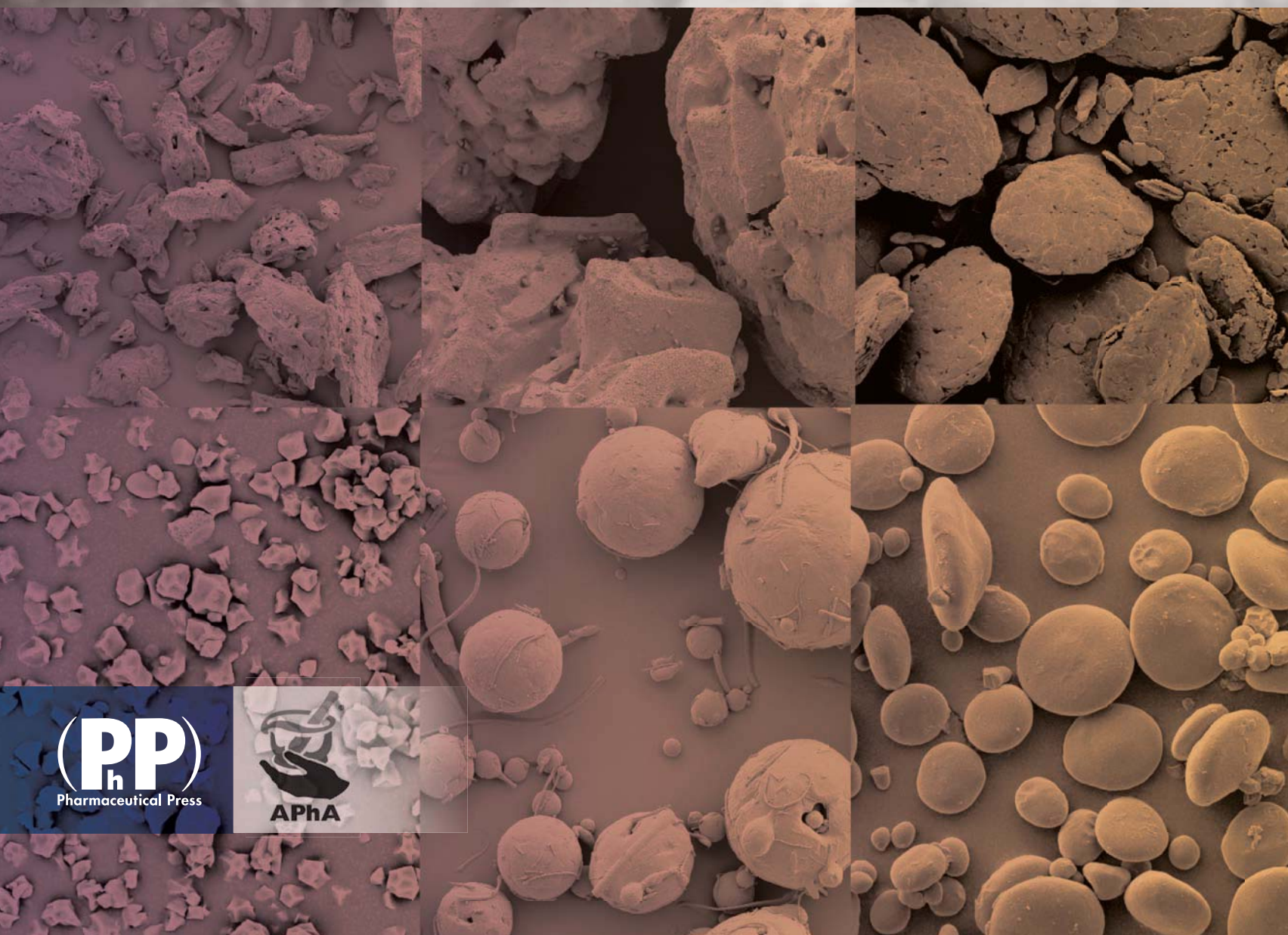


# Handbook of Pharmaceutical Excipients

Sixth edition

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



**(PP)**  
Pharmaceutical Press



# Handbook of Pharmaceutical Excipients

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SIXTH EDITION

*Edited by*

**Raymond C Rowe** BPharm, PhD, DSC, FRPharmS, FRSC, CPhys, MInstP

**Chief Scientist**

*Intelligensys Ltd, Stokesley, North Yorkshire, UK*

**Paul J Sheskey** BSc, RPh

**Application Development Leader**

*The Dow Chemical Company, Midland, MI, USA*

**Marian E Quinn** BSc, MSc

**Development Editor**

*Royal Pharmaceutical Society of Great Britain, London, UK*



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# Preface

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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 Pharmacopoeia, Japanese Pharmacopoeia, and the United States Pharmacopoeia/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 Pharmacopoeia (PhEur), Japanese Pharmacopoeia (JP), and the United States Pharmacopoeia/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 transmittance 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

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

## Notice to Readers

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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

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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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---

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**Gary Moss**  
University of Hertfordshire  
Hertfordshire, UK

