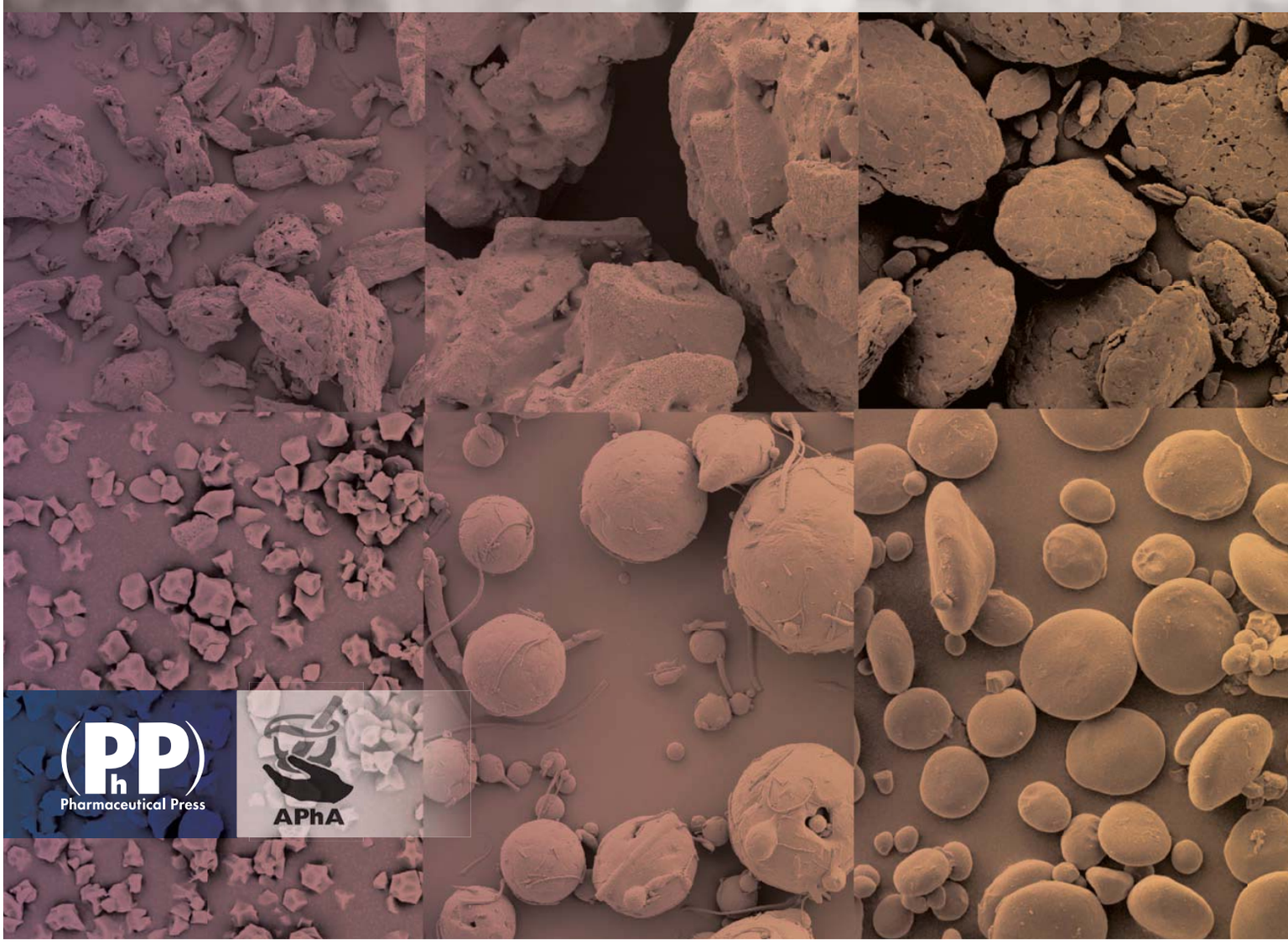
Handbook of Pharmaceutical Excipients

Sixth edition

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



Pharmaceutical Press
APhA

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SIXTH EDITION

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Preface

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

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

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

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

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

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Arrangement

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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.

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14 Safety

Hydrogenated castor oil is used in oral and topical pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

Acute oral toxicity studies in animals have shown that hydrogenated castor oil is a relatively nontoxic material. Irritation tests with rabbits show that hydrogenated castor oil causes mild, transient irritation to the eye.

