SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RAD: 14-134651- -4 **FECHA**: 2015-06-19 10:06:51
DEP: 2020 DIRECCION DE NUEVAS CREACIONES **EVE:** 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II **FOLIOS**: 8
ACT: 476 TRASTITULARSOLI

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
JUAN PABLO CADENA SARMIENTO

Asunto: Radicación: 14-134651- -4
Trámite: 11
Evento: 378
Actuación: 476
Oficio: 6813
Folios: 8

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/US2012/067172				
Fecha de Presentación Internacional	30/11/2012				

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

1. Documentos estudiados

Descripción:	Radicado No. 14-134651-00000-0000	20/junio/2014
Reivindicaciones:	Radicado No. 14-134651-00000-0000	20/junio/2014
Prioridad:	US 61/566,109	2/diciembre/2011
	US 61/653,439	31/mayo/2012
	US 61/647,288	15/mayo/2012
	US 61/670,419	11/julio/2012

2. Análisis de la Prioridad

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

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se

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estudiarán las cubiertas por la tasa pagada. En el presente caso, se tiene en cuenta la totalidad del capítulo reivindicatorio (Radicado No. 14-134651-00000-0000) para el examen de patentabilidad.

Título de la solicitud: "COMPOSICIONES FARMACÉUTICAS DE 7-(6-(2-HIDROXIPROPAN-2-IL)PIRIDIN-3-IL)-1-((TRANS)-4-METOXICICLOHEXIL)-3,4-DIHIDROPIRAZINO[2,3-B]PIRAZIN-2(1H)-ONA, UNA FORMA SÓLIDA DE LAS MISMAS Y MÉTODOS DE SU USO".

El problema planteado en esta solicitud consiste en la necesidad de identificar los posibles polimorfos del compuesto 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona.

Para resolver este problema técnico la solicitud en estudio proporciona una composición farmacéutica que comprende 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona y la forma A de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/4985; A61K9/00; A61K9/20; A61K9/28; A61P35/00; C07D487/04.

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 23 a 26 no es patentable de acuerdo con el Art citado.

5. De la solicitud de patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 carece de concisión y sustento descriptivo debido a que abarca agentes para los cuales no existe información en la descripción que evidencie una verdadera posesión por parte de la solicitante. Esto se debe al uso de las siguientes expresiones: "una sal", "isotopólogo", "metabolito" o "forma sólida". Las expresiones son generales y abarcan un número indeterminado de compuestos, la descripción no enseña la manera de obtener todos estos agentes, no divulga sus estructuras ni las características fisicoquímicas de los polimorfos. De igual forma, un metabolito es un producto que surge de un proceso biológico que se desarrolla luego de la ingesta de un agente y por lo tanto su obtención no obedece a un desarrollo inventivo ya que no se ha generado por efecto del investigador para resolver un problema técnico sino que obedece al efecto de las enzimas relacionadas con el metabolismo, por lo cual el metabolito no es patentable.

La reivindicación 1 reclama una composición pero no divulga los elementos técnicos esenciales que caracterizan este tipo de productos. Una composición debe caracterizarse por sus activos, sus excipientes y las proporciones de los mismos que permiten lograr el efecto técnico.

La expresión "una cantidad efectiva" no es aceptable ya que no limita el alcance de la solicitud. Se sugiere a la solicitante limitar la concentración con fundamento en la materia ejemplificada y ensayada.

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Las reivindicaciones 1, 16 y 27 reclaman una forma sólida del compuesto 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona y la forma A de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona, sin embargo no se realiza una caracterización adecuada de dichos sólidos. Esta Superintendencia aclara a la solicitante que una forma cristalina se puede definir apropiadamente en una reivindicación, por sus parámetros fisicoquímicos, tales como:

1. El patrón de difracción de Rayos X en mono cristal, que es específico de cada polimorfo, por lo cual, si la reivindicación caracteriza el polimorfo mediante este patrón, no se exigirá otro dato.
2. El patrón de difracción de Rayos X en polvo (DRXP), el cual debe presentar por lo menos 20 picos correspondientes a las intensidades de los haces difractados o a los espacios interplanares dhkl según los índices de Miller (hkl) medidos de acuerdo con el ángulo de difracción de Bragg 2θ en el intervalo más representativo comprendido entre 5° hasta 90°.
3. Las espectroscopías Raman e IR.
4. La espectroscopía RMN-C13
5. Los métodos de análisis térmico: TGA, DTA y DSC

La difracción de rayos X es la técnica más útil para el estudio de cristales en lo que atañe a la estructura cristalina, dado que los patrones de difracción de los diversos polimorfos presentan siempre notables diferencias, por lo que deben incluir los picos de intensidad más representativa para el caso del cristal reivindicado. En consecuencia se recomienda al solicitante hacer una correcta caracterización del cristal desde la reivindicación independiente.

Las reivindicación 28 caracteriza una forma sólida del compuesto 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona y la forma A de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona, mediante 4 picos de difracción de rayos X. Esta caracterización es inapropiada ya que como se indicó anteriormente, la solicitante debe caracterizar cada polimorfo por sus propiedades fisicoquímicas, siendo la más aceptada el espectro de difracción de rayos X, y para cada cristal se debe presentar los picos de mayor intensidad, los cuales se consideran los más representativos. Es pertinente señalar que menos de diez picos del espectro de difracción de rayos X son insuficientes para caracterizar de manera inequívoca un sólido cristalino de un compuesto dado. Esto es evidenciado por Bhattacharya[1] que provee un gráfico comparativo (fig. 11) mediante el cual superpone los difractogramas XRPD de dos polimorfos de ibandronato sódico. A través de esto Bhattacharya *et al.,* demuestran que diferentes polimorfos de un compuesto dado pueden compartir incluso tres picos principales de XRPD. De acuerdo con Bhattacharya, alrededor de diez de los picos más fuertes del XRPD junto con sus tolerancias son necesarios para identificar una forma cristalina única.

La expresión “alrededor de” utilizada en el pliego reivindicatorio es ambigua y no limita el alcance de la solicitud. Se le sugiere a la solicitante limitar la reclamación a rangos definidos que sean una solución al problema técnico.

Las reivindicaciones 8, 9, 12 y 13 utilizan los nombres AVICEL PH 102® y AC-DI-SOL ®, la mención de marcas registradas no es aceptada debido a que los componentes de una formulación deben definirse mediante sus nombres químico o DCI.

1. H.G. Brittain. “Polymorphism in Pharmaceutical Solids”. Segunda Edición, Informa Healthcare,NY, 2009. Págs. 334 y 335.

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La reivindicación 21 indica que la composición esta revestida de película, sin embargo no se describe la composición de dicha película, por lo cual la reivindicación carece de concisión y sustento descriptivo.

La expresión "sustancialmente pura" es ambigua y no limita el alcance de la solicitud. La pureza puede definirse mediante el porcentaje impurezas presentes.

6. Unidad de invención (Art 25 D 486)

La Solicitud no cumple con el Requisito de Unidad de Invención porque se refiere a 2 Grupos Inventivos.

Los Grupos Inventivos están definidos por las siguientes características **esenciales**:

1° Composiciones farmacéuticas que comprenden 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona y la forma A de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona, ácido esteárico y monohidrato de lactosa (Reiv. 1 a 15 y 17 a 22).
2° La forma sólida denominada "A" de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona y la forma A de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona y composiciones que la comprenden (Reiv. 16 y 27 a 32).

No se guarda un concepto común inventivo porque los polimorfos del agente 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino [2,3-6] pirazin-2(1H)-ona y la forma A de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-6]pirazin-2(1H)-ona poseen propiedades fisicoquímicas diferentes al compuesto base, de igual forma, la composición reclamada no requiere del polimorfo "A" como elemento esencial de la misma.

7. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: 2 de diciembre de 2011 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	US2010216781	"mTOR kinase inhibitors for oncology indications and diseases associated with the mTOR/PI3K/AKT pathway "	26/agosto/2010
D2	US2011137028	"Methods of synthesis and purification of heteroaryl compounds "	9/junio /2011
D3	Raymond C Rowe, Pharmaceutical press. 2009	Handbook of Pharmaceutical Excipients	2009

D1[2] divulga el compuesto 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona, sus isotopólogos,

2http://worldwide.espacenet.com/publicationDetails/biblio?CC=WO&NR=2007134876&KC=&FT=E&locale=en_EP

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sales y metabolitos y composiciones que lo comprenden (Ejemplo 9, C, Reiv. 48 y 49).

D2[3] enseña el compuesto 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona, sus isotopólogos, sales y metabolitos y composiciones que lo comprenden (Ejemplo 9, C, Reiv. 42). Igualmente, la anterioridad indica que el el sólido aislado fue combinado con hidroxi-tolueno butilaldehído (BHT) (Párr. 0545).

D3 divulga la utilidad del monohidrato de lactosa y del ácido esteárico como excipientes para la elaboración de formas farmacéuticas.

8. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

Grupo inventivo 2

La reivindicación 27 consiste en la forma sólida de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona, denominada forma “A”.

Características esenciales	D2
Reiv. 27: La forma A sólida de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona.	La forma sólida de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4- metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona. (Párr. 0545)

Las características esenciales de la forma sólida A de la reivindicación 27 habían sido divulgadas previamente en el documento D2, el cual enseña que el sólido obtenido con el proceso de síntesis es combinado con hidroxitolueno butilado (BHT), tal como lo indica la solcitante en la descripción, la forma A reclamada se obtiene mediante la mezcla de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona con BHT (Párr. 00172), en consecuencia, el sólido obtenido en D2 corresponde al sólido reclamado en la presente solicitud

En consecuencia, la reivindicación 27 carece de novedad, según lo divulgado en el documento D1.

Las reivindicaciones dependientes 28 a 32 y 16 no mencionan alguna característica que haga nueva la forma sólida de la reivindicación 27, por lo cual se considera que no son nuevas.

Nivel inventivo (Art18 D486)

Grupo inventivo 1:

La reivindicación 1 consiste una composición farmacéutica caracterizada porque comprende una cantidad de 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona, una sal isotopólogo, metabolito o forma sólida del mismo, junto con ácido esteárico y monohidrato de

3 http://worldwide.espacenet.com/publicationDetails/biblio?CC=WO&NR=2004089988&KC=&FT=E&locale=en_EP

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lactosa.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1	D3
Una composición farmacéutica caracterizada porque comprende:	Divulga composiciones que comprenden el compuesto 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona, una sal isotopólogo o metabolito.	Enseña el uso del ácido esteárico y del monohidrato de lactosa en la elaboración de preparaciones farmacéuticas. (Págs. 359 y 697)
7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona, una sal isotopólogo, metabolito o forma sólida del mismo,	7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona, una sal isotopólogo o metabolito.	
junto con ácido esteárico y monohidrato de lactosa.	Ácido esteárico y lactosa (Párrs 0461 y 0475)	

Los documentos D1 y D3 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque:

D1 enseña el compuesto 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona, una sal isotopólogo, metabolito y composiciones que lo comprenden (Ejemplo 9, C, Reiv. 48 y 49), la anterioridad indica que este agente puede estar formulado junto con excipientes como el ácido esteárico y la lactosa (Párrs 0461 y 0475). Las formulaciones divulgadas en D1 proveen medicamentos útiles para el tratamiento de enfermedades asociadas con Mtor/PI3K/AKT cinasa.

La diferencia entre la invención, definida en la reivindicación 1 y la composición de D1 consiste en que la anterioridad no divulga una composición específica que comprenda estos tres agentes.

Estas diferencias no parecen conceder un efecto técnico inesperado o una ventaja a la composición reclamada en esta solicitud porque no presentar una mayor afinidad como inhibidor de mTOR cinasa o una ventaja farmacocinética, según lo establecido en la descripción.

El problema técnico objetivo de esta solicitud consiste en la necesidad de composiciones del agente 7-(6-(2-hidroxipropan-2-il)piridin-3-il)-1-((trans)-4-metoxiciclohexil)-3,4-dihidropirazino[2,3-b]pirazin-2(1H)-ona alternativas a las ya conocidas en el documento D1.

Sin embargo, la utilización de monohidrato de lactosa en formulaciones farmacéuticas como aglutinante, diluyente o agente de relleno ya se había divulgado en D3 (Págs. 364 y 365). De igual forma, D3 indica que el ácido esteárico es un excipiente útil en la elaboración de tabletas como agente lubricante en una concentración entre el 1 a 3% (Pág. 697).

En consecuencia, la persona del oficio normalmente versada en la materia, seleccionaría excipientes como el monohidrato de lactosa y el ácido esteárico del documento D3 para obtener formulaciones alternativas a las descritas en el documento D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo

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cual se considera obvia.

De manera que la solución propuesta por esta solicitud en la reivindicación 1 y en las reivindicaciones dependientes 2 –15, 17-22 es obvia y no tiene nivel inventivo.

9. Conclusión

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

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US2010216781	1 a 15 y 17 a 22	Nivel inventivo
D2	US2011137028	16 y 27 a 32	Novedad
D3	Raymond C Rowe, Pharmaceutical press. 2009	1 a 15 y 17 a 22	Nivel inventivo

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En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente 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.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

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 2015-06-23

Elaboró: Emilse Cano Urrego
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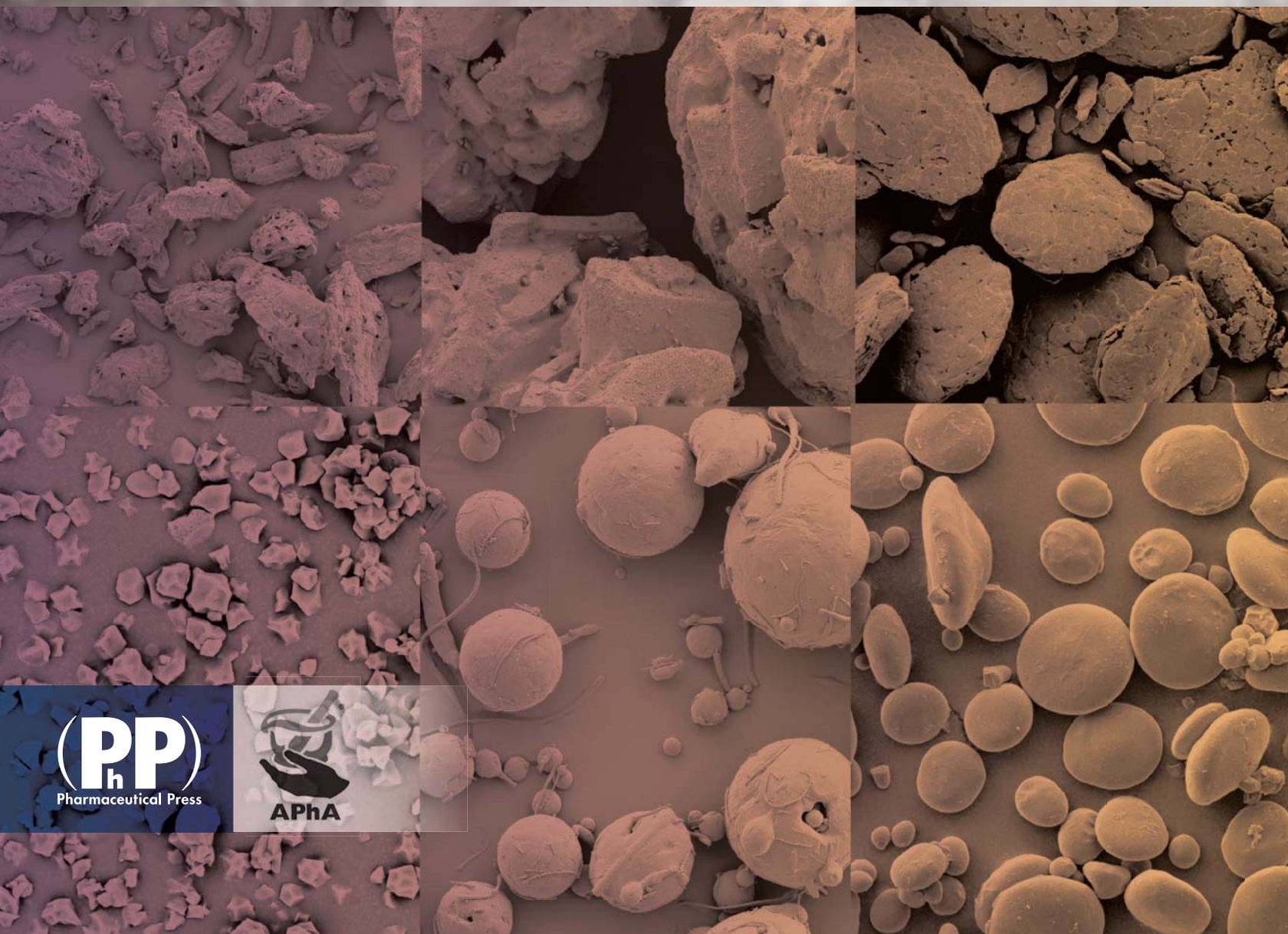
Handbook of Pharmaceutical Excipients

Sixth edition

Edited by
Raymond C Rowe, Paul J Sheskey and Marian E Quinn



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APhA

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Preface

Pharmaceutical dosage forms contain both pharmacologically active compounds and excipients added to aid the formulation and manufacture of the subsequent dosage form for administration to patients. Indeed, the properties of the final dosage form (i.e. its bioavailability and stability) are, for the most part, highly dependent on the excipients chosen, their concentration and interaction with both the active compound and each other. No longer can excipients be regarded simply as inert or inactive ingredients, and a detailed knowledge not only of the physical and chemical properties but also of the safety, handling and regulatory status of these materials is essential for formulators throughout the world. In addition, the growth of novel forms of delivery has resulted in an increase in the number of the excipients being used and suppliers of excipients have developed novel coprocessed excipient mixtures and new physical forms to improve their properties. The *Handbook of Pharmaceutical Excipients* has been conceived as a systematic, comprehensive resource of information on all of these topics.

The first edition of the *Handbook* was published in 1986 and contained 145 monographs. This was followed by the second edition in 1994 containing 203 monographs, the third edition in 2000 containing 210 monographs and the fourth edition in 2003 containing 249 monographs. Since 2000, the data has also been available on CD-ROM, updated annually, and from 2004 online. The fifth edition with its companion CD-ROM, *Pharmaceutical Excipients 5*, contained 300 monographs and was published in 2006. This new edition contains 340 excipient monographs with a new text design and enhanced online features, compiled by over 140 experts in pharmaceutical formulation or excipient manufacture from Australia, Europe, India, Japan, and the USA. All the monographs have been reviewed and revised in the light of current knowledge. There has been a greater emphasis on including published data from primary sources although some data from laboratory projects included in previous editions have been retained where relevant. Variations in test methodology can have significant effects on the data generated (especially in the case of the compactability of an excipient), and thus cause confusion. As a consequence, the editors have been more selective in including data relating to the physical properties of an excipient. However, comparative data that show differences between either source or batch of a specific excipient have been retained as this was considered relevant to the behavior of a material in practice. Over the past few years, there has been an increased emphasis on the harmonization of excipients. For information on the current status for each excipient selected for harmonization, the reader is directed to the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website (http://www.edqm.eu), and also the General Information Chapter 8 in the JP XV. The Suppliers Directory (Appendix I) has also been completely updated with many more international suppliers included.

In a systematic and uniform manner, the *Handbook of Pharmaceutical Excipients* collects essential data on the physical properties of excipients such as: boiling point, bulk and tap density, compression characteristics, hygroscopicity, flowability, melting point, moisture content, moisture-absorption isotherms, particle size distribution, rheology, specific surface area, and solubility. Scanning electron microphotographs (SEMs) are also included for many of the excipients. This edition contains over 130 near-infrared (NIR) spectra specifically generated for the *Handbook*. The *Handbook* contains information from various international sources and personal observation and comments from monograph authors, steering committee members, and the editors.

All of the monographs in the *Handbook* are thoroughly cross-referenced and indexed so that excipients may be identified by either a chemical, a nonproprietary, or a trade name. Most monographs list related substances to help the formulator to develop a list of possible materials for use in a new dosage form or product. Related substances are not directly substitutable for each other but, in general, they are excipients that have been used for similar purposes in various dosage forms.

The *Handbook of Pharmaceutical Excipients* is a comprehensive, uniform guide to the uses, properties, and safety of pharmaceutical excipients, and is an essential reference source for those involved in the development, production, control, or regulation of pharmaceutical preparations. Since many pharmaceutical excipients are also used in other applications, the *Handbook of Pharmaceutical Excipients* will also be of value to persons with an interest in the formulation or production of confectionery, cosmetics, and food products.

Arrangement

The information consists of monographs that are divided into 22 sections to enable the reader to find the information of interest easily. Although it was originally intended that each monograph contain only information about a single excipient, it rapidly became clear that some substances or groups of substances should be discussed together. This gave rise to such monographs as 'Coloring Agents' and 'Hydrocarbons'. In addition, some materials have more than one monograph depending on the physical characteristics of the material, e.g. Starch versus Pregelatinized Starch. Regardless of the complexity of the monograph they are all divided into 22 sections as follows:

1 Nonproprietary Names
2 Synonyms
3 Chemical Name and CAS Registry Number
4 Empirical Formula and Molecular Weight
5 Structural Formula
6 Functional Category
7 Applications in Pharmaceutical Formulation or Technology
8 Description
9 Pharmacopeial Specifications
10 Typical Properties
11 Stability and Storage Conditions
12 Incompatibilities
13 Method of Manufacture
14 Safety
15 Handling Precautions
16 Regulatory Status
17 Related Substances
18 Comments
19 Specific References
20 General References
21 Authors
22 Date of Revision

Descriptions of the sections appear below with information from an example monograph if needed.

Section 1, Nonproprietary Names, Lists the excipient names used in the current British Pharmacopoeia, European Pharmacopeia, Japanese Pharmacopeia, and the United States Pharmacopeia/National Formulary.

Section 2, Synonyms, Lists other names for the excipient, including trade names used by suppliers (shown in italics). The inclusion of one supplier's trade name and the absence of others should in no way be interpreted as an endorsement of one supplier's product over the other. The large number of suppliers internationally makes it impossible to include all the trade names.

Section 3, Chemical Name and CAS Registry Number, Indicates the unique Chemical Abstract Services number for an excipient along with the chemical name, e.g., Acacia [9000-01-5].

Sections 4 and 5, Empirical Formula and Molecular Weight and Structural Formula, Are self-explanatory. Many excipients are not pure chemical substances, in which case their composition is described either here or in Section 8.

Section 6, Functional Category, Lists the function(s) that an excipient is generally thought to perform, e.g., diluent, emulsifying agent, etc.

Section 7, Applications in Pharmaceutical Formulation or Technology, Describes the various applications of the excipient.

Section 8, Description, Includes details of the physical appearance of the excipient, e.g., white or yellow flakes, etc.

Section 9, Pharmacopeial Specifications, Briefly presents the compendial standards for the excipient. Information included is obtained from the British Pharmacopoeia (BP), European Pharmacopeia (PhEur), Japanese Pharmacopeia (JP), and the United States Pharmacopeia/National Formulary (USP/USP–NF). Information from the JP, USP and USP–NF are included if the substance is in those compendia. Information from the PhEur is also included. If the excipient is not in the PhEur but is included in the BP, information is included from the BP. Pharmacopeias are continually updated with most now being produced as annual editions. However, although efforts were made to include up-to-date information at the time of publication of this edition, the reader is advised to consult the most current pharmacopeias or supplements.

Section 10, Typical Properties, Describes the physical properties of the excipient which are not shown in Section 9. All data are for measurements made at 20°C unless otherwise indicated. Where the solubility of the excipient is described in words, the following terms describe the solubility ranges:

Very soluble	1 part in less than 1
Freely soluble	1 part in 1–10
Soluble	1 part in 10–30
Sparingly soluble	1 part in 30–100
Slightly soluble	1 part in 100–1000
Very slightly soluble	1 part in 1000–10 000
Practically insoluble or insoluble	1 part in more than 10 000

For this edition, near-infrared (NIR) reflectance spectra of samples as received (i.e. the samples were not dried or reduced in particle size) were measured using a FOSS NIRSystems 6500 spectrophotometer (FOSS NIRSystems Inc., Laurel, MD, USA) fitted with a Rapid Content Analyser against a ceramic standard supplied with the instrument. The instrument was controlled by Vision (version 2.22) software. Spectra were recorded over the wavelength range 1100–2498 nm (700 data points) and each saved spectrum was the average of 32 scans. Solid powdered samples were measured in glass vials of approximately 20 mm diameter. Each sample was measured in triplicate and the mean spectrum taken. When more than one batch of a material was available, the mean of all the batches is presented. Liquid samples were measured by transflectance using a gold reflector (2 × 0.5 mm optical path-length, FOSS) placed in a 45 mm silica reflectance cell against air as the reference. Spectra are presented as plots of (a) $\log(1/R)$ *vs* wavelength (dashed line, scale on right-hand side) and (b) second-derivative $\log(1/R)$ *vs* wavelength (solid line, scale on left-hand side). R is the reflectance and $\log(1/R)$ represents the apparent absorbance. Second-derivative spectra were calculated from the $\log(1/R)$ values using an 11 point Savitzky-Golay filter with second-order polynomial smoothing.

Note, peak positions and amplitudes in the second-derivative spectrum are very sensitive to the method used to calculate the second-derivative.

Where practical, data typical of the excipient or comparative data representative of different grades or sources of a material are included, the data being obtained from either the primary or the manufacturers' literature. In previous editions of the *Handbook* a laboratory project was undertaken to determine data for a variety of excipients and in some instances this data has been retained. For a description of the specific methods used to generate the data readers should consult the appropriate previous edition(s) of the *Handbook*.

Section 11, Stability and Storage Conditions, Describes the conditions under which the bulk material as received from the supplier should be stored. In addition some monographs report on storage and stability of the dosage forms that contain the excipient.

Section 12, Incompatibilities, Describes the reported incompatibilities for the excipient either with other excipients or with active ingredients. If an incompatibility is not listed it does not mean it does not occur but simply that it has not been reported or is not well known. Every formulation should be tested for incompatibilities prior to use in a commercial product.

Section 13, Method of Manufacture, Describes the common methods of manufacture and additional processes that are used to give the excipient its physical characteristics. In some cases the possibility of impurities will be indicated in the method of manufacture.

Section 14, Safety, Describes briefly the types of formulations in which the excipient has been used and presents relevant data concerning possible hazards and adverse reactions that have been reported. Relevant animal toxicity data are also shown.

Section 15, Handling Precautions, Indicates possible hazards associated with handling the excipient and makes recommendations for suitable containment and protection methods. A familiarity with current good laboratory practice (GLP) and current good manufacturing practice (GMP) and standard chemical handling procedures is assumed.

Section 16, Regulatory Status, Describes the accepted uses in foods and licensed pharmaceuticals where known. However, the status of excipients varies from one nation to another, and appropriate regulatory bodies should be consulted for guidance.

Section 17, Related Substances, Lists excipients similar to the excipient discussed in the monograph.

Section 18, Comments, Includes additional information and observations relevant to the excipient. Where appropriate, the different grades of the excipient available are discussed. Comments are the opinion of the listed author(s) unless referenced or indicated otherwise.

Section 19, Specific References, Is a list of references cited within the monograph.

Section 20, General References, Lists references which have general information about this type of excipient or the types of dosage forms made with these excipients.

Section 21, Authors, Lists the current authors of the monograph in alphabetical order. Authors of previous versions of the monograph are shown in previous printed editions of the text.

Section 22, Date of Revision, Indicates the date on which changes were last made to the text of the monograph.

Acknowledgments

A publication containing so much detail could not be produced without the help of a large number of pharmaceutical scientists based world-wide. The voluntary support of over 140 authors has been acknowledged as in previous editions, but the current editors would like to thank them all personally for their contribution. Grateful thanks also go to the members of the International Steering Committee who advised the editors and publishers on all aspects of the *Handbook* project.Many authors and Steering Committee members have been involved in previous editions of the *Handbook*. For others, this was their first edition although not, we hope, their last. We extend our thanks to all for their support. Thanks are also extended to Roger Jee, Kelly Palmer, and Tony Moffat at The School of Pharmacy, University of London for supplying the NIR spectra, to Pfizer PGRD, Sandwich, UK for supplying SEMs, and to excipient manufacturers and suppliers who provided helpful information on their products.

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Raymond C Rowe, Paul J Sheskey, Marian E Quinn
July 2009

Notice to Readers

The *Handbook of Pharmaceutical Excipients* is a reference work containing a compilation of information on the uses and properties of pharmaceutical excipients, and the reader is assumed to possess the necessary knowledge to interpret the information that the *Handbook* contains. The *Handbook of Pharmaceutical Excipients* has no official status and there is no intent, implied or otherwise, that any of the information presented should constitute standards for the substances. The inclusion of an excipient, or a description of its use in a particular application, is not intended as an endorsement of that excipient or application. Similarly, reports of incompatibilities or adverse reactions to an excipient, in a particular application, may not necessarily prevent its use in other applications. Formulators should perform suitable experimental studies to satisfy themselves and regulatory bodies that a formulation is efficacious and safe to use.

While considerable efforts were made to ensure the accuracy of the information presented in the *Handbook*, neither the publishers nor the compilers can accept liability for any errors or omissions. In particular, the inclusion of a supplier within the Suppliers Directory is not intended as an endorsement of that supplier or its products and, similarly, the unintentional omission of a supplier or product from the directory is not intended to reflect adversely on that supplier or its product.

Although diligent effort was made to use the most recent compendial information, compendia are frequently revised and the reader is urged to consult current compendia, or supplements, for up-to-date information, particularly as efforts are currently in progress to harmonize standards for excipients.

Data presented for a particular excipient may not be representative of other batches or samples.

Relevant data and constructive criticism are welcome and may be used to assist in the preparation of any future editions or electronic versions of the *Handbook*. The reader is asked to send any comments to the Editor, Handbook of Pharmaceutical Excipients, Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN, UK, or Editor, Handbook of Pharmaceutical Excipients, American Pharmacists Association, 2215 Constitution Avenue, NW, Washington, DC 20037-2985, USA.

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New Monographs

The following new monographs have been added to the *Handbook of Pharmaceutical Excipients*, 6th edition.