**Marian E Quinn**  
Royal Pharmaceutical Society of Great Britain  
London, UK

**Raymond C Rowe**  
Intelligensys Ltd  
Stokesley, UK

**Niklas Sandler**  
University of Helsinki  
Helsinki, Finland

**Shirish A Shah**  
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Gifu, Japan

**Paul J Weller**  
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London, UK

# Editorial Staff

---

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# Contributors

---

**O AbuBaker**  
GlaxoSmithKline Inc  
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**KS Alexander**  
University of Toledo  
Toledo, OH, USA

**LV Allen Jr**  
International Journal of Pharmaceutical Compounding  
Edmond, OK, USA

**FA Alvarez-Nunez**  
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**GE Amidon**  
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**GP Andrews**  
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**NA Armstrong**  
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**TI Armstrong**  
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Havant, Hampshire, UK

**AC Bentham**  
Pfizer Global R&D  
Sandwich, Kent, UK

**M Bond**  
Danisco (UK) Ltd  
Redhill, Surrey, UK

**MC Bonner**  
University of Bradford  
Bradford, UK

**CG Cable**  
Royal Pharmaceutical Society of Great Britain  
Edinburgh, UK

**AM Campeta**  
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**WG Chambliss**  
University of Mississippi  
University, MS, USA

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**R Chen**  
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**JH Collett**  
University of Manchester  
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**W Cook**  
Pfizer Global R&D  
Kent, UK

**A Cram**  
Pfizer Global R&D  
Kent, UK

**TC Dahl**  
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**PD Daugherty**  
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**A Day**  
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**HJ de Jong**  
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**E Draganoiu**  
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**S Edge**  
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**C Egger**  
Rockwood Pigments  
Turin, Italy