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

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Accepted in the USA as an indirect food additive. Included in the FDA Inactive Ingredients Database (oral capsules, tablets, and sublingual tablets).

Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Castor oil; vegetable oil, hydrogenated.

18 Comments

Various different grades of hydrogenated castor oil are commercially available, the composition of which may vary considerably. *Sterotex K* (Karlshamns Lipid Specialities), for example, is a mixture of hydrogenated castor oil and hydrogenated cottonseed oil. *See* Vegetable Oil, hydrogenated for further information.

The EINECS number for hydrogenated castor oil is 232-292-2.

19 Specific References

1 Kline CH. Thixcin R-thixotrope. *Drug Cosmet Ind* 1964; **95**(6): 895–897.
2 Yonezawa Y *et al*. Release from or through a wax matrix system. III: Basic properties of release through the wax matrix layer. *Chem Pharm Bull (Tokyo)* 2002; **50**(6): 814–817.
3 Vergote GJ *et al*. An oral controlled release matrix pellet formulation containing microcrystalline ketoprofen. *Int J Pharm* 2002; **219**: 81–87.
4 Danish FQ, Parrott EL. Effect of concentration and size of lubricant on flow rate of granules. *J Pharm Sci* 1971; **60**: 752–754.
5 Hölzer AW, Sjögren J. Evaluation of some lubricants by the comparison of friction coefficients and tablet properties. *Acta Pharm Suec* 1981; **18**: 139–148.

20 General References

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21 Author

RT Guest.

22 Date of Revision

11 February 2009.

Cellulose, Microcrystalline

1 Nonproprietary Names

BP: Microcrystalline Cellulose
JP: Microcrystalline Cellulose
PhEur: Cellulose, Microcrystalline
USP-NF: Microcrystalline Cellulose

2 Synonyms

Avicel PH; *Cellets*; *Celex*; cellulose gel; hellulosum microcristallinum; *Celphere*; *Ceolus KG*; crystalline cellulose; E460; *Emcocel*; *Ethispheres*; *Fibrocel*; *MCC Sanaq*; *Pharmacel*; *Tabulose*; *Vivapur*.

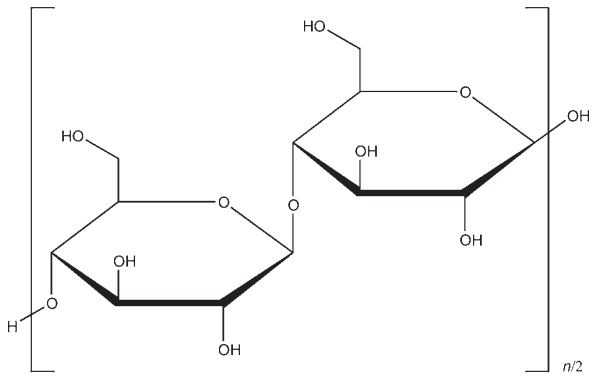
3 Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000
where $n \approx 220$.

5 Structural Formula



6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

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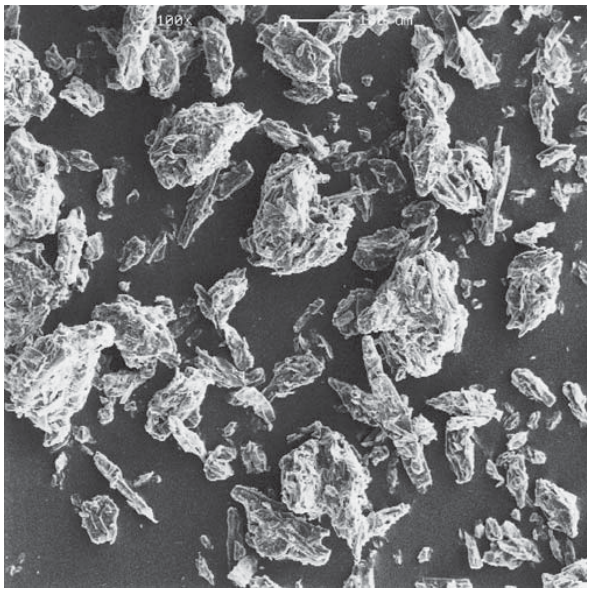
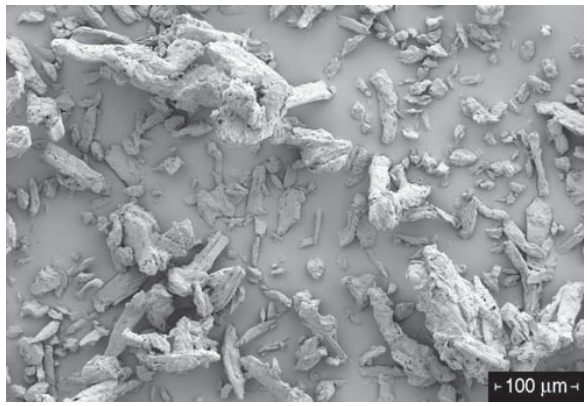
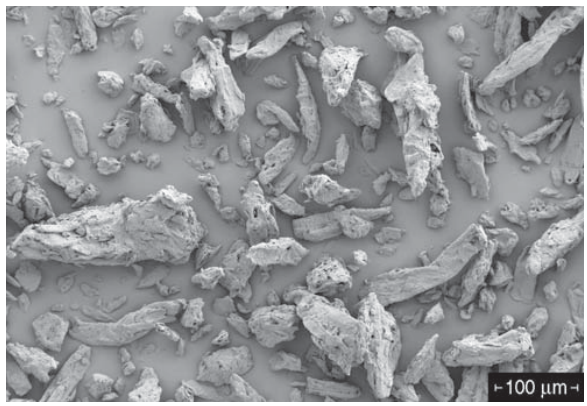
SEM 1: Excipient: microcrystalline cellulose; manufacturer: JRS Pharma LP; lot no.: 98662; magnification: 100×.



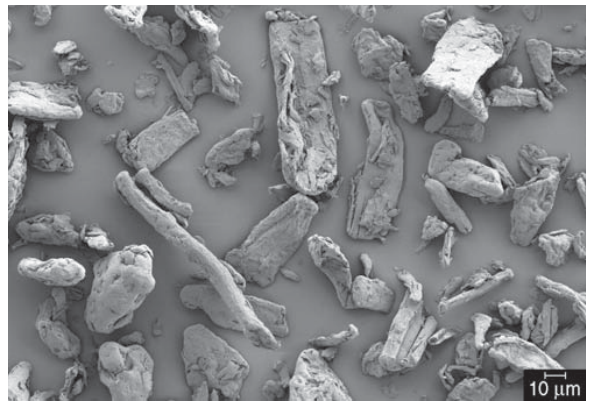
SEM 2: Excipient: microcrystalline cellulose (*Avicel PH-101*); manufacturer: FMC Biopolymer. magnification: 200×; voltage: 3 kV.



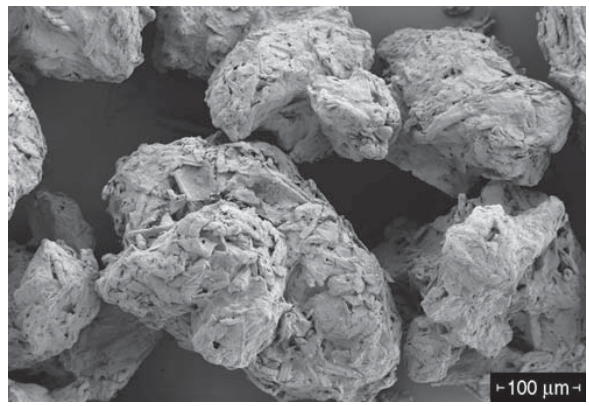
SEM 3: Excipient: microcrystalline cellulose (*Avicel PH-102*); manufacturer: FMC Biopolymer. magnification: 200×; voltage: 3 kV.



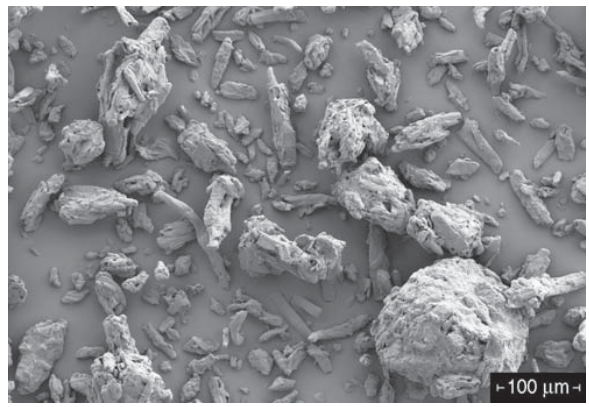
SEM 4: Excipient: microcrystalline cellulose (*Avicel PH-105*); manufacturer: FMC Biopolymer. magnification: 500×; voltage: 3 kV.



SEM 5: Excipient: microcrystalline cellulose (*Avicel PH-200*); manufacturer: FMC Biopolymer. magnification: 200×; voltage: 3 kV.



SEM 6: Excipient: microcrystalline cellulose (*Avicel PH-302*); manufacturer: FMC Biopolymer. magnification: 200×; voltage: 3 kV.



7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.[1–7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.

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Microcrystalline cellulose is also used in cosmetics and food products; *see* Table I.

8 Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for microcrystalline cellulose.

Test	JP XV	PhEur 6.3	USP32–NF27
Identification	+	+	+
Characters	+	+	–
pH	5.0–7.5	5.0–7.5	5.0–7.5
Bulk density	+	–	+
Loss on drying	⩽7.0%	⩽7.0%	⩽7.0%
Residue on ignition	⩽0.1%	–	⩽0.1%
Conductivity	+	+	+
Sulfated ash	–	⩽0.1%	–
Ether-soluble substances	⩽0.05%	⩽0.05%	⩽0.05%
Water-soluble substances	+	⩽0.25%	⩽0.25%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Microbial limits	+	+	+
Aerobic	$\leqslant 10^3$ cfu/g	$\leqslant 10^3$ cfu/g	$\leqslant 10^3$ cfu/g
Molds and yeasts	$\leqslant 10^2$ cfu/g	$\leqslant 10^2$ cfu/g	$\leqslant 10^2$ cfu/g
Solubility	–	+	–
Particle size distribution	–	–	+

10 Typical Properties

Angle of repose

49° for *Ceolus KG*;

34.4° for *Emcocel 90M*.[9]

Density (bulk)

0.337 g/cm^3;

0.32 g/cm^3 for *Avicel PH-101*;[10]

0.80 ± 5 g/cm^3 for *Cellets 100*, *200*, *350*, *500*, *700*, *1000*;

0.29 g/cm^3 for *Emcocel 90M*;[9]

0.26–0.31 g/cm^3 for *MCC Sanaq 101*;

0.28–0.33 g/cm^3 for *MCC Sanaq 102*;

0.29–0.36 g/cm^3 for *MCC Sanaq 200*;

0.34–0.45 g/cm^3 for *MCC Sanaq 301*;

0.35–0.46 g/cm^3 for *MCC Sanaq 302*;

0.13–0.23 g/cm^3 for *MCC Sanaq UL-002*;

0.29 g/cm^3 for *Vivapur 101*.

Density (tapped)

0.478 g/cm^3;

0.45 g/cm^3 for *Avicel PH-101*;

0.35 g/cm^3 for *Emcocel 90M*.[9]

Density (true) 1.512–1.668 g/cm^3;

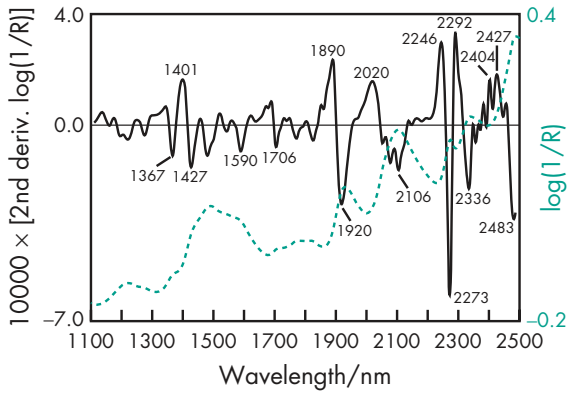

Figure 1: Near-infrared spectrum of cellulose, microcrystalline measured by reflectance.

1.420–1.460 g/cm^3 for *Avicel PH-102*.[11]

Flowability 1.41 g/s for *Emcocel 90M*.[9]

Melting point Chars at 260–270°C.

Moisture content Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.[12] *See* Table III.

NIR spectra *see* Figure 1.

Particle size distribution Typical mean particle size is 20–200 µm. Different grades may have a different nominal mean particle size; *see* Table III.

Solubility Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Specific surface area

1.06–1.12 m^2/g for *Avicel PH-101*;

1.21–1.30 m^2/g for *Avicel PH-102*;

0.78–1.18 m^2/g for *Avicel PH-200*.

11 Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

13 Method of Manufacture

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14 Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.[13]

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Table III: Properties of selected commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size (μm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH-101 [(a)]	50	60	⩽1.0	⩽5.0
		200	⩽30.0	
Avicel PH-102 [(a)]	100	60	⩽8.0	⩽5.0
		200	⩾45.0	
Avicel PH-103 [(a)]	50	60	⩽1.0	⩽3.0
		200	⩽30.0	
Avicel PH-105 [(a)]	20	400	⩽1.0	⩽5.0
Avicel PH-112 [(a)]	100	60	⩽8.0	⩽1.5
Avicel PH-113 [(a)]	50	60	⩽1.0	⩽1.5
		200	⩽30.0	
Avicel PH-200 [(a)]	180	60	⩾10.0	⩽5.0
		100	⩾50.0	
Avicel PH-301 [(a)]	50	60	⩽1.0	⩽5.0
		200	⩽30.0	
Avicel PH-302 [(a)]	100	60	⩽8.0	⩽5.0
		200	⩾45.0	
Celex 101 [(b)]	75	60	⩽1.0	⩽5.0
		200	⩾30.0	
Ceolus KG-802 [(c)]	50	60	⩽0.5	⩽6.0
		200	⩽30.0	
Emcocel 50M [(d)]	50	60	⩽0.25	⩽5.0
		200	⩽30.0	
Emcocel 90M [(d)]	91	60	⩽8.0	⩽5.0
		200	⩾45.0	
MCC Sanaq 101[(e)]	50	60	⩽1.0	⩽6.0
		200	⩽30.0	
MCC Sanaq 102[(e)]	100	60	⩽8.0	⩽6.0
		200	⩾45.0	
MCC Sanaq 200[(e)]	180	60	⩾10.0	⩽6.0
		100	⩾50.0	
MCC Sanaq 301[(e)]	50	60	⩽1.0	⩽6.0
		200	⩾30.0	
MCC Sanaq 302[(e)]	100	60	⩽8.0	⩽6.0
		200	⩾45.0	
MCC Sanaq UL-002[(e)]	50	60	<0.5	⩽6.0
		100	<5.0	
		200	<5.0–30.0	
Vivapur 101 [(d)]	50	60	⩽1.0	⩽5.0
		200	⩽30.0	
Vivapur 102 [(d)]	90	60	⩽8.0	⩽5.0
		200	⩾45.0	
Vivapur 12 [(d)]	160	38	⩽1.0	⩽5.0
		94	⩽50.0	

Suppliers:
(a) FMC Biopolymer
(b) International Specialty Products
(c) Asahi Kasei Corporation
(d) JRS Pharma
(e) Pharmatrans Sanaq AG

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the workplace exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.[14]

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; oral capsules, powders, suspensions, syrups, 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

Microcrystalline cellulose and carrageenan; microcrystalline cellulose and carboxymethylcellulose sodium; microcrystalline cellulose and guar gum; powdered cellulose; silicified microcrystalline cellulose.

Microcrystalline cellulose and carrageenan

Synonyms *Lustre Clear.*

Comments *Lustre Clear* (FMC Biopolymer) is an aqueous film coating combining microcrystalline cellulose and carrageenan.

Microcrystalline cellulose and guar gum

Synonyms *Avicel CE-15.*

Comments *Avicel CE-15* (FMC Biopolymer) is a coprocessed mixture of microcrystalline cellulose and guar gum used in chewable tablet formulations.

18 Comments

Microcrystalline cellulose 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.

Several different grades of microcrystalline cellulose are commercially available that differ in their method of manufacture,[15,16] particle size, moisture, flow, and other physical properties.[17–29] The larger-particle-size grades generally provide better flow properties in pharmaceutical machinery. Low-moisture grades are used with moisture-sensitive materials. Higher-density grades have improved flowability.

Several coprocessed mixtures of microcrystalline cellulose with other excipients such as carrageenan, carboxymethylcellulose sodium, and guar gum are commercially available; *see* Section 17.

Celphere (Asahi Kasei Corporation) is a pure spheronized microcrystalline cellulose available in several different particle size ranges. *Balocel Sanaq* (Pharmatrans Sanaq AG) is an excipient used mainly in the production of pellets and granulates in direct tableting, which contains lactose, microcrystalline cellulose, and sodium carboxymethylcellulose.

According to PhEur 6.3, microcrystalline cellulose has certain functionality related characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient. Non-mandatory testing procedures have been described for particle size distribution (2.9.31 or 2.9.38) and powder flow (2.9.36).

A specification for microcrystalline cellulose is contained in the Food Chemicals Codex (FCC).[30] The PubChem Compound ID (CID) for microcrystalline cellulose is 14055602.

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22 Date of Revision

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Lactose, Anhydrous

1 Nonproprietary Names

BP: Anhydrous Lactose
JP: Anhydrous Lactose
PhEur: Lactose, Anhydrous
USP-NF: Anhydrous Lactose

2 Synonyms

Anhydrous 60M; *Anhydrous Direct Tableting (DT)*; *Anhydrous DT High Velocity*; *Anhydrous Impalpable*; *Lactopress Anhydrous*; *Lactopress Anhydrous 250*; lactosum anhydricum; lattosio; milk sugar; *SuperTab 21AN*; *SuperTab 22AN*; saccharum lactis.

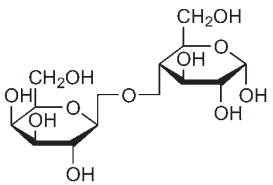
3 Chemical Name and CAS Registry Number

O-β-D-Galactopyranosyl-(1→4)-β-D-glucopyranose [63-42-3]

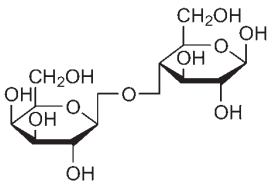
4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$ 342.30

5 Structural Formula



Anhydrous α-lactose



Anhydrous β-lactose

The PhEur 6.5 and USP32–NF27 describe anhydrous lactose as O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose; or a mixture of O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose and O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose. The JP XV describes anhydrous lactose as β-lactose or a mixture of β-lactose and α-lactose, and defines these as per the PhEur and USP–NF.

6 Functional Category

Directly compressible tablet excipient; dry powder inhaler carrier; lyophilization aid; tablet and capsule diluent; tablet and capsule filler.

7 Applications in Pharmaceutical Formulation or Technology

Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous injections.

See also Lactose, Inhalation; Lactose, Monohydrate; Lactose, Spray-Dried.

8 Description

Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous β-lactose and anhydrous α-lactose. Anhydrous lactose typically contains 70–80% anhydrous β-lactose and 20–30% anhydrous α-lactose.

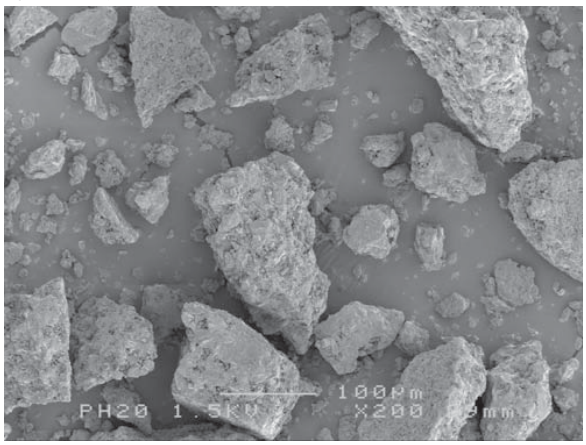
9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

10 Typical Properties

Brittle fracture index 0.0362
Bonding index 0.0049 (at compression pressure 177.8 MPa)[1]
Density (true) 1.589 g/cm^3 for anhydrous β-lactose
Density (bulk) 0.71 g/cm^3 for *SuperTab 21AN*; 0.66 g/cm^3 for *Super-Tab 22AN*.

SEM 1: Excipient: *SuperTab 21AN*; manufacturer: DMV-Fonterra Excipients; magnification: 200×; voltage: 1.5 kV.



SEM 2: Excipient: *SuperTab 22AN*; manufacturer: DMV-Fonterra Excipients; magnification: 55×; voltage: 1.5 kV.

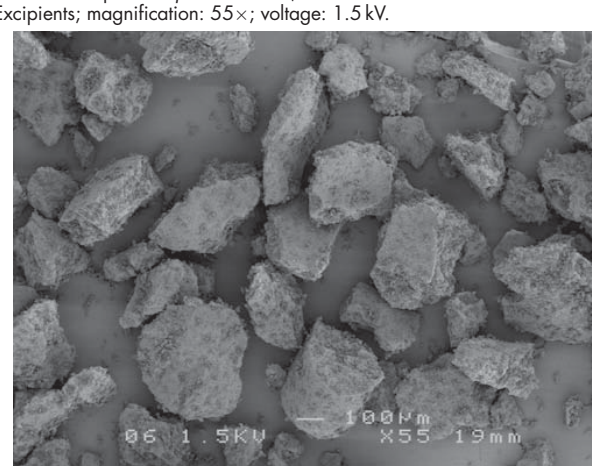


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Table I: Pharmacopeial specifications for lactose anhydrous.

Test	JP XV	PhEur 6.5	USP32–NF27
Identification	+	+	+
Appearance/color of solution	+	+	+
Characters	—	+	—
Optical rotation	+54.4° to +55.9°	+54.4° to +55.9°	+54.4° to +55.9°
Acidity or alkalinity	+	+	+
Heavy metals	⩽5 ppm	⩽5 ppm	⩽5 μg/g
Protein and light absorbing impurities/substances	+	—	+
Absorbance			
210–220 nm	⩽0.25	⩽0.25	⩽0.25
270–300 nm	⩽0.07	⩽0.07	⩽0.07
400 nm	⩽0.04	⩽0.04	⩽0.04
Loss on drying	⩽0.5%	+[a]	⩽0.5%
Water	⩽1.0%	⩽1.0%	⩽1.0%
Residue on ignition	⩽0.1%	—	⩽0.1%
Sulfated ash	—	⩽0.1%	—
Microbial limit			
Aerobic bacteria	⩽100 cfu/g	10^2 cfu/g	⩽100 cfu/g
Fungi and yeast	⩽50 cfu/g	—	⩽50 cfu/g
Absence of *Escherichia coli*	+	+	+
Absence of *Salmonella*	+	—	—
Isomer ratio	+	+[a]	+

(a) Not a mandatory test.

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Density (tapped) 0.88 g/cm^3 for *SuperTab 21AN*; 0.78 g/cm^3 for *Super-Tab 22AN*.

Melting point

223.0°C for anhydrous α-lactose;

252.2°C for anhydrous β-lactose;

232.0°C (typical) for commercial anhydrous lactose.

NIR spectra *see* Figure 1.

Particle size distribution *see* Table II.

Permanent deformation pressure 521.0 MPa (at compression pressure 177.8 MPa)[1]

Reduced modulus of elasticity 5315 (at compression pressure 177.8 MPa)[1]

Solubility Soluble in water; sparingly soluble in ethanol (95%) and ether; 40 g/100 mL at 25°C for typical Sheffield Pharma Ingredients products.

Specific rotation $[\alpha]_D^{25}$ = 54.4° to 55.9°

Tensile strength 2.577 MPa (at compression pressure 177.8 MPa)[1] Methods for characterizing the mechanical properties of compacts of pharmaceutical ingredients are specified in the *Handbook of Pharmaceutical Excipients*, 3rd edn.[1]

11 Stability and Storage Conditions

Mold growth may occur under humid conditions (80% RH and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; *see* Section 12. At 80°C and 80% RH, tablets containing anhydrous lactose have been shown to expand 1.2 times after one day.[2]

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

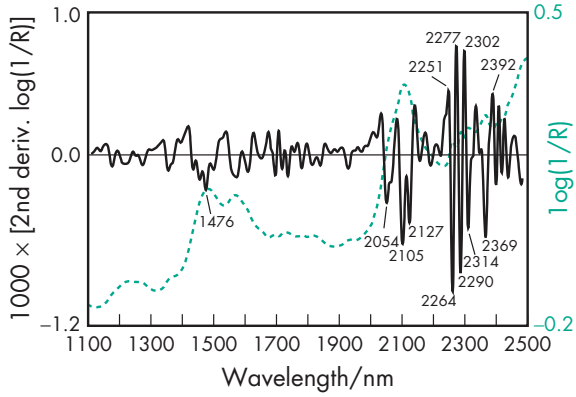

Figure 1: Near-infrared spectrum of lactose anhydrous measured by reflectance.

12 Incompatibilities

Lactose anhydrous is incompatible with strong oxidizers. When mixtures containing a hydrophobic leukotriene antagonist and anhydrous lactose or lactose monohydrate were stored for six weeks at 40°C and 75% RH, the mixture containing anhydrous lactose showed greater moisture uptake and drug degradation.[3]

Studies have also shown that in blends of roxifiban acetate (DMP-754) and lactose anhydrous, the presence of lactose anhydrous accