets (MCT)—These are compressed tablets made by more than one compression cycle

Layered Tablets—Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation The operation may be repeated to produce multilayered tablets of two or three layers Special tablet presses are required to make layered tablets such as the Versa press (*Stokes/Pennwalt*)

Press Coated Tablets—Such tablets, also referred to as dry coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets They have all the advantages of compressed tablets, ie, slotting, monogramming, speed of disintegration etc, while retaining the attributes of sugar coated tablets in masking the taste of the drug substance in the core tablets An example of a press coated tablet press is the *Manesty* Drycota Press coated tablets also can be used to separate incompatible drug substances, in addition, they can provide a means of giving an enteric coating to the core tablets Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms

Controlled-Release Tablets—Compressed tablets can be formulated to release the drug slowly over a prolonged period of time Hence, these dosage forms have been referred to as *prolonged release* or *sustained release* dosage forms as well These tablets (as well as capsule versions) can be categorized into three types (1) those that respond in some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively slowly controlled manner, and (3) those that combine combinations of mechanisms to release portions of drug, such as repeat action tablets The performance of these systems is described in more detail in Chapter 47

Tablets for Solution—Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tablets for Solution

Effervescent Tablets In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric or citric In the presence of water, these additives react, liberating carbon dioxide that acts as a disintegrator and produces effervescence Except for small quantities of lubricants present, effervescent tablets are soluble

Compressed Suppositories or Inserts - Occasionally, vaginal suppositories, such as Metronidazole Tablets, are prepared by compression Tablets for this use usually contain lactose as the diluent In this case, as well as for any tablet intended for administration other than by swallowing, the label must indicate the manner in which it is to be used

Buccal and Sublingual Tablets—These are small, flat, oval tablets Tablets intended for buccal administration by inserting into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet Progesterone Tablets may be administered in this way

Some newer approaches use tablets that melt at body temperatures The matrix of the tablet is solidified while the drug is in solution After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate limiting step in the absorption of poorly soluble compounds Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride, or erythrityl tetranitrate, are placed under the tongue Sublingual tablets dissolve rapidly, and the drug substances are absorbed readily by this form of administration

MOLDED TABLETS OR TABLET TRITURATES (TT)
Tablet triturates usually are made from moist material, using a triturate mold that gives them the shape of cut sections of a cylinder Such tablets must be completely and rapidly soluble The problem arising from compression of these tablets is the failure to find a lubricant that is completely water soluble

Dispensing Tablets (DT)—These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids thus circumventing the necessity to weigh small quantities These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form

Hypodermic Tablets (HT)—Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection Their use in this manner should be discouraged, since the resulting solutions are not sterile Large quantities of these tablets continue to be made, but for oral administration No hypodermic tablets ever have been recognized by the official compendia

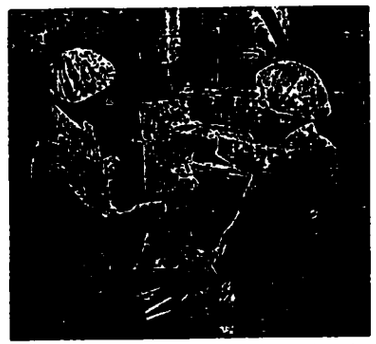


Figure 45-1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly)

Compressed Tablets (CT)

For medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics These characteristics include the ability to flow freely, cohesiveness, and lubrication The ingredients such as disintegrants designed to break the tablet up in gastrointestinal (GI) fluids and controlled release polymers designed to slow drug release ideally should possess these characteristics or not interfere with the desirable performance traits of the other excipients Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material that is to be compressed into tablets

The basic mechanical unit in all tablet compression equipment includes a lower punch that fits into a die from the bottom and an upper punch, with a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity (see Fig 45-2) The tablet is formed by pressure applied on the punches and subsequently is ejected from the die The weight of the tablet is determined by the volume of the material that fills the die cavity Therefore, the ability of the granulation to flow freely into the die is important to ensure a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper If the tablet granulation does not possess adequate properties, the tablet after compression will crumble and fall apart on handling As the punches must move freely within the die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow the removal of the compressed tablets

There are three general methods of tablet preparation the wet granulation method the dry granulation method, and direct compression The method of preparation and the added ingredients are selected to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets After compression, the tablet

Figure 45-2. Basic mechanical unit for tablet compression lower punch, die, and upper punch (courtesy, Vector/Colton)

lets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics, and uniformity, which also are influenced both by the method of preparation and by the added materials present in the formulation In the preparation of compressed tablets, the formulator also must be cognizant of the effect that the ingredients and methods of preparation may have on the availability of the active ingredients and, hence, the therapeutic efficacy of the dosage form In response to a request by physicians to change a documented tablet so that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score Subsequent use of the tablet, containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response On the other hand literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet that, although containing the same quantity of drug substance, gave the desired clinical response at half its original dose Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed [3,4,10] See Chapters 38, 53, and 58

TABLET INGREDIENTS

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials The latter are known as adjuvants or *excipients* They may be classified according to the purpose they play in the finished tablet The first group contains those that help to impart satisfactory processing and compression characteristics to the formulation These include diluents, binders, glidants, and lubricants The second group of added substances helps to give additional desirable physical characteristics to the finished tablet Included in this group are disintegrants, colors, and, in the case of chewable tablets, flavors and sweetening agents and in the case of controlled-release tablets, polymers or waxes or other solubility retarding materials

Although the term *inert* has been applied to these added materials, it is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them Preformulation studies demonstrate their influence on stability, bioavailability, and the processes by which the dosage forms are prepared The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain The result is called the *Handbook of Pharmaceutical Excipients* This reference now is distributed widely throughout the world [16]

Diluents

Frequently, the single dose of the active ingredient is small, and an inert substance is added to increase the bulk to make the tablet a practical size for compression Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet, hence, it is obvious that another material must be added to make tableting possible Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar Certain dihydric salts, such as mannitol, lactose, sorbitol sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing Such tablets commonly are called *chewable tablets* Upon chewing properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel, and leave no unpleasant aftertaste in the mouth Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flowability and compressibility These are discussed under *Direct Compression* page 869

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations Usually, these have been selected on the basis of experience and cost factors However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered, eg, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the GI tract When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems Highly absorbent substances, eg, bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids, and the synthetic estrogens These drug substances may be adsorbed after administration The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant results in tablets that discolor on aging

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas However, its presence in 5 to 15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling

Many ingredients are used for several different purposes, even within the same formulation, eg, corn starch can be used in paste form as a binder When added in drug or suspension form, it is a good disintegrant Even though these two uses are to achieve opposite goals some tablet formulas use corn starch in both ways In some controlled release formulas, the polymer hydroxypropylmethylcellulose (HPMC) is used both as an aid to prolong the release from the tablet as well as a film-former in the tablet coating Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary to use them rationally

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators They impart a cohesiveness to the tablet formulation that ensures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size Materials commonly used as binders include starch, gelatin, and sugars such as sucrose, glucose, dextrose, molasses, and lactose Natural and synthetic gums that have been used include acacia, sodium alginate extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum, and larch arabogalactan Other agents that may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water, and alcohol

The quantity of binder used has considerable influence on the characteristics of the compressed tablets The use of too much binder or too strong a binder will make a hard tablet that will not disintegrate easily and will cause excessive wear of punches and dies Differences in binders used for CT Tolbutamide resulted in differences in hypoglycemic effects observed clinically Materials that have no cohesive qualities of their own will require a stronger binder than those with these qualities Alcohol and water are not binders in the true sense of the word, but because of their solvent action on some ingredients such as lactose, starch, and celluloses, they change the powdered material to granules, and the residual moisture retained enables the materials to adhere together when compressed

Binders are used both as a solution and in a dry form, depending on the other ingredients in the formulation and the method of preparation However, several *pregelatinized* starches available are intended to be added in the dry form so that water alone can be used as the granulating solution The same amount of binder in solution will be more effective than if it were dispersed in a dry form and moistened with the solvent By the latter procedure, the binding agent is not as effective in reaching and wetting each of the particles within the mass of powders. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film that must be penetrated before the powders can be wetted by the binder solution After wetting, a certain period of time is necessary to dissolve the binder completely and make it completely available for use Since powders differ with respect to the ease with which they can be wetted and their rate of solubilization, it is preferable to incorporate the binding agent in solution. By this technique it often is possible to gain effective binding with a lower concentration of binder

The direct-compression method for preparing tablets (see page 869) requires a material that is not only free-flowing but also sufficiently cohesive to act as a binder This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose, and polyvinylpyrrolidone It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium

STARCH PASTE—Corn starch in used widely as a binder The concentration may vary from 10 to 20%. It usually is prepared as it is to be used, by dispersing corn starch in sufficient cold purified water to make a 5 to 10% *w/w* suspension and warming in a water bath with continuous stirring until a translucent paste forms It has been observed that during paste formation, not all of the starch is hydrolyzed Starch paste then is not only useful as a binder, but also as a method to incorporate some disintegrant inside the granules

GELATIN SOLUTION—Gelatin generally is used as a 10 to 20% solution; gelatin solutions should be prepared freshly as needed and used while warm or they will solidify The gelatin is added to cold purified water and allowed to stand until it is hydrated. It then is warmed in a water bath to dissolve the gelatin, and the solution is made up to the final volume on a weight basis to give the concentration desired

CELLULOSIC SOLUTIONS—Various celluloses have been used as binders in solution form Hydroxypropylmethylcellulose (HPMC) has been used widely in this regard Typical of a number of cellulosics, HPMC is more soluble in cold water than hot It also is more dispersable in hot water than cold. Hence, to obtain a good, smooth gel that is free from lumps or *fisheyes*, it is necessary to add the HPMC in hot, almost boiling water and, under agitation, cool the mixture down as quickly as possible, as low as possible Other water-soluble cellulosics such as hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) have been used successfully in solution as binders

Not all cellulosics are soluble in water Ethylcellulose can be used effectively when dissolved in alcohol or as a dry binder that then is wetted with alcohol It is used as a binder for materials that are moisture-sensitive

POLYVINYLPYRROLIDONE—PVP can be used as an aqueous or alcoholic solution, and this versatility has increased its popularity Concentrations range from 2% and vary considerably

It will be noted that binder solutions usually are made up to weight rather than volume This is to enable the formulator to determine the weight of the solids that have been added to the tablet granulation in the binding solution This becomes part of the total weight of the granulation and must be taken into consideration in determining the weight of the compressed tablet, which will contain the stated amount of the therapeutic agent

As can be seen by the list of binders in this chapter, most modern binders used in solution are polymeric Because of this, the flow or spreadability of these solutions becomes important when selecting the appropriate granulating equipment The rheology of polymeric solutions is a fascinating subject in and of itself and should be considered for these materials

Lubricants

Lubricants have a number of functions in tablet manufacture They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity, and may improve the rate of flow of the tablet granulation Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, and polyethylene glycol (PEG) Most lubricants, with the exception of talc, are used in concentrations below 1% When used alone, talc may require concentrations as high as 5% Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can result in *waterproofing* the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance.

The addition of the proper lubricant is highly desirable if the material to be tableted tends to stick to the punches and dies Immediately after compression, most tablets have the tendency to expand and will bind and stick to the side of the die The choice of the proper lubricant will overcome this effectively

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily The lubricant should be divided finely by passing it through a 60- to 100 mesh nylon cloth onto the granulation. In production this is called *bolting* the lubricant After adding the lubricant, the granulation is tumbled or mixed gently to distribute the lubricant without coating the particles too well or breaking them down to finer particles Some research has concluded that the order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form Thus, attention to the mixing process itself is just as important as the selection of lubricant materials

These process variables can be seen in the prolonged blending of a lubricant in a granulation Overblending materially can affect the hardness, disintegration time, and dissolution performance of the resultant tablets

The quantity of lubricant varies, being as low as 0.1% and, in some cases, as high as 5% Lubricants have been added to the granulating agents in the form of suspensions or emulsions This technique serves to reduce the number of operational procedures and thus reduce the processing time

In selecting a lubricant, proper attention must be given to its compatibility with the drug agent Perhaps the most widely investigated drug is acetylsalicylic acid Different talcs varied significantly the stability of aspirin Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order hydrogenated vegetable oil, stearic acid, talc, and aluminum stearate

The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine, and Carbowax 4000 However, it has been suggested that formulations used to prepare water-soluble tablets may represent a number of compromises between compression efficiency and water solubility While magnesium stearate is one of the most widely used lubricants, its hydrophobic properties can retard disintegration and dissolution To overcome these waterproofing characteristics, sodium lauryl sulfate sometimes is included One compound found to have the lubricating properties of magnesium stearate without its disadvantages is magnesium lauryl sulfate Its safety for use in pharmaceuticals has not been established

Glidants

A glidant is a substance that improves the flow characteristics of a powder mixture These materials always are added in the dry state just prior to compression (ie, during the lubrication step) Colloidal silicon dioxide Cab-o-sil *(Cabot)* is the most commonly used glidant and generally is used in low concentrations of 1% or less Talc (asbestos-free) also is used and may serve the dual purpose of lubricant/glidant.

It is especially important to optimize the order of addition and the mixing process for these materials, to maximize their effect and to make sure that their influence on the lubricant(s) is minimized

Disintegrants

A disintegrant is a substance or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration The active ingredient must be released from the tablet matrix as efficiently as possible to allow rapid dissolution Materials serving as disintegrants have been classified chemically as starches, clays, celluloses, algins, gums, and cross-linked polymers

The oldest and still the most popular disintegrants are corn and potato starch that have been well dried and powdered Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix However, others have suggested that its disintegrating action in tablets is due to capillary action rather than swelling, the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action Starch, 5%, is suggested, but if more rapid disintegration is desired, this amount may be increased to 10 or 15% Although it might be expected that disintegration time would decrease as the percentage of starch in the tablet increased, this does not appear to be the case for tolbutamide tablets In this instance, there appears to be a critical starch concentration for different granulations of the chemical When their disintegration effect is desired, starches are added to the powder blends in the dry state

A group of materials known as *super disintegrants* have gained in popularity as disintegrating agents The name comes from the low levels (2 to 4%) at which they are completely effective. Croscarmellose, crospovidone, and sodium starch glycolate represent examples of a cross-linked cellulose, a cross-linked polymer, and a cross-linked starch, respectively

The development of these disintegrants fostered new theories about the various mechanisms by which disintegrants act Sodium starch glycolate swells 7- to 12 fold in less than 30 sec Croscarmellose swells 4- to 8-fold in less than 10 sec The starch swells equally in all three dimensions, while the cellulose swells only in two dimensions, leaving fiber length essentially the same Since croscarmellose is the more efficient disintegrating agent, it is postulated that the rate, force, and extent of swelling play an important role in these disintegrants that work by swelling Cross linked PVP swells little but returns to its original boundaries quickly after compression Wicking, or capillary action, also is postulated to be a major factor in the ability of cross-linked PVP to function [17-19]

In addition to the starches, a large variety of materials have been used and are reported to be effective as disintegrants This group includes Veegum HV, methylcellulose, agar, bentonite, cellulose and wood products, natural sponge, cation exchange resins, alginic acid, guar gum, citrus pulp, and carboxymethylcellulose [20] Sodium lauryl sulfate in combination with starch also has been demonstrated to be an effective disintegrant In some cases the apparent effectiveness of surfactants in improving tablet disintegration is postulated as due to an increase in the rate of wetting.

The disintegrating agent usually is mixed with the active ingredients and diluents prior to granulation In some cases it may be advantageous to divide the starch into two portions one part is added to the powdered formula prior to granulation, and the remainder is mixed with the lubricant and added prior to compression Incorporated in this manner, the starch serves a double purpose the portion added to the lubricant rapidly breaks down the tablet to granules, and the starch mixed with the active ingredients disintegrates the granules into smaller particles Veegum has been shown to be more effective as a disintegrator in sulfathiazole tablets when a part of the quantity is added after granulation and only a small amount before granulation Likewise, the montmorillonite clays were found to be good tablet disintegrants when added to prepared granulations as powder They are much less effective as disintegrants when incorporated within the granules

Factors other than the presence of disintegrants can affect the disintegration time of compressed tablets significantly The binder, tablet hardness, and the lubricant have been shown to influence the disintegration time Thus, when the formulator is faced with a problem concerning the disintegration of a compressed tablet, the answer may not lie in the selection and quantity of the disintegrating agent alone.

The evolution of carbon dioxide is also an effective way to cause the disintegration of compressed tablets Tablets containing a mixture of sodium bicarbonate and an acidulant such as tartaric or citric acid will effervesce when added to water Sufficient acid is added to produce a neutral or slightly acidic reaction when disintegration in water is rapid and complete One drawback to the use of the effervescent type of disintegrator is that such tablets must be kept in a dry atmosphere at all times during manufacture, storage, and packaging Soluble, effervescent tablets provide a popular form for dispensing aspirin and noncaloric sweetening agents

Coloring Agents

Colors in compressed tablets serve functions other than making the dosage form more esthetic in appearance Color helps the manufacturer to control the product during its preparation as well as serving as a means of identification to the user The wide diversity in the use of colors in solid dosage forms makes it possible to use color as an important category in the identification code developed by the AMA to establish the identity of an unknown compressed tablet in situations arising from poisoning

All colorants used in pharmaceuticals must be approved and certified by the FDA For several decades colorants have been subjected to rigid toxicity standards, and as a result, a number of colorants have been removed from an approved list of Food, Drug and Cosmetic Act (FD&C) colors, or *delisted* Several have been listed as well The colorants currently approved in the US are listed in Table 45-1 Each country has its own list of approved colorants, and formulators must consider this in designing products for the international market [1]

Any of the approved, certified, water soluble FD&C dyes, mixtures of the same, or their corresponding lakes may be used to color tablets A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal resulting in an insoluble form of the dye In some instances multiple dyes are used to give a purposefully heterogeneous coloring in the form of speckling to compressed tablets The dyes available do not meet all the criteria required for the ideal pharmaceutical colorants The photosensitivity of several of the commonly used colorants and their lakes has been investigated, as well as the protection afforded by a number of glasses used in packaging tablets

Another approach for improving the photostability of dyes has been in the use of ultraviolet-absorbing chemicals in the tablet formulations with the dyes The Di-Pac line *(Amstar)* is a series of commercially available colored, direct-compression sugars

Table 45-1. Colors Approved for Use in the US in Oral Dosage Forms[a,b]

COLOR	OTHER NAMES	COLOR INDEX NO (1971)	USE RESTRICTION (US)
FD&C Red 40	Allura red	16035	FDA certification on each lot of dye
D&C Red 33	Acid fuchsin D Naphtalone red 8	17200	ADI 0-0 75 mg ADI 0-1 0 mg
D&C Red 36			None
Canthaxanthin	Food orange 8	40850	FDA certification on each lot of dye
D&C Red 22	Eosin Y	45380	FDA certification on each lot of dye
D&C Red 28	Phloxine B	45410	FDA certification on each lot of dye
D&C Red 3	Erythrosine	45430	None
Cochineal extract	Natural red 4 Carmine	75470	ADI 0–5 mg elemental iron
Iron oxide—red	—	77491	None
FD&C Yellow 6	Sunset yellow FCF Yellow orange S	15985	Label declaration and FDA certification on each lot of dye
FD&C Yellow 5	Tartrazine	19140	FDA certification on each lot of dye
D&C Yellow 10	Quinoline yellow WS	47005	
Beta-carotene	—	40800	ADI 0–5 mg elemental iron
Iron oxide—yellow	—	77492	FDA certification on each lot of dye
FD&C Blue 1	Brilliant blue FCF	42090	None
FD&C Blue 2	Indigotine Indigo carmine	73015	FDA certification on each lot of dye
FD&C Green 3	Fast green FCF	42035	ADI 0–5 mg elemental iron
Iron oxide—black	—	77499	None
Caramel	Burnt sugar		None
Titanium dioxide		77891	

[a] Abbreviations ADI, acceptable daily intake (per kg body weight) CI color index numbers of 1971 (US), D&C, Drug and Cosmetic Dyes (US), FD&C, Food Drug and Cosmetic Dyes (US), FDA, Food and Drug Administration (US)
[b] As of February, 1988 and subject to revision

The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulating process Another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with the other ingredients If the insoluble lakes are used, they may be blended with the other dry ingredients Frequently during drying, colors in wet granulations migrate, resulting in an uneven distribution of the color in the granulation After compression, the tablets will have a mottled appearance due to the uneven distribution of the color Migration of colors may be reduced by drying the granulation slowly at low temperatures and stirring the granulation while it is drying The affinity of several water soluble, anionic, certified dyes for natural starches has been demonstrated, in these cases this affinity should aid in preventing color migration

Other additives have been shown to act as dye-migration inhibitors Tragacanth (1%), acacia (3%), attapulgite (5%), and talc (7%) were effective in inhibiting the migration of FD&C Blue No 1 in lactose In using dye lakes, the problem of color migration is avoided since the lakes are insoluble Prevention of mottling can be helped also by the use of lubricants and other additives that have been colored similarly to the granulation prior to their use The problem of mottling becomes more pronounced as the concentration of colorants increases Color mottling is an undesirable characteristic common to many commercial tablets

Flavoring Agents

In addition to the sweetness that may be afforded by the diluent of the chewable tablet, eg, mannitol or lactose, artificial sweetening agents may be included Formerly, the cyclamates, either alone or in combination with saccharin, were used widely With the banning of the cyclamates and the indefinite status of saccharin, new natural sweeteners are being sought Aspartame *(Searle)*, has found applications in pharmaceutical formulations Sweeteners other than the sugars have the advantage of reducing the bulk volume, considering the quantity of sucrose required to produce the same degree of sweetness Being present in small quantities, they do not affect markedly the physical characteristics of the tablet granulation

POWDER COMPACTION

Compressed tablets became a commercially viable and efficient dosage form with the invention of tablet machines In 1843 William Brockendon, a British inventor, author, artist, and watchmaker, received British Patent #9977 for *Shaping Pills, Lozenges, and Black Lead by Pressure in Dies* [2] In over 150 years of tablet manufacture, the basic process has not changed Surprisingly, improvements have been made only with regards to speed of manufacture and quality control

The process of compaction has several identifiable phases As can be seen in Figure 45-3, when powders undergo compression (a reduction in volume), the first process to occur is a consolidation of the powders During this consolidation phase, the powder particles adopt a more efficient packing order The

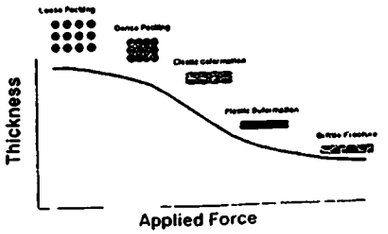


Figure 45-3 The stages of powder compaction

second phase of the compaction process is elastic, or reversible deformation. If the force were to be removed during this phase, the powder would recover completely to the efficiently packed state. For most pharmaceutical powders, this phase is very short in duration and very difficult to identify on most instrumented tablet presses. The third phase of compaction is plastic, or irreversible, deformation of the powder bed. It is this phase of the compaction process that is the most critical in tablet formation. If too much force is applied to the powder, brittle fracture occurs. If the force was applied too quickly, fracture and debonding during stress relaxation can occur.

In 1950, Stewart reported on the importance of plastic flow and suggested that if a material has significant plastic flow under compression, it will be more likely to form a compact.[23] David and Augsburger evaluated stress-relaxation data, using the Maxwell model of viscoelastic behavior in an attempt to quantify the rate of plastic deformation of some direct compression excipients.[24] Jones has used the term *contact time* to describe the total time for which a moving punch applies a detectable force to the die contents during the compression and compression event, excluding ejection.[25]

Rees and Rue evaluated three parameters: stress relation during compaction, effect of contact time on tablet density, and rate of application of diametrical compression on tablet deformation.[26]

Jones[25] outlined numerous techniques to evaluate the compactability of powders. Because of the completeness of his review, these parameters are discussed below.

Tablet Strength—Compression Pressure Profile

Most formulators use tablet *hardness*, or tensile strength, as a measure of the cohesiveness of a tablet. With even the simplest of instrumented tablet presses, it is possible to plot tensile strength versus the force applied to the tablet. Figure 45-4 illustrates such a plot. These plots can be useful in identifying forces that can cause fracture and can lead to a quick, tangible assessment of the compatibility of the formulation. However, there are many limitations to this method, as these plots cannot predict *lamination* or *capping*. In addition, the cohesiveness of a tablet can change upon storage, in either a positive or negative direction.

Tablet Friability

This test is discussed later in the chapter, and there have been many suggestions about how they should be performed. Many formulators believe this is an important indicator of cohesiveness but is of limited value in predicting failure in the field.

Changes in Bed Density during Compression

As applied stress (force) increases, elastic and plastic deformation of the particles occurs, which results in plastic flow and a reduction in inter- and intraparticulate void spaces. This lowers the overall compact density.

For highly cohesive systems, the reduction in void space may yield a compact of sufficient strength for insertion into a capsules shell. However, the inherent cohesiveness for most drugs and excipients is not suitable alone for tablet manufacture.

The Heckel equation is given below. K can be considered equal to the reciprocal of the mean yield pressure, and A is a function of the original compact volume and is related to the densification and particle rearrangement prior to bonding.

$$\log\left[1/(1-D)\right] = KP + A$$

where D is the relative density at pressure P, and K and A are constants.

Hersey and Rees[26] have classified Heckel plots into two categories. Figure 45-5 shows both types of Heckel plots. Type 2 differs from Type 1 in that above a certain pressure a single linear relationship occurs irrespective of the initial bed density. This is independent of particle size and is probable due to fragmentation of particles and their subsequent compaction by plastic deformation. For Type 1 materials, no such fracture occurs, but adjacent particles simply deform plastically.

The pressure at which the plots transition to a linear portion is approximately equal to the minimum pressure required to form a coherent compact.

Changes in Surface Area during Compression

Bulk powders change their state of packing during compaction, and individual particles fracture and/or plastically deform. During this process the surface area of the powders and the compact as whole changes. Conventional nitrogen absorption techniques can estimate these changes. Although this can be tedious, these measurements can give a means of examining lamination tendency.

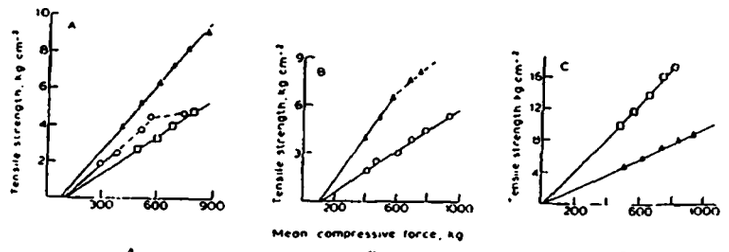


Figure 45-4 Tensile strength of compacts prepared from different crystal forms. *A* Barbitone (104–152 μm)—○, Form I; □, Form II; △, Form III. *B* Sulfathiazole (104–152 μm)—○, Form I; △, Form II. *C* Aspirin (250–353 μm) △, Form I; □, Form IV (courtesy, Summers et al[27]).

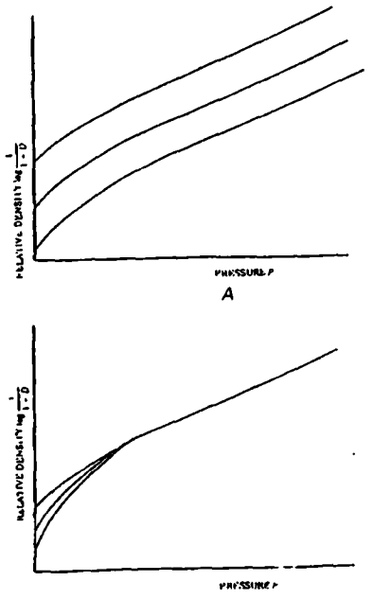


Figure 45-5 Heckel plots. *A* Type I. *B* Type II (courtesy, Jones[25]).

Stress Relaxation

The experimental technique consists of holding the compression process at a point of maximum compression and observing the compression force over various periods of time. By increasing the duration of this period (dwell time), plastic flow is maximized, and tablet strength increases.

Stress Transmissions during Compression

If the stresses in the upper punch, lower punch, and die wall are monitored, as in Figure 45-6, a general plot can be constructed showing the relationship between these forces. The elastic limit is reached at point *A*. At point *B*, the applied force is released, and the transmitted force on the wall of the die falls rapidly. The upper punch ceases to contact the powder/compact at point *C*, where the transmitted force falls rapidly to a residual force, point *D*. The force needed to eject the tablet from the die must be greater than the residual force holding it to the sides of the die. Therefore, residual forces tend to be proportional to ejection forces. In addition, these plots can give a good assessment of the elastic component of the compaction process of a powder.

Work and Compaction

Force-displacement (F D) curves are useful in determining the work involved in forming a compact. Curves, such as shown in Figure 45-7,[28] represent the work of the compression process, but all compacts expand somewhat during decompression, and this force is transferred back to the punch. Therefore, by performing a second compression of the compact, the second result can be subtracted from the first for a *corrected F D curve*. The corrected curve represents the work associated with plastic deformation during powder compaction, as well as a determination of the work of friction of the die wall and the work of elastic deformation.

GRANULATION METHODS

Wet Granulation

The most widely used and most general method of tablet preparation is the wet granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on a large scale. The steps in the wet method are weighing, mixing, granulation, screening the damp mass, drying, dry screening, lubrication, and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluent, and disintegrant are mixed or blended well. For small batches the ingredients may be mixed in stainless steel bowls or mortars. Small scale blending also can be carried out on a large piece of paper by holding the opposite edges and tumbling the material back and forth. The powder blend may be sifted through a screen of suitable fineness to remove or break up lumps. This screening also affords additional mixing. The screen selected always should be of the same type of wire or cloth that will not affect the potency of the ingredients through interaction. For example, the stability of ascorbic acid is affected deleteriously by even small amounts of copper, thus care must be taken to avoid contact with copper or copper containing alloys.

For larger quantities of powder, the Patterson Kelley twin-shell blender and the double-cone blender offer a means of precision blending and mixing in short periods of time (Fig 45-8). Twin-shell blenders are available in many sizes from laboratory models to large production models. Planetary mixers, eg, the Glen mixer and the Hobart mixer, have served their

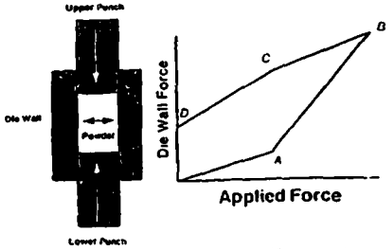


Figure 45-6 Transmitted stresses during tablet compaction.

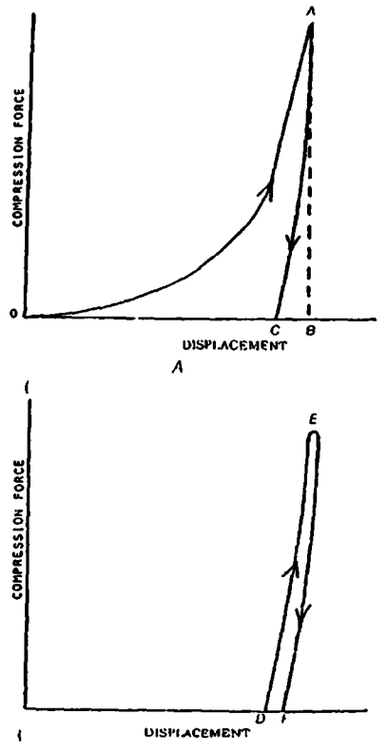


Figure 45-7 Typical forces. *A* Displacement (f–D) curve, *B* displacement (f–D), second compression (courtesy, Jones[29])

function in the pharmaceutical industry for many years (Fig 45-9). On a large scale, ribbon blenders also are employed frequently and may be adapted for continuous-production procedures. Mass mixers of the sigma-blade type have been used widely in the pharmaceutical industry.

Rapidly increasing in popularity are the high-speed, high shear mixers such as the Lodige/Littleford, Thosso, Fielder, and Baker Perkins. For these mixers a full range of sizes are available. The processing of granulations in these machines is generally faster than in conventional granulators. However, control over the process is critical, and scale-up issues may become extremely important.[30] Fluid-bed granulation (discussed below) also is gaining wide acceptance in the industry. For both of these types of processing, slight modifications to the following procedures are required.

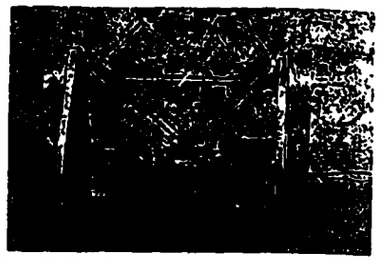


Figure 45-8 Twin-shell blender for solids or liquid-solids blending (courtesy, Patterson-Kelley)

Solutions of the binding agent are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is overwetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

The wet granulation is forced through a 6- or 8-mesh screen. Small batches can be forced through by hand using a manual screen. For larger quantities, one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, Colton rotary granulator, Fitzpatrick comminuting mill, or Stokes tornado mill. See Figure 45-10. In comminuting mills the granulation is forced through the sieving device by rotating hammers, knives, or oscillating bars. Most

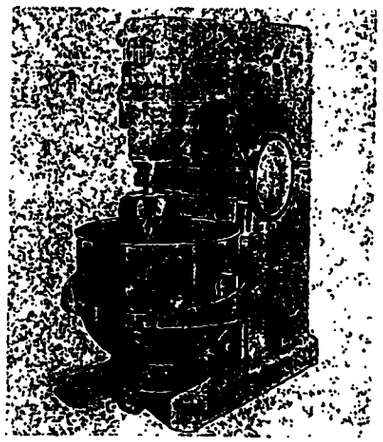


Figure 45-9. The Glen powder mixer (courtesy, Am Machine)

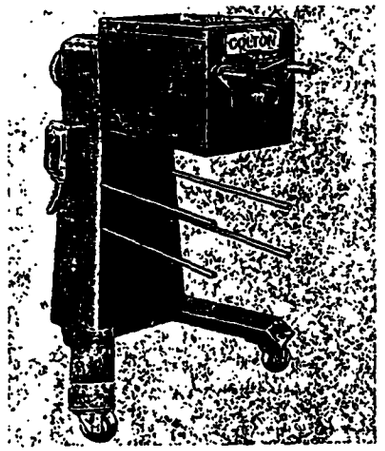


Figure 45-10 Rotary granulator and sifter (courtesy, Vector/Colton)

high-speed mixers are equipped with a chopper blade that operates independently of the main mixing blades and can replace the wet milling step, ie, can obviate the need for a separate operation.

For tablet formulations in which continuous production is justified, extruders such as the Reitz extructor have been adapted for the wet granulation process. The extruder consists of a screw mixer with a chamber where the powder is mixed with the binding agent, and the wet mass gradually is forced through a perforated screen, forming threads of the wet granulation. The granulation then is dried by conventional methods. A semiautomatic, continuous process using the Reitz extructor has been described for the preparation of the antacid tablet Gelusil (*Warner-Lambert*).

Moist materials from the wet milling step is placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. See Figure 45-11. While tray drying was the most widely used method of drying tablet granulations in the past, fluid-bed drying is now equally popular. Notable among the newer methods being introduced are the fluid-bed dryers. In drying tablet granulation by fluidization, the material is suspended and agitated in a warm air stream while the granulation is maintained in motion. Drying tests comparing the fluidized bed and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time, the fluidization method is claimed to have other advantages such as better control of drying temperatures, decreased handling costs, and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed. See Figure 45-12.[31]

The application of radio frequency drying and infrared drying to tablet granulations has been reported as successful for most granulations tried. These methods readily lend themselves to continuous granulation operations. The study of drying methods for tablet granulations led to the development of the Rovac dryer system by Ciba pharmacists and engineers. The dryer is similar in appearance to the cone blender except for the heating jacket and vacuum connections. By excluding oxygen and using the lower drying temperatures made possible by drying in a vacuum, opportunities for degradation of the ingredients during the drying cycle are minimized. A greater uniformity of residual moisture content is achieved because of the moving bed, controlled temperature, and controlled time period of the drying cycle. Particle-size distribution can be controlled by varying the speed of rotation and drying temperature as well as by comminuting the granulation to the desired granule size after drying.

In drying granulations it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients, such as gums, in a hydrated state. Also, the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process, an effort is made to obtain a uniform moisture content. In addition to the importance of moisture content of the granulation in its handling during the manufacturing steps, the stability of the products containing moisture sensitive active ingredients may be related to the moisture content of the products.

Previously it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression. This is also true for water-soluble drug substances, resulting in tablets unsatisfactory as to content uniformity. Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present as granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies.

After drying the granulation is reduced in particle size by passing it through a smaller mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. The following sizes are suggested:

Tablets up to ¼ inch diameter – use 20 mesh
Tablets ¼ to ⅝ inch, use 16 mesh
Tablets ⅝ to ¾ inch use 14 mesh
Tablets ¾ inch and larger use 12-mesh

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a stainless steel spatula. With larger quantities, any of the comminuting mills with screens corresponding to those just mentioned may be used. Note that the smaller the tablet, the finer the dry granulation to enable more uniform filling of the die cavity; large granules give an irregular fill to a comparatively small die cavity. With compressed tablets of sodium bicarbonate, lactose, and magnesium trisilicate, a relationship has been demonstrated between the particle size of the granulated material and the disintegration time and capping of the resultant tablets. For a sulfathiazole granulation, however, the particle size distribution did not appear to influence hardness or disintegration.

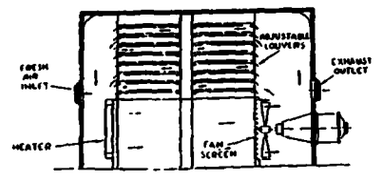


Figure 45-11 Cross section of tray dryer

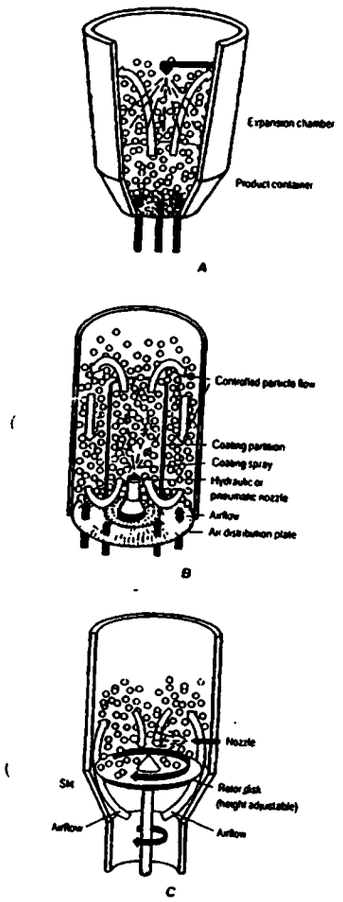


Figure 45-12. Three versions of fluidized bed granulation and drying. *A* Top-spray method used in conventional fluid-bed granulation coaters, *B* bottom-spray method used in Wurster air-suspension columns, *C* tangential-spray method used in rotary fluid-bed coaters/granulators (courtesy, Aster Publ, adapted from Reference 31)

After dry granulation, the lubricant is added as a fine powder. It usually is screened onto the granulation through 60- or 100-mesh nylon cloth to eliminate small lumps as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation very gently, preferably in a blender using a tumbling action. Gentle action is desired to maintain the uniform granule size resulting from the granulation step. It has been claimed that too much fine powder is not desirable because fine powder may not feed into the die evenly, consequently, variations in weight and density result. Fine powders, commonly designated as *fines*, also blow out around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Fines, however, at a level of 10 to 20%, traditionally are sought by the tablet formulator. The presence of some fines is necessary for the proper filling of the die cavity. Now, even higher concentrations of fines are used successfully in tablet manufacture. Most investigators agree that no general limits exist for the amount of fines that can be present in a granulation, it must be determined for each specific formula.

Many formulators once believed (and some still believe) that overblending resulted in an increased amount of fines and, hence, caused air entrapment in the formula. The capping and laminating of tablets associated with overblending lubricants was thought to be caused by these air pockets. Most scientists now recognize that a more plausible explanation has to do with the function of the lubricants themselves. Since the very nature of a lubricant tends to make surfaces less susceptible to adhesion, overblending prevents the intergranular bonding that takes place during compaction.

Fluid-Bed Granulation

A new method for granulating evolved from the fluid-bed drying technology described earlier. The concept was to spray a granulating solution onto the suspended particles, which then would be dried rapidly in the suspending air. The main benefit from this system is the rapid granulation and drying of a batch. The two main firms that developed this technology are *Glatt* and *Aeromatic*. The design of these systems is basically the same with both companies (see Fig. 45-12). In this method, particles of an inert material or the active drug are suspended in a vertical column with a rising air stream, while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in a tablet granulation that is ready for compression after the addition of the lubricant. An obvious advantage exists, since granulating and drying can take place in a single piece of equipment. It should be noted, however, that many of the mixers discussed previously can be supplied with a steam jacket and vacuum and can provide the same advantage.

In these systems a granulating solution or solvent is sprayed into or onto the bed of suspended particles. The rate of addition of the binder, temperature in the bed of particles, temperature of the air, volume, and moisture of the air all play an important role in the quality and performance of the final product. Many scientists feel that this method is an extension of the wet-granulation method, as it incorporates many of its concepts. However anyone who has developed a formulation in a fluid-bed system knows that the many operating parameters involved make it somewhat more complex.[31] In addition to its use for the preparation of tablet granulations, this technique also has been proposed for the coating of solid particles as a means of improving the flow properties of small particles. Researchers have observed that, in general, fluid-bed granulation yields a less dense particle than conventional methods, and this can affect subsequent compression behavior. A large-scale fluid-bed granulation process has been described for Tylenol (*McNeil*). Methods for the preparation of compressed tablets have been reviewed in the literature.[32]

In the *Merck* facility at Elkton, VA, the entire tablet-manufacturing process based on a wet-granulation method is computer-controlled. By means of a computer, the system weighs the ingredients, blends, granulates, dries, and lubricates to prepare a uniform granulation of specified particle size and particle-size distribution. The computer directs the compression of the material into tablets with exacting specifications for thickness, weight, and hardness. After compression, the tablets are coated with a water-based film coating. The computer controls and monitors all flow of material. The plant represents the first totally automated pharmaceutical manufacturing facility. See Figure 45-13.

Although the Merck facility represents the most fully automated production operation, there are many others throughout the industry that have parts of the operation (such as a coating, compressing, or fluid-bed granulation process) operating under a high degree of sophistication and automation. This is the trend for the future. Equipment suppliers work closely with individual pharmaceutical companies in designing specialized and unique systems.

Dry Granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression, or double-compression. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication, and compression. The active ingredient, diluent (if required), and part of the lubricant are blended. One of the constituents, either the active ingredient or the diluent, must have cohesive properties. Powdered material contains a considerable amount of air, under pressure this air is expelled, and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug.

When slugging is used, large tablets are made as slugs because fine powders flow better into large cavities. Also, producing large slugs decreases production time. ¾ to 1 in are the most practical sizes for slugs. Sometimes, to obtain the pressure that is desired the slug sizes are reduced to ½ in. The punches should be flat faced. The compressed slugs are comminuted through the desirable mesh screen either by hand or, for larger quantities, through the Fitzpatrick or similar comminuting mill. The lubricant remaining is added to the granulation and blended gently, and the material is compressed into tablets. Aspirin is a good example of where slugging is satisfactory. Other materials such as aspirin combinations, acetophenetidin, thiamine hydrochloride, ascorbic acid, magnesium hydroxide, and other antacid compounds may be treated similarly.

Results comparable to those accomplished by the slugging process also are obtained with compacting mills. In the compaction method the powder to be densified passes between high pressure rollers that compress the powder and remove the air. The densified material is reduced to a uniform granule size and compressed into tablets after the addition of a lubricant. Excessive pressures that may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate. Compaction mills available include the Chilsonator (*Fitzpatrick*), Roller Compactor (*Vector*), and the Compactor Mill (*Allis Chalmers*).

Direct Compression

As its name implies, direct compression consists of compressing tablets directly from powdered material without modifying the

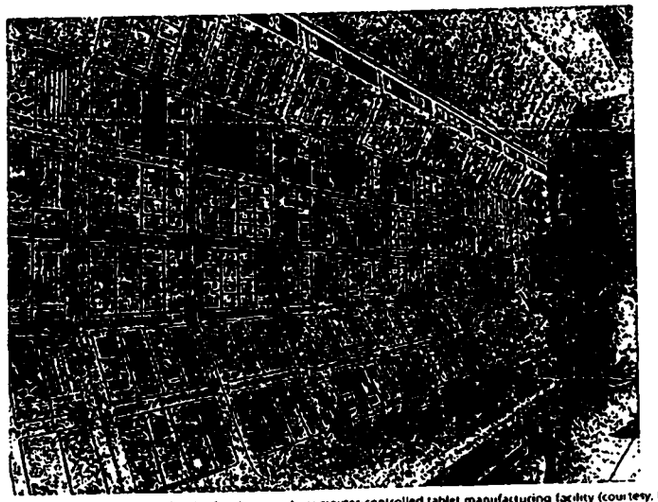


Figure 45-13. Computer control room for the first large-scale computer-controlled tablet manufacturing facility (courtesy, Merck).

physical nature of the material itself Formerly, direct compression as a method of tablet manufacture was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals such as potassium salts (chlorate, chloride bromide, iodide, nitrate, permanganate), ammonium chloride, and methenamine These materials possess cohesive and flow properties that make direct compression possible

Since the pharmaceutical industry constantly is making efforts to increase the efficiency of tableting operations and reduce costs by using the smallest amount of floor space and labor as possible for a given operation, increasing attention is being given to this method of tablet preparation Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of imparting the characteristics required for compression and the use of force-feeding devices to improve the flow of powder blends

For tablets in which the drug itself constitutes a major portion of the total tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed directly. Direct compression for tablets containing 25% or less of drug substances frequently can be used by formulating with a suitable diluent that acts as a carrier or vehicle for the drug [32-34]

Direct-compression vehicles or carriers must have good flow and compressible characteristics. These properties are imparted to them by a preprocessing step such as wet granulation, slugging, spray drying, spheronization, or crystallization These vehicles include processed forms of most of the common diluents including dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol, and microcrystalline cellulose These commercially available direct-compression vehicles may contain small quantities of other ingredients (eg, starch) as processing aids Dicalcium phosphate dihydrate (Di-Tab, *Stauffer*) in its unmilled form has good flow properties and compressibility It is a white, crystalline agglomerate insoluble in water and alcohol The chemical is odorless, tasteless, and nonhygroscopic Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression It also may contain small quantities of dextrin, starch, or invert sugar It is a white crystalline powder with a sweet taste and complete water solubility It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness One commercial source is Di Pac *(Amstar)* prepared by the cocrystallization of 97% sucrose and 3% dextrins Some forms of lactose meet the requirements for a direct compression vehicle. Hydrous lactose does not flow, and its use is limited to tablet formulations prepared by the wet-granulation method Both anhydrous lactose and spray dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present. Mannitol is a popular diluent for chewable tablets because of its pleasant taste and mouth feel resulting from its negative heat of solution In its granular form *(ICI Americas)* it has good flow and compressible qualities It has a low moisture content and is not hygroscopic.

The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (Avicel, *FMC*) This nonfibrous form of cellulose is obtained by spray drying washed, acid treated cellulose and is available in several grades that range in average particle size from 20 to 100 μm It is water-insoluble, but the material has the ability to draw fluid into a tablet by capillary action, it swells on contact and thus acts as a disintegrating agent The material flows well and has a degree of self lubricating qualities, thus requiring a lower level of lubricant than other excipients

Forced-flow feeders are mechanical devices, available from pharmaceutical equipment manufacturers, designed to deaerate light and bulky material Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure By increasing the density of the powder, higher uniformity in tablet weights is obtained See Figure 45-14

Recently, many companies have reversed their optimism for some direct-compression systems Some formulations made by direct compression were not as *forgiving* as the older wet-granulated products were As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations Interest in direct compression also is stimulating basic research on the flowability of powders with and without additives Direct compression formulas are included in the formula section found on pages 878 to 881

Related Granulation Processes

SPHERONIZATION—Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations Since the particles are round, they have good flow properties when dried They can be formulated to contain sufficient binder to impart cohesiveness for tableting Spheronization equipment such as the Marumerizer *(Luwa)* and the CF-Granulator *(Vector)* is commercially available A wet granulation containing the drug substance, diluent (if required), and binder, is passed first through an extruding machine to form rod-shaped cylindrical segments ranging in diameter from 0 5 to 12 mm The segment diameter and the size of the final spherical particle depend on the extruder screen size After extrusion the segments are placed into the Marumerizer where they are shaped into spheres by centrifugal and frictional forces on a rotating plate (see Fig 45 15) The pellets then are dried by conventional methods, mixed with suitable lubricants, and compressed into tablets or used as capsule-fill material Microcrystalline cellulose has been shown to be an effective diluent and binder in granulations to be spheronized [35-38] The advantages of the process include the production of granules, regular in shape, size, and surface characteristics; low friability resulting in fewer fines and less dust, and the ability to regulate the size of the spheres within a narrow particle-size distribution.

Spheres also can be produced by fluid-bed granulation techniques and by other specialized equipment such as the

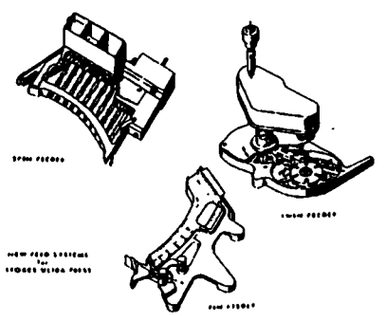


Figure 45-14 Feeding devices designed to promote flow of granulations for high speed machines (courtesy, Stokes/Pennwalt)

Figure 45-15. The inside of a QJ-400 Marumerizer (courtesy, Luwa).

CF-Granulator *(Vector)* These processes, however, must begin with crystals or nonpareil seeds followed by buildup Exact results, such as sphere density, are different for the various methods and could be important in product performance. These processes can be run as batches or continuously.

SPRAY-DRYING—A number of tableting additives suitable for direct compression have been prepared by the drying process known as spray-drying The method consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets The feed liquid may be a solution, slurry emulsion, gel, or paste, provided it is pumpable and capable of being atomized As shown in Figure 45-16, the feed is sprayed into a current of warm filtered air The air supplies the heat for evaporation and conveys the dried product to the collector; the air is then exhausted with the moisture. As the liquid droplets present a large surface area to the warm air, local heat and transfer coefficients are high

The spray-dried powder particles are homogeneous, approximately spherical in shape, nearly uniform in size, and frequently hollow. The latter characteristic results in low bulk density with a rapid rate of solution Being uniform in size and spherical, the particles possess good flowability. The design and operation of the spray-dryer can vary many characteristics of the final product, such as particle size and size distribution, bulk and particle densities, porosity, moisture content, flowability, and friability. Among the spray-dried materials available for direct compression formulas are lactose, mannitol, and flour Another application of the process in tableting is spray-drying the combination of tablet additives as the diluent, disintegrant, and binder The spray dried material then is blended with the active ingredient or drug, lubricated, and compressed directly into tablets

Since atomization of the feed results in a high surface area, the moisture evaporates rapidly The evaporation keeps the product cool and as a result the method is applicable for drying heat-sensitive materials Among heat-sensitive pharmaceuticals successfully spray-dried are the amino acids, antibiotics as aureomycin, bacitracin, penicillin, and streptomycin, ascorbic acid, cascara extracts, liver extracts, pepsin and similar enzymes, protein hydrolysates, and thiamine [39]

Frequently, spray-drying is more economical than other processes, since it produces a dry powder directly from a liquid and eliminates other processing steps as crystallization, precipitation, filtering or drying, particle size reduction, and particle classifying By the elimination of these steps, labor, equipment costs, space requirements and possible contamination of the product are reduced Intrinsic factor concentrate obtained from hog mucosa previously was prepared by *Lederle*, using a salt-precipitation process followed by a freeze-drying By using spray-drying it was possible to manufacture a high grade material by a continuous process The spherical particles of the product facilitated its subsequent blending with vitamin B_{12} Similar efficiencies have been found in processes producing magnesium trisilicate and dihydroxyaluminum sodium carbonate, both chemicals are used widely in antacid preparations

Encapsulation of chemicals also can be achieved using spray-drying equipment The process is useful in coating one material on another to protect the interior substance or to control the rate of its release The substance to be coated can be either liquid or solid but must be insoluble in a solution of the coating material The oil-soluble vitamins, A and D, can be coated with a variety of materials such as acacia gum to prevent their deterioration Flavoring oils and synthetic flavors are coated to give the so called dry flavors

SPRAY-CONGEALING—Also called spray-chilling, spray-congealing is a technique similar to spray drying It consists of melting solids and reducing them to beads or powder by spraying the molten feed into a stream of air or other gas The same basic equipment is used as with spray drying, although no source of heat is required Either ambient or cooled air is used, depending on the freezing point of the product. For example, monoglycerides and similar materials are spray congealed with air at 50°F A closed-loop system with refrigeration cools and recycles the air. Using this process, drugs can be dissolved or suspended in a molten wax and spray-congealed, the resultant material then can be adapted for a prolonged-release form of the drug

Among the carbohydrates used in compressed tablets, mannitol is the only one that possesses high heat stability Mannitol melts at 167° and, either alone or in combination with other carbohydrates, can be fused and spray congealed. Selected drugs have been shown to be soluble in these fused mixtures, and the resultant spray congealed material possesses excellent flow and compression characteristics

TABLET MACHINES

As mentioned previously, the basic mechanical unit in tablet compression involves the operation of two steel punches within a steel die cavity The tablet is formed by the pressure exerted on the granulation by the punches within the die cavity, or cell The tablet assumes the size and shape of the punches and die used See Figures 45 17 and 45-18 While round tablets are used more generally, oval, capsule-form, square, triangular, or other irregular shapes may be used Likewise, the curvature of

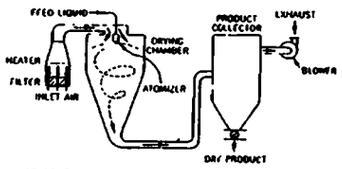


Figure 45-16 Typical spray-drying system (courtesy, Bowen Eng)

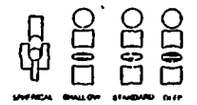


Figure 45-17 Concave punches

Table 45-3. High-Speed Rotary Tablet Machines (continued)

MACHINE MODEL	TOOL SETS	MAXIMUM TABLET DIAMETER (INCHES)	PRESS SPEED (TABLETS/MIN)	DEPTH OF FILL (INCHES)
Gemini	55	16	2200–7700	16
	67	11	2680–9380	16
	73	8	2920–10,200	16
Elizabeth-Hata equipment				
AP-45-LDU	45	17	1800–6300	8–18
AP 55 LDU	55	13	2200–7700	8–18
AP-65-LDU	65	11	2600–9100	8–18
AP-71-LDU	71	11	2840–9940	8–18
51 XLDU	51	17	2040–7140	8–18
65-XLDU	61	13	2440–8540	8–18

d---ll time permitted on the high-speed machine. These devices a- llustrated in Figure 45-14. Presses with triple compression points (see Table 45-3) permit the partial compaction of material before final compaction. This provides for partial deaeration and particle orientation of material before final compression. This helps in the direct compacting of materials and reduces laminating and capping due to entrapped air.

Multilayer Rotary Tablet Machines

The rotary tablet machines also have been developed into models capable of producing multiple-layer tablets; the machines are able to make 1, 2 or 3-layer tablets (Versa Press, *Stokes/*

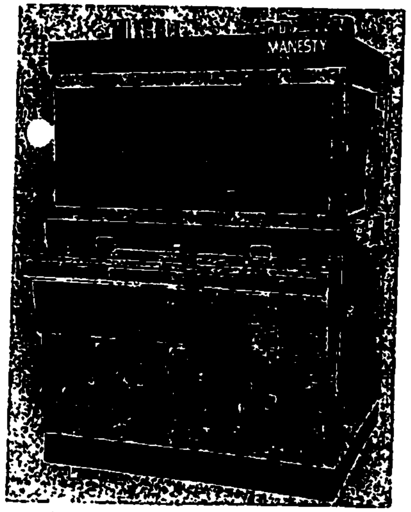


Figure 45-25 Rotapress Mark IIA. Designed for improvements in sound reduction, operator safety, cleanliness, and operational convenience, note the control panel on front of machine (courtesy, Thomas/Manesty)

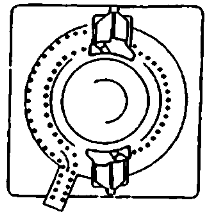


Figure 45-26 The movement of tablets on die table of a double rotary press (courtesy, Vector/Colton)

Pennwalt). Stratified tablets offer a number of advantages. Incompatible drugs can be formed into a single tablet by separating the layers containing them with a layer of inert material. It has permitted the formulation of time-delay medication and offers a wide variety of possibilities in developing color combinations that give the products identity.

Originally, the tablets were prepared by a single-compression method. The dies were filled with the different granulations in successive layers, and the tablet was formed by a single compression stroke. The separation lines of the tablets prepared by this method tended to be irregular. In the machines now available for multilayer production the granulation receives a precompression stroke after the first and second fill, which lightly compacts the granulation and maintains a well defined surface of separation between each layer. The operator is able to eject either precompressed layer with the machine running at any desired speed for periodic weight and analysis checks.

Other multiple-compression presses can receive previously compressed tablets and compress another granulation around the preformed tablet. An example of a press with this capability is the Manesty Drycota *(Thomas/Manesty)*. Pressure-coated tablets can be used to separate incompatible drug substances and also to give an enteric coating to the core tablets.

Capping and Splitting of Tablets

The splitting or capping of tablets is one of great concern and annoyance in tablet making. It is quite difficult to detect while the tablets are being processed but can be detected easily by vigorously shaking a few in the cupped hands. A slightly chipped tablet does not necessarily mean that the tablet will cap or split.

There are many factors that may cause a tablet to cap or split.

Excess *fines* or powder, which traps air in the tablet mixture.

Deep markings on tablet punches. Many designs or scores on punches are too broad and deep. Hairline markings are just as appropriate as deep, heavy markings.

Worn and imperfect punches. Punches should be smooth and buffed. Nicked punches often cause capping. The development of fine feather edges on tablets indicates wear on punches.

Worn dies. Dies should be replaced or reversed. Dies that are chrome-plated or have tungsten carbide inserts wear longer and give better results than ordinary steel dies.

Too much pressure. By reducing the pressure on the machines the condition may be corrected.

Unsuitable formula. It may be necessary to change the formula.

Moist and soft granulation. This type of granulation will not flow freely into the dies, thus giving uneven weights and soft or capped tablets.

Poorly machined punches. Uneven punches are detrimental to the tablet machine itself and will not produce tablets of accurate weight. One punch out of alignment may cause one tablet to split or cap on every revolution.

split: ruptura, grieta, hendidura

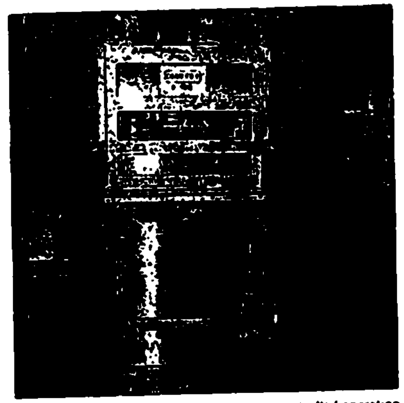


Figure 45-27. Courtoy R-100 with computer-controlled operation

Instrumented Tablet Presses

Compressional and ejectional forces involved in tablet compression can be studied by attaching strain gauges to the punches and other press components involved in compression. The electrical output of the gauges has been monitored by telemetry or use of a dual-beam oscilloscope equipped with camera.[42,43] Instrumentation permits a study of the compaction characteristics of granulations, their flowabilities, and the effect of formulation additives, such as lubricants, as well as differences in tablet press design, as shown in Figures 45-27 to 45-30. Physical characteristics of tablets, such as hardness, friability, disintegration time, and dissolution rate, are influenced not only by the nature of the formulation but by the compressional force as well.

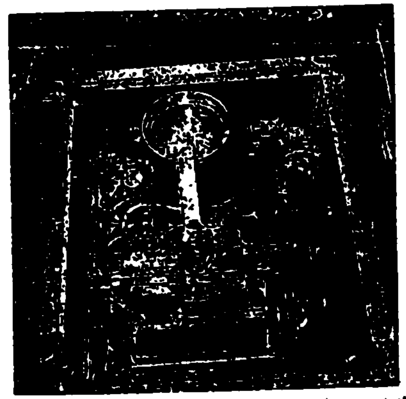


Figure 45-28. Direct weighing of tablets produced gives actual weight feedback for the controller of the Courtoy R 100 (seen in the bottom left of Fig 45-27)

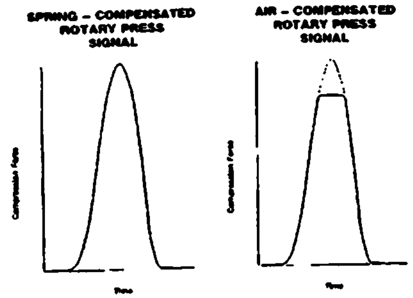


Figure 45-29 Force-time curves for two types of tablet press

As can be seen in Figures 45-29 and 45-30, the rate and duration of compaction forces can be quantified. The rate of force application has a profound effect on powder consolidation within the die and, hence, efficiency of packing and powder compaction. The rate of release of force, or *decompression* has a direct effect on the ability of the tablet to withstand relaxation. A prominent hypothesis, fostered by Hiestand[44-46] and later Luenberger[46], suggested that capping and laminating of tablets is caused by too-rapid stress relaxation or decompression. This explains why slowing a tablet press and using tapered dies is useful in such situations. Most prominent pharmaceutical scientists have embraced this theory and largely have discounted air entrapment as a cause of capping and laminating.

Figure 45-30 presents an interesting set of plots. Walter and Augsburger reported that as compaction force rises, the steel tooling actually compresses in accommodation to the forces applied. The forces used to produce a tablet are considerable and should be monitored and understood.[47] Therefore, definition of the compressional force and duration of force (dwell time) giving a satisfactory tablet for a formulation provides an in-process control for obtaining both tablet to tablet and lot-to-lot uniformity (see Figs 45-24 and 45-31).

Instrumentation has led to the development of on line, automatic, electromechanical tablet weight-control systems capa-

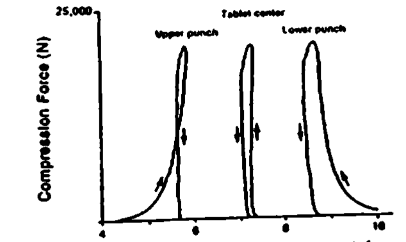


Figure 45-30 Plot showing the upper and lower punch forces as functions of the position of the punch face within the die. A biaxial force/displacement curve also shown is a plot of the position of the tablet center as a function of the compression force

ble of continuously monitoring the weights of tablets as they are produced. Units are available commercially (Thomas Tablet Sentinel *(Thomas Eng)*, Pettn Compression Force Monitor *(Raymond Auto)*, Vali-Tab *(Stokes/Pennwalt)*) and are applicable to single or rotary tablet machines. Most commercial presses today can be delivered with some sort of instrumentation attached. When tablet weights vary from preset limits, the monitor automatically will adjust the weight control mechanism to reestablish weights within acceptable limits. If the difficulty continues, the unit will activate an audible warning signal or an optional shut-down relay on the press (see Figs 45-27 and 45-28). Most production model tablet presses come equipped with complete instrumentation (optional) and with options for statistical analysis and print out of compression/ejection signals. The techniques and applications of press instrumentation have been reviewed.[48,49]

Contamination Control

While good manufacturing practices used by the pharmaceutical industry for many years have stressed the importance of cleanliness of equipment and facilities for the manufacture of drug products, the penicillin contamination problem resulted in renewed emphasis on this aspect of manufacturing. Penicillin, as either an airborne dust or residual quantities remaining in equipment, is believed to have contaminated unrelated products in sufficient concentrations to cause allergic reactions in individuals hypersensitive to penicillin who received these products. This resulted in the industry spending millions of dollars to change or modify buildings, manufacturing processes, equipment, and standard operating procedures to eliminate penicillin contamination.

With this problem has come renewed emphasis on the dust problem, material handling, and equipment cleaning in dealing with drugs, especially potent chemicals. Any process using chemicals in powder form can be a dusty operation; the preparation of compressed tablets and encapsulation fall in this category. In the design of tablet presses attention is being given to the control and elimination of dust generated in the tableting process. In the Perfecta press shown in Figure 45-32, the pressing compartment is completely sealed off from the outside environment, making cross contamination nearly impossible. The pressing compartment can be kept dust-free by the air supply and vacuum equipment developed for the machine. It removes airborne dust and granular particles that have not been compressed, thus keeping the circular pressing compartment and the upper and lower punch guides free of dust.

Drug manufacturers have the responsibility to make certain that microorganisms present in finished products are unlikely to cause harm to the patient and will not be deleterious to the product. An outbreak of *Salmonella* infections in Scandinavian countries was traced to thyroid tablets that had been prepared

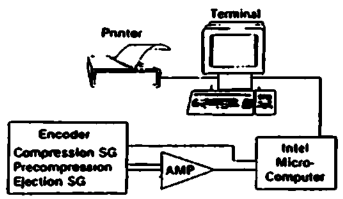


Figure 45-31. Schematic of an instrumentation system using a microcomputer as developed by Schering-Plough

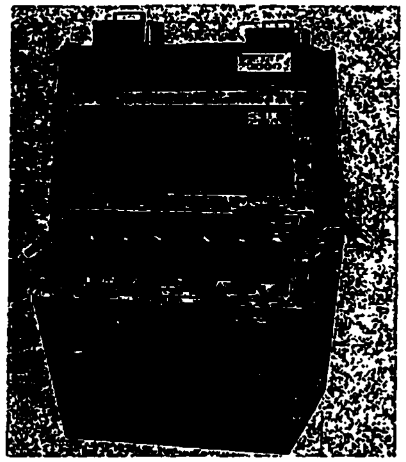


Figure 45-32. Fette Perfecta 3000 high speed tablet press with pressing compartment completely sealed off from outside environment, making cross contamination impossible (courtesy, Raymond Auto)

from contaminated thyroid powder. This concern eventually led to the establishment of microbial limits for raw materials of animal or botanical origin, especially those that readily support microbial growth and are not rendered sterile during subsequent processing. Harmful microorganisms when present in oral products include *Salmonella* spp, *Escherichia coli*, certain *Pseudomonas* spp such as *P aeruginosa*, and *Staphylococcus aureus*. The compendia have microbial limits on raw materials such as aluminum hydroxide gel, corn starch, thyroid, acacia, and gelatin.

These represent examples of the industry's efforts to conform with the intent of current good manufacturing practice as defined by the FDA.

Tablet Formulations

WET GRANULATION

CT Acetaminophen, 300 mg

INGREDIENTS	IN EACH	IN 10 000
Acetaminophen	300 mg	3000 g
Polyvinylpyrrolidone	22.5 mg	225 g
Lactose	61 75 mg	617 5 g
Alcohol SD3A—200 proof	4 5 mL	45 L
Stearic acid	9 mg	90 g
Talc	13 5 mg	135 g
Corn starch	43 25 mg	432 5 g

Blend acetaminophen, polyvinylpyrrolidone, and lactose together; pass through a 40-mesh screen. Add the alcohol slowly, and knead well. Screen the wet mass through a 4-mesh screen. Dry the granulation at 50° overnight. Screen the dried granulation through a 20 mesh screen. Bolt the stearic acid, talc, and cornstarch through a 60 mesh screen prior to mixing by tumbling with the granulation. Compress, using 7/16-inch standard concave punch. Ten tablets should weigh 4 5 g (courtesy, Abbott)

CT Ascorbic Acid USP, 50 mg

INGREDIENTS	IN EACH	IN 7000
Ascorbic acid USP (powder No 80)*	55 mg	385 g
Lactose	21 mg	147 g
Starch (potato)	13 mg	91 g
Ethylcellulose N 100 (80–105 cps)	16 mg	112 g
Starch (potato)	7 mg	49 g
Talc	6 5 mg	45 5 g
Calcium stearate (impalpable powder)	1 mg	7 g
Weight of granulation		836.5 g

* Includes 10% in excess of label claim

Granulate the first three ingredients with ethylcellulose (5%) dissolved in anhydrous ethyl alcohol, adding additional anhydrous alcohol to obtain good, wet granules. Wet-screen through a #8 stainless steel screen and dry at room temperature in an air-conditioned area. Dry-screen through a #20 stainless steel screen and incorporate the remaining three ingredients. Mix thoroughly and compress. Use a flat, beveled, 1/4-inch punch. Twenty tablets should weigh 2 39 g.

Chewable Antacid Tablets

INGREDIENTS	IN EACH	IN 10,000
Magnesium trisilicate	500 mg	5000 g
Aluminum hydroxide, dried gel	250 mg	2500 g
Mannitol	300 mg	3000 g
Sodium saccharin	2 mg	20 g
Starch paste, 5%	qs	qs
Oil of peppermint	1 mg	10 g
Magnesium stearate	10 mg	100 g
Corn starch	10 mg	100 g

Mix the magnesium trisilicate and aluminum hydroxide with the mannitol. Dissolve the sodium saccharin in a small quantity of purified water, then combine this with the starch paste. Granulate the powder blend with the starch paste. Dry at 140°F and screen through 16-mesh screen. Add the flavoring oil, magnesium stearate, and corn starch, mix well. Age the granulation for at least 24 hr and compress, using a 5/8-inch, flat face, bevel-edge punch (courtesy, *Atlas*)

CT Hexavitamin

INGREDIENTS	IN EACH	IN 7000
Ascorbic acid USP (powder)*	82 5 mg	577 5 g
Thiamine mononitrate USP (powder)*	2 4 mg	16 8 g
Riboflavin*	3 3 mg	23 1 g
Nicotinamide USP (powder)*	22 mg	154 g
Starch	13 9 mg	97 4 g
Lactose	5 9 mg	41 2 g
Zein	6 4 mg	45 g
Vitamin A acetate	6250 U	
Vitamin D_2* (use Pfizer crystalets medium granules containing 500,000 U vitamin A acetate and 50,000 U vitamin D_2/g)	625 U	87.5 g
Magnesium stearate		7 5 g
Weight of granulation		1050 g

* Includes the following in excess of label claim: ascorbic acid 10%, thiamine mononitrate 20%, riboflavin 10%, nicotinamide 10%, and vitamin A acetate–vitamin D_2 crystalets 25%

Thoroughly mix the first six ingredients and granulate with zein (10% in ethyl alcohol, adding additional alcohol if necessary to obtain good, wet granules). Wet-screen through a #8 stainless steel screen and dry at 110 to 120°F. Dry-screen through a #20 stainless steel screen and add the vitamin crystalets. Mix thoroughly, lubricate, and compress. Ten tablets should weigh 1 60 g. Coat with syrup.

CT Theobromine-Phenobarbital

INGREDIENTS	IN EACH	IN 7000
Theobromine	325 mg	2275 g
Phenobarbital	33 mg	231 g
Starch	39 mg	273 g
Talc	8 mg	56 g
Acacia (powder)	8 mg	56 g
Stearic acid	0 7 mg	4.9 g
Weight of granulation		2895 9 g

Prepare a paste with the acacia and an equal weight of starch. Use this paste for granulating the theobromine and phenobarbital. Dry and put through a 12 mesh screen, add the remainder of the material, mix thoroughly, and compress into tablets, using a 13/32-inch concave punch. Ten tablets should weigh 4 13 g

FLUID-BED GRANULATION

CT Ascorbic Acid USP, 50 mg

INGREDIENTS	IN EACH	IN 10,000
Ascorbic acid USP (powder no 80)*	55 mg	550 g
Lactose	21 mg	210 g
Starch (potato)	13 mg	130 g
Ethylcellulose N100 (80–105 cps)	16 mg	160 g
Starch (potato)	7 mg	70 g
Talc	6 5 mg	65 g
Calcium stearate	1 mg	10 g
Weight of granulation		1195.0 g

* Includes 10% in excess of claim

Add the first three ingredients to the granulator. Mix for 5 to 15 min or until well mixed. Dissolve the ethylcellulose in anhydrous ethanol and spray this solution and any additional ethanol into the fluidized mixture. Cease spraying when good granules are produced. Dry to approximately 3% moisture. Remove the granules and place them in a suitable blender. Sequentially add the remaining three ingredients with mixing steps in between each addition. Compress using a flat, beveled, 1/4-inch punch. Twenty tablets should weigh 2.39 g

Sustained-Release (SR) Procainamide Tablets

INGREDIENTS	IN EACH	IN 10 000
Procainamide	500 mg	5000 g
HPMC 2208, USP	300 mg	3000 g
Carnauba wax	60 mg	600 g
HPMC 2910, USP	30 mg	300 g
Magnesium stearate	4 mg	40 g
Stearic acid	11 mg	110 g
Talc	5 mg	50 g
Weight of granulation		9100 g

Place the first three ingredients in the granulator and mix for 5 to 15 min. Dissolve the HPMC in water (mix in hot water, then cool down) and spray into the fluidized mixture. Dry to approximately 5% moisture. Sequentially add the last three ingredients, with mixing steps in between each addition. Compress, using capsule-shaped tooling. Ten tablets should weigh 9 1 g

DRY GRANULATION

CT Acetylsalicylic Acid

INGREDIENTS	IN EACH	IN 7000
Acetylsalicylic Acid (crystals 20-mesh)	0 325 g	2275 g
Starch		226 8 g
Weight of granulation		2501 8 g

Dry the starch to a moisture content of 10%. Thoroughly mix this with the acetylsalicylic acid. Compress into slugs. Grind the slugs to 14- to 16-mesh size. Recompress into tablets, using a 13/32-inch punch. Ten tablets should weigh 3 575 g

CT Sodium Phenobarbital

INGREDIENTS	IN EACH	IN 7000
Phenobarbital sodium	65 mg	455 g
Lactose (granular, 12-mesh)	26 mg	182 g
Starch	20 mg	140 g
Talc	20 mg	140 g
Magnesium stearate	0.3 mg	2.1 g
Weight of granulation		919.1 g

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a ⅝ inch concave punch. Ten tablets should weigh 1.3 g.

CT Vitamin B Complex

INGREDIENTS	IN EACH	IN 10,000
Thiamine mononitrate*	0.733 mg	7.33 g
Riboflavin*	0.733 mg	7.33 g
Pyridoxine hydrochloride	0.333 mg	3.33 g
Calcium pantothenate*	0.4 mg	4 g
Nicotinamide	5 mg	50 g
Lactose (powder)	75.2 mg	752 g
Starch	21.9 mg	219 g
Talc	20 mg	200 g
Stearic acid (powder)	0.701 mg	7.01 g
Weight of granulation		1250 g

* Includes 10% in excess of label claim.

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a ⅝ inch concave punch. Ten tablets should weigh 1.25 g.

Sufficient tartaric acid should be used in these tablets to adjust the pH to 4.5.

DIRECT COMPRESSION

APC Tablets

INGREDIENTS	IN EACH	IN 10,000
Aspirin (40-mesh crystal)	224 mg	2240 g
Phenacetin	160 mg	1600 g
Caffeine (anhyd USP gran)	32 mg	320 g
Compressible sugar (Di-Pac*)	93.4 mg	934 g
Sterotex	7.8 mg	78 g
Silica gel (Syloid 244*)	2.8 mg	28 g

* Amstar
* Dawson Chem

Blend ingredients on a twin-shell blender for 15 min and compress on a ⅝-inch standard concave punch (courtesy, *Amstar*).

CT Ascorbic Acid USP, 250 mg

INGREDIENTS	IN EACH	IN 10,000
Ascorbic Acid USP (Merck, fine crystals)	255 mg	2550 g
Microcrystalline cellulose*	159 mg	1590 g
Stearic acid	9 mg	90 g
Colloidal silica*	2 mg	20 g
Weight of granulation		4250 g

* Avicel PH-101
* Cab-O-Sil

Blend all ingredients in a suitable blender. Compress, using ⅝₁₆ inch standard concave punch. Ten tablets should weigh 4.25 g (courtesy, *FMC*).

Breath Freshener Tablets

INGREDIENTS	IN EACH	IN 10,000
Wintergreen oil	0.6 mg	6 g
Menthol	0.85 mg	8.5 g
Peppermint oil	0.3 mg	3 g
Silica gel (Syloid 244*)	1 mg	10 g
Sodium saccharin	0.3 mg	3 g
Sodium bicarbonate	14 mg	140 g
Mannitol USP (granular)	180.95 mg	1809.5 g
Calcium stearate	2 mg	20 g

* Dawson Chem

Mix the flavor oils and menthol until liquid. Adsorb onto the silica gel. Add the remaining ingredients. Blend and compress on ⅜-inch, flat face bevel-edge punch to a thickness of 3.1 mm (courtesy, *Atlas*).

Chewable Antacid Tablets

INGREDIENTS	IN EACH	IN 10,000
Aluminum hydroxide and magnesium carbonate, codried gel*	325 mg	3250 g
Mannitol USP (granular)	675 mg	6750 g
Microcrystalline cellulose*	75 mg	750 g
Corn starch	30 mg	300 g
Calcium stearate	22 mg	220 g
Flavor	qs	qs

* Reheis F-MA 11
* Avicel

Blend all ingredients in a suitable blender. Compress, using a ⅝ inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

Chewable Multivitamin Tablets

INGREDIENTS	IN EACH	IN 10,000
Vitamin A USP (dry, stabilized form)	5000 USP units	50 million units
Vitamin D dry, stabilized form)	400 USP units	4 million units
Ascorbic Acid USP	60.0 mg	600 g
Thiamine Hydrochloride USP	1 mg	10 g
Riboflavin USP	1.5 mg	15 g
Pyridoxine Hydrochloride USP	1 mg	10 g
Cyanocobalamin USP	2 μg	20 mg
Calcium Pantothenate USP	3 mg	30 g
Niacinamide USP	10 mg	100 g
Mannitol USP (granular)	236.2 mg	2362 g
Corn starch	16.6 mg	166 g
Sodium saccharin	1.1 mg	11 g
Magnesium stearate	6.6 mg	66 g
Talc USP	10 mg	100 g
Flavor	qs	qs

Blend all ingredients in a suitable blender. Compress, using a ⅜ inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

CT Ferrous Sulfate

INGREDIENTS	IN EACH	IN 7000
Ferrous Sulfate USP (crystalline)	0.325 g	2275 g
Talc		0.975 g
Sterotex		1.95 g
Weight of granulation		2277.93 g

Grind to 12- to 14-mesh, lubricate and compress. Coat immediately to avoid oxidation to the ferric state with 0.410 gr of tolu balsam (dissolved in alcohol) and 0.060 gr of salol and chalk. Use a deep, concave, ⅜₁₆ inch punch. Ten tablets should weigh 3.25 g.

CT Methenamine

INGREDIENTS	IN EACH	IN 7000
Methenamine (12- to 14-mesh crystals)	0.325 g	2275 g
Weight of granulation		2275 g

Compress directly, using a ⅜₁₆ inch punch. Ten tablets should weigh 3.25 g.

CT Phenobarbital USP, 30 mg

INGREDIENTS	IN EACH	IN 10,000
Phenobarbital	30.59 mg	305.9 g
Microcrystalline cellulose*	30.59 mg	305.9 g
Spray-dried lactose	69.16 mg	691.6 g
Colloidal silica*	1.31 mg	13.3 g
Stearic acid	1.33 mg	13.3 g
Weight of granulation		1330 g

* Avicel-PH 101
* QUSO F-22

Screen the phenobarbital to break up lumps and blend with the microcrystalline cellulose. Add spray-dried lactose and blend finally, add the stearic acid and colloidal silica, blend to obtain a homogeneous mixture. Compress, using a ⅜₁₆ inch, shallow, concave punch. Ten tablets should weigh 1.33 g (courtesy, *FMC*).

Molded Tablets or Tablet Triturates (TT)

Tablet triturates are small, discoid masses of molded powders weighing 30 to 250 mg each. The base consists of lactose, β-lactose, mannitol, dextrose, or other rapidly soluble materials. It is desirable in making tablet triturates to prepare a solid dosage form that is rapidly soluble, as a result they are generally softer than compressed tablets.

This type of dosage form is selected for a number of drugs because of its rapidly dissolving characteristic. Nitroglycerin in many concentrations is prepared in tablet triturate form since the molded tablet rapidly dissolves when administered by placing under the tongue. Potent alkaloids and highly toxic drugs used in small doses are prepared as tablet triturates that can serve as dispensing tablets to be used as the source of the drug in compounding other formulations or solutions. Narcotics in the form of hypodermic tablets originally were made as tablet triturates because they rapidly dissolve in sterile water for injection prior to administration. Today with stable injections of narcotics available, there is no longer any justification for their use in this manner. Although many hypodermic tablets currently are made, they are used primarily for oral administration.

Tablet triturates are made by forcing a moistened blend of the drug and diluent into a mold, extruding the formed mass, which is allowed to dry. This method is essentially the same as it was when introduced by Fuller in 1878. Hand molds may vary in size, but the method of operation is essentially the same. Molds consist of two plates made from polystyrene plastic, hard rubber, nickel plated brass, or stainless steel. The mold plate contains 50 to 500 carefully polished perforations. The other plate is fitted with a corresponding number of projecting pegs or punches that fit the perforations in the mold plate. The mold plate is placed on a flat surface, the moistened mass is forced into the perforations, and the excess is scraped from the top surface. The mold plate is placed over the plate with the corresponding pegs and lowered. As the plates come together, the pegs force the tablet triturates from the molds. They remain on the tops of the pegs until dry, and they can be handled (see Fig. 45-33). In some hand molds, as shown in Figure 45-34, the pegs are forced down onto the plate holding the moist trituration.

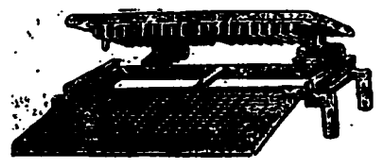


Figure 45-34. Tablet triturate mold (courtesy, Vector/Colton).

FORMULATION

In developing a formula it is essential to know the blank weight of the mold that is to be used. To determine this, the weight of the diluent that exactly fills all the openings in the mold is determined by experiment. This amount of diluent is weighed and placed aside. The total amount of the drug required is determined by multiplying the number of perforations in the plate used in the previous experiment by the amount of drug desired in each tablet. The comparative bulk of this medication is compared with that of an equal volume of diluent and that quantity of diluent is removed and weighed. The drug and the remaining diluent are mixed by trituration, and the resulting triturate is moistened and forced into the openings of the mold. If the perforations are not filled completely, more diluent is added, its weight noted, and the formula written from the results of the experiments.

It is also permissible in the development of the formula to weigh the quantity of medication needed for the number of tablets represented by the number of perforations in the mold, triturate with a weighed portion (more than ½) of the diluent, moisten the mixture, and press it into the perforations of the mold. An additional quantity of the diluent is moistened immediately and also forced into the perforations in the plate until they are filled completely. All excess diluent is removed, the trial tablets are forced from the mold, then triturated until uniform, moistened again, if necessary, and remolded. When these tablets are dried thoroughly and weighed, the difference between their total weight and the weight of medication taken will indicate the amount of diluent required and accordingly supply the formula for future use for that particular tablet triturate.

For proper mixing procedures of the medication with the diluent see Chapter 37.

Figure 45-33. Hand-molding tablet triturates (courtesy, Merck).

PREPARATION

The mixed powders are moistened with a proper mixture of alcohol and water, although other solvents or moistening agents such as acetone, petroleum benzin, and various combinations of these may be used in specific cases, the agent of choice depends on the solvent action that it will exert on the powder mixture. Often the moistening agent is 50% alcohol, but this concentration may be increased or decreased depending on the constituents of the formula. Care must be used in adding the solvent mixture to the powder. If too much is used, the mass will be soggy and will require a long time to dry, and the finished tablet will be hard and slowly soluble, if the mass is too wet, shrinkage will occur in the molded tablets, finally, a condition known as creeping will be noticed. Creeping is the concentration of the medication on the surface of the tablet caused by capillarity and rapid evaporation of the solvent from the surface. Because molded tablets by their very nature are quite friable, an inaccurate strength in each tablet may result from creeping if powder is lost from the tablet's surface. On the other hand, if an insufficient amount of moistening agent is used, the mass will not have the proper cohesion to make a firm tablet. The correct amount of moistening agent can be determined initially only by experiment.

Pharmaceutics: The Science of Dosage Form Design

EDITED BY

Michael E. Aulton BPharm PhD MPS
Reader in Pharmacy, Leicester Polytechnic, Leicester, UK

EDINBURGH LONDON MELBOURNE AND NEW YORK 1988

CHURCHILL LIVINGSTONE
Medical Division of Pearson Professional Ltd
Distributed in the United States of America by
Churchill Livingstone Inc., 650 Avenue of the Americas,
New York, 10011, and associated companies, branches
and representatives throughout the world.

First published 1988
Reprinted 1989
Reprinted 1990
Reprinted 1991
Reprinted 1992
Reprinted 1994 (twice)
Reprinted 1995
Reprinted 1996 (twice)

ISBN 0-443-03643-8

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloguing in Publication Data
A catalog record is available from the Library of Congress

Produced by Longman Asia Ltd, Hong Kong
NPCC/10

18

M H Rubinstein

Tablets

TABLETS AS A DOSAGE FORM

In December 1843 a patent was granted to the Englishman, William Brockedon, for a machine to compress powders to form compacts. This very simple device consisted essentially of a hole (or die) bored through a piece of metal within which the powder was compressed between two cylindrical punches, one was inserted into the base of the die and at a fixed depth, the other was inserted at the top of the die and struck with a hammer. The invention was first used to produce compacts of potassium bicarbonate and caught the imagination of a number of pharmaceutical companies. Later, Wellcome in Britain was the first company to use the term tablet to describe this compressed dosage form. The *British Pharmacopoeia* defines tablets as being circular in shape with either flat or convex faces and prepared by compressing the medicament or mixture of medicaments, usually with added substances. Tablets are now the most popular dosage form, accounting for

some 70% of all ethical pharmaceutical preparations produced. Indeed the importance of tablets as a form of drug administration can be seen from the fact that the *British Pharmacopoeia* (BP) in 1932 included only one tablet monograph (glyceryl trinitrate), which rapidly increased to 82 in the 1953 BP. By 1963 the BP had 183 tablet preparations, and in 1973 this figure had risen to 310 and to 384 in the 1980 edition.

Advantages of compressed tablets

The compressed tablet has a number of advantages as a dosage form. It enables an accurate dosage of medicament to be administered simply. It is easy to transport in bulk and carry by the patient. The tablet is a uniform final product as regards weight and appearance, and is usually more stable than liquid preparations. The release rate of the drug from a tablet can be tailored to meet pharmacological requirements. Finally, the major advantage of the compressed tablet as a dosage form is that tablets can be mass produced simply and quickly and the resultant manufacturing cost is therefore very much lower when compared with other dosage forms.

Types of tablet

Several categories of tablet can be distinguished dependent on the mode of use. The commonest type are those intended to be swallowed whole. A less common type of tablet is that formulated to allow dissolution or dispersion in water prior to administration. Many tablets are formulated to be effervescent and have become increasingly widely used in recent years because of their more rapid release of medicament and reduced chance of causing gastric irritation. Some tablets are designed to be chewed and used where buccal absorption is desired. Alternatively they may be intended to dissolve slowly in the mouth, e.g. lozenges or under the tongue (sublingual). There are now available many types of tablets which provide for the release of the drug to be delayed or allow a controlled, sustained rate of release. Many of these preparations are highly sophisticated and are referred to as 'complete drug delivery systems'. Tablets can also be coated so as to protect the drug against decomposition or to disguise or minimize the unpleasant taste of certain medicaments (see Chapter 40 for further details). Coating also enhances the appearance of tablets and makes them more readily identifiable. In addition, coatings can be applied which are resistant to gastric juices but which readily dissolve in the small intestine. These 'enteric' coatings can protect drugs against decomposition in the acid environment of the stomach. The coating process has traditionally involved the application of surface layers of sucrose so as to build up a thick sugar coat around the tablets. This process can take several days. For this reason the spray application of a film of material is now becoming more popular. This film coating technique can be carried out in a coating pan or alternatively in specialized fluidized bed equipment. Compressed coating around a tablet core has also been developed. These compression machines can produce multilayer tablets with different ingredients in each layer, so that potentially incompatible ingredients can be formulated in the same tablet.

Essential properties of tablets

The major advantage of tablets as a dosage form is that they provide an accurate dosage of medicament. Each tablet must contain a known amount of drug and this must be checked by content uniformity tests. Tablets must also be uniform in weight, appearance and diameter. Another prerequisite of tablets for oral use is that when they are swallowed whole they should readily disintegrate in the stomach. This property represents a great paradox in formulation, since tablets should be produced with sufficient strength to withstand the rigors of processing, coating and packing, yet be capable of rapid breakdown when administered in order to release the drug rapidly. This disintegration involves the bursting apart of the compact by aqueous fluids penetrating the fine residual pore structure of the tablet. These fluids come into contact with tablet components that either swell or release gases and so break apart the intact tablet. Perhaps the most significant property of tablets is that of dissolution rate. The active ingredient must be available pharmacologically

and since drugs cannot be absorbed into the blood stream from the solid state, the active ingredient must first dissolve in the gastric or intestinal fluids before absorption can take place (see Chapter 9 for further discussion). Thus dissolution of the drug from tablets into aqueous fluids is a very important property of solid dosage forms (Chapter 5). Tablets should also be stable to air and the temperature of the environment over a reasonable period of time and, in addition, light and moisture should not affect tablet properties. Finally tablets should be reasonably robust and be capable of withstanding normal patient handling and handling during transport. The formulation of a tablet is thus designed so that the final tablet has all these essential properties.

TABLET FORMULATION

Influence of tableting method on formulation

The majority of tablets are not composed solely of the drug. Various materials are usually added that make the powder system more compressible. Indeed powders intended for compression into tablets must possess two essential properties: fluidity and compressibility.

Powder fluidity

Fluidity is required so that the material can be transported through the hopper of a tableting machine. If adequate fluidity does not exist, this gives rise to 'arching', 'bridging' or 'rat-holing' (see Chapter 36). Fluidity is also essential so that adequate filling of the dies occurs in the tableting machine to produce tablets of a consistent weight. If the powder formulation does not flow satisfactorily, variable die filling will result, which will produce tablets that vary in weight and strength and therefore steps must be taken to ensure that fluidity is maintained. Powder flow can be improved mechanically by the use of vibrators. However, the use of these devices can cause powder segregation and stratification and much care needs to be exercised. A better method to enhance powder fluidity is to incorporate a glidant into the formulation (see later). Materials such as fumed silicon dioxide are excellent flow promoters even in concentrations of less than 0.01%. Another way to improve powder flow is to make the particles as spherical as possible, for example by spray drying or by the use of spheronization machines such as the marumarizor. The most popular method of increasing the flow properties of powders is by granulation. Most powdered materials can be granulated and the improvement in flow can be quite startling. Icing sugar, for example, will not flow, but if it is granulated with water it flows more easily.

Powder compressibility

Compressibility is the property of forming a stable, intact compact mass when pressure is applied. Paracetamol is poorly compressible whereas lactose compresses well. The physics of powder compression and why some materials compact better than others is a subject on its own and is described in Chapter 39. Much research work is in progress to characterize compaction behaviour but suffice to say that little is known about why some materials compress better than others. It is known, however, that in nearly all cases, granulation improves compressibility.

The need for granulation prior to compression

Granulation is the process of particle size enlargement of powdered ingredients (see Chapter 37 for details) and is carried out to confer fluidity and compressibility to powder systems. In addition the ideal properties of a granule include the following:

1 When compacted a tablet granulation should confer physical strength and form to the tablets. The granulation should be capable of being subjected to high compression pressures without defects forming.
2 A good granulation should have a uniform distribution of all the ingredients in the formulation.
3 The particle size range of the granulation should be log normally distributed. There should be a small percentage of both fine and coarse particles.
4 Granules should be as near spherical shape as possible and robust enough to withstand handling, without breaking down.

5 The granulation should be relatively dust free thus minimizing powder spread during tableting.

Tableting methods

The preparation of tablets can be divided into (a) dry methods and (b) wet methods. Dry methods include direct compression, slugging and roller compaction, and wet methods include wet granulation. The reader is referred to Chapter 39 for details.

Direct compression

Dry methods and in particular direct compression are superior to those methods employing liquids, since dry processes do not require the equipment and handling expenses required in wetting and drying procedures and can avoid hydrolysis of water-sensitive drugs. Some drugs, for example aspirin, can be tableted without further treatment, but the vast majority of drugs require the addition of a direct compression vehicle to aid compression. Great interest in direct compression has been evident in recent years and this has resulted in a wide range of direct compression tablet formulations being introduced. A direct compression vehicle is an inert substance which can be compacted with no difficulty and which may do so even when fairly large quantities of drugs are mixed with it. Materials currently available as direct compression diluents may be divided into three groups according to their disintegration properties and their flow characteristics:

1 disintegration agents with poor flow, e.g. microcrystalline cellulose, microfine cellulose and directly compressible starch,
2 free flowing materials which do not disintegrate, e.g. dibasic calcium phosphate,
3 free-flowing powders which disintegrate by dissolution, e.g. spray-dried lactose, anhydrous lactose, spray-crystallized maltose, dextrose, sucrose, dextrose, mannitol and amylose.

Tablets are produced by mixing the drug with the compression vehicle in a blender. The powder mix is then compressed directly on a tableting machine. The process of direct compression is described in Chapter 39.

Direct compression vehicles should be free flowing, physiologically inert, tasteless, colourless, and have a good mouth feel. Vehicles should also improve the compressibility of poorly compressible drugs, be relatively inexpensive and be capable of being reworked with no loss of flow or compressibility. Finally, direct compression diluents should promote rapid disintegration, be white and able to produce tablets containing a high proportion of non-compressible material (known as *capacity*). In practice, no one single material fulfils all these criteria and it may be necessary to blend two or more compression aids together.

The quantity of medicament which can be mixed with the carrier so that direct compression properties are retained is governed by the capacity of the carrier. The more compressible the active ingredient, the greater the proportion that can be carried successfully by the vehicle. When considering the capacity potential, it is normal to consider the active ingredient as being non-compressible. Generally, unless the drug itself is easily compressible, the amount of drug present is limited to a maximum of about 25% of the tablet weight. Another potential problem with direct compression is static electricity.

The formulation and release of drugs from tablets prepared by direct compression has been extensively investigated. Fox *et al.* (1963) made a detailed study of the tableting properties of microcrystalline cellulose. It was found that extremely hard tablets could be made with ease with no sign of lubrication difficulties. Flowability was very good and tablets exhibited excellent friability and rapid disintegration time. The dissolution of phenobarbitone and prednisone from directly compressed tablets and from tablets prepared by wet granulation was investigated by Kim (1970). It was found that, in general, tablets prepared from soluble direct compression vehicles containing a disintegrant showed faster dissolution times than those prepared by wet granulation. Bolhuis and Lerk (1973) evaluated eleven excipients and found that microcrystalline cellulose and extra fine lactose had the best overall properties.

Microcrystalline cellulose (MCC) is perhaps the most widely used direct compression excipient. It exhibits the highest capacity and compressibility of all known direct compression vehicles (Mendell,

1972), however, its flow properties are relatively poor MCC is chemically an inert material and is compatible with most drugs Its high initial moisture content and its hygroscopicity may preclude its use with very moisture-sensitive drugs. However, there is some evidence that MCC may in fact stabilize drugs susceptible to hydrolysis, by perhaps acting as a moisture scavenging agent (Sixsmith, 1976). This has been demonstrated for ascorbic acid and aspirin. It has been reported that MCC has a specific stabilizing effect on nitroglycerine tablets (Richman *et al* , 1965). It was later found by Goodhart *et al.* (1976), after a very comprehensive study, that nitroglycerine tablets formulated with MCC produced tablets with superior stability and more uniform content than tablets prepared by the popularly used moulded technique.

Another popular direct compression excipient is *dibasic calcium phosphate*, a comparatively cheap insoluble diluent with good flow properties Khan and Rhodes (1972a, b) and Khan and Rooke (1976) have examined its compressional, disintegration and dissolution properties in the presence of various disintegrants. They have shown that a cationic ion exchange resin and sodium starch glycollate are effecive disintegrants for dibasic calcium phosphate system even at low concentration. Dibasic calcium phosphate is slightly alkaline, so must not be used where the active ingredient is sensitive to pH values of 7.3 or above. Shah and Arambulo (1974) have shown from accelerated stability tests that dibasic calcium phosphate (Emcompress) was probably unsuitable for ascorbic acid and thiamine hydrochloride, since deteriorating crushing strength and disintegration properties resulted as well as chemical degradation in the case of ascorbic acid. Calcium salts in general have been shown to adversely effect the absorption properties of several drugs including tetracycline and they should not, therefore, be coformulated Khan and Rhodes (1976) have shown that for directly compressing griseofulvin, dicalcium phosphate yielded tablets of better weight uniformity than MCC. Direct compression formulations of ampicillin have been successfully produced by Niazi *et al.* (1976) and shown to be better than similar tablets produced by moist granulation.

Dry granulation

Granulation by compression or slugging is one of the dry methods which has been used for many years for moisture- or heat-sensitive ingredients The blend of powders is forced into dies of a large heavy-duty tableting press and compacted The compacted masses are called 'slugs'. An alternative technique is to squeeze the powder blend into a solid cake between rollers. This is known as *roller compaction*. The slugs or roller compacts are then milled and screened in order to produce a granular form of tableting material which flows more uniformly than the original powder mix These processes are described in more detail in Chapters 37 and 39

Slugging has the advantage over direct compression in that once the slugs are formed, no segregation of drug and excipient can occur In addition the method is useful for hydrolysable and thermolabile drugs Although used, slugging is a lengthy process and involves a relatively high capital investment since heavy-duty presses are expensive Compared with other granulation processes, the throughput is slow

The effect of various tablet formulations and processing factors on the rate of dissolution of salicylic acid tablets prepared by slugging was investigated by Levy *et al.* (1963). It was found that the dissolution rate increased with decreasing granule size and starch content of the granules. Increasing the slugging pressure of granules caused an increase in dissolution rate due to fracturing of the harder granules into smaller particles with greater specific surface area Langridge and Wells (1980) have recently shown that precompression or slugging of a mixture of microcrystalline cellulose and dicalcium phosphate dihydrate significantly reduced compressibility of both excipients. Although slugging is one of the oldest and most widely used processes for tableting, it has received very little scientific attention.

Wet granulation

Tableting by the wet granulation process is the most widely used method for pharmaceutical materials The technique involves a number of stages which are described in detail in Chapter 39. The wet granulation process has a number of advantages over the other granulation methods but it is not readily suitable for hydrolysable and/or thermolabile drugs such as antibiotics. During the development of a tablet formulation, all the physical variables which can affect the resultant granules have to be considered also so as to minimize the effect of process variation on the quality of the final product.

Influence of granulation media In wet granulation, the binder is normally incorporated as a solution or mucilage The choice of the liquid phase will depend upon the properties of the materials to be granulated *Water* is the most widely used binder vehicle but non-aqueous granulation using *isopropanol, ethanol* or *methanol* may be preferred if the drug is readily hydrolysed Changes in drug solubility resulting from a change in solvent have been shown by Wells and Walker (1983) to affect granule strength due to solute migration.

In wet granulation, granule growth is initiated by the formation of liquid bridges between primary particles (see Chapter 37) Soluble excipients will dissolve in the binder solution to increase the liquid volume available for wet granulation, consequently granules of large mean size are formed. The soluble components recrystallize on drying to form a greater number of solid bridges If one of the components absorbs water, this reduces the volume of binder liquid available to form wet granules and so smaller granules will result (Jaiyeoba and Spring, 1980) Thus the choice of binder vehicle can affect the characteristics of the dry granules

Influence of binder concentration and volume Techniques of binder addition to powders include the incorporation of a concentrated binder solution followed by additional fluid, which maintains a standard binder content Shubair and Dungwall (1976) studied the rate of release of erythrosine from lactose tablets without disintegrant or lubricant. It was found that release rate was inversely related to starch binder content Release rates decreased progressively from 2 to 10% w/w mucilage, but an unexpected rapid release followed use of 20% w/w starch mucilage Further research did not indicate that poor binder distribution gave a complete explanation, since addition of water to dilute the 20% w/w mucilage to 10% w/w did not reduce the dissolution rate Therefore the method of incorporation of the binder may also have an effect on drug release. The effect of increasing the volume of binder fluid used to granulate blends of lactose and boric acid, has been investigated by Opakunle and Spring (1976) Increasing the volume of binder fluid produced stronger granules, thought to be due to the formation of more binder bonds and the presence of more recrystallized bridges Thus the amount of binder fluid must be very closely controlled in order to produce granules of a consistent hardness

Tablet excipients

A tablet does not just contain the active ingredient but also includes other substances, known as excipients, which have specific functions The various classes of excipients which are normally incorporated into tablet formulations are discussed here

Diluents

Diluents or 'bulking agents' are 'inert' substances which are added to the active ingredient in sufficient quantity to make a reasonably sized tablet. This agent may not be necessary if the dose of the drug per tablet is high Generally, a tablet should weigh at least 50 mg and therefore very low dose drugs will invariably require a diluent to bring the overall tablet weight to at least 50 mg. The principal substance employed as a diluent is *lactose* It has a pleasant taste, rapidly dissolves in water, absorbs very little moisture and is fairly neutral in reaction. Its main disadvantage is that it is somewhat expensive and has poor flow characteristics Lactose deforms easily under pressure and, as a result of this ductility, good tablets are normally produced. The spray-dried form of lactose flows much more readily and is used as a direct compression vehicle *Dicalcium phosphate* is another diluent that is used extensively as a tablet diluent It is insoluble in water and makes good hard, white granules It absorbs even less moisture than lactose and is therefore used with hygro-

scopic drugs such as pethidine hydrochloride. The *starches* are used as diluents and as binding agents. They are available as finely divided powders and aid the disintegration process. Starches contain up to 14% moisture and can therefore lead to stability problems for a moisture sensitive drug. Another very popular diluent is *microcrystalline cellulose*. This substance is supplied as a free-flowing ingredient and is normally used as a direct compression vehicle. It has disintegrating properties and requires less lubricant in the formulation than other diluents. *Dextrose* has been used as a bulking agent, but the granules produced are much softer and not very white. In addition, dextrose absorbs moisture. *Sucrose* is very hygroscopic and goes sticky on exposure to moisture. Its pleasant taste makes it especially useful in lozenges. *Mannitol* is another sugar which, although expensive, is very quick dissolving and is therefore used for tablets that have to be dissolved, e.g. glyceryl trinitrate tablets. Since it has a negative heat of solution, it is used for chewable tablets because it imparts a pleasant taste and a cooling sensation when sucked or chewed. Table 18.1 summarizes the commonly used diluents.

Table 18.1 Tablet diluents used in the wet granulation process

Diluent	*Comment*
Dextrose	Hygroscopic
Dicalcium phosphate	Inexpensive, insoluble in water
α-Lactose BP	Inexpensive, relatively inert, the most frequently used diluent
Mannitol	Freely soluble, used particularly for chewable tablets
Microcrystalline cellulose	Excellent compression properties, has some disintegrating ability
Sodium chloride	Freely soluble, used for solution tablets
Sucrose	Sweet taste but hygroscopic; may be diluted with lactose

Courtesy of N. A. Armstrong

Adsorbents

Adsorbents are substances included in a formulation that are capable of holding quantities of fluids in an apparently dry state. Oil-soluble drugs, fluid extracts or oils can be mixed with adsorbents and then granulated and compressed into tablets. *Fumed silica, microcrystalline cellulose, magnesium carbonate, kaolin* and *bentonite* are examples of adsorbents commonly employed.

Moistening agents

In wet granulation, a moistening agent is required which is usually *water*. If the formulated powder contains sucrose, for example, it may only be necessary to add water, since sucrose rapidly dissolves and acts as its own binding agent. In cases where water cannot be used because the drug is hydrolysed, then alcohol is often substituted. Absolute alcohol is expensive and thus *industrial methylated spirits* is used. Care must be taken to remove all traces of the solvent during drying or the tablets will possess an alcoholic odour. *Isopropyl alcohol* is an alternative moistening agent. It is difficult, however, to remove the last traces from granules and it possesses an objectionable odour.

Binding agents (adhesives)

The substances that act as adhesives to bind powders together in the wet granulation process are known as binders. They also help to bind granules together during compression. If too little binding agent is included in a formulation, soft granules result. Conversely, too much binding agent produces large, hard granules.

Binding agents can be added in two ways depending on the method of granulation.

1. as a powder in the formulation as in 'slugging' or in dry granulation methods,
2. as a solution to the mixed powders as in wet granulation.

There are not many examples of (1) since most substances require some moisture present to make them adhesive.

Common binding agents include starch mucilage and gelatin solution. *Starch* is a good and popular binder and needs to be present in an amount equal to 2%. It is incorporated as a mucilage in water. When dry, the starch binder is insoluble in water, unlike gelatin which remains soluble in the dry state. *Gelatin* is often used as a binder in lozenges. Among the other most

important binders is *polyvinylpyrrolidone* (PVP). This substance is soluble both in water and in alcohol and has been shown to release drugs faster than with other binders. Rubinstein and Rughani (1978), using four binders in a tablet formulation of frusemide, showed how the choice of binder affects dissolution rate. They observed t_{50} values between 3.65 minutes with PVP to 117 minutes with starch mucilage. Other less common binders include *hydrolysed gelatin*, derivatives of seaweed (such as *alginic acid, sodium alginate* and calcium alginate) and cellulose derivatives (in particular *ethyl cellulose* and *hydroxypropylmethylcellulose*).

Common binders used in the wet granulation process are listed in Table 18.2.

Table 18.2 Adhesives (binders) used in the wet granulation process

Adhesive	*Concentration in granulating fluid (% w/v)*	*Comments*
Acacia mucilage	up to 20	Yields very hard granules
Gelatin	5–20	Forms gel in cold, therefore warm solution used, strong adhesive, often used in lozenge granules
Glucose	up to 50	Strong adhesive; hygroscopic, so tablet may weaken in humid conditions
Polyvinyl pyrrolidone (PVP)	2–10	Soluble in water and in some organic solvents, therefore can be used for anhydrous granulation
Starch mucilage	5–10	Often used warm, a very commonly used adhesive
Sucrose	up to 70	Hygroscopic, tablets may harden on storage

Courtesy of N. A. Armstrong

Glidants

Glidants are materials which are added to tablet formulations in order to improve the flow properties of the granulations. They act by reducing interparticulate friction. The most commonly used and effective glidant is *fumed* (or *colloidal*) *silica*. Flow of granules can be dramatically improved by the addition of less than 0.1% w/w of this material to powders and granules. Fumed silica is thought to act by lodging in the surface irregularities of the particles or granules, which effectively smooths the particle surface.

Lubricants

These agents are required to prevent adherence of the granules to the punch faces and dies. They also ensure smooth ejection of the tablet from the die. Many lubricants also enhance the flow properties of the granules. Talc and magnesium stearate appear to be more effective as punch lubricants than stearic acid, which is more effective as a die lubricant.

Magnesium stearate is the most popular lubricant used and is normally effective on its own as both a die and a punch lubricant. It is incorporated by blending with the dry granules prior to compression, up to a concentration of about 1% w/w. A thin layer of magnesium stearate around the granule is just as effective as a thick layer from the lubrication point of view, but increased magnesium stearate quantities reduce the disintegration time, retard drug dissolution and also reduce the bonding forces between granules to produce soft tablets. The reduction in drug release properties is due to the hydrophobic nature of magnesium stearate preventing drug dissolution. It has been shown (Bolhuis *et al.*, 1975) that the extent of mixing time greatly affects the distribution of magnesium stearate around the tablet granules. An increase in mixing time produces a more uniform distribution of lubricant, but adversely affects tablet hardness and dissolution. For many drugs, magnesium stearate is chemically incompatible (e.g. aspirin) and therefore *talc* or *stearic acid* is often used. Microcrystalline cellulose requires less lubricant for effective lubrication of granules, since to some extent it acts as its own lubricant.

Table 18.3 lists the commonly used tablet glidants and lubricants.

Disintegrating agents

Disintegrants are always added to tablets to promote breakup of the tablets when placed in an

Table 18.3 Commonly used tablet glidants and lubricants

Substance	Lubricant or glidant	Concentration in tablet (% w/w)	Comments
Stearates, e.g. magnesium, calcium, stearic acid	Lubricant	0.25–1	Reduce tablet strength, prolong disintegration, insoluble in water, excellent lubricant properties; magnesium stearate is very widely used
Talc	Lubricant and glidant	1–2	Insoluble but not hydrophobic, only a moderate lubricant
Polyethylene glycol	Lubricant	2–5	Molecular weights 4000–6000, soluble in water, moderately effective
Liquid paraffin	Lubricant	up to 5	Dispersion problems, inferior to stearates
Sodium lauryl sulphate	Lubricant	0.5–5	Moderate lubricant with wetting properties, often used in conjunction with stearates
Colloidal silica	Glidant	0.1–0.5	Excellent glidant
Starch	Glidant	2–10	Primary function is that of a disintegrant
Magnesium lauryl sulphate	Lubricant	1–2	Water soluble

Courtesy of N. A. Armstrong.

aqueous environment. The object of a disintegrant is to cause the tablet to disintegrate rapidly so as to increase the surface area of the tablet fragments and so promote rapid release of the drug. Wagner (1969) proposed a scheme which related tablet breakup to drug dissolution and absorption (Fig. 18.1) which had been referred to previously in Chapter 9. Release rate of the drug is greater from disintegrated particles than from the intact tablet or tablet fragments. Thus, a good disintegrant will quickly break up a tablet into primary particles and ensure that the drug is assimilated at a fast rate. The disintegration test, which is included in all pharmacopoeias, measures the time it takes for a tablet to break down and pass through a standard screen.

Disintegrants can act by swelling in the presence of water to burst open the tablet. Starch is the commonest disintegrant in tablet formulation and is believed to act by swelling. However, other effective disintegrants do not swell in contact with water and the mechanisms by which disintegrants act is the subject of some controversy. It is believed that disintegrants that do not swell exert their disintegrating action by capillary action. Liquid is drawn up through capillary pathways within the tablet and ruptures the interparticulate bonds. This action serves to break the tablet apart. Lowenthal (1973) has discussed in detail the various mechanisms of disintegration.

Starch can be incorporated in many ways into a formulation. For example, all the starch can be added to the other ingredients and the homogeneous mix wet granulated. Alternatively, about two-thirds of the starch can be added before wet granulation and the remainder added in dry form to the dried granules. Starch can be added in dry form all at once to the dried granules. This last method is not popular because too much starch between the granules inhibits bonding, with the result that a soft tablet is produced. The advantage of incorporating some of the starch outside the dry granules, is that the disintegration time is improved in tablets possessing water repellant drugs, since the surrounding starch acts as a pathway for water penetration into the tablet and for the pushing apart of granules due to the expansion of a localized high concentration of starch.

Other common disintegrants include *cation exchange resins* (Amberlite IRP 88), *cross-linked polyvinylpyrrolidone* (Polyplasdone XL), *modified starches* (sodium starch glycollate) and *cellulose materials* (Avicel) (see Table 18.4).

Specific formulation requirements of other compressed dosage forms

Lozenges

Lozenges are compressed tablets, usually at least 18 mm in diameter, which do not contain a disintegrant and which are sucked to dissolve in the mouth. Generally there are two types, depending on the required action. The first type produces a local effect in the mouth or throat. Usually this type of lozenge contains an antiseptic (e.g. benzalkonium) or antibiotic. These lozenges must be palatable and slowly soluble. The formulation thus contains some sucrose in fine powder, lactose and

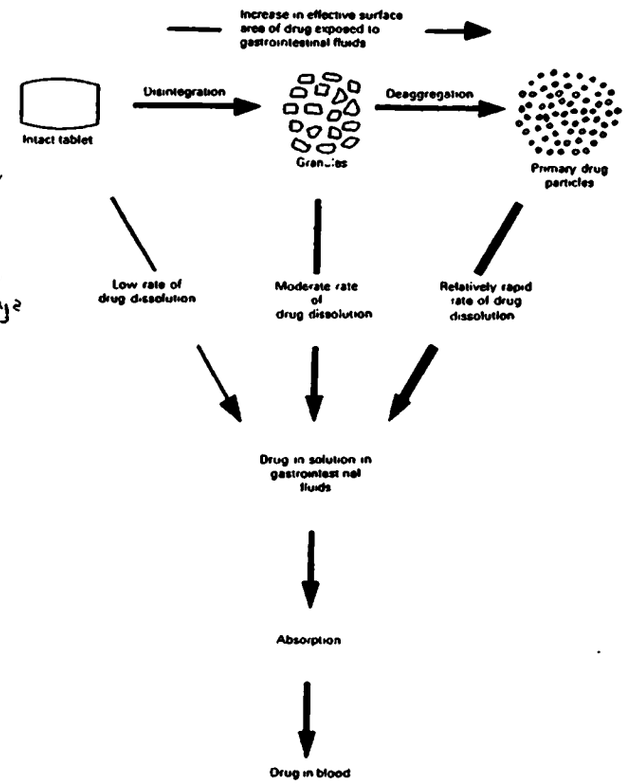


Fig. 18.1 Diagrammatic representation of the disintegration and dissolution steps prior to absorption of a poorly soluble drug from a tablet. (After Wells and Rubinstein, 1976)

Table 18.4 Tablet disintegrants

Material	Concentration in tablet (% w/w)	Comments
Alginic acid and alginates	2–10	
Carbon dioxide		Created in situ in effervescent tablets
Ion exchange resins		Amberlite (R)
Magnesium aluminium silicate	up to 10	Veegum (R), often slightly coloured
Microcrystalline cellulose	up to 10	Avicel (R), lubricant properties, directly compressible
Modified corn starch		Starch 1500 (R)
Sodium dodecyl sulphate	0.5–5	Primarily a wetting agent but this aids disintegration
Sodium carboxymethylcellulose	1–2	Nymcel (R)
Sodium starch glycollate	1–10	Primojel (R), Explotab (R)
Starch	2–10	Potato and maize starches are most frequently used
Modified cellulose gum	2	Ac-di-sol (R)
Cross linked polyvinylpyrrolidone		Polyplasdone XL (R)

Courtesy of N. A. Armstrong

gelatin solution to impart a smooth taste. The formulation is compressed between flat-faced punches to allow greater pressures to be applied. Flavours are normally incorporated to assist palatability. The second type of lozenge produces a systemic effect. An example is a lozenge containing vitamin supplements (multivitamin tablets) which is required to be sucked and is a palatable way of administering vitamins. Again flavours are normally included to make the lozenge more acceptable.

Effervescent tablets

Quick dissolution of the active ingredient in water can be very effectively achieved if the tablet is broken apart by the internal liberation of carbon dioxide. This also serves to increase palatability. By combining alkali metal carbonates or bicarbonates with tartaric or citric acid, carbon dioxide can be liberated when the tablet is placed in water. These effervescent mixtures have been known for over 250 years and the famous Rochelle salt (potassium sodium tartrate) dates back to 1731. Effervescent tablets can be produced by wet fusion and heat fusion. With the wet fusion technique, citric acid is moistened and added to sodium bicarbonate and granulated in a suitable mixer, the moist citric acid acting to partially fuse the powders. The granules are then tableted and the tablets dried in ovens at 70 °C, before being packaged in moisture-proof containers or aluminium foil. The heat fusion technique requires all the powders to be blended dry, with the citric acid being in the form of citric acid monohydrate. The mixed powders are then heated to liberate the water of crystallization in the citric acid, which acts as the granulating agent. The mass is further mixed, whilst being heated, to produce granules which are compressed into tablets.

A water-soluble lubricant is normally used in effervescent tablets to prevent an insoluble 'scum' forming on the water surface. Sweetness is achieved with saccharin, since sucrose is hygroscopic and adds too much bulk to the tablets.

Chewable tablets

For patients who have difficulty in swallowing tablets whole or for children who have not yet learned to wash tablets down with water, chewable tablets present an attractive alternative, with the added advantage that this type of medication can be taken at any time or place when water is not available. Mannitol is normally used as a chewable base diluent, since it has a pleasant, cooling sensation in the mouth and can mask the taste of some objectionable medicaments.

Chewable tablets are prepared by wet granulation. The granules should not be too hard and normally contain a high proportion of flavouring agents to aid palatability, which can include chocolate bases. A disintegrating agent is not required, since the teeth perform this function. Antacid tablets are invariably presented as tablets that should be chewed to obtain quick indigestion relief.

Sublingual and buccal tablets

Tablets placed under the tongue (sublingual) or in the side of the cheek (buccal) can produce an immediate systemic effect by enabling the drug to be directly absorbed through the mucosa. Examples are isoprenaline sulphate (Bronchodilator) and glyceryl trinitrate tablets (vasodilator). These tablets are usually small and flat, do not contain a disintegrant and are compressed lightly to produce a fairly soft tablet. Sucrose is used to impart sweetness.

Implants

Implants are very small pellets composed of drug substance only without excipients. They are normally about 2–3 mm in diameter and are prepared in an aseptic manner to be sterile. Implants are inserted into body tissues by surgical procedures, where they are very slowly absorbed over a period of months. Implant pellets are used largely for the administration of hormones such as stilboestrol, testosterone and dioxycortone acetate. Implants are produced on a single punch machine, normally hand operated. The machine must be appropriately sterilized. The die is filled by hand, since the drug does not normally flow. The particle size of the drug is important and is usually kept large to produce a slow rate of absorption. In addition the implants are made very hard to achieve a gradual release.

Multilayer tablets

A multilayer tablet consists of several different granulations that are compressed, on top of each other, to form a single tablet composed of two or more layers. Each layer is fed from a separate feed frame with individual weight control. Multilayer tablets are mainly used for incompatible substances, for example, phenylephedrine hydrochloride and ascorbic acid in admixture with paracetamol. Paracetamol and phenylephedrine hydrochloride are contained in one layer and paracetamol and ascorbic acid in the other. In spite of the intimate contact at the surface between the two layers, virtually no reaction takes place. Dust extraction is essential during compression to avoid cross-contamination. Each layer, in a multilayer tablet, is individually compressed lightly after each fill. This avoids the granules intermixing if the machine vibrates.

Sustained-release tablets

The advantages, disadvantages and formulation requirements of sustained-release tablets are discussed in the following section. For further details, see the Biopharmaceutics part of this book, particularly Chapters 9 and 11.

Sustained-release tablets

Advantages and disadvantages as a dosage form

In recent years there has been a large increase in the development and use of sustained-release tablets which are designed to release the drug slowly after ingestion. The main factor in the more widespread use of these types of dosage forms is that patient compliance is improved, since only one or two tablets need to be taken daily. Thus the frequency with which the patient has to take these tablets to obtain the desired effect is considerably reduced. In addition, the drug's activity can be extended to take effect throughout the night, so that the patient need not be awakened until morning. A single daily dosage has advantages with psychiatric patients, since this patient group generally forgets to take their medication regularly, and for patients in hospital a decrease in the number of doses administered can result in a time saving for nurses. Another advantage sometimes expressed for sustained-release tablets is that this type of medication reduces the severity or frequency of untoward side effects. Aspirin, for example, has been shown to produce less gastric bleeding when formulated as a sustained-release formulation than conventional

aspirin preparations (Treadwell *et al.* 1973). Generally, a sustained-release tablet produces a more constant blood level of drug than repeated doses of a conventional tablet and this may be clinically very significant (see Chapter 11). Aminophylline has a very narrow therapeutic blood level range and many daily dosages must be given in order that the correct therapeutic blood level can be maintained. In practice, this means that conventional tablets must be administered at precise time intervals, which is very inconvenient for the patient. Formulating aminophylline as a sustained-release tablet has resulted in a 12-hourly dosage regimen and the constant blood level that has been achieved has reduced the incidence of toxicity due to blood level peaking. Thus a more efficient utilization of the drug in the body can be effected with some sustained-release formulations.

Although there is no doubt that sustained-release tablets have many advantages to the patient, there are disadvantages with this type of medication. The cost of prolonged action tablets is more per unit dose than conventional dosage forms. Some drugs, such as riboflavin and ferrous sulphate, are more efficiently absorbed in particular regions of the gastrointestinal tract and therefore sustained-release tablets are not very useful, because they release the drug throughout the intestinal tract. Accidental poisoning with sustained-release dosage forms does present special treatment problems not seen with conventional oral tablets. The slow release of the drug into the gastrointestinal tract and its extended absorption, often results in slow clearance of drug from the body. The physical size of the dosage form may present problems. Some patients do experience difficulty in swallowing a 600–650 mg sustained-release tablet and it is often difficult to formulate the tablets so that the overall tablet weight is very much lower than this. In isolated cases, large tablets have been reported lodged in the oesophagus. Sustained-release tablets of potassium chloride have been known to cause ulceration due to delayed gastrointestinal transit time (McCall, 1975). Variability of absorption can be a troublesome problem with sustained-release tablets. After ingestion the tablet should release quantities of drug at much later times to maintain drug absorption over an extended period. This involves a triggering mechanism and the mechanism may exist in the dosage form itself or in the gastrointestinal tract of the patient. Sustained-release tablets can fail because poor formulation can result in all the drug being released at once, or they fail because inconsistent amounts of drug are released. It has been known for sustained-release tablets to be recovered from the faeces of some subjects.

Types of sustained-release tablets

Attempts have been made to classify sustained-release dosage forms according to their mode of release or the blood level–time profiles that they produce. These differences are discussed in Chapter 11. Suffice it to say here that the BNF presently refers to all such preparations as 'sustained release'.

Formulation of sustained-release tablets

Sustained-release tablets can consist of two parts, an immediately available dose and a sustaining part, containing many times the therapeutic dose, for protracted blood drug levels. The immediately available dose is normally directly added to the sustaining part of the tablet or alternatively is incorporated in the tablet coating with the sustaining portion in the core of the tablet. The heart of the system resides with the sustaining portion of the tablet and various methods have been used to retard drug release.

Methods of achieving sustained-release

Diffusion-controlled release Diffusion entails the movement of drug molecules from a region of high concentration in the tablet to one of a lower concentration in the gastrointestinal fluids. The rate at which diffusion occurs will depend upon the surface area, the diffusional pathway, the drug concentration gradient and the diffusion coefficient of the system. In any one dosage form these factors will be kept constant so that a predetermined diffusion rate of drug out of the tablet will be achieved. In practice, diffusion-controlled release can be produced by formulating the drug in an insoluble matrix. The gastrointestinal fluids penetrate the matrix and drug diffuses out of the matrix and is absorbed. Alternatively, the drug particles can be coated with a polymer coat of defined thickness. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of fluid into the surrounding liquid. In both cases a constant concentration of drug and a constant area of diffusion, together with a constant diffusional pathway, are essential to achieve a constant drug release rate.

With matrix tablets the initial dose is normally placed in the coat of the tablet. The coat and the matrix can be tableted together by compression coating or the coat can be applied using a coating pan or air-suspension technique. In non-coated systems the initial dose is normally tableted with the matrix granulation. Matrices can be composed of polymeric materials such as methylcellulose or insoluble plastic inert substances such as methyl methacrylate. Higuchi (1962) found that for matrix tablets a plot of the square root of time against amount of drug released produced a straight line and this square root plot is often used to record the dissolution rate of matrix tablets.

Dissolution-controlled release Dissolution can be employed as the rate-limiting step in sustained-release tablets. Drugs with poor dissolution rates are inherently prolonged, but with water-soluble drugs it is possible to incorporate a water-insoluble carrier into the tablet formulation to reduce dissolution. Prolonged drug action can also be achieved by leaving out the disintegrating agent in the tablet formulation. Encapsulated drug products also utilize dissolution to control release. With these products, individual drug particles or granules are coated with a slowly soluble coating material such as polyethylene glycol of varying thickness. The time required for dissolution of the coat is proportional to the coating thickness. The coated particles can be compressed directly into tablets. A pulsed dosing effect is obtained by tableting a small number of different thickness coated particles or more usually by utilizing a spectrum of different thickness coatings.

Release controlled by ion exchange Ion exchange materials are water-insoluble resinous materials containing salt-forming groups. Either anionic or cationic groups can be used to produce the desired ion exchange resin. The drug-charged resin is prepared by mixing the resin with drug solution, then washing to remove contaminant ions and then dried to form beads or particles which are tableted. Drug release is achieved in the presence of a high concentration of appropriately charged ions in the gastrointestinal tract; the drug molecule is exchanged and diffused out of the resin to the gastrointestinal fluids. The method is attractive because it relies only on the ionic environment of the resin and not on pH, enzyme content, etc. at the absorption site. The main disadvantage with this type of sustained-release product is that whereas in theory the ionic content of the gastrointestinal tract should remain constant, in practice the ionic content varies with diet and water content, and therefore variable drug release results.

Release controlled by osmotic pressure With this technique, a semipermeable membrane is placed around a tablet or drug particle which allows transport of water into the centre of the tablet by osmosis. As a result of increased internal pressure, drug solution is then pumped out of the tablet through a small hole in the tablet coating. The delivery rate is contant provided that excess drug is present inside the tablet but rapidly declines parabolically to zero once the concentration drops to below saturation. The size of the delivery orifice is very important and this is bored with the use of a laser beam. Since the mechanism is based on osmotic pressure, the system delivers drug at a rate independent of stirring rate and environment pH, factors which make this system an attractive proposition for prolonged drug release from the gastrointestinal tract.

FORMULATION FACTORS AFFECTING THE RELEASE OF A DRUG FROM TABLETS

The effective surface area of the drug

The dissolution rate of a drug is directly related to the surface area exposed to the dissolution media. In order therefore to increase the dissolution rate for a given amount of drug, the effective surface area has to be increased. This can

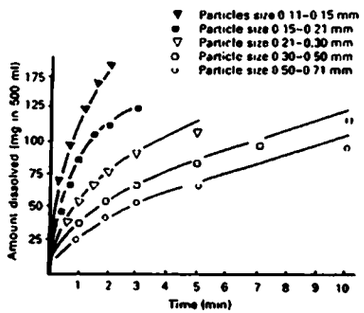


Fig. 18.2 Effect of particle size of phenacetin on dissolution rate (Fuhrhop, P. (1974) Influence of formulation on dissolution rate. In *Dissolution Technology*, L. J. Leeson and J. T. Carstensen, eds, pp. 106–146, Academy of Pharmaceutical Science, American Pharmaceutical Association, Washington, DC)

simply be accomplished by decreasing the particle size of the drug. See earlier discussion under 'Disintegrating agents' and Fig. 18.1.

Figure 18.2 clearly depicts this phenomenon. For the five size ranges examined, the amount of drug dissolving increases as the particle size decreases and surface area increases. However, if the drug is hydrophobic a reduction in particle size may produce a smaller effective surface area and a reduction in dissolution rate. Many *in vitro* studies have also demonstrated the importance of the effective surface area of drug particles. Figure 18.3 shows the effect of administering three different particle sizes of phenacetin on the plasma levels of healthy adult volunteers. Both the rate and extent of phenacetin availability increase as particle size decreases. The effect of particle size reduction on the bioavailability of nitrofurantoin is shown in Fig. 18.4. The microcrystalline form, particle size less than 10 μm, is more rapidly and completely absorbed from tablets than is the macrocrystalline form (74–177 μm) from capsules.

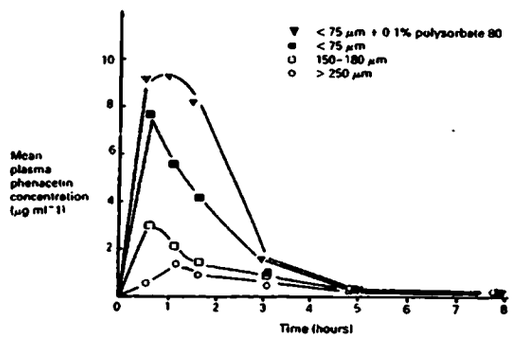


Fig. 18.3 Mean plasma phenacetin concentrations in six adult volunteers following administration of 1.5 g doses (Prescott, L. F., Steel, R. F. and Ferrier, W. R. (1970) The effect of particle size on the absorption of phenacetin in man. *Clin. Pharmac. Ther.*, **11**, 496–504)

Effect of binding agents

Binding agents are incorporated into tablets during granulation in order to improve the flowability of the drug and to enhance compressibility. These agents coat the drug particles and therefore the rate of solution of the binder in water can determine the release rate from the tableted drug.

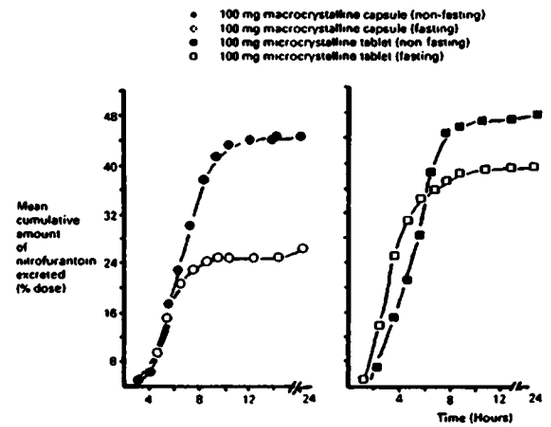


Fig. 18.4 Mean cumulative urinary excretion of nitrofurantoin after oral administration of a 100 mg capsule or tablet (Rietz, T. R., Sequeira, J. A. and Tembo, A. V. (1974) Effect of food on nitrofurantoin absorption. *Clin. Pharmac. Ther.*, **16**, 63–68)

Wells (1980) measured the dissolution rates of chlorpropamide tablets containing starch, hydrolysed gelatin, methylhydroxyethylcellulose (MHEC) and polyvinylpyrrolidone (PVP) as binders. It was found that tablets containing soluble binders (hydrolysed gelatin and PVP) had rapid dissolution rates whereas slow and incomplete disintegration of tablets formulated with starch paste led to protracted release of drug. MHEC produced macrogranular breakdown which gave rise to very slow release rates.

Effect of disintegrants

In order for a drug to be released rapidly from a solid dosage form, the tablet or capsule must disintegrate quickly to liberate a large effective surface area of drug to the dissolving medium. Disintegrants act by either bursting open the tablet and/or by promoting the rapid ingress of water into the centre of the tablet or capsule. In many cases capillarity and therefore the rate of water penetration predominates in causing disruption. Wells (1980) has found that chlorpropamide tablets containing sodium starch glycollate were superior in dissolution properties from similar tablets containing microcrystalline cellulose and cross-linked polyvinylpyrrolidone. The ion exchange resin Amberlite was found to promote rapid disintegration of chlorpropamide tablets, but dissolution rates were found to be inferior to sodium starch glycollate. Measurement of the swelling capacity and hydration capacity of the disintegrants (Table 18.5) indicated that

Table 18.5 Swelling and hydration characteristics of tablet disintegrants

Disintegrant	*Swelling capacity*	*Hydration capacity*
Starch	1.025	1.5620
Microcrystalline cellulose (Elcema)	1.020	4.1778
Cross-linked polyvinylpyrrolidone	1.780	4.8099
Amberlite	2.048	3.7443
Sodium starch glycollate	>3	∞

Amberlite and sodium starch glycollate possesses high swelling capacities and in the case of sodium starch glycollate an exceptionally high hydration capacity

Effect of lubricants

Most tablets contain a lubricating agent to prevent the dosage form sticking to the processing machinery. Figure 18.5 shows the effect of lubricant on the dissolution rate of salicylic acid tablets. The hydrophilic lubricant sodium lauryl sulphate allowed the drug to dissolve more rapidly than the control tablet containing no lubricant. However, incorporation of the popular hydrophobic lubricant magnesium stearate produced a decrease in dissolution rate. The most effective lubricants are very hydrophobic and they must therefore be properly formulated to avoid reducing dissolution rate and bioavailability.

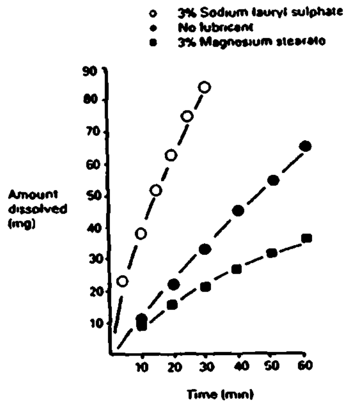


Fig 18.5 Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets (Levy, G and Gumtow, R H (1963) Effect of certain tablet formulation factors on dissolution rate of the active ingredient III Tablet lubricants *J pharm. Sci*, 52, 1139–1141)

Effect of diluents

Rubinstein and Birch (1977) examined the release rate and bioavailability of 5 mg bendrofluazide tablets containing four different excipients: sorbitol, lactose, calcium orthophosphate and calcium hydrogen orthophosphate. The calcium salts were generally found to be superior to the other diluents Sorbitol was shown to markedly decrease the release rate of bendrofluazide This excipient dissolves very slowly and therefore release of the drug occurs by erosion. The calcium salts on the other hand were shown to promote the rapid disintegration of the tablets and therefore to liberate the drug quickly from the dosage form

Effect of granule size

Rubinstein and Blane (1977) examined the effect of granule size on the *in vitro* and *in vivo* properties of bendrofluazide tablets 5 mg Extensive investigations showed that in general granule size was not a critical factor affecting the pharmaceutical properties of the tablets.

REFERENCES

Bolhuis, G K and Lerk, C F. (1973) *Pharm Weekblad*, 108, 496

Bolhuis, G K., Lerk, C F., Zuurman, H T and De Boer, A. H (1975) *Pharm Weekblad*, 110, 317

Fox, C D, Richman, M. D, Reier, G E. and Shangraw, R (1963) *Drug Cosmet Ind*, 92, 161

Goodhart, F W, Gucluyildiz, H, Daly, R E., Chafetz, L and Nunger, F. C (1976) *J pharm Sci*, 65, 1466

Higuchi, T (1962) *J pharm Sci*, 52, 1145

Jaiyeoba, K T and Spring, M. S (1980) *J Pharm Pharmac.*, 32, 386

Khan, K A and Rhodes, C. T (1972a) *Pharm Acta Helv*, 47, 153

Khan, K A. and Rhodes, C. T (1972b) *Pharm Acta Helv*, 47, 594

Khan, K. A and Rooke, D. J (1976) *J Pharm, Pharmac*, 28, 633.

Khan, K A and Rhodes, C T (1976) *Drug Dev. Comm*, 2, 77

Kim, Y (1970) Ph D Thesis, University of Maryland, Maryland, USA

Langridge, L R and Wells, J I. (1980) Paper presented at the British Pharmaceutical Technology Conference, London, April 1980

Levy, G, Antkowiak, J M, Procknal, J A and White, D C (1963) *J pharm. Sci*, 52, 1047

Lowenthal, W. (1973) *Pharm Acta Helv*, 48, 589

McColl, A J (1975) *Br med J*, 3, 5

Mendell, E J. (1972) *Mfg Chem Aerosol News*, 43(3), 47, 43(4), 40, 43(5), 43, 43(6), 31

Naas, S, El-Rashidy, R M and Eskhwas, F (1976) *Drug Dev Comm*, 2, 41

Opakunle, W O and Spring, M. S (1976) *J Pharm. Pharmac*, 28, 806

Richman, M D, Fox, C D and Shangraw, R F. (1965) *J. pharm Sci*, 54, 447

Rubinstein, M H and Birch, M (1977) *Drug Dev Ind Pharm*, 3(5) 439

Rubinstein, M H and Blane, M C, *Pharm Acta Helv*, 52, 5

Rubinstein, M H and Rughani, J M (1978) *Drug Dev Ind Pharm*, 4, 541

Shah, D H. and Arambulo, A S (1974) *Drug Dev Comm*, 1, 495.

Shubair, M. S and Dingwall, D (1976) *Mfg Chem Aerosol News*, 47, 52

Sixsmith, M D (1976) *Mfg Chem Aerosol News*, 46, 27

Treadwell, B L J, Carroll, D G and Pomare, E W (1973) *N Z med J*, 78, 435

Wagner, J G (1969) *J. pharm Sci.*, 58, 1253

Wells, J I (1980) Ph D Thesis, Liverpool Polytechnic.

Wells, J I and Rubinstein, M H (1976) *Pharm J*, 217, 629–631

Wells, J I and Walker, C V (1983) *Int J Pharm*, 15, 97

JOURNAL OF PHARMACEUTICAL SCIENCES

SEPTEMBER 1983
VOLUME 72 NUMBER 9

RESEARCH ARTICLES

Effect of Intergranular *versus* Intragranular Cornstarch on Tablet Friability and *In Vitro* Dissolution

Z. T. CHOWHAN * and I.-C. YANG

Received March 22, 1982, from the *Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304.* Accepted for publication August 18, 1982.

Abstract □ The effect of blending dry cornstarch *versus* wet granulation with the drug and other excipients on friability and *in vitro* dissolution of a ticlopidine hydrochloride tablet formulation was studied. The friability of the tablets was reduced by wet granulating cornstarch with the drug and other excipients compared with the dry blending. The dissolution rate and the tablet-to-tablet variability was improved by incorporating cornstarch in the wet-granulation stage. The lactose placebo tablets, which were wet granulated with either a binder solution or without a binder, also showed reduced tablet friability due to the incorporation of cornstarch in the wet-granulation step. Examination of the tablet cross sections under the scanning electron microscope indicated clumping of starch grains when starch was blended in the dry form. Starch grains were well embedded in the other materials of the tablet and not readily visible when starch was wet granulated with the other excipients. This results in better bonding, fewer weak points, and better homogeneity of the starch disintegrator within the tablet, which accounts for better friability and improved dissolution.

Keyphrases □ Ticlopidine hydrochloride—tablet friability, *in vitro* dissolution, effect of inter- *versus* intragranular cornstarch □ Cornstarch—inter- *versus* intragranular, effect on tablet friability and *in vitro* dissolution, ticlopidine hydrochloride □ Dissolution—*in vitro*, ticlopidine hydrochloride, effect of inter- *versus* intragranular corn starch, friability

Starch USP is a common excipient in compressed tablets, both as a disintegrator and as a binder. Cornstarch is one of the most common disintegrating agents used in tablet formulations today. When added in the dry state to the dry granulation, it acts as a disintegrator. In the paste or dry form, when added before wet granulation, its function is that of a disintegrator and binder.

The mechanism of action of starches is not well understood. In aspirin tablets (1) where contact of starch grains was continuous in the interparticle spaces, disintegration was rapid and effective even when void spaces were eliminated. Where contact was not continuous, disintegration was slower, and appeared to depend on the degree of contact between starch grains and aspirin particles and on the size of interparticle spaces. The primary mechanism appeared to be a swelling action. Capillarity *per se* did not appear to have a disintegrating effect. Ingram and Lowenthal (2) could not find any measurable correlations between starch grain damage and disintegration time or between starch swelling and compressional force. Outside of compressional force, the inherent effect of the tablet ingredients was the only factor that appeared to affect disintegration. In a later study, Lowenthal and Burruss (3) discounted pore diameter and porosity of the tablet as a mechanism of action of starch as a disintegrator. A significant swelling of the starch grains was not observed (4) when pressure-deformed grains were moistened with water. Thus, the regaining of the shape of starch grains was apparently not the mechanism of action as a tablet disintegrator. Observations by scanning electron microscope (5) indicated that rupture of the tablet surface occurred where starch agglomerates were found. It was postulated that water hydrates the hydroxyl groups of the starch molecules, causing them to move apart. The slight swelling that occurs is due to a rapid hydration step and a slower sorption step after the addition of water. Channels or pores lined with starch were not evident. The conditions for rapid tablet disintegration were sufficient agglomerates, low pressure, and presence of water.

In wet-granulated tablet formulations, starch is usually added in the dry form prior to compression. This general practice is based perhaps on the swelling theory of the mechanism of action of starch as a disintegrator which is generally discounted. The data in the literature strongly suggest that disintegration is influenced by a wide variety

0022-3549/83/0900-0983$01.00/0

Table I—Formulations Used in This Study [a]

Ingredients	Formulation		
	A	B	C
Ticlopidine hydrochloride	250.00	-	-
Microcrystalline cellulose	87.35	—	87.35
Lactose	—	337.35	255.85
Citric acid	3.90	3.90	3.90
Starch	39.00	39.00	39.00
Povidone	7.80	7.80	.
Stearic acid		..	3.90
Magnesium stearate	1.95	1.95	

[a] Milligrams of ingredient per tablet.

of factors that are specific only for a given tablet formulation; it is difficult to determine the mechanism of action of starch as a tablet disintegrator.

Recent studies from these laboratories (6) suggested that the friability of compressed tablets was reduced by incorporating 80% cornstarch in the wet-granulation step compared with the dry blending. This paper examines the effects of intragranular *versus* intergranular cornstarch on tablet friability and *in vitro* dissolution.

EXPERIMENTAL

Materials—The drug, ticlopidine hydrochloride[1], was 99.0% pure. The excipients used were microcrystalline cellulose[2] NF, povidone[3] USP,

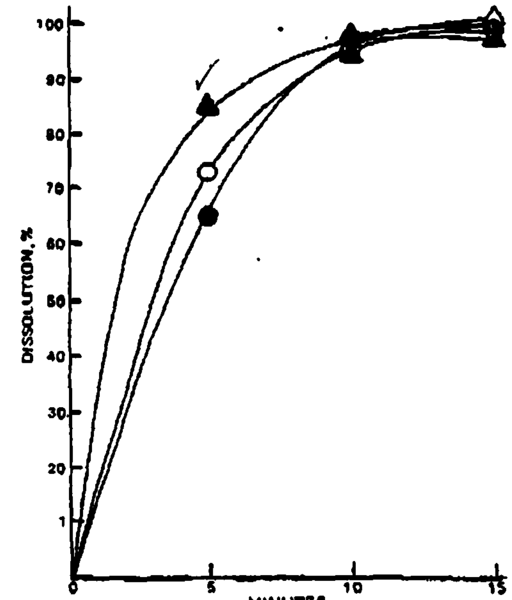


Figure 1—*Dissolution profiles of ticlopidine hydrochloride tablets (formulation A) showing the effect of adding cornstarch before wet granulation versus blending it with the dry granulation. The granulation moisture content was 2.1%, and tablet crushing strength was 15 Strong Cobb units. Key:* ~~*(O) starch dry blended, with extra-deep concave*~~ *punches; (●) starch dry blended, with standard concave punches; (△) starch wet granulated, with extra-deep concave punches; (▲) starch wet granulated, with standard concave punches.*

[1] 5-(o-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride; Sanofi Research Co., New York, NY 10019.
[2] Avicel pH 101, FMC Corp.
[3] GAF Corp., New York, NY 10020.

Table II—Effect of the Addition of Starch During Wet Granulation or Blending with the Dry Granulation on Friability of Tablets Compressed with Standard Concave Punches [a]

Punch	Tablet Friability, %	
	Starch Blended with Dry Granulation	Starch Wet Granulated with Other Materials
Standard concave	0.27	0.0025
Extra-deep concave	0.136	0.0100

[a] Using formulation A with a granulation moisture of 2% and tablet crushing strength of 15 Strong Cobb units.

citric acid[4] USP, stearic acid[5] powder NF, cornstarch[6] NF, lactose[7] USP, and magnesium stearate[4] NF.

Granulation—The formulations used in this study are given in Table I. The drug and the appropriate excipients were mixed together in a small, planetary mixer for 10 min. Citric acid and povidone in formulations A and B and citric acid alone in formulation C were dissolved in water. These solutions were used to granulate the powder mixture. After 10 min of mixing, the granulation was passed through a 1.-mm aperture and dried in a forced-air oven at 50° until the desired moisture levels were obtained. The dried granulation was forced through a 1.2-mm aperture screen. The lubricant and the disintegrator were blended with the granulation for 5 min. The granulations were stored in tightly closed, glass bottles. The moisture content of the final granulation was determined prior to compression.

Compression—The compression was carried out by means of a single-punch tablet machine[8]. The punches and die were 10.32 mm in diameter. Standard concave and extra-deep concave punches were used for compression. The target compression weight was 390 mg/tablet. The tablet crushing strength was determined[9] immediately after compression. For each determination, 10 tablets were tested and the mean was calculated.

Granulation Moisture—The granulation was exposed to a 125-W

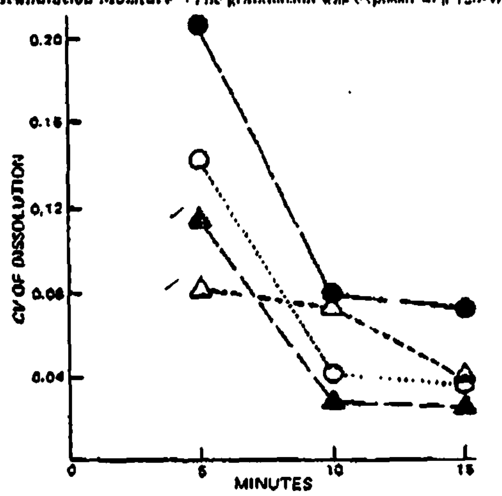


Figure 2—*Coefficient of variation of dissolution showing the effect of adding cornstarch before wet granulation versus blending it with the dry granulation (formulation A). The granulation moisture content was 2.1%, and the tablet crushing strength was 15 Strong Cobb units. Key: (O) starch dry blended, with extra-deep concave punches; (●) starch dry blended, with standard concave punches; (△) starch wet granulated, with extra-deep concave punches; (▲) starch wet granulated, with standard concave punches.*

[4] Mallinckrodt, Inc., St. Louis, MO 63147.
[5] Emery Industries, Inc., Cincinnati, OH 45232.
[6] Staley Manufacturing Co., Decatur, Ill.
[7] Regular Grade; Foremost Co., San Francisco, CA 94104.
[8] Stokes Model F4.
[9] Schleuniger-2E Hardness Tester; Vector Corp., Marion, IA 52302.

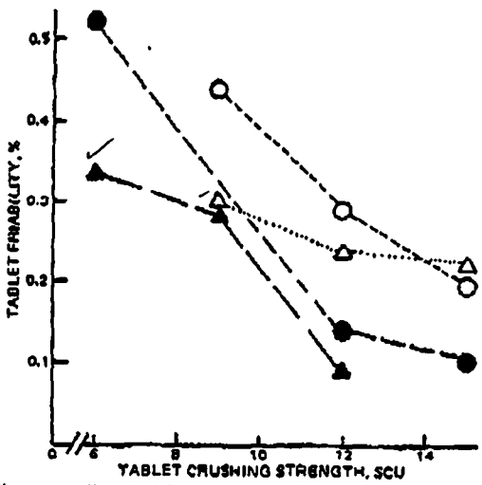


Figure 3—*Effect of adding cornstarch during wet granulation versus blending with the dry granulation on friability of placebo tablets (formulation B). The granulation moisture content was 2.0%. Key: (○) starch dry blended, with standard concave punches; (●) starch dry blended with extra-deep concave punches; (△) starch wet granulated, with standard concave punches; (▲) starch wet granulated, with extra-deep concave punches.*

IR lamp for 15 min at a 90-V setting in a moisture balance[10]. The percent weight loss on drying was read directly from the instrument.

Tablet Friability—A Roche-type friabilator was used. Twenty tablets were brushed with a soft, camel's hair brush to remove all adhering particles. After accurate weighing, the tablets were placed in the drum. The drum was rotated for 4 min (100 revolutions), the tablets were removed, brushed to remove adhering particles, and accurately weighed. The test was carried out in duplicate, and the mean percent friability was calculated.

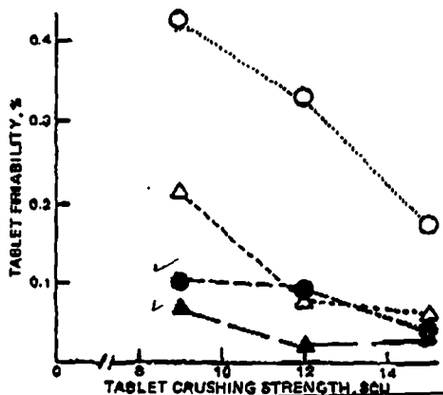


Figure 4—*Effect of adding cornstarch during wet granulation versus blending with the dry granulation on friability of placebo tablets (formulation C). The granulation moisture content was 3.0%. Key: (○) starch dry blended, with standard concave punches; (●) starch dry blended, extra-deep concave punches; (△) starch wet granulated, with standard concave punches; (▲) starch wet granulated, with extra-deep concave punches.*

[10] Cenco Central Scientific Co., Chicago, IL 60621.

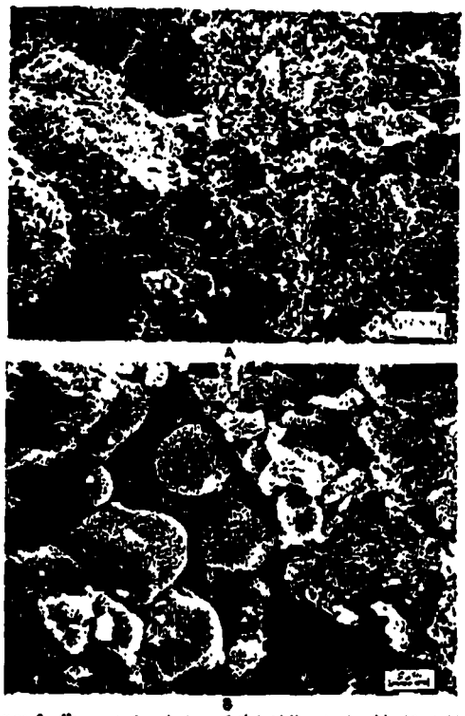


Figure 5—*Cross-sectional view of ticlopidine hydrochloride tablets compressed with the standard concave punches using formulation A. Starch was dry blended. Key: (A) ~400X (original magnification); (B) ~200X (original magnification).*

***In Vitro* Dissolution**—*The in vitro* dissolution was determined by the USP Method II as reported earlier (6). For each determination, six tablets were tested. This apparatus consisted of 1 NF paddles driven by a multiple-spindle drive with a variable-speed control[11]; round-bottom, plastic resin kettles[12] measuring 1 liter; and a water bath. The dissolution

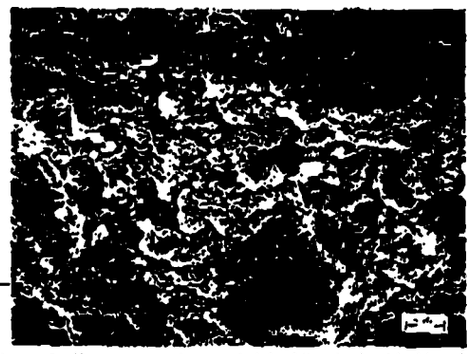


Figure 6—*Cross-sectional view of ticlopidine hydrochloride tablets compressed with the standard concave punches using formulation A. Starch was wet granulated [~200X (original magnification)].*

[11] Model 7299, Hanson Research Corp., Northridge, Calif.
[12] Kimax, Indianapolis, Ind.

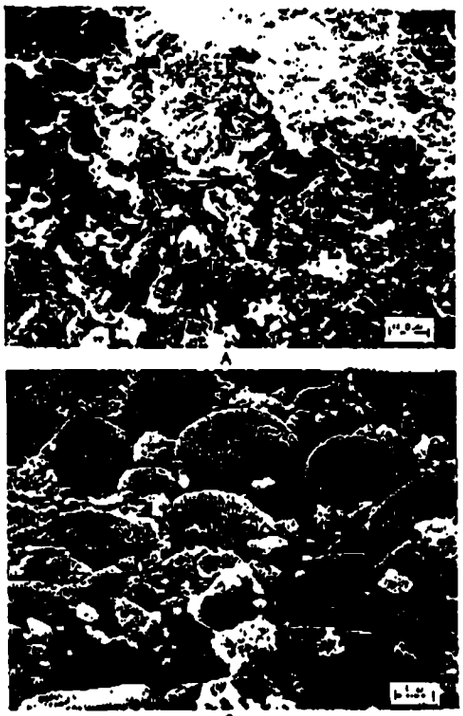


Figure 7—*Cross-sectional view of ticlopidine hydrochloride tablets compressed with the extra-deep concave punches using formulation A. Starch was dry blended. Key: (A) ~400X (original magnification); (B) ~2000X (original magnification).*

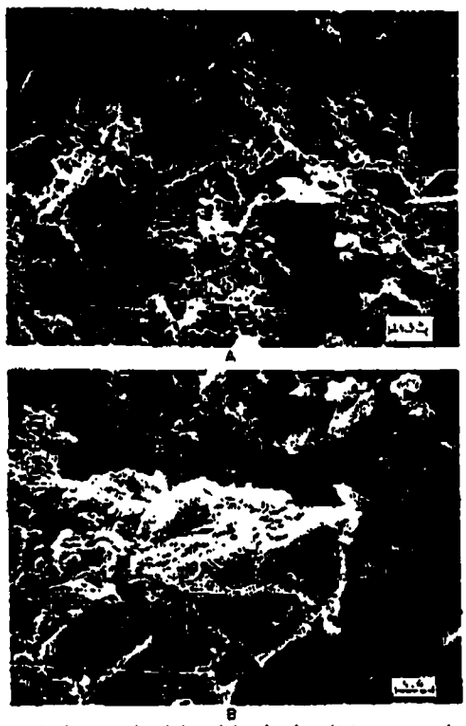


Figure 9—*Cross-sectional view of the placebo tablets compressed with extra-deep concave punches using formulation B. Starch was (A) dry blended or (B) wet granulated (~2000X (original magnification)).*

medium was 700 ml of deionized water equilibrated at 37° and stirred at 50 rpm. The dissolved drug was analyzed by recording the absorbance at 238 nm, using an automated monitoring system consisting of a peristaltic pump[14], 1-mm spectrophotometer flow cells, and automatic sample changer/spectrophotometer[14]. The absorbances were plotted on a recorder every minute until complete dissolution was achieved. The dissolution apparatus was calibrated using USP dissolution calibrator tablets (prednisone, 50 mg). The mean dissolution and the standard deviations were within the required range.

Scanning Electron Micrographs.—Cross sections of the tablets were obtained by cutting tablets axially with a sharp razor blade. The tablet cross sections were mounted on cylindrical specimen stubs with double-stick tape[15] with the inner side surface up. Surface conductivity on the tablet sample was obtained with a silver paint in a vacuum evaporator. The samples were viewed at an oblique angle of 30° in a scanning electron microscope[16]. The photographs were taken using self-developing film[17].

Figure 8—*Cross-sectional view of ticlopidine hydrochloride tablets compressed with the extra-deep concave punches using formulation A. Starch was wet granulated (~2000X (original magnification)).*

RESULTS AND DISCUSSION

The results of the friability of ticlopidine hydrochloride tablets (formulation A) are given in Table II. The starch was either added during the wet-granulation process (a) blended in the dry form with the dry granules. The tablet crushing strength and the granulation moisture were both controlled in these studies[18]. The compression was carried out with standard concave and extra-deep concave punches. The results indicate that the friability of the tablets compressed from granulations in which starch was incorporated in the wet-granulation process was lower compared with the friability of the tablets containing starch in the dry-blended form. Extra-deep concave punches showed a much larger effect

[13] Model 3810; Harvard Apparatus, Millis, Mass.
[14] Model 20; Beckman Instruments, Fullerton, Calif.
[15] Scotch Tape; Minnesota Mining and Manufacturing Co., St. Paul, MN 55101.
[16] SEM Model Alpha-9; International Scientific Instruments, Inc., Santa Clara, CA 95050.
[17] Type 52 Polapan; Polaroid Corp.
[18] Data to be published.

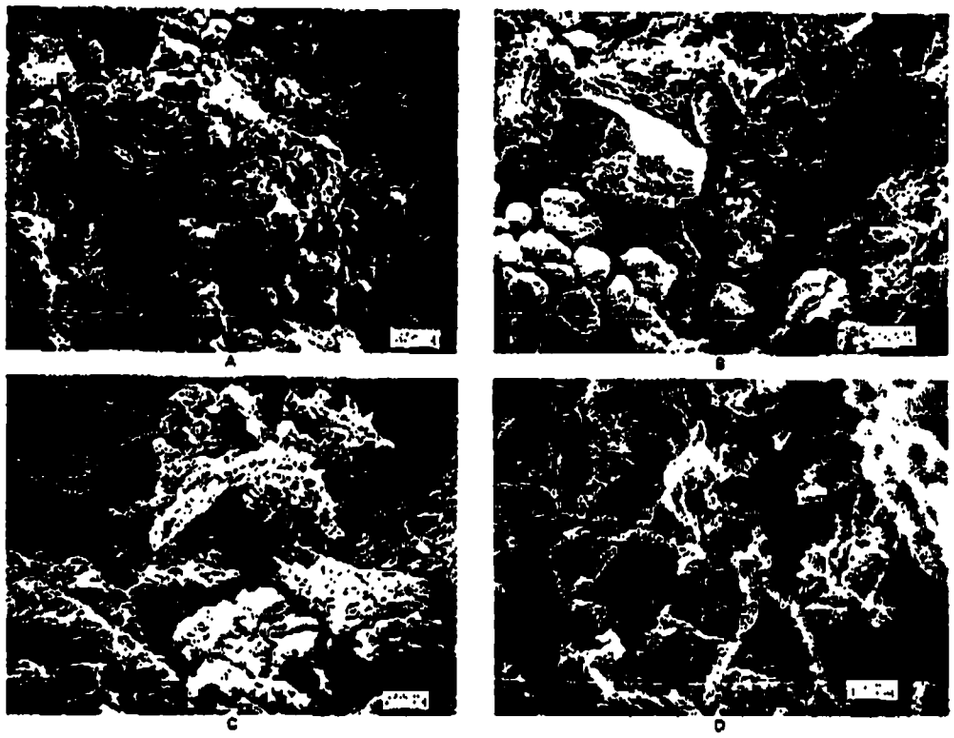


Figure 10—*Cross-sectional view of the placebo tablets compressed with the standard concave punches using formulation C. Key: (A) Starch was dry blended (~100× (original magnification)); (B) starch was dry blended (~300× (original magnification)); (C) starch was wet granulated (~400× (original magnification)); (D) starch was wet granulated (~3000× (original magnification)).*

in reducing tablet friability compared with the standard concave punches as a result of the differences in processing starch.

Figure 1 gives the dissolution profiles of ticlopidine hydrochloride tablets (formulation A) resulting from granulations in which starch was either blended in the dry form or wet granulated with the drug and other excipients. For both punch tip geometries, the initial dissolution rate of the tablets compressed from granulations containing starch in the wet-granulation stage was higher compared with the tablets that were compressed from granulations containing starch in the dry form.

The coefficients of variation (CV) of these tablets as a function of the dissolution time are given in Fig. 2. At all time points studied, the dissolution coefficient of variation of standard convex tablets was smaller for tablets containing starch in the wet-granulated form compared with the tablets containing starch in the dry-blended form. The dissolution coefficient of variation of extra-deep convex tablets compressed from granules containing wet-granulated starch was smaller only at the 5-min time point. At later time points, the punch tip geometry effects discussed earlier (6) override, at least in part, the starch-processing effects.

Placebo tablets (formulations B and C) were compressed with both punch tip geometries to confirm the nonspecificity of the effect on tablet friability caused by the mode of addition of starch. The results of the friability of formulation B placebo tablets at various crushing strengths under controlled granulation moisture are given in Fig. 3. The tablets compressed with the granulation containing wet-granulated starch were less friable compared with the tablets compressed from granulations containing starch in the dry-blended form. At higher crushing strengths, these differences were small. This was true with both punch tip geometries. In agreement with an earlier report (6), the friability of extra-deep convex tablets was smaller than the friability of standard convex tablets.

Granulations were made without a wet binder (formulation C) to study the influence of the mode of the starch addition on tablet friability. Figure 4 gives the results of the tablet friability at various crushing strengths at a controlled moisture content. For both punch tip geometries, the friability of the tablets compressed from granulations containing wet-granulated starch was smaller than the tablets compressed from granulations containing starch in the dry-blended form. The friability of the extra-deep convex tablets was much smaller than the friability of the standard convex tablets.

These results suggest definite advantages of incorporating starch as a disintegrator in the wet granulated part of the formulation of tablets containing soluble drugs and/or soluble major excipients for improving tablet friability and *in vitro* dissolution. It is also important to point out that the wet granulations containing starch must be dried below 60° to prevent gelatinization of the starch.

To investigate the mechanism by which the incorporation of starch in the wet granulation improved tablet friability and *in vitro* dissolution, a scanning electron microscope was used to examine the cross sections of the tablets. Figure 5 is a cross sectional view of ticlopidine hydrochloride tablets (formulation A) containing starch in the dry blended form compressed with the standard concave punches. Starch grains, mostly deformed, appeared in clumps with some loose, fine granules. The clumping of the starch grains was not observed when cross sections of the tablet containing starch as a part of the wet granulation were examined (Fig. 6). The starch grains were well distributed in the drug-excipient granules showing good contact with the powders.

Because of the dependence of the axial and radial movement of the powders on punch tip geometry, cross sections of the extra-deep convex tablets were examined to study its effect on the distribution of starch granules within the tablet. Clumps of starch grains with some loose, fine granules were observed (Fig. 7) when starch was dry blended with the dry granules. Starch did not appear to adhere to the flat or to the other materials

in the tablet. This results in weaker points within the tablets and fine cracks around the agglomerates. Higher tablet friability and higher tablet-to-tablet variability in dissolution could be explained as resulting from clumping of starch grains and weaker points around these agglomerates. The cross-sectional view of the tablet compressed from granules containing starch in the wet-granulation stage is shown in Fig. 6. No clumping of the starch grains was seen. The materials were well distributed in the tablet matrix. Comparisons of the two punch tip geometries revealed no major differences in the distribution of starch resulting from the differential particle movement during compression (compare Figs. 5 and 6 with Figs. 7 and 8).

Figure 9 gives cross-sectional views of the placebo tablet compressed with the standard concave punches (formulation B). Tablets containing dry blended starch showed only a few starch grains (Fig. 9A) compared with the largely fused lactose (Fig. 9B) for tablets compressed from wet-granulated starch.

The cross-sectional views of the tablets compressed from formulation C without a wet binder are shown in Fig. 10. Similar to ciclopidine hydrochloride tablets, clumping of starch grains was observed when starch was dry blended (Fig. 10A and B). Starch grains do not adhere to themselves or to the other materials in the tablet. This is in contrast to the case when starch was wet granulated with other excipients using water (Fig. 10C and D). Agglomerates or even isolated starch grains were not observed. The starch was well embedded in the soluble excipient, lactose, which on drying crystallized out.

In conclusion, this study suggests that the tablet friability and *in vitro* dissolution improved by incorporating starch in the wet-granulation stage of formulations containing a soluble drug and/or a soluble major excipient. This improvement in tablet friability and *in vitro* dissolution is due to a better bonding, fewer weak points, and better homogeneity of the disintegrator, starch, within the tablet.

REFERENCES

(1) N. R. Patel and R. Hopponen, *J. Pharm. Sci.*, 55, 1065 (1966).
(2) J. T. Ingram and W. Lowenthal, *J. Pharm. Sci.*, 57, 893 (1968).
(3) W. Lowenthal and R. A. Burruss, *J. Pharm. Sci.*, 60, 1825 (1971).
(4) W. Lowenthal, *J. Pharm. Sci.*, 61, 455 (1972).
(5) W. Lowenthal and J. H. Wood, *J. Pharm. Sci.*, 62, 287 (1973).
(6) Z. T. Chowhan, J.-C. Yang, A. A. Amaro, L.-H. Chi, and Y. P. Chow, *J. Pharm. Sci.*, 71, 1371 (1982).

Application of the Ammonia Gas-Sensing Electrode: Determination of Drugs Having a Carbothionamido Group by Decomposition with Acid

SHOICHIRO TAGAMI * and **HIROMI MAEDA**

Received April 19, 1982, from the *Toyama Medical and Pharmaceutical University, Sugitani, Toyama, Japan.* Accepted for publication August 4, 1982.

Abstract □ A method to determine drugs having a carbothionamido group using an ammonia gas-sensing electrode is described. To obtain analytical accuracy, the effect of factors that influence the potential is also discussed. Ethionamide or prothionamide was refluxed with 20% HCl to give ammonium chloride, hydrogen sulfide, and a carboxylic acid. The ammonia, which evolved at pH > 11, was determined. A linear calibration plot was obtained within the drug concentration range of 2×10^{-5}–1×10^{-3} *M*.

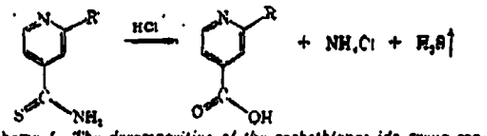
Keyphrases □ **Ammonia gas-sensing electrode**—determination of carbothionamido groups, acid decomposition of ethionamide and prothionamide □ **Ethionamide**—carbothionamido group, determination using ammonia gas-sensing electrode, acid decomposition □ **Prothionamide**—carbothionamido group, determination using ammonia gas-sensing electrode, acid decomposition

In recent years, the development of gas-permeable membrane electrodes has led to their widespread use in the analytical field (1). Although electrodes that use immobilized enzymes on the membrane are employed for the determination of organic and biological compounds, few applications to drug analysis have been reported in the literature, and no pharmacopeia has yet introduced their use for assays. Therefore, a previous paper (2) described procedures for the determination of drugs having a carboxyamido group (ethenzamide, nicotinamide, pyrazinamide, and salicylamide).

The present paper describes the determination of drugs having a carbothionamido group in an analogous way and describes in detail the operations and handling of the ammonia gas-sensing electrode. The carbothionamido group decomposes into ammonium chloride, hydrogen sulfide, and a carboxylic acid on heating with hydrochloric acid (Scheme I). It may thus be possible to utilize the ammonia gas-sensing electrode to determine the ammonia derived from the ammonium chloride during the decomposition.

EXPERIMENTAL

Apparatus and Reagents—Direct potentiometric measurements were made at 20° in an 80-ml cell equipped with a magnetic stirrer, using a pH/mV meter[1] with a recorder[2] and ammonia gas-sensing electrodes A[3] and B[4]. Ethionamide[5], prothionamide[6], and ammonium chloride[7] were analytical grade or certified quality and were dried *in vacuo* at room temperature for 5 hr. Other chemicals used were reagent grade. Ammonium chloride solutions of 0.001–1 *M* and ammonium chloride solutions of 0.01–0.1 *M* saturated with ammonium picrate were used as internal filling solutions.



Scheme I—The decomposition of the carbothionamido group-containing compounds ethionamide (R = C_2H_5) and prothionamide (R = C_3H_7).

[1] Model F-7ss, Hitachi-Horiba Instruments, Horiba Co., Kyoto.
[2] Model PDR-2ss, Toa Dempa Co., Tokyo.
[3] Model 95-09, Orion Research Inc., Cambridge.
[4] Daiichi Seiyaku Co., Tokyo (lot CA 7921B05).
[5] Lederle-Japan Ltd., Tokyo (lot CA 7917905; assay, 100.2%).
[6] E. Merck, Darmstadt (lot 0274854; assay, 99.8%).

0022-3549/83/0900-0988$01.00/0

240

~~240~~

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	04-108760
	Trámite	011
	Evento	001
	Actuación	430
	Oficio	12483
	Folios	007

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap.I ☐	Cap. II ☒
No. Sol. Internacional		PCT/EP03/008732	
Fecha de Presentación Internal.		07-08-2003	

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 le comunica:

1. Documentos estudiados

Descripción:	Folios 25-37	como se radicó inicialmente
	Folios 178-190	como se radicó el 03-07-2008
Reivindicaciones:	Folios 38-41	como se radicó inicialmente
	Folios 134-136	como se radicó el 18-01-2007
	Folios 191-194	como se radicó el 03-07-2008
Oposición:	Folios 73-88	como se radicó el 04-07-2006 Opositor Tecnoquímicas S.A.
Prioridad:	Folio 1	EP, 02028745.4, 20-12-2002
Respuesta del solicitante:	Folios 110-132	como se radicó el 18-10-2006
	Folios 162-176	como se radicó el 03-07-2008

2. Objeto de la invención

Título de la solicitud: FORMULACIONES DE DOSIS ALTAS DE IBANDRONATO (folio 1).

El problema técnico planteado en la solicitud está relacionado con la necesidad de proporcionar una composición farmacéutica solida oral con dosis altas de ibandronato, que disuelva fácilmente y sea estable en su almacenamiento respecto a temperatura y humedad (folios 27-28; pág. 3-4).

Para **solucionar este problema técnico** la solicitud en estudio proporciona una composición farmacéutica para tableta que contiene hasta 250 mg, especialmente 150 mg o 100 mg de ácido ibandrónico o una de sus sales fisiológicamente seguras, en la que el desintegrante, la sustancia activa y parte del material de relleno forman el granulado, es decir el desintegrante está en la fase intragranular.

Adicionalmente, tal composición para tableta tiene en la fase extragranular el resto del material de relleno o diluente, lubricantes y reguladores de flujo; siendo la tableta o núcleo comprimido preferiblemente recubierto con una película de recubrimiento.

Asimismo, se provee un proceso para la preparación de tales composiciones farmacéuticas en forma de tableta basado en un proceso de granulación en lecho fluidizado, con las posteriores etapas de mezcla con los demás excipientes y compresión para formar la tableta o núcleo comprimido.

El objeto de la presente solicitud de patente se relaciona con la Clasificación internacional de Patentes (IPC): A61K31/663, A61K9/20, A61K9/28.

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

En la reivindicación 1, en la frase "*contiene como sustancia activa hasta 250 mg*" el término "*hasta*" no es conciso, ya que significa que la sustancia activa puede estar entre 0 mg a 250 mg, incluyendo así dosis bajas del activo, lo que no corresponde con el problema técnico planteado que está relacionado con dosis altas del mismo; por tanto, es necesario que dicho término sea retirado y se deje un valor fijo o un rango del contenido del activo en la composición, acorde con las composiciones que soportan la invención, las cuales enseñan composiciones con 100 y 150 mg de ácido ibandrónico (folios 188, 190; pág. 11, 13, ej. 1 y 2).

En la reivindicación 1, es necesario cambiar la expresión no concisa "*o sales fisiológicamente seguras del mismo*" por "*o una de sus sales fisiológicamente seguras*".

En las reivindicaciones 2 y 3, es necesario cambiar la expresión "*grano de comprimido*" por "*núcleo comprimido*", ya que se refiere es a la tableta comprimida o núcleo.

Las reivindicaciones 6 y 7 que reclaman composiciones específicas, deben ser dependientes de la 1 puesto que están basadas en las características esenciales de la 1, correspondiendo a los ej. 2 y 1, respectivamente, que soportan la invención en la descripción (folios 188, 190; pág. 11, 13).

La reivindicación 9 caracteriza inadecuadamente una composición por ser obtenida mediante un proceso dado, ya que una composición debe caracterizarse por los elementos que la comprenden como son activo y excipientes.

Se requiere al Solicitante hacer las aclaraciones necesarias.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 20-12-2002, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de publicación
D1	US 6294196	Pharmaceutical composition containing diphosphonic acid or salt thereof.	2001-09-25
D4	Bibliografía 1	Effect of intergranular versus Intragranular cornstarch on tablet friability and in vitro dissolution	09-1983

Bibliografía 1: Z. T. Chowean et al., "Effect of intergranular versus Intragranular cornstarch on tablet friability and in vitro dissolution", Journal of pharmaceutical sciences, 1983, vol. 72 number 9, page. 983-988.

D1 http://worldwide.espacenet.com/searchResults?NUM=US6294196&DB=EPODOC&locale=en_EP&ST=number&compact=false, se relaciona con formas farmacéuticas sólidas conteniendo como sustancia activa un ácido bifosfónico o una sal fisiológicamente compatible de éste, donde la sustancia activa está en forma granulada opcionalmente con otros adyuvantes en la fase interna y donde un lubricante está en la fase externa; así como también se relaciona con procesos para preparación de tal forma farmacéutica (resumen y col.1).

D4 en folios 234-239, se relaciona con el efecto del almidón (*desintegrante*) intergranular (*extragranular*) frente al intragranular sobre la friabilidad y disolución de tabletas, divulgando como efecto la reducción de la friabilidad y la mejor disolución de las tabletas que incorporan el desintegrante, el fármaco y otros excipientes en la granulación húmeda (intragranular) en comparación con la mezcla del desintegrante a los gránulos ya secos (extragranular); enseñando que tales resultados de mejor friabilidad y disolución cuando el desintegrante está en la parte intragranular se dan debido a la mejor unión o enlazamiento entre partículas, existencia de menos puntos débiles y mejor homogeneidad del desintegrante dentro de la tableta (folio 234; pág. 983, resumen).

5. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo18 D486)

- Se solicita en la reivindicación 1-7 y 9, una composición farmacéutica que contiene hasta 250 mg de ácido ibandrónico o una de sus sales fisiológicamente seguras, en la que el desintegrante se adiciona al granulado junto con la sustancia activa y con parte del material de relleno.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica

SOLICITUD	D1
Composición farmacéutica oral que contiene	Composición farmacéutica oral que contiene
hasta 250 mg ácido ibandrónico o una de sus sales fisiológicamente seguras	(0,25-100) mg ácido ibandrónico o una de sus sales fisiológicamente seguras (col. 4, lín. 14-20 y 64-66)
Y donde el granulado contiene: - el desintegrante - la sustancia activa - y parte del material de relleno	Y donde el granulado contiene: - la sustancia activa - y parte del material de relleno Estando el desintegrante en la parte extragranular (col. 8-9, ej. 6)

El estado de la técnica más cercano es D1 que divulga composiciones farmacéuticas para formas sólidas (tabletas recubiertas o capsulas) que contienen entre (0,25-100) mg de acido ibandrónico o una de sus sales fisiológicamente seguras (col. 4, lín. 14-20 y 64-66), donde el granulado contiene la sustancia activa y parte del material de relleno, estando el desintegrante en la parte extragranular (col. 8-9, ej. 6).

La diferencia de la solicitud con D1 es que el desintegrante está en la parte intragranular.

El efecto técnico que logra tal diferencia es que la composición sólida de acido ibandrónico es fácilmente disuelta y posee estabilidad en su almacenamiento con respecto a temperatura y humedad (folio 181; pág. 4, párrafo 1), sin que tabletas de tal composición presenten agrietamiento (folios 125-126; pág. 16-17 de respuesta).

243

~~243~~

Así, el Problema Técnico Objetivo está relacionado con la necesidad de obtener una composición solida de acido ibandrónico, que disuelva fácilmente y sea estable en su almacenamiento con respecto a temperatura y humedad, sin que tabletas de tal composición presenten agrietamiento.

Sin embargo, se aclara primero que es reconocido por la persona del oficio normalmente versada en la materia que el desintegrante (p.ej. almidón, crospovidona) puede estar en la parte intragranular, en la parte extragranular o estar dividido entre éstas dos; siendo también conocido que cuando el desintegrante está en la parte extragranular, es decir adicionado a los gránulos ya secos, se inhibe el enlace o cohesión entre los gránulos, resultando en una tableta blanda (folio 229; pág. 312, col 2), es decir, que la tableta es fácilmente agrietable a condiciones de humedad y temperatura elevadas no adecuadas en su almacenamiento.

Segundo, que D4 divulga que incorporar el desintegrante en la parte intragranular (adicionado en la mezcla para granulación húmeda) reduce la friabilidad (*al aumentar el grado de cohesión*) y aumenta la velocidad de disolución de tabletas comprimidas, en comparación con las que contienen el desintegrante en la parte extragranular (adicionado a los gránulos ya secos); puesto que, cuando el desintegrante está en la parte intragranular se encuentra mejor distribuido (homogéneamente) entre las partículas de fármaco y excipientes del granulado, generando un mejor contacto y enlace entre las partículas y menos puntos débiles en la tableta, mientras que cuando el desintegrante está en la parte extragranular (mezclado con los gránulos ya secos), el desintegrante no se adhiere a sí mismo ni a los otros materiales y se forman agrupamientos de partículas de desintegrante, lo cual resulta en puntos más débiles dentro de la tableta y en finas grietas alrededor de los aglomerados, generando así una alta variabilidad en los resultados de friabilidad y disolución tableta a tableta (folios 238-239; pág. 987 col 2, 988 col 1-2).

En consecuencia, la composición farmacéutica reclamada es obvia, porque la persona del oficio normalmente versada en la materia enfrentada al problema de obtener una composición solida de acido ibandrónico, que disuelva fácilmente y sea estable en su almacenamiento con respecto a temperatura y humedad, sin que tabletas de tal composición presenten agrietamiento, cambiaría con expectativa razonable el desintegrante de la parte extragranular según composiciones de D1 a la parte intragranular (en la mezcla para granulación húmeda) como ya lo conoce el experto y como se revela en D4, para lograr de esta forma la composición objeto de la solicitud; por tanto, la composición reivindicada carece de nivel inventivo.

- Se solicita en la reivindicación 8, un proceso de preparación de la composición de la reivindicación 1.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica

SOLICITUD	D1
Proceso de preparación de la composición de la 1 (*tabletas*)	Proceso de preparación de una tableta de ácido ibandrónico (col. 9)
Disolver el aglutínate (PVP) en agua	Disolver el aglutínate (PVP) en agua
Cargar en una cámara de lecho fluidizado el principio activo, desintegrante (crospovidona) y parte del material de relleno	Cargar en una cámara de lecho fluidizado el principio activo y parte del material de relleno
Granular por aspersión a (60-80)°C con la solución de aglutinante	Granular por aspersión con la solución de aglutinante
Secar el material granulado entre (60-80)°C y pasar el material seco a través de un tamiz	Secar el material granulado y pasar el material seco a través de un tamiz
Mezclar el granulado con el resto de material de relleno, el lubricante y el regulador de flujo	Mezclar el granulado con el desintegrante (crospovidona), el resto de material de relleno, el lubricante y el regulador de flujo
Comprimir la mezcla en núcleos de tabletas y realizar el recubrimiento de los mismos con la mezcla de recubrimiento	Comprimir la mezcla en núcleos de tabletas y realizar el recubrimiento de los mismos con la mezcla de recubrimiento

244

El estado de la técnica más cercano es D1 que divulga un proceso de preparación de tabletas de ácido ibandrónico por medio de granulación húmeda en un granulador de lecho fluidizado que comprende: mezclar el principio activo con parte del material de relleno, granular esta mezcla con una solución acuosa del aglutinante, secar el granulado una cámara de lecho fluidizado, pasar este material por un tamiz, mezclar el granulado con el desintegrante, el resto de material de relleno, el lubricante y el regulador de flujo, comprimir tal mezcla en tabletas y recubrir éstas con el material de recubrimiento (folios 142-143; col. 8-9, ej. 6).

La diferencia de la solicitud con D1 es que indica que el desintegrante se adiciona en la parte intragranular y que la temperatura de granulación y de secado es de (60-80) °C.

Y el efecto técnico que logra tal diferencia es que permite obtener una composición sólida (en tableta) de acido ibandrónico que es fácilmente disuelta y posee estabilidad en su almacenamiento con respecto a temperatura y humedad (folio 181; pág. 4, párrafo 1), sin que tabletas de tal composición presenten agrietamiento (folios 125-126; pág. 16-17 de respuesta).

Así, el Problema Técnico Objetivo está relacionado con la necesidad de cómo obtener una composición solida en forma de tableta de acido ibandrónico, que disuelva fácilmente y sea estable en su almacenamiento con respecto a temperatura y humedad, sin que tabletas de tal composición presenten agrietamiento.

Sin embargo, se aclara primero que es reconocido por la persona del oficio normalmente versada en la materia que el desintegrante (p.ej. almidón, crospovidona) puede adicionarse en la parte intragranular, en la parte extragranular o estar dividido entre éstas dos; siendo también conocido que cuando el desintegrante está en la parte extragranular, es decir, adicionado a los gránulos ya secos, se inhibe el enlace o cohesión entre los gránulos, resultando en una tableta blanda (folio 229; pág. 312, col 2), es decir, que la tableta es fácilmente agrietable a condiciones de humedad y temperatura altas no adecuadas en su almacenamiento. Igualmente, es conocido que las temperaturas de granulación y secado específicas en un proceso de granulación húmeda, pueden ser determinadas de acuerdo a ensayos de pre formulación que permitan obtener un granulado con un contenido de humedad uniforme y apropiada para su manejo y estabilidad (folio 218: pág. 867, col. 2).

Segundo, que D4 divulga que incorporar el desintegrante en la parte intragranular (incorporado en la mezcla para granulación húmeda) reduce la friabilidad (*al aumentar el grado de cohesión*) y aumenta la velocidad de disolución de tabletas comprimidas, en comparación con las que contienen el desintegrante en la parte extragranular (adicionado a los gránulos ya secos); puesto que, cuando el desintegrante está en la parte intragranular se encuentra mejor distribuido (homogéneamente) entre las partículas de fármaco y excipientes del granulado, generando un mejor contacto y enlace entre las partículas y menos puntos débiles en la tableta, mientras que cuando el desintegrante está en la parte extragranular (mezclado con los gránulos ya secos), el desintegrante no se adhiere a sí mismo ni a los otros materiales y forma agrupamientos de partículas de desintegrante, lo cual resulta en puntos mas débiles dentro de la tableta y en finas grietas alrededor de los aglomerados, generando así una alta variabilidad en los resultados de friabilidad y disolución tableta a tableta (folios 238-239; pág. 987 col 2, 988 col 1-2).

Por ende, el proceso reclamado es obvio, porque la persona del oficio normalmente versada en la materia enfrentada al problema de cómo obtener una composición solida en forma de tableta de acido ibandrónico, que disuelva fácilmente y sea estable en su almacenamiento con respecto a temperatura y humedad, sin que

tabletas de tal composición presenten agrietamiento, cambiaría con expectativa razonable el desintegrante de la parte extragranular según proceso de obtención de composiciones de D1 a la parte intragranular (adicionándolo en la mezcla de granulación húmeda) como ya lo conoce el experto y como se revela en D4, y determinaría mediante ensayos de rutina la temperatura optima de granulación y secado de los gránulos, para lograr de esta forma el proceso de la solicitud; por ende, el proceso reivindicado carece de nivel inventivo.

6. Respuesta al solicitante

El solicitante anexa un nuevo capitulo descriptivo (folios 178-190) y capitulo reivindicatorio (folios 191-194), cambiando en la pág. 12 de la descripción y en la reivindicación 8 las expresiones "*rociar en granulado*" y "*granos de comprimido*" por las expresiones "*granular por aspersión*" y "*núcleos de comprimidos*", respectivamente; capítulos que son aceptados por esta oficina.

- En relación con la falta de claridad el solicitante señala que ha cambiando en la pág. 12 de la descripción y en la reivindicación 8 las expresiones "*rociar en granulado*" y "*granos de comprimido*" por las expresiones "*granular por aspersión*" y "*núcleos de comprimidos*", respectivamente; obedeciendo a una corrección de evidentes errores cometidos durante la traducción (folios 165-166; pág. 4-5 de respuesta).

  Al respecto, se aclara que tales términos erróneamente traducidos sólo se corrigieron en la pág. 12 de la descripción y en la reivindicación 8, pero que en las demás partes donde se mencionan estos términos no se corrigieron, p. ej. en las reivindicaciones 2 y 3; por tanto es necesario revisar y corregir.

- En relación con el nivel inventivo, el solicitante señala de manera separada consideraciones frente a cada documento:

  - Que D1 enseña composiciones que incluyen en la fase externa un agente desintegrante (crospovidona) y un agente lubricante, mientras que la fase interna contiene la sustancia activa (ácidos bifosfónicos) junto con adyuvantes como enlazadores y material de relleno. Pero que las composiciones de la solicitud se caracterizan por porque la sustancia activa está mezclada con el desintegrante y una parte del material de relleno, lo que permite aumentar sorprendentemente la estabilidad de la composiciones al evitar los efectos adversos generados por la humedad durante su almacenamiento, evitando así la tendencia la agrietamiento, como se muestra en los resultados obtenidos (folio 168-169; pág. 7-8 de respuesta).

  - Que D2 enseña composiciones que contienen a) entre (0,5 a 40) % de un acido bifosfónico y b) entre (69-99,5) % de excipientes como diluyentes, enlazantes, desintegrantes, lubricantes y ceras; pero que la composición reclamada en la solicitud no incluye una cera como recubrimiento, por lo cual considera que el nivel inventivo de la materia reclamada no es afectado por las enseñanzas de D2 (folios 171-172; pág. 10-11 de respuesta).

  - Que D3 enseña un proceso para formar un granulado a partir de sustancias solidas en polvo, pero que no enseña las proporciones de ingredientes necesarios para obtener una tableta con alto contenido de ingrediente activo, ni la ubicación de los diferentes ingredientes para obtener un producto estable, por lo que considera que este documento no afecta el nivel inventivo de la materia reclamada (folio 173; pág. 12 de respuesta).

En relación a las anteriores observaciones del solicitante, se aclara que en efecto la diferencia de la solicitud con D1 es que el desintegrante está en la parte intragranular.

Y el efecto técnico logrado por tal diferencia es que la composición sólida de acido ibandrónico es fácilmente disuelta y posee estabilidad en su almacenamiento con respecto a temperatura y humedad (folio 181; pág. 4, párrafo 1), sin que tabletas de tal composición presenten agrietamiento (folios 125-126; pág. 16-17 de respuesta).

No obstante, se aclara que se han cambiado los documentos D2 y D3 por el documento D4, dado que es comúnmente reconocido por la persona del oficio normalmente versada en la materia que el desintegrante (p.ej. almidón, crospovidona, entre otros) puede estar en la parte intragranular, en la parte extragranular o estar dividido entre éstas dos; y que también es conocido que cuando el desintegrante está en la parte extragranular (adicionado a los gránulos ya secos) se inhibe el enlace o cohesión entre los gránulos y genera una tableta blanda (folio 229; pág. 312, col 2), es decir, que la tableta es fácilmente agrietable a condiciones de humedad y temperatura elevadas no adecuadas en su almacenamiento.

Por tanto, la materia reclamada es afectada por D1 (desintegrante en la fase extragranular) y D4, ya que D4 que enseña mejor friabilidad (*por aumento del grado de cohesión*) y disolución de tabletas que contienen el desintegrante en la fase intragranular en comparación con las que lo contienen en la fase extragranular, tal como se explica en el análisis de nivel inventivo.

7. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US 629419	1-9	Nivel inventivo
D4	Bibliografía 1	1-9	Nivel inventivo

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 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.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 01 AGO. 2011

CONCEPTO TECNICO No. 2032	EXAMINADOR TECNICO Código No. 202079