**T Farrell**  
Colorcon Inc  
West Point, PA, USA

**RA Ferraina**  
Pfizer Global R&D  
Groton, CT, USA

**RT Forbes**  
University of Bradford  
Bradford, UK

**SO Freers**  
Grain Processing Corporation  
Muscatine, IA, USA

**B Fritzsching**  
BENEO-Palatinit GmbH  
Mannheim, Germany

**GP Frunzi**  
Time-Cap Labs Inc  
Farmingdale, NY, USA

**LY Galichet**  
London, UK

**PL Goggin**  
Pfizer Global R&D  
Kent, UK

**S Gold**  
AstraZeneca  
Macclesfield, Cheshire, UK

**SR Goskonda**  
Sunnyvale, CA, USA

**RT Guest**  
GlaxoSmithKline  
Ware, Hertfordshire, UK

**RT Gupta**  
SNDT Women's University  
Mumbai, India

**VK Gupta**  
Covidien  
Webster Groves, MO, USA

**A Guy**  
Balchem Encapsulates  
New Hampton, NY, USA

**S Haley**  
AstraZeneca  
Macclesfield, Cheshire, UK

**BC Hancock**  
Pfizer Inc  
Groton, CT, USA

**BA Hanson**  
Schering-Plough Research Institute  
Summit, NJ, USA

**KP Hapgood**  
Monash University  
Clayton, Victoria, Australia

**O Häusler**  
Roquette Europe  
Lestrem, France

**X He**  
GlaxoSmithKline  
Research Triangle Park, NC, USA

**SL Hem**  
Purdue University  
West Lafayette, IN, USA

**L Hendricks**  
Innophos Inc  
Cranbury, NJ, USA

**JC Hooton**  
AstraZeneca  
Macclesfield, Cheshire, UK

**P Hoppu**  
University of Helsinki  
Helsinki, Finland

**WL Hulse**  
University of Bradford  
Bradford, UK

**JT Irwin**  
Perrigo Company  
Allegan, MI, USA

**M Isreb**  
University of Bradford  
Bradford, UK

**H Ito**  
NOF Corporation  
Hyogo-ken, Japan

**BR Jasti**  
University of the Pacific  
Stockton, CA, USA

**BA Johnson**  
Pfizer Inc  
Groton, CT, USA

**DS Jones**  
The Queen's University Belfast  
Belfast, UK

**M Julien**  
Gattefosse SAS  
Saint-Priest, France

**MA Kabir**  
Schering-Plough Consumer Healthcare  
Memphis, TN, USA

**JS Kaerger**  
Aeropharm GmbH  
Rudolstadt, Germany

**AS Kearney**  
GlaxoSmithKline Inc  
King of Prussia, PA, USA

**VL Kett**  
The Queen's University of Belfast  
Belfast, UK

**AH Kibbe**  
Wilkes University School of Pharmacy  
Wilkes-Barre, PA, USA

**PB Klepak**  
Reheis Inc  
Berkeley Heights, NJ, USA

**DD Ladipo**  
Pfizer Global R&D  
Groton, CT, USA

**WJ Lambert**  
Pacira Pharmaceuticals Inc  
San Diego, CA, USA

**BA Langdon**

Pfizer Global R&D  
Groton, CT, USA

**D Law**

Abbott Laboratories  
North Chicago, IL, USA

**MG Lee**

MHRA  
London, UK

**CS Leopold**

University of Hamburg  
Hamburg, Germany

**X Li**

University of the Pacific  
Stockton, CA, USA

**EB Lindblad**

Brenntag Biosector  
Frederikssund, Denmark

**O Luhn**

BENEO-Palatinit GmbH  
Mannheim, Germany

**PE Luner**

Pfizer Inc  
Groton, CT, USA

**BR Matthews**

Alcon Laboratories (UK) Ltd  
Hertfordshire, UK

**JS Maximilien**

Pfizer Global R&D  
Kent, UK

**CP McCoy**

The Queen's University of Belfast  
Belfast, UK

**C Medina**

Amgen Inc  
Thousand Oaks, CA, USA

**R Milallos**

University of Toledo  
Toledo, OH, USA

**MA Mitchell**

Pfizer Inc  
St Louis, MO, USA

**RC Moreton**

FinnBrit Consulting  
Waltham, MA, USA

**GL Mosher**

Verrow Pharmaceuticals Inc  
Lenexa, KS, USA

**G Moss**

University of Hertfordshire  
Hertfordshire, UK

**C Mroz**

Colorcon Ltd  
Dartford, Kent, UK

**MP Mullarney**

Pfizer Inc  
Groton, CT, USA

**K Murakami**

Tomita Pharmaceutical Co Ltd  
Tokushima-ken, Japan

**S Murdande**

Pfizer Inc  
Groton, CT, USA

**BJ Murphy**

Pfizer Inc  
Groton, CT, USA

**RG Nause**

Pfizer Inc  
Groton, CT, USA

**S Nema**

Pfizer Global R&D  
Chesterfield, MO, USA

**S Obara**

Shin-Etsu Chemical Co. Ltd  
Niigata, Japan

**A Palmieri**

University of Florida  
Gainesville, FL, USA

**MA Pellett**

Wyeth Consumer Healthcare  
Havant, Hampshire, UK

**L Peltonen**

University of Helsinki  
Helsinki, Finland

**Y Peng**

AstraZeneca Pharmaceuticals  
Wilmington, DE, USA

**M Penning**

Mainz, Germany

**JD Pipkin**

CyDex Pharmaceuticals Inc  
Lenexa, KS, USA

**P Plumb**

AstraZeneca  
Macclesfield, Cheshire, UK

**F Podczeck**

Tyne and Wear, UK

**P Pople**

SNDT Women's University  
Mumbai, India

**W Qu**

University of Tennessee  
Memphis, TN, USA

**ME Quinn**  
Royal Pharmaceutical Society of Great Britain  
London, UK

**A Rajabi-Siahboomi**  
Colorcon Inc  
West Point, PA, USA

**RD Reddy**  
Pfizer Inc  
Groton, CT, USA

**JP Reo**  
Schering-Plough Consumer Healthcare  
Memphis, TN, USA

**MA Repka**  
University of Mississippi  
University, MS, USA

**B Richard**  
Pacira Pharmaceuticals Inc  
San Diego, CA, USA

**TL Rogers**  
The Dow Chemical Co  
Bomlitz, Germany

**RC Rowe**  
Intelligensys Ltd  
Stokesley, UK

**T Sakurai**  
Ueno Fine Chemicals Industry Ltd  
Osaka-shi, Japan

**N Sandler**  
University of Helsinki  
Helsinki, Finland

**B Sarsfield**  
Bristol-Myers Squibb  
New Brunswick, NJ, USA

**M Savolainen**  
University of Copenhagen  
Copenhagen, Denmark

**A Schoch**  
BENEO-Palatinit GmbH  
Mannheim, Germany

**DR Schoneker**  
Colorcon Inc  
West Point, PA, USA

**J Schrier**  
Pacira Pharmaceuticals Inc  
San Diego, CA, USA

**CJ Sciarra**  
Sciarra Laboratories  
Hicksville, NY, USA

**JJ Sciarra**  
Sciarra Laboratories  
Hicksville, NY, USA

**N Seido**  
Takasago International Corporation  
Tokyo, Japan

**HC Shah**  
SNDT Women's University  
Mumbai, India

**SA Shah**  
ICON Development Solutions  
Phoenix, AZ, USA

**U Shah**  
Solvay Pharmaceuticals Inc  
Marietta, GA, USA

**RM Shanker**  
Pfizer Inc  
Groton, CT, USA

**JJ Sheng**  
AstraZeneca  
Wilmington, DE, USA

**PJ Sheskey**  
The Dow Chemical Company  
Midland, MI, USA

**AJ Shukla**  
University of Tennessee  
Memphis, TN, USA

**J Shur**  
University of Bath  
Bath, UK

**D Simon**  
Roquette Frères  
Lestrem, France

**A Singh**  
University of Mississippi  
MS, USA

**KK Singh**  
SNDT Women's University  
Mumbai, India

**JLP Soh**  
Pfizer Global R&D  
Kent, UK

**RA Storey**  
AstraZeneca  
Macclesfield, Cheshire, UK

**C Sun**  
University of Minnesota College of Pharmacy  
Minneapolis, MN, USA

**AK Taylor**  
Baton Rouge  
LA, USA

**J Teckoe**  
Colorcon Ltd  
Dartford, Kent, UK

**MS Tesconi**  
Wyeth Research  
Pearl River, NY, USA

**D Thassu**  
UCB Pharma Inc  
Rochester, NY, USA

**F Tian**  
University of Copenhagen  
Copenhagen, Denmark

**S Tiwari**  
Colorcon Inc  
West Point, PA, USA

**N Trivedi**  
Covidien  
Webster Groves, MO, USA

**BF Truitt**  
Bilcare Inc  
Pheonixville, PA, USA

**CK Tye**  
Pfizer Inc  
Groton, CT, USA

**HM Unvala**  
Bayer Corp  
Myerstown, PA, USA

**D Wallick**  
The Dow Chemical Company  
Midland, MI, USA

**PJ Weller**  
Royal Pharmaceutical Society of Great Britain  
London, UK

**P Ying**  
Pacira Pharmaceuticals Inc  
San Diego, CA, USA

**PM Young**  
University of Sydney  
Sydney, NSW, Australia

**D Zhang**  
Merck Co Inc  
Rahway, NJ, USA

---

## About the Editors

---

### **Raymond C Rowe**

BPharm, PhD, DSC, FRPharmS, FRSC, CPhys, MInstP

Raymond Rowe has been involved in the *Handbook of Pharmaceutical Excipients* since the first edition was published in 1986, initially as an author then as a Steering Committee member. In addition to his position as Chief Scientist at Intelligensys, UK, he is also Professor of Industrial Pharmaceutics at the School of Pharmacy, University of Bradford, UK. He was formerly Senior Principal Scientist at AstraZeneca, UK. In 1998 he was awarded the Chiroscience Industrial Achievement Award, and in 1999 he was the British Pharmaceutical Conference Science Chairman. He has contributed to over 350 publications in the pharmaceutical sciences including a book and eight patents.

### **Paul J Sheskey**

BSc, RPh

Paul Sheskey has been involved in the *Handbook of Pharmaceutical Excipients* as an author and member of the Steering Committee since the third edition. He is an Application Development Leader in

the Dow-Wolff Cellulosics R&D Group at The Dow Chemical Company in Midland, Michigan, USA. Paul received his BSc degree in pharmacy from Ferris State University. Previously, he has worked as a research pharmacist in the area of solid dosage form development at the Perrigo Company and the Upjohn (Pfizer) Company. Paul has authored numerous journal articles in the area of pharmaceutical technology. He is a member of the AAPS and the Controlled Release Society.

### **Marian E Quinn**

BSc, MSc

Marian Quinn joined the publications department of the Royal Pharmaceutical Society of Great Britain in 2007 for the sixth edition of the *Handbook of Pharmaceutical Excipients*, having previously worked on the 34th and 35th editions of *Martindale: The Complete Drug Reference*. She has also previously worked at the National Institute for Medical Research, Blackwell Publishing, and Elsevier. Marian received her BSc (Hons) degree in microbiology from the University of Surrey, and her MSc in molecular genetics from the University of Leicester.

# New Monographs

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

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

# Related Substances

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

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

# Units of Measurement

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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<sup>2</sup>) =  $6.4516 \times 10^{-4}$  square meter (m<sup>2</sup>)  
1 square foot (ft<sup>2</sup>) =  $9.29030 \times 10^{-2}$  square meter (m<sup>2</sup>)  
1 square yard (yd<sup>2</sup>) =  $8.36127 \times 10^{-1}$  square meter (m<sup>2</sup>)

## Density

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

## Energy

1 kilocalorie (kcal) =  $4.1840 \times 10^3$  joules (J)

## Force

1 dyne (dynes) =  $1 \times 10^{-5}$  newton (N)

## Length

1 angstrom (Å) =  $10^{-10}$  meter (m)  
1 inch (in) =  $2.54 \times 10^{-2}$  meter (m)  
1 foot (ft) =  $3.048 \times 10^{-1}$  meter (m)  
1 yard (yd) =  $9.144 \times 10^{-1}$  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 × °F) + 32 Fahrenheit (°F)

Fahrenheit (°F) = (0.556 × °C) + 32 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<sup>2</sup>/s)

## Volume

1 cubic inch (in<sup>3</sup>) =  $1.63871 \times 10^{-5}$  cubic meter (m<sup>3</sup>)

1 cubic foot (ft<sup>3</sup>) =  $2.83168 \times 10^{-2}$  cubic meter (m<sup>3</sup>)

1 cubic yard (yd<sup>3</sup>) =  $7.64555 \times 10^{-1}$  cubic meter (m<sup>3</sup>)

1 pint (UK) =  $5.68261 \times 10^{-4}$  cubic meter (m<sup>3</sup>)

1 pint (US) =  $4.73176 \times 10^{-4}$  cubic meter (m<sup>3</sup>)

1 gallon (UK) =  $4.54609 \times 10^{-3}$  cubic meter (m<sup>3</sup>)

1 gallon (US) =  $3.78541 \times 10^{-3}$  cubic meter (m<sup>3</sup>)



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## 21 Authors

S Edge, JS Kaerger, J Shur.