Adipic Acid
Ammonium Chloride
Butylene Glycol
Calcium Acetate
Calcium Chloride
Calcium Hydroxide
Calcium Lactate
Calcium Silicate
Cellulose, Microcrystalline and Carboxymethylcellulose Sodium
Ceresin
Coconut Oil
Corn Starch and Pregelatinized Starch
Glycine
Hydrophobic Colloidal Silica
Hydroxypropyl Betadex
Lactose, Inhalation
Lactose, Monohydrate and Corn Starch
Lactose, Monohydrate and Microcrystalline Cellulose
Lactose, Monohydrate and Povidone
Lactose, Monohydrate and Powdered Cellulose
Maleic Acid
Methionine
Myristyl Alcohol
Neotame
Pentetic Acid
Phospholipids
Poly(DL-Lactic Acid)
Polyoxylglycerides
Potassium Alum
Propylparaben Sodium
Safflower Oil
Sodium Carbonate
Sodium Formaldehyde Sulfoxylate
Sodium Thiosulfate
Sucrose Octaacetate
Sulfur Dioxide
Tagatose
Tricaprylin
Triolein
Vitamin E Polyethylene Glycol Succinate

Related Substances

Acetic acid *see* Acetic Acid, Glacial
Activated attapulgite *see* Attapulgite
Aleuritic acid *see* Shellac
d-Alpha tocopherol *see* Alpha Tocopherol
d-Alpha tocopheryl acetate *see* Alpha Tocopherol
dl-Alpha tocopheryl acetate *see* Alpha Tocopherol
d-Alpha tocopheryl acid succinate *see* Alpha Tocopherol
dl-Alpha tocopheryl acid succinate *see* Alpha Tocopherol
Aluminum distearate *see* Aluminum Monostearate
Aluminum tristearate *see* Aluminum Monostearate
Anhydrous citric acid *see* Citric Acid Monohydrate
Anhydrous sodium citrate *see* Sodium Citrate Dihydrate
Anhydrous sodium propionate *see* Sodium Propionate
Aqueous shellac solution *see* Shellac
Artificial vinegar *see* Acetic Acid, Glacial
Aspartame acesulfame *see* Aspartame
Bacteriostatic water for injection *see* Water
Bentonite magma *see* Bentonite
Beta tocopherol *see* Alpha Tocopherol
Beta-carotene *see* Coloring Agents
n-Butyl lactate *see* Ethyl Lactate
Butylparaben sodium *see* Butylparaben
Calcium acetate monohydrate *see* Calcium Acetate
Calcium ascorbate *see* Sodium Ascorbate
Calcium cyclamate *see* Sodium Cyclamate
Calcium diorthosilicate *see* Calcium Silicate
Calcium polycarbophil *see* Polycarbophil
Calcium propionate *see* Sodium Propionate
Calcium sorbate *see* Sorbic Acid
Calcium sulfate hemihydrate *see* Calcium Sulfate
Calcium trisilicate *see* Calcium Silicate
Calcium trisodium pentetate *see* Pentetic Acid
Capric acid *see* Lauric Acid
Carbon dioxide-free water *see* Water
Cationic emulsifying wax *see* Wax, Nonionic Emulsifying
Ceratonia extract *see* Ceratonia
Cetylpyridinium bromide *see* Cetylpyridinium Chloride
Chlorhexidine acetate *see* Chlorhexidine
Chlorhexidine gluconate *see* Chlorhexidine
Chlorhexidine hydrochloride *see* Chlorhexidine
Chlorodifluoromethane *see* Chlorodifluoroethane (HCFC)
Chlorophenoxyethanol *see* Phenoxyethanol
Corn syrup solids *see* Maltodextrin
m-Cresol *see* Cresol
o-Cresol *see* Cresol
p-Cresol *see* Cresol
Crude olive-pomace oil *see* Olive Oil
Cyclamic acid *see* Sodium Cyclamate
De-aerated water *see* Water
Dehydrated alcohol *see* Alcohol
Delta tocopherol *see* Alpha Tocopherol
Denatured alcohol *see* Alcohol
Dextrose anhydrous *see* Dextrose
Diazolidinyl urea *see* Imidurea
Dibasic potassium phosphate *see* Sodium Phosphate, Dibasic
Diethylene glycol monopalmitostearate *see* Ethylene Glycol Stearates
Dilute acetic acid *see* Acetic Acid, Glacial
Dilute alcohol *see* Alcohol
Dilute ammonia solution *see* Ammonia Solution
Dilute hydrochloric acid *see* Hydrochloric Acid
Dilute phosphoric acid *see* Phosphoric Acid
Dilute sulfuric acid *see* Sulfuric Acid
Dimethyl-β-cyclodextrin *see* Cyclodextrins
Dioctyl phthalate *see* Dibutyl Phthalate
Dipotassium edetate *see* Edetic Acid
Docusate calcium *see* Docusate Sodium
Docusate potassium *see* Docusate Sodium
Dodecyl gallate *see* Propyl Gallate
Dodecyltrimethylammonium bromide *see* Cetrimide
Edetate calcium disodium *see* Edetic Acid
Eglumine *see* Meglumine
Ethyl gallate *see* Propyl Gallate
Ethyl linoleate *see* Linoleic Acid
Ethylene glycol monopalmitate *see* Ethylene Glycol Stearates
Ethylene glycol monostearate *see* Ethylene Glycol Stearates
Ethylparaben potassium *see* Ethylparaben
Ethylparaben sodium *see* Ethylparaben
Extra virgin olive oil *see* Olive Oil
Fine virgin olive oil *see* Olive Oil
Fuming sulfuric acid *see* Sulfuric Acid
Gamma tocopherol *see* Alpha Tocopherol
Glyceryl triisooctanoate *see* Tricaprylin
Glycine hydrochloride *see* Glycine
Hard water *see* Water
Hesperidin *see* Neohesperidin Dihydrochalcone
Hexadecyltrimethylammonium bromide *see* Cetrimide
High-fructose syrup *see* Fructose
Hyaluronic acid *see* Sodium Hyaluronate
Hydrogenated lanolin *see* Lanolin
Hydrogenated vegetable oil, type II *see* Vegetable Oil, Hydrogenated
2-Hydroxyethyl-β-cyclodextrin *see* Cyclodextrins
3-Hydroxypropyl-β-cyclodextrin *see* Hydroxypropyl Betadex
Indigo carmine *see* Coloring Agents
Invert sugar *see* Sucrose
Isotrehalose *see* Trehalose
Laccaic acid B *see* Shellac
Lampante virgin olive oil *see* Olive Oil
Lanolin alcohols ointment *see* Petrolatum and Lanolin Alcohols
DL-Leucine *see* Leucine
Liquefied phenol *see* Phenol
Liquid fructose *see* Fructose
Magnesium carbonate anhydrous *see* Magnesium Carbonate
Magnesium carbonate hydroxide *see* Magnesium Carbonate
Magnesium lauryl sulfate *see* Sodium Lauryl Sulfate
Magnesium metasilicate *see* Magnesium Silicate
Magnesium orthosilicate *see* Magnesium Silicate
Magnesium trisilicate anhydrous *see* Magnesium Trisilicate
D-Malic acid *see* Malic Acid
L-Malic acid *see* Malic Acid
d-Menthol *see* Menthol
l-Menthol *see* Menthol
D-Methionine *see* Methionine
DL-Methionine *see* Methionine
Methyl lactate *see* Ethyl Lactate
Methyl linoleate *see* Linoleic Acid
Methyl methacrylate *see* Polymethacrylates
Methyl oleate *see* Ethyl Oleate
Methylparaben potassium *see* Methylparaben
Methylparaben sodium *see* Methylparaben
N-Methylpyrrolidone *see* Pyrrolidone
Microcrystalline cellulose and carrageenan *see* Cellulose, Microcrystalline

Microcrystalline cellulose and guar gum *see* Cellulose, Microcrystalline
Microcrystalline cellulose spheres *see* Sugar Spheres
Modified lanolin *see* Lanolin
Monobasic potassium phosphate *see* Sodium Phosphate, Monobasic
Montmorillonite *see* Magnesium Aluminum Silicate
Neotrehalose *see* Trehalose
Normal magnesium carbonate *see* Magnesium Carbonate
NPTAB see Sugar Spheres
Octyl gallate *see* Propyl Gallate
Oleyl oleate *see* Oleyl Alcohol
Olive-pomace oil *see* Olive Oil
Palmitin *see* Palmitic Acid
Pentasodium pentetate *see* Pentetic Acid
Pharmaceutical glaze *see* Shellac
Phenoxypropanol *see* Phenoxyethanol
Polacrilin *see* Polacrilin Potassium
Poly(methyl methacrylate) *see* Polymethacrylates
Potassium bisulfite *see* Potassium Metabisulfite
Potassium myristate *see* Myristic Acid
Potassium propionate *see* Sodium Propionate
Powdered fructose *see* Fructose
Propan-1-ol *see* Isopropyl Alcohol
(*S*)-Propylene carbonate *see* Propylene Carbonate
Propylparaben potassium *see* Propylparaben
Purified bentonite *see* Bentonite
Purified stearic acid *see* Stearic Acid
Quaternium 18-hectorite *see* Hectorite
Rapeseed oil *see* Canola Oil
Refined almond oil *see* Almond Oil
Refined olive-pomace oil *see* Olive Oil
Saccharin ammonium *see* Saccharin
Saccharin calcium *see* Saccharin
Safflower glycerides *see* Safflower Oil
Self-emulsifying glyceryl monostearate *see* Glyceryl Monostearate
Sodium bisulfite *see* Sodium Metabisulfite
Sodium borate anhydrous *see* Sodium Borate
Sodium carbonate decahydrate *see* Sodium Carbonate
Sodium carbonate monohydrate *see* Sodium Carbonate
Sodium edetate *see* Edetic Acid
Sodium erythorbate *see* Erythorbic Acid
Sodium glycinate *see* Glycine
Sodium laurate *see* Lauric Acid
Sodium myristate *see* Myristic Acid
Sodium palmitate *see* Palmitic Acid
Sodium sorbate *see* Sorbic Acid
Sodium sulfite heptahydrate *see* Sodium Sulfite
Soft water *see* Water
Spermaceti wax *see* Wax, Cetyl Esters
Stearalkonium hectorite *see* Hectorite
Sterile water for inhalation *see* Water
Sterile water for injection *see* Water
Sterile water for irrigation *see* Water
Sugartab see Sugar, Compressible
Sunset yellow FCF *see* Coloring Agents
Synthetic paraffin *see* Paraffin
DL-Tagatose *see* Tagatose
L-Tagatose *see* Tagatose
Tartrazine *see* Coloring Agents
Theobroma oil *see* Suppository Bases, Hard Fat
Tocopherols excipient *see* Alpha Tocopherol
Tribasic sodium phosphate *see* Sodium Phosphate, Dibasic
Trimethyl-β-cyclodextrin *see* Cyclodextrins
Trimethyltetradecylammonium bromide *see* Cetrimide
Trisodium edetate *see* Edetic Acid
Virgin olive oil *see* Olive Oil
Water for injection *see* Water
White petrolatum *see* Petrolatum
Zinc formaldehyde sulfoxylate *see* Sodium Formaldehyde Sulfoxylate
Zinc propionate *see* Sodium Propionate
Zinc trisodium pentetate *see* Pentetic Acid

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Abbreviations

Some units, terms, and symbols are not included in this list as they are defined in the text. Common abbreviations have been omitted. The titles of journals are abbreviated according to the general style of the *Index Medicus*.