## 22 Date of Revision

27 February 2009.

# 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

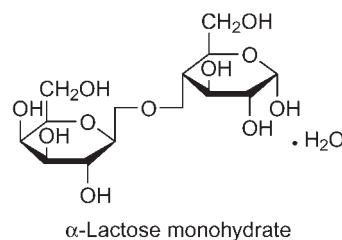
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [5989-81-1]; [10039-26-6]; [64044-51-5]

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<sub>12</sub>H<sub>22</sub>O<sub>11</sub>·H<sub>2</sub>O 360.31

## 5 Structural Formula



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.<sup>(1–9)</sup> 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  $\alpha$ -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.  $\alpha$ -lactose monohydrate,  $\beta$ -lactose anhydrous, and  $\alpha$ -lactose anhydrous. The stable crystalline forms of lactose are  $\alpha$ -lactose monohydrate,  $\beta$ -lactose anhydrous, and stable  $\alpha$ -lactose anhydrous.

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting;  $\alpha$ -lactose is approximately 20% as sweet as sucrose, while  $\beta$ -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).<sup>(10)</sup>

### Bonding index

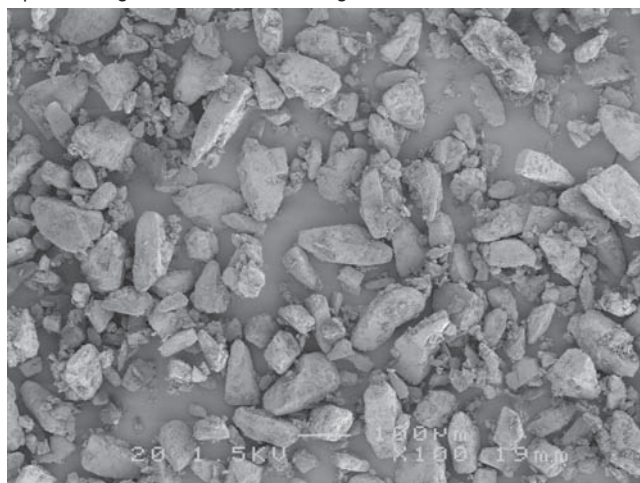
0.0081 (at compression pressure 189.5 MPa);

0.0052 (at compression pressure 191.0 MPa).<sup>(10)</sup>

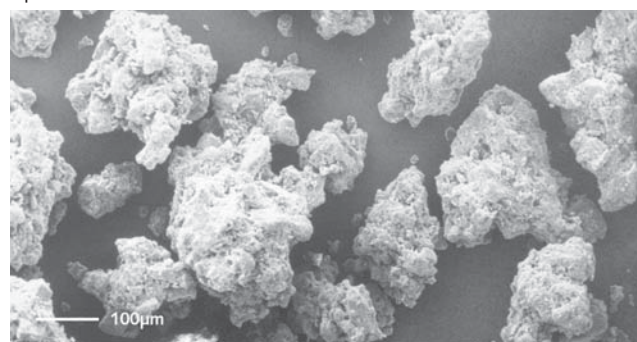
**Density (true)** 1.545 g/cm<sup>3</sup> ( $\alpha$ -lactose monohydrate)

**Density (bulk)** *see* Table II.

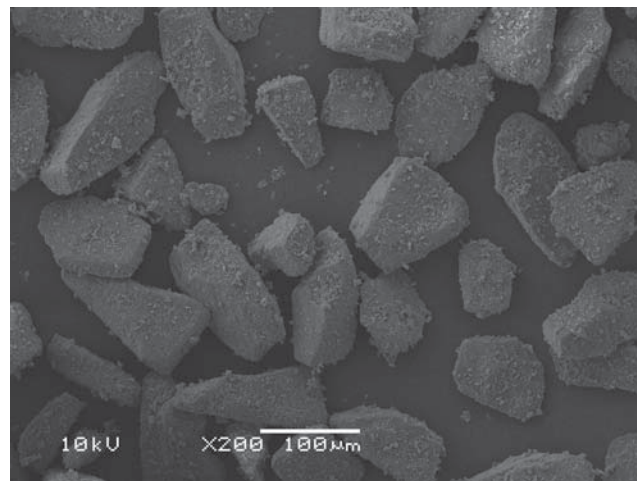
**SEM 1:** Excipient: *Pharmatose 125M*; manufacturer: DMV-Fonterra Excipients; magnification: 100 $\times$ ; voltage: 1.5 kV.



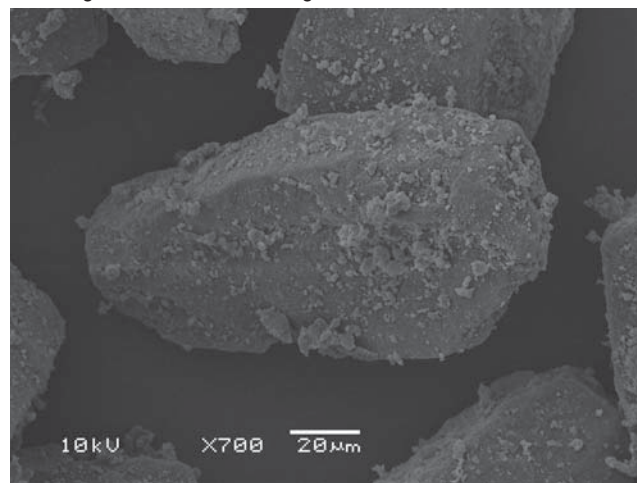
**SEM 2:** Excipient: *SuperTab 30GR*; manufacturer: DMV-Fonterra Excipients.



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



**SEM 4:** Excipient: *Lactochem Crystals*; manufacturer: Friesland Foods Domo; magnification: 700 $\times$ ; 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  $\alpha$ -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% <sup>(a)</sup> | 4.5–5.5%              | 4.5–5.5%             |
| Sulfated ash                                      | —                       | ≤0.1%                 | —                    |
| Residue on ignition                               | ≤0.1%                   | —                     | ≤0.1%                |
| Loss on drying                                    | ≤0.5% <sup>(b)</sup>    | —                     | ≤0.5% <sup>(c)</sup> |
| Microbial limit                                   |                         |                       |                      |
| Aerobic bacteria                                  | ≤100 cfu/g              | 10 <sup>2</sup> cfu/g | ≤100 cfu/g           |
| Fungi and yeast                                   | ≤50 cfu/g               | —                     | ≤50 cfu/g            |
| Absence of <i>Escherichia coli</i>                | +                       | +                     | +                    |
| Absence of <i>Salmonella</i>                      | +                       | —                     | —                    |

(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).<sup>(10)</sup>**Reduced modulus of elasticity**

1472 (at compression pressure 189.5 MPa);

5155 (at compression pressure 191.0 MPa).<sup>(10)</sup>**Solubility** see Table IV.**Specific rotation**  $[\alpha]_D^{20} = +54.4^\circ$  to  $+55.9^\circ$  as a 10% w/v solution.Lactose exhibits mutarotation, and an equilibrium mixture containing 62%  $\beta$ -lactose and 38%  $\alpha$ -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).<sup>(10)</sup>**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.<sup>(10)</sup>**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

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

| Supplier/grade                      | Density (bulk) (g/cm <sup>3</sup> ) | Density (tapped) (g/cm <sup>3</sup> ) | Water content (%) |
|-------------------------------------|-------------------------------------|---------------------------------------|-------------------|
| <b>DMV-Fonterra Excipients</b>      |                                     |                                       |                   |
| 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                                  | —                 |
| <b>Friesland Foods Domo</b>         |                                     |                                       |                   |
| 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                                  | —                 |
| <b>Meggles GmbH</b>                 |                                     |                                       |                   |
| 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               |
| Primalac 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               |
| <b>Sheffield Pharma Ingredients</b> |                                     |                                       |                   |
| Monohydrate 80M                     | 0.66                                | 0.92                                  | 4.8–5.2           |
| Monohydrate Impalpable              | 0.53                                | 0.81                                  | 4.8–5.2           |

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.

## 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.<sup>(11)</sup> 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.<sup>(12)</sup>

Lactose is also incompatible with amino acids, amfetamines,<sup>(13)</sup> and lisinopril.<sup>(14)</sup>

## 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 <sup>(a)</sup> | —       | —                  | —                  | —                  | —       |
| 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 <sup>(b)</sup> | —                  | 100 <sup>(c)</sup> | —       |
| Friesland Foods Domo          |                                        |        |                      |        |        |                      |                    |                      |         |                    |                    |                    |         |
| Lactochem Coarse Crystals     | —                                      | —      | —                    | —      | —      | —                    | 30–80              | —                    | ≥65     | —                  | ≥90 <sup>(d)</sup> | —                  | —       |
| 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 <sup>(e)</sup> | —      | —      | —                    | —                  | ≥95 <sup>(f)</sup>   | —       | —                  | —                  | —                  | —       |
| Lactochem Powder              | —                                      | —      | —                    | —      | 65–80  | ≥85 <sup>(g)</sup>   | ≥95                | —                    | —       | —                  | —                  | —                  | —       |
| Lactochem Fine Powder         | —                                      | —      | 55–80 <sup>(e)</sup> | —      | ≥80    | —                    | ≥98                | —                    | —       | —                  | —                  | —                  | —       |
| Lactochem Extra Fine Powder   | —                                      | —      | ≥90 <sup>(e)</sup>   | —      | —      | —                    | ≥99 <sup>(h)</sup> | —                    | —       | —                  | —                  | —                  | —       |
| Lactochem Super Fine Powder   | —                                      | —      | ≥95                  | —      | —      | —                    | —                  | —                    | —       | —                  | —                  | —                  | —       |
| Lactochem Microfine           | 90                                     | —      | —                    | —      | —      | —                    | —                  | —                    | —       | —                  | —                  | —                  | —       |
| Meggle GmbH                   |                                        |        |                      |        |        |                      |                    |                      |         |                    |                    |                    |         |
| CapsuLac 60                   | —                                      | —      | —                    | —      | —      | 5                    | 15                 | —                    | 60      | —                  | 99                 | 100 <sup>(i)</sup> | —       |
| GranuLac 70                   | —                                      | —      | —                    | —      | —      | 50                   | —                  | —                    | —       | —                  | 99.5               | 100 <sup>(i)</sup> | —       |
| GranuLac 140                  | —                                      | 30     | —                    | —      | —      | 90                   | 100                | —                    | —       | —                  | —                  | —                  | —       |
| GranuLac 200                  | —                                      | 55     | —                    | —      | —      | 96                   | —                  | —                    | —       | —                  | —                  | —                  | —       |
| GranuLac 230                  | —                                      | 75     | —                    | 96     | —      | 99.5                 | —                  | —                    | —       | —                  | —                  | —                  | —       |
| PrismaLac 40                  | —                                      | —      | —                    | —      | —      | —                    | —                  | 4                    | —       | —                  | —                  | 85 <sup>(j)</sup>  | 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 <sup>(c)</sup> | —       |
| Tablettose 80                 | —                                      | —      | —                    | 13     | —      | —                    | —                  | 53 <sup>(a)</sup>    | —       | —                  | 93                 | 100 <sup>(i)</sup> | —       |
| Tablettose 100                | —                                      | —      | —                    | 12     | —      | 22                   | 42                 | —                    | 77      | —                  | 98                 | 100 <sup>(c)</sup> | —       |
| Sheffield Pharma Ingredients) |                                        |        |                      |        |        |                      |                    |                      |         |                    |                    |                    |         |
| Monohydrate 80M               | —                                      | —      | —                    | —      | 24–65  | 69–85 <sup>(g)</sup> | —                  | ≥99 <sup>(a)</sup>   | —       | —                  | —                  | —                  | —       |
| Monohydrate Impalpable        | —                                      | —      | 64–80                | —      | ≥94    | ≥99 <sup>(g)</sup>   | —                  | —                    | —       | —                  | —                  | —                  | —       |

(a) &lt;180 µm.

(b) &lt;355 µm.

(c) &lt;500 µm.

(d) &lt;425 µm.

(e) &lt;53 µm.

(f) &lt;212 µm.

(g) &lt;106 µm.

(h) ≤125 µm.

(i) &lt;630 µm.

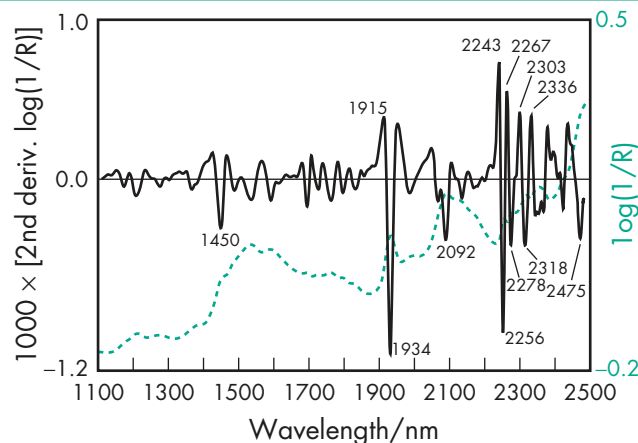


**Figure 1:** Near-infrared spectrum of lactose monohydrate measured by reflectance.

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.

$\alpha$ -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  $\alpha$ -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.<sup>(15–18)</sup> 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.<sup>(15,16)</sup> In one of the studies,<sup>(15)</sup> 75% of the subjects had symptoms with 12 g of lactose (equivalent to 250 mL of milk). In another,<sup>(16)</sup> 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.<sup>(17)</sup>

Most adults consume about 25 g of lactose per day (500 mL of milk) without symptoms.<sup>(18,19)</sup> 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.<sup>(20)</sup>

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.<sup>(21)</sup>

LD<sub>50</sub> (rat, IP): >10 g/kg

LD<sub>50</sub> (rat, oral): >10 g/kg

LD<sub>50</sub> (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.<sup>(5,8,9)</sup> A number of co-processed excipients which contain lactose are available for direct-compression applications: co-processed lactose and starch (*Starlac*, Meggle/Roquette Frères),<sup>(22)</sup> lactose and microcrystalline cellulose (*Microcelac*, Meggle);<sup>(23)</sup> lactose and cellulose powder (*Cellactose*, Meggle),<sup>(24,25)</sup> lactose, povidone, and crospovidone (*Ludipress*, *Ludipress LCE*, BASF).<sup>(26)</sup>

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.<sup>(27–29)</sup> For example,  $\alpha$ -lactose becomes anhydrous at approximately 120°C.  $\alpha$ -Lactose monohydrate may also contain a small quantity of the  $\beta$ -form.

A specification for lactose is included in the Food Chemicals Codex (FCC).<sup>(30)</sup>

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

S Edge, AH Kibbe, J Shur.

## 22 Date of Revision

10 March 2009.



# 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; *Tego-stearic*.

## 3 Chemical Name and CAS Registry Number

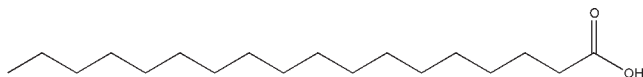
Octadecanoic acid [57-11-4]

## 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;<sup>(1–3)</sup> see Table I, although it may also be used as a binder<sup>(4)</sup> 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.<sup>(5)</sup>

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.<sup>(6,7)</sup> 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)*  $\approx 0.537 \text{ g/cm}^3$

*Density (tapped)*  $0.571 \text{ g/cm}^3$

*Density (true)*  $0.980 \text{ g/cm}^3$

*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

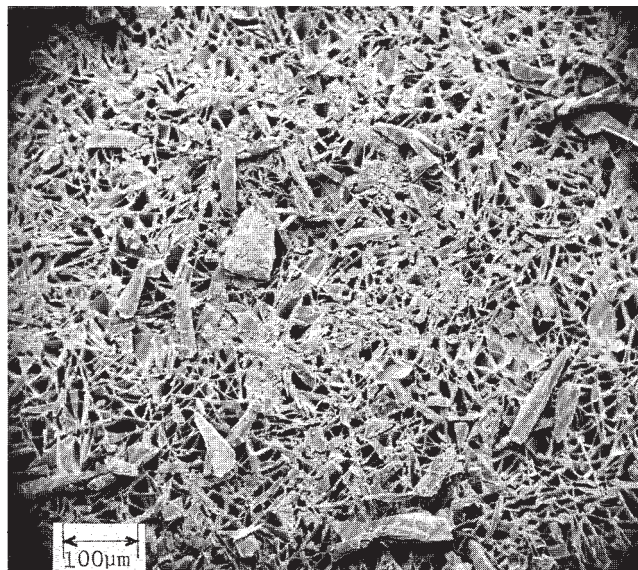
*Saponification value* 200–220

*Solubility* Freely soluble in benzene, carbon tetrachloride, chloroform, and ether; soluble in ethanol (95%), hexane, and propylene glycol; practically insoluble in water.<sup>(8)</sup>

*Specific surface area*

0.51–0.53 m<sup>2</sup>/g

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



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

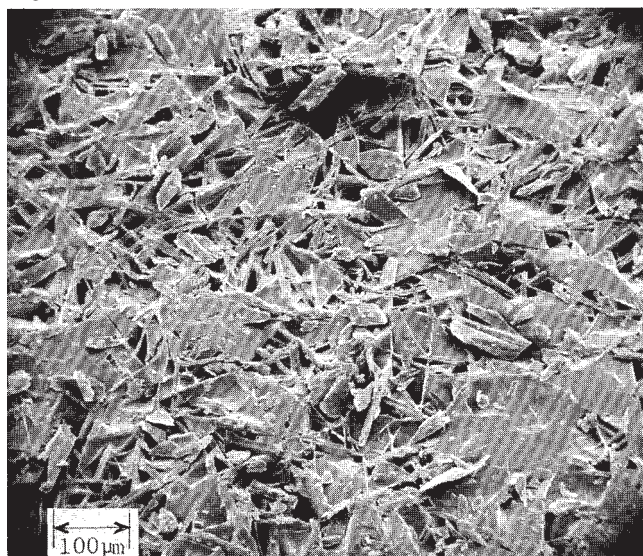


**Table II:** Pharmacopeial specifications for stearic acid.

| 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%    | —          |
| Congeeing 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.

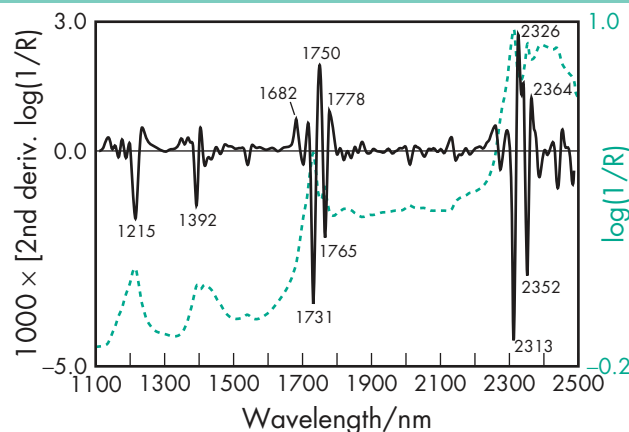


**Figure 1:** Near-infrared spectrum of stearic acid measured by reflectance.

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,<sup>(9)</sup> 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.<sup>(10)</sup>

## 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<sub>50</sub> (mouse, IV): 23 mg/kg<sup>(11)</sup>

LD<sub>50</sub> (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<sup>3</sup> at 70°C

**Flash point** 196°C

**Iodine number** ≤1.5

**Melting point** 66–69°C

**Refractive index**  $n_D^{20} = 1.4299$

**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.<sup>(12)</sup> Stearic acid is highly soluble in structurally diverse solvents. Stearic acid/solvent packing within a 24.8?<sup>3</sup> cubic volume explains the stoichiometry of stearic acid solubility at multiple temperatures in multiple solvents.<sup>(13)</sup>

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.<sup>(14)</sup>

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.<sup>(15)</sup>

A specification for stearic acid is contained in the Food Chemicals Codex (FCC).<sup>(16)</sup>

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

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## 21 Author

LV Allen Jr.

## 22 Date of Revision

25 February 2009.