≈	approximately.
Ad	Addendum.
ADI	acceptable daily intake.
approx	approximately.
atm	atmosphere.
BAN	British Approved Name.
bp	boiling point.
BP	British Pharmacopoeia.
BS	British Standard (specification).
BSI	British Standards Institution.
cal	calorie(s).
CAS	Chemical Abstract Service.
CFC	chlorofluorocarbon.
cfu	colony-forming unit
cm	centimeter(s).
cm^2	square centimeter(s).
cm^3	cubic centimeter(s).
cmc	critical micelle concentration.
CNS	central nervous system.
cP	centipoise(s).
cSt	centistoke(s).
CTFA	Cosmetic, Toiletry, and Fragrance Association.
d	particle diameter (d_{10} at 10 percentile; d_{50} at 50 percentile; d_{90} at 90 percentile).
D&C	designation applied in USA to dyes permitted for use in drugs and cosmetics.
DoH	Department of Health (UK).
DSC	differential scanning calorimetry.
EC	European Community.
e.g.	*exemplit gratia*, 'for example'.
EINECS	European Inventory of Existing Commercial Chemical Substances.
et al	*et alii*, 'and others'.
EU	European Union.
FAO	Food and Agriculture Organization of the United Nations.
FAO/WHO	Food and Agriculture Organization of the United Nations *and the* World Health Organization.
FCC	Food Chemicals Codex.
FDA	Food and Drug Administration of the USA.
FD&C	designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.
FFBE	Flat face beveled edge.
g	gram(s).
GMP	Good Manufacturing Practice.
GRAS	generally recognized as safe by the Food and Drug Administration of the USA.
HC	hydrocarbon.
HCFC	hydrochlorofluorocarbon.
HFC	hydrofluorocarbon.
HIV	human immunodeficiency virus.
HLB	hydrophilic–lipophilic balance.
HSE	Health and Safety Executive (UK).
i.e.	*id est*, 'that is'.
IM	intramuscular.
INN	International Nonproprietary Name.
IP	intraperitoneal.
ISO	International Organization for Standardization.
IU	International Units.
IV	intravenous.
J	joule(s).
JP	Japanese Pharmacopeia.
JPE	Japanese Pharmaceutical Excipients
kcal	kilocalorie(s).
kg	kilogram(s).
kJ	kilojoule(s).
kPa	kilopascal(s).
L	liter(s).
LAL	*Limulus* amoebocyte lysate.
LC_{50}	a concentration in air lethal to 50% of the specified animals on inhalation.
LD_{50}	a dose lethal to 50% of the specified animals or microorganisms.
Ld_{Lo}	lowest lethal dose for the specified animals or microorganisms.
m	meter(s).
m^2	square meter(s).
m^3	cubic meter(s).
M	molar.
max	maximum.
MCA	Medicines Control Agency (UK).
mg	milligram(s).
MIC	minimum inhibitory concentration.
min	minute(s) *or* minimum.
mL	milliliter(s).
mm	millimeter(s).
mM	millimolar.
mm^2	square millimeter(s).
mm^3	cubic millimeter(s).
mmHg	millimeter(s) of mercury.
mmol	millimole(s).
mN	millinewton(s).
mol	mole(s).
mp	melting point.
mPa	millipascal(s).
MPa	megapascal(s).
μg	microgram(s).
μm	micrometer(s).
N	newton(s) *or* normal (concentration).
NIR	near-infrared.
nm	nanometer(s).
o/w	oil-in-water.
o/w/o	oil-in-water-in-oil.
Pa	pascal(s).
pH	the negative logarithm of the hydrogen ion concentration.
PhEur	European Pharmacopeia.
pK_a	the negative logarithm of the dissociation constant.
pph	parts per hundred.
ppm	parts per million.
psia	pounds per square inch absolute.
R	reflectance.
RDA	recommended dietary allowance (USA).
rpm	revolutions per minute.
s	second(s).
SC	subcutaneous.
SEM	scanning electron microscopy *or* scanning electron microphotograph.

SI	Statutory Instrument *or* Système International d'Unites (International System of Units).
TD_{Lo}	lowest toxic dose for the specified animals or microorganisms.
TPN	total parental nutrition.
TWA	time weighted average.
UK	United Kingdom.
US *or* USA	United States of America.
USAN	United States Adopted Name.
USP	The United States Pharmacopeia.
USP–NF	The United States Pharmacopeia National Formulary.
UV	ultraviolet.
v/v	volume in volume.
v/w	volume in weight.
WHO	World Health Organization.
w/o	water-in-oil.
w/o/w	water-in-oil-in-water.
w/v	weight in volume.
w/w	weight in weight.

Units of Measurement

The information below shows imperial to SI unit conversions for the units of measurement most commonly used in the *Handbook*. SI units are used throughout with, where appropriate, imperial units reported in parentheses.

Area

1 square inch (in^2) = 6.4516×10^{-4} square meter (m^2)
1 square foot (ft^2) = 9.29030×10^{-2} square meter (m^2)
1 square yard (yd^2) = 8.36127×10^{-1} square meter (m^2)

Density

1 pound per cubic foot (lb/ft^3) = 16.0185 kilograms per cubic meter (kg/m^3)

Energy

1 kilocalorie (kcal) = 4.1840×10^3 joules (J)

Force

1 dyne (dynes) = 1×10^{-5} newton (N)

Length

1 angstrom (Å) = 10^{-10} meter (m)
1 inch (in) = 2.54×10^{-2} meter (m)
1 foot (ft) = 3.048×10^{-1} meter (m)
1 yard (yd) = 9.144×10^{-1} meter (m)

Pressure

1 atmosphere (atm) = 0.101325 megapascal (MPa)
1 millimeter of mercury (mmHg) = 133.322 pascals (Pa)
1 pound per square inch (psi) = 6894.76 pascals (Pa)

Surface tension

1 dyne per centimeter (dyne/cm) = 1 millinewton per meter (mN/m)

Temperature

Celsius (°C) = (1.8 × °C) + 32 Fahrenheit (°F)
Fahrenheit (°F) = (0.556 × °F) –17.8 Celsius (°C)

Viscosity (dynamic)

1 centipoise (cP) = 1 millipascal second (mPa s)
1 poise (P) = 0.1 pascal second (Pa s)

Viscosity (kinematic)

1 centistoke (cSt) = 1 square millimeter per second (mm^2/s)

Volume

1 cubic inch (in^3) = 1.63871×10^{-5} cubic meter (m^3)
1 cubic foot (ft^3) = 2.83168×10^{-2} cubic meter (m^3)
1 cubic yard (yd^3) = 7.64555×10^{-1} cubic meter (m^3)
1 pint (UK) = 5.68261×10^{-4} cubic meter (m^3)
1 pint (US) = 4.73176×10^{-4} cubic meter (m^3)
1 gallon (UK) = 4.54609×10^{-3} cubic meter (m^3)
1 gallon (US) = 3.78541×10^{-3} cubic meter (m^3)

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21 Authors

S Edge, JS Kaerger, J Shur.

22 Date of Revision

27 February 2009.

L

Lactose, Monohydrate

1 Nonproprietary Names

BP: Lactose
PhEur: Lactose Monohydrate
JP: Lactose Hydrate
USP-NF: Lactose Monohydrate

2 Synonyms

CapsuLac; *GranuLac*; *Lactochem*; lactosum monohydricum; *Monohydrate*; *Pharmatose*; *PrismaLac*; *SacheLac*; *SorboLac*; *SpheroLac*; *SuperTab 30GR*; *Tablettose*.

For grades, *see* Tables II and III.

3 Chemical Name and CAS Registry Number

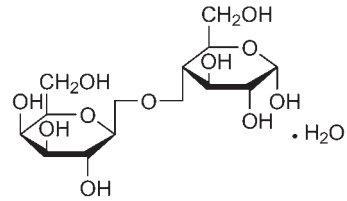
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [5989-81-1]; [10039-26-6]; [64044-51-5]

CAS Registry numbers for lactose monohydrate are [5989-81-1] (lactose monohydrate), [10039-26-6] (lactose monohydrate, cyclic), and [64044-51-5] (lactose monohydrate, open form).

4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}{\cdot}H_2O$ 360.31

5 Structural Formula



α-Lactose monohydrate

The USP32–NF27 describes lactose monohydrate as a natural disaccharide, obtained from milk, which consists of one galactose and one glucose moiety. The PhEur 6.5 and JP XV describe lactose monohydrate as the monohydrate of O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose. It is stated in the USP32–NF27 that lactose monohydrate may be modified as to its physical characteristics, and may contain varying proportions of amorphous lactose.

6 Functional Category

Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

7 Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler and diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas.[1–9] Lactose is also used as a diluent in dry-powder inhalation; *see*Lactose, Inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used.

Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1 : 3) to prepare sugar-coating solutions. It may also be used in intravenous injections.

Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions.

Direct-compression grades of lactose monohydrate are available as granulated/agglomerated α-lactose monohydrate, containing small amounts of anhydrous lactose.

Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation.

Other directly compressible lactoses are spray-dried lactose and anhydrous lactose; *see* Lactose, Spray-Dried and Lactose, Anhydrous.

8 Description

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous, and stable α-lactose anhydrous.

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

10 Typical Properties

Brittle fracture index

0.0749 (at compression pressure 189.5 MPa);
0.0883 (at compression pressure 191.0 MPa).[10]

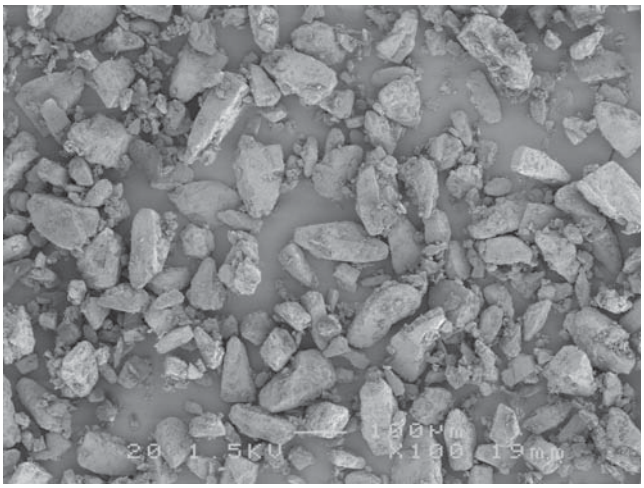
Bonding index

0.0081 (at compression pressure 189.5 MPa);
0.0052 (at compression pressure 191.0 MPa).[10]

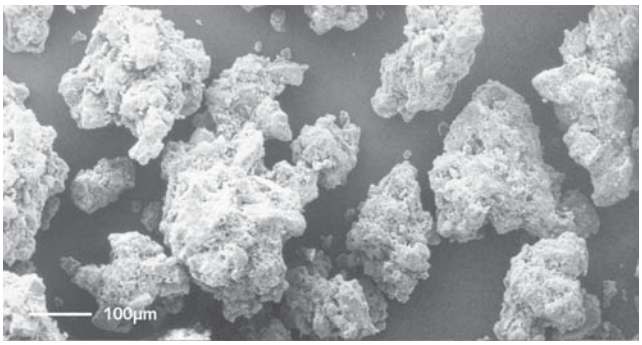
Density (true) 1.545 g/cm^3 (α-lactose monohydrate)

Density (bulk) *see* Table II.

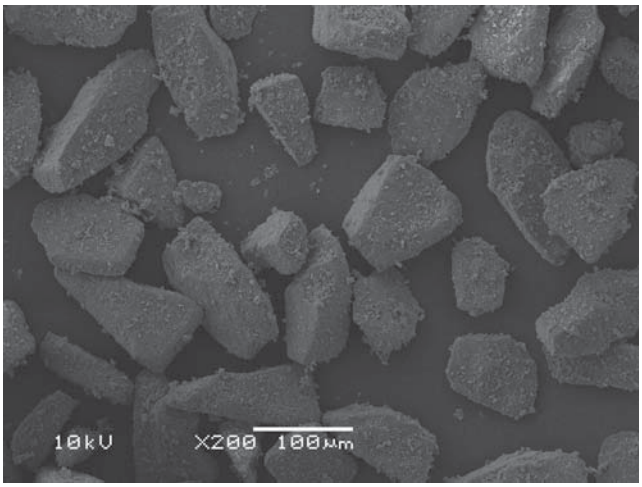
SEM 1: Excipient: *Pharmatose 125M*; manufacturer: DMV-Fonterra Excipients; magnification: 100×; voltage: 1.5 kV.



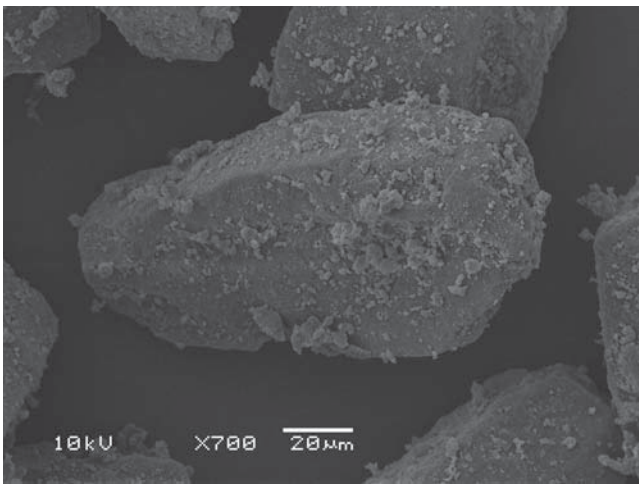
SEM 2: Excipient: *SuperTab 30GR*; manufacturer: DMV-Fonterra Excipients.



SEM 3: Excipient: *Lactochem Crystals*; manufacturer: Friesland Foods Domo; magnification: 200×; voltage: 10 kV.



SEM 4: Excipient: *Lactochem Crystals*; manufacturer: Friesland Foods Domo; magnification: 700×; voltage: 10 kV.



Density (tapped) *see* Table II.

Loss on drying Typically 0.2% for *Monohydrate 80M*, *Monohydrate Impalpable*; and 0.1–0.2% for Meggle products.

Melting point 201–202°C (for dehydrated α-lactose monohydrate)

Moisture content Lactose monohydrate contains approximately 5% w/w water of crystallization and normally has a range of 4.5–5.5% w/w water content. *See* Table II.

NIR spectra *see* Figure 1.

Table I: Pharmacopeial specifications for lactose, monohydrate.

Test	JP XV	PhEur 6.5	USP32–NF27
Identification	+	+	+
Characters	+	+	—
Appearance/color of solution	+	+	+
Acidity or alkalinity	+	+	+
Specific optical rotation	+54.4° to +55.9°	+54.4° to +55.9°	+54.4° to +55.9°
Protein and light-absorbing impurities/substances	+	—	+
Absorbance			
at 210–220 nm	⩽0.25	⩽0.25	⩽0.25
at 270–300 nm	⩽0.07	⩽0.07	⩽0.07
at 400 nm	⩽0.04	⩽0.04	⩽0.04
Heavy metals	⩽5 ppm	⩽5 ppm	⩽5 μg/g
Water	4.5–5.5%[a]	4.5–5.5%	4.5–5.5%
Sulfated ash	—	⩽0.1%	—
Residue on ignition	⩽0.1%	—	⩽0.1%
Loss on drying	⩽0.5%[b]	—	⩽0.5%[c]
Microbial limit			
Aerobic bacteria	⩽100 cfu/g	10^2 cfu/g	⩽100 cfu/g
Fungi and yeast	⩽50 cfu/g	—	⩽50 cfu/g
Absence of *Escherichia coli*	+	+	+
Absence of *Salmonella*	+	—	—

(a) 4.0–5.5% for granulated powder.
(b) For the granulated powder, not more than 1.0%.
(c) Modified monohydrate form, not more than 1.0%.

Particle size distribution *see* Table III.
Permanent deformation pressure

370.0 MPa (at compression pressure 189.5 MPa);

485.0 MPa (at compression pressure 191.0 MPa).[10]

Reduced modulus of elasticity

1472 (at compression pressure 189.5 MPa);

5155 (at compression pressure 191.0 MPa).[10]

Solubility *see* Table IV.
Specific rotation $[\alpha]_D^{20}$ = +54.4° to +55.9° as a 10% w/v solution. Lactose exhibits mutarotation, and an equilibrium mixture containing 62% β-lactose and 38% α-lactose is obtained instantly on the addition of a trace of ammonia.
Tensile strength 2.987 MPa (at compression pressure 189.5 MPa); 2.517 MPa (at compression pressure 191.0 MPa).[10]
Water content *see* Table II.

Methods for characterizing the mechanical properties of compacts of pharmaceutical ingredients are specified in the *Handbook of Pharmaceutical Excipients*, 3rd edn.[10]

Table IV: Solubility of lactose.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Ether	Practically insoluble
Water	1 in 5.24
	1 in 3.05 at 40°C
	1 in 2.30 at 50°C
	1 in 1.71 at 60°C
	1 in 0.96 at 80°C

11 Stability and Storage Conditions

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; *see* Section 12. The purities of different lactoses can vary and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also differ.

Solutions show mutarotation; *see* Section 10.

Lactose should be stored in a well-closed container in a cool, dry place.

Table II: Typical physical properties of selected commercially available lactose, monohydrate.

Supplier/grade	Density (bulk) (g/cm³)	Density (tapped) (g/cm³)	Water content (%)
DMV-Fonterra Excipients			
Pharmatose 50M	0.70	0.82	—
Pharmatose 60M	0.80	0.98	—
Pharmatose 70M	0.81	1.02	—
Pharmatose 80M	0.75	0.92	—
Pharmatose 90M	0.72	0.90	—
Pharmatose 100M	0.73	0.88	—
Pharmatose 110M	0.72	0.88	—
Pharmatose 125M	0.68	0.85	—
Pharmatose 130M	0.65	0.96	—
Pharmatose 150M	0.62	0.90	—
Pharmatose 200M	0.57	0.84	—
Pharmatose 350M	0.54	0.80	—
Pharmatose 450M	0.48	0.74	—
SuperTab 30GR	0.53	0.66	—
Friesland Foods Domo			
Lactochem Coarse Crystals	0.75	0.88	—
Lactochem Crystals	0.74	0.86	—
Lactochem Fine Crystals	0.73	0.85	—
Lactochem Extra Fine Crystals	0.73	0.86	—
Lactochem Coarse Powder	0.71	0.95	—
Lactochem Regular Powder	0.62	0.92	—
Lactochem Powder	0.64	0.89	—
Lactochem Fine Powder	0.61	0.84	—
Lactochem Extra Fine Powder	0.45	0.74	—
Lactochem Super Fine Powder	0.47	0.74	—
Meggle GmbH			
CapsuLac 60	0.59	0.70	5.2
GranuLac 70	0.72	0.90	5.2
GranuLac 140	0.66	0.89	5.2
GranuLac 200	0.54	0.80	5.2
GranuLac 230	0.47	0.76	5.2
PrismaLac 40	0.47	0.54	5.2
SacheLac 80	0.60	0.71	5.2
SorboLac 400	0.36	0.78	5.2
SpheroLac 100	0.69	0.84	5.2
Tablettose 70	0.51	0.62	5.2
Tablettose 80	0.57	0.72	5.2
Tablettose 100	0.54	0.74	5.2
Sheffield Pharma Ingredients			
Monohydrate 80M	0.66	0.92	4.8–5.2
Monohydrate Impalpable	0.53	0.81	4.8–5.2

12 Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products.[11] The Maillard interaction has also been shown to occur between lactose and secondary amine. However, the reaction sequence stops with the formation of the imine, and no yellow-brown coloration develops.[12]

Lactose is also incompatible with amino acids, amfetamines,[13] and lisinopril.[14]

13 Method of Manufacture

Lactose is a natural disaccharide consisting of galactose and glucose, and is present in the milk of most mammals. Commercially, lactose is produced from the whey of cows' milk; whey being the

Table III: Particle size distribution of selected commercially available lactose, monohydrate.

Supplier/grade	Typical particle size distribution (%)												
	<10 μm	<32 μm	<45 μm	<63 μm	<75 μm	<100 μm	<150 μm	<200 μm	<250 μm	<315 μm	<400 μm	<600 μm	<800 μm
DMV-Fonterra Excipients													
Pharmatose 50M	—	—	—	—	—	—	—	⩽20	—	—	⩾80	—	—
Pharmatose 60M	—	—	—	—	⩽5	—	10–20	—	40–65	—	—	⩾98	—
Pharmatose 70M	—	—	—	—	5–13	—	25–45	—	60–80	—	—	⩾98	—
Pharmatose 80M	—	—	—	—	—	⩽20	—	—	70–90	⩾95	—	—	—
Pharmatose 90M	—	—	—	⩽15	—	15–30	55–90	—	—	100	—	—	—
Pharmatose 100M	—	—	—	⩽15	—	—	60–80	—	⩾99	—	—	—	—
Pharmatose 110M	—	—	—	⩽20	—	30–60	75–90	—	—	100	—	—	—
Pharmatose 125M	—	—	⩽40	40–70	—	⩾90	⩾97	—	—	—	—	—	—
Pharmatose 130M	—	—	—	—	⩽50	—	—	80–90[a]	—	—	—	—	—
Pharmatose 150M	—	—	⩽50	—	—	⩾70	⩾85	—	—	100	—	—	—
Pharmatose 200M	—	—	50–65	—	—	⩾90	⩾96	—	⩾99	—	—	—	—
Pharmatose 350M	—	—	⩾60	—	—	⩾96	—	—	100	—	—	—	—
Pharmatose 450M	—	—	⩾90	⩾98	—	—	100	—	—	—	—	—	—
SuperTab 30GR	—	—	—	—	⩽30	—	40–70	—	—	⩾90[b]	—	100[c]	—
Friesland Foods Domo													
Lactochem Coarse Crystals	—	—	—	—	—	—	30–80	—	⩾65	—	⩾90[d]	—	—
Lactochem Crystals	—	—	—	—	5–30	—	55–95	—	⩾90	—	—	—	—
Lactochem Fine Crystals	—	—	—	—	⩽30	—	—	—	⩾90	—	—	—	—
Lactochem Extra Fine Crystals	—	—	—	—	10–45	—	—	—	⩾99	—	—	—	—
Lactochem Coarse Powder	—	—	—	—	15–50	—	⩾75	—	⩾98	—	—	—	—
Lactochem Regular Powder	—	—	20–42[e]	—	—	—	—	⩾95[f]	—	—	—	—	—
Lactochem Powder	—	—	—	—	65–80	⩾85[g]	⩾95	—	—	—	—	—	—
Lactochem Fine Powder	—	—	55–80[e]	—	⩾80	—	⩾98	—	—	—	—	—	—
Lactochem Extra Fine Powder	—	—	⩾90[e]	—	—	—	⩾99[h]	—	—	—	—	—	—
Lactochem Super Fine Powder	—	—	⩾95	—	—	—	—	—	—	—	—	—	—
Lactochem Microfine	90	—	—	—	—	—	—	—	—	—	—	—	—
Meggle GmbH													
CapsuLac 60	—	—	—	—	—	5	15	—	60	—	99	100[i]	—
GranuLac 70	—	—	—	—	—	50	—	—	—	—	99.5	100[i]	—
GranuLac 140	—	30	—	—	—	90	100	—	—	—	—	—	—
GranuLac 200	—	55	—	—	—	96	—	—	—	—	—	—	—
GranuLac 230	—	75	—	96	—	99.5	—	—	—	—	—	—	—
PrismaLac 40	—	—	—	—	—	—	—	4	—	—	—	85[i]	100
SacheLac 80	—	—	—	—	—	5	—	—	63	—	100	—	—
SorboLac 400	—	95	—	99.5	—	—	—	—	—	—	—	—	—
SpheroLac 100	—	—	—	9	—	—	78	98	99.5	—	—	—	—
Tablettose 70	—	—	—	1	—	—	25	56	—	—	97	100[c]	—
Tablettose 80	—	—	—	13	—	—	—	53[a]	—	—	93	100[i]	—
Tablettose 100	—	—	—	12	—	22	42	—	77	—	98	100[c]	—
Sheffield Pharma Ingredients)													
Monohydrate 80M	—	—	—	—	24–65	69–85[g]	—	⩾99[a]	—	—	—	—	—
Monohydrate Impalpable	—	—	64–80	—	⩾94	⩾99[g]	—	—	—	—	—	—	—

(a) <180 μm.
(b) <355 μm.
(c) <500 μm.
(d) <425 μm.
(e) <53 μm.
(f) <212 μm.
(g) <106 μm.
(h) ⩽125 μm.
(i) <630 μm.

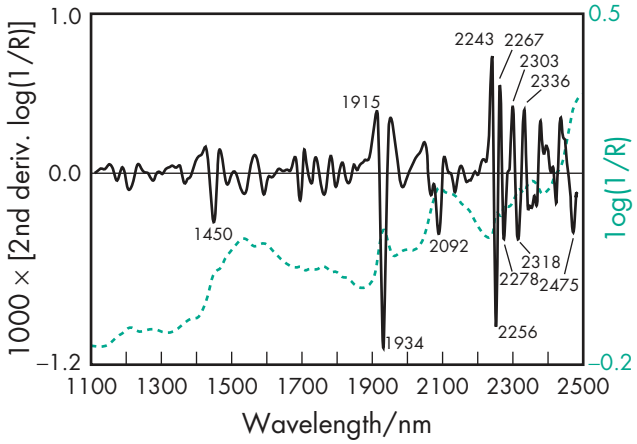


Figure 1: Near-infrared spectrum of lactose monohydrate measured by reflectance.

residual liquid of the milk following cheese and casein production. Cows' milk contains 4.4–5.2% lactose; lactose constitutes 38% of the total solid content of milk.

α-Lactose monohydrate is prepared by crystallization from supersaturated solutions below 93.5°C. Various crystalline shapes are prism, pyramidal, and tomahawk; these are dependent on the method of precipitation and crystallization. Direct compression grades of α-lactose monohydrate are prepared by granulation/agglomeration and spray-drying.

14 Safety

Lactose is widely used in pharmaceutical formulations as a filler and filler-binder in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely attributed to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase.[15–18] This results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence. In lactose-tolerant individuals, lactase hydrolyzes lactose in the small intestine to glucose and galactose, which are then absorbed. Lactase levels are normally high at birth, and levels decline rapidly in early childhood. Malabsorption of lactose (hypolactasia) may occur at an early age (4–8 years) and varies among different ethnic groups. Lactose is excreted unchanged when administered intravenously.

The symptoms of lactose intolerance are caused by the osmotic effect of the unabsorbed lactose, which increases water and sodium levels in the lumen. Unabsorbed lactose, upon reaching the colon, can be fermented by colonic flora, which produces gas, causing abdominal distension and discomfort. A lactose tolerance test has been developed based on the measurement of blood glucose level and the hydrogen level in the breath. However, its usefulness has been questioned as the test is based on a 50 g dose of lactose.

Approximately 10–20% of lactose-intolerant individuals, in two studies, showed clinical symptoms of intolerance after ingestion of 3–5 g of lactose.[15,16] In one of the studies,[15] 75% of the subjects had symptoms with 12 g of lactose (equivalent to 250 mL of milk). In another,[16] eight out of 13 individuals developed diarrhea after the administration of 20 g of lactose, and nine out of 13 after the administration of 25 g.

Lower doses of lactose produce fewer adverse effects, and lactose is better tolerated if taken with other foods. As a result, there is a significant population with lactose malabsorption who are still able to ingest normal amounts of lactose, such as that in milk, without the development of adverse side effects.[17]

Most adults consume about 25 g of lactose per day (500 mL of milk) without symptoms.[18,19] When symptoms appear, they are usually mild and dose-related. The dose of lactose in most pharmaceuticals seldom exceeds 2 g per day. It is unlikely that severe gastrointestinal symptoms can be attributed to the lactose in a conventional oral solid-dosage form, especially in adults who have not previously been diagnosed as severely lactose-intolerant. However, anecdotal reports of drug-induced diarrhea due to lactose intolerance have been made following administration of pharmaceutical preparations containing lactose.

It has also been suggested that lactose intolerance may have a role in irritable bowel syndrome, but this role is currently unclear.[20]

In the past, there have been concerns over the transmissible spongiform encephalopathies (TSE) contamination of animal-derived products. However, in the light of current scientific knowledge, and irrespective of geographical origin, milk and milk derivatives are reported as unlikely to present any risk of TSE contamination; TSE risk is negligible if the calf rennet is produced in accordance with regulations.[21]

LD_{50} (rat, IP): >10 g/kg
LD_{50} (rat, oral): >10 g/kg
LD_{50} (rat, SC): >5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive generation of dust, or inhalation of dust, should be avoided.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (IM, IV, and SC: powder for injections; oral: capsules and tablets; inhalation preparations; vaginal preparations). Included in non-parenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lactose, anhydrous; lactose, inhalation; lactose, monohydrate and corn starch; lactose, monohydrate and microcrystalline cellulose; lactose, monohydrate and povidone; lactose, monohydrate and powdered cellulose; lactose, spray-dried.

18 Comments

Lactose monohydrate is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter 1196 in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

A number of different grades of lactose are commercially available that vary in their physical properties, and many studies have been reported in the literature comparing the behavior of these various materials in different formulations.[5,8,9] A number of co-processed excipients which contain lactose are available for direct-compression applications: co-processed lactose and starch (*Starlac*, Meggle/Roquette Fréres),[22] lactose and microcrystalline cellulose (*Microcelac*, Meggle);[23] lactose and cellulose powder (*Cellactose*, Meggle),[24,25] lactose, povidone, and crospovidone (*Ludipress*, *Ludipress LCE*, BASF).[26]

Lactose may exhibit complex thermoanalytical transitions because of its several crystalline, as well as amorphous, forms. Differential scanning calorimetry (DSC) can be used effectively to characterize the composition.[27–29] For example, α-lactose becomes anhydrous at approximately 120°C. α-Lactose monohydrate may also contain a small quantity of the β-form.

A specification for lactose is included in the Food Chemicals Codex (FCC).[30]

The EINECS number for lactose is 200-559-2. The PubChem Compound ID (CID) for lactose monohydrate includes 62223 and 104938.

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21 Authors

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22 Date of Revision

10 March 2009.

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Stearic Acid

1 Nonproprietary Names

BP: Stearic Acid
JP: Stearic Acid
PhEur: Stearic Acid
USP-NF: Stearic Acid

2 Synonyms

Acidum stearicum; cetylacetic acid; *Crodacid*; *Cristal G*; *Cristal S*; *Dervacid*; E570; *Edenor*; *Emersol*; *Extra AS*; *Extra P*; *Extra S*; *Extra ST*; 1-heptadecanecarboxylic acid; *Hystrene*; *Industrene*; *Kortacid 1895*; *Pearl Steric*; *Pristerene*; stereophanic acid; *Tegostearic*.

3 Chemical Name and CAS Registry Number

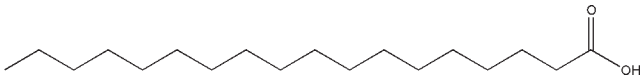
Octadecanoic acid [57-11-4]

4 Empirical Formula and Molecular Weight

$C_{18}H_{36}O_2$ 284.47 (for pure material)

The USP32–NF27 describes stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$). In the USP32–NF27, the content of stearic acid is not less than 40.0% and the sum of the two acids is not less than 90.0%. The USP32–NF27 also contains a monograph for purified stearic acid; *see* Section 17. The PhEur 6.5 contains a single monograph for stearic acid but defines stearic acid 50, stearic acid 70, and stearic acid 95 as containing specific amounts of stearic acid ($C_{18}H_{36}O_2$); *see* Section 9.

5 Structural Formula



6 Functional Category

Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant;[1–3] *see* Table I, although it may also be used as a binder[4] or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used in enteric tablet coatings and as a sustained-release drug carrier.[5]

In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams.[6,7] The partially neutralized stearic acid forms a creamy base when mixed with 5–15 times its own weight of aqueous liquid, the appearance and plasticity of the cream being determined by the proportion of alkali used.

Stearic acid is used as the hardening agent in glycerin suppositories.

Stearic acid is also widely used in cosmetics and food products.

Table I: Uses of stearic acid.

Use	Concentration (%)
Ointments and creams	1–20
Tablet lubricant	1–3

8 Description

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor (with an odor threshold of 20 ppm) and taste suggesting tallow.

See also Section 13.

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

10 Typical Properties

Acid value 195–212
Boiling point 383°C
Density (bulk) ≈0.537 g/cm^3
Density (tapped) 0.571 g/cm^3
Density (true) 0.980 g/cm^3
Flash point 113°C (closed cup)
Melting point 69–70°C
Moisture content Contains practically no water.
NIR spectra *see* Figure 1.
Partition coefficient Log (oil : water) = 8.2
Refractive index 1.43 at 80°C
Saponification value 200–220
Solubility Freely soluble in benzene, carbon tetrachloride, chloroform, and ether; soluble in ethanol (95%), hexane, and propylene glycol; practically insoluble in water.[8]
Specific surface area
0.51–0.53 m^2/g

SEM 1: Excipient: stearic acid, 95% (*Emersol 153*); manufacturer: Emery Industries; lot no.: 18895; magnification: 120×; voltage: 10 kV.

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SEM 2: Excipient: stearic acid, food grade (*Emersol 6332*); manufacturer: Emery Industries; lot no.: 18895; magnification: 120×; voltage: 10 kV.

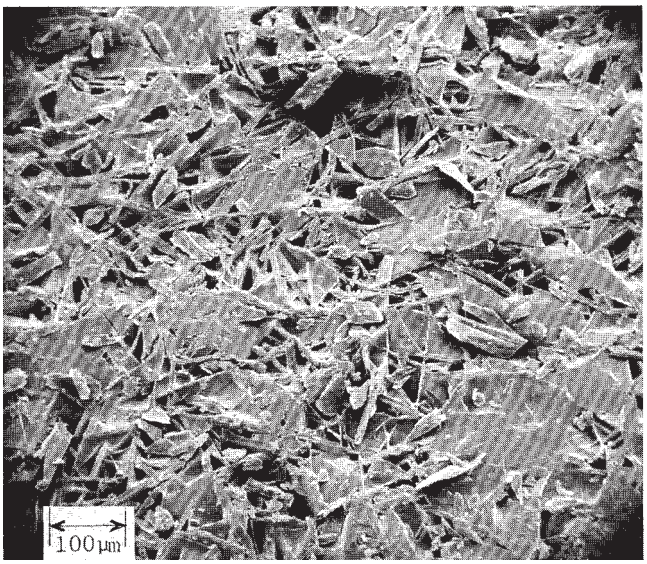

Table II: Pharmacopeial specifications for stearic acid.

Test	JP XV	PhEur 6.5	USP32–NF27
Identification	—	+	—
Characters	—	+	—
Acidity	—	+	—
Acid value	194–210	194–212	—
Appearance	—	+	—
Content of stearic acid	—	+	⩾40.0%
Stearic acid 50	—	40–60%	—
Stearic acid 70	—	60–80%	—
Stearic acid 95	—	⩾90.0%	—
Content of stearic and palmitic acids	—	+	⩾90.0%
Stearic acid 50	—	⩾90.0%	—
Stearic acid 70	—	⩾90.0%	—
Stearic acid 95	—	⩾96.0%	—
Congealing temperature	56.0–72.0°C	—	⩾54°C
Freezing point	—	+	—
Stearic acid 50	—	53–59°C	—
Stearic acid 70	—	57–64°C	—
Stearic acid 95	—	64–69°C	—
Iodine value	⩽4.0	+	⩽4.0
Stearic acid 50	—	⩽4.0%	—
Stearic acid 70	—	⩽4.0%	—
Stearic acid 95	—	⩽1.5%	—
Nickel	—	⩽1 ppm	—
Residue on ignition	⩽0.1%	—	⩽0.1%
Heavy metals	⩽20 ppm	—	⩽0.001%
Neutral fat or paraffin	+	—	+
Mineral acid	+	—	+

See also Section 17 and Table III.

11 Stability and Storage Conditions

Stearic acid is a stable material; an antioxidant may also be added to it; *see* Section 13. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Stearic acid is incompatible with most metal hydroxides and may be incompatible with bases, reducing agents, and oxidizing agents.

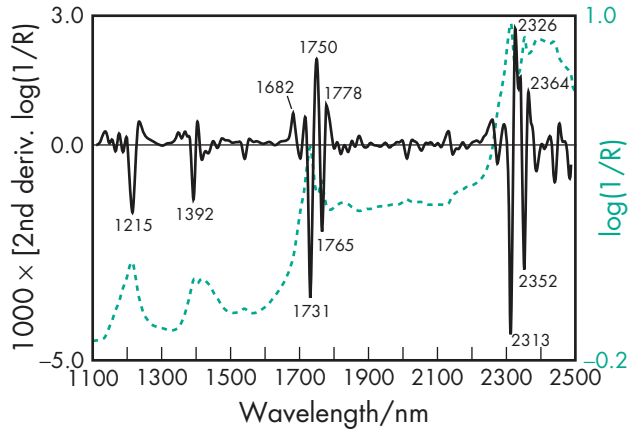

Figure 1: Near-infrared spectrum of stearic acid measured by reflectance.

Ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts.

A number of differential scanning calorimetry studies have investigated the compatibility of stearic acid with drugs. Although such laboratory studies have suggested incompatibilities, e.g. with naproxen,[9] they may not necessarily be applicable to formulated products.

Stearic acid has been reported to cause pitting in the film coating of tablets applied using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid.[10]

13 Method of Manufacture

Stearic acid is manufactured by hydrolysis of fat by continuous exposure to a countercurrent stream of high-temperature water and fat in a high-pressure chamber. The resultant mixture is purified by vacuum steam distillation and the distillates are then separated using selective solvents.

Stearic acid may also be manufactured by the hydrogenation of cottonseed and other vegetable oils; by the hydrogenation and subsequent saponification of olein followed by recrystallization from alcohol; and from edible fats and oils by boiling with sodium hydroxide, separating any glycerin, and decomposing the resulting soap with sulfuric or hydrochloric acid. The stearic acid is then subsequently separated from any oleic acid by cold expression.

Stearic acid is derived from edible fat sources unless it is intended for external use, in which case nonedible fat sources may be used. The USP32–NF27 states that stearic acid labeled solely for external use is exempt from the requirement that it be prepared from edible sources. Stearic acid may contain a suitable antioxidant such as 0.005% w/w butylated hydroxytoluene.

14 Safety

Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. Stearic acid is generally regarded as a nontoxic and nonirritant material. However, consumption of excessive amounts may be harmful.

LD_{50} (mouse, IV): 23 mg/kg[11]
LD_{50} (rat, IV): 21.5 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Stearic acid dust may be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and a dust respirator are recommended. Stearic acid is combustible.

Table III: Specifications of different stearic acid grades.

Product	Stearic acid content (%)	Melting range (°C)	Acid value	Iodine value	Saponification value	Unsaponifiable matter (%)
Hystrene 5016	44	54.5–56.5	206–210	⩽0.5	206–211	⩽0.2
Hystrene 7018	68.5	61.0–62.5	200–205	⩽0.5	200–206	⩽0.2
Hystrene 9718	90	66.5–68.0	196–201	⩽0.8	196–202	⩽0.3
Industrene 7018	65	58.0–62.0	200–207	⩽1.5	200–208	⩽0.5
Industrene 8718	87	64.5–67.5	196–201	⩽2.0	196–202	⩽1.5

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe (fatty acids). Included in the FDA Inactive Ingredients Database (sublingual tablets; oral capsules, solutions, suspensions, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium stearate; magnesium stearate; polyoxyethylene stearates; purified stearic acid; zinc stearate.

Purified stearic acid

Empirical formula $C_{18}H_{36}O_2$
Molecular weight 284.47
CAS number [57-11-4]
Synonyms Octadecanoic acid
Acid value 195–200
Boiling point 361°C
Density 0.847 g/cm^3 at 70°C
Flash point 196°C
Iodine number ⩽1.5
Melting point 66–69°C
Refractive index n_D^{80} = 1.4299
Solubility Soluble 1 in 5 parts benzene, 1 in 6 parts carbon tetrachloride, 1 in 2 parts chloroform, 1 in 15 parts ethanol, 1 in 3 parts ether; practically insoluble in water.
Vapor density (relative) 9.80 (air = 1)
Comments The USP32–NF27 describes purified stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$), which together constitute not less than 96.0% of the total content. The content of $C_{18}H_{36}O_2$ is no less than 90.0% of the total.

18 Comments

Stearic acid is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

A wide range of different grades of stearic acid are commercially available that have varying chemical compositions and hence different physical and chemical properties; *see* Table III.[12] Stearic acid is highly soluble in structurally diverse solvents. Stearic acid/solvent packing within a 24.8 ?^{3} cubic volume explains the stoichiometry of stearic acid solubility at multiple temperatures in multiple solvents.[13]

In one study the release of an active drug in a formulation containing stearic acid was independent of compression pressure in the range 1–7 tons; the particle size of the stearic acid did have a significant influence on the drug release.[14]

A potential application of stearic acid is in the preparation of 'cushioning pellets', composed of stearic acid : microcrystalline cellulose (4 : 1 w/w). The use of these pellets may avoid rupture of the coating of pellets during the compression step of manufacturing.[15]

A specification for stearic acid is contained in the Food Chemicals Codex (FCC).[16]

The EINECS number for stearic acid is 200-313-4.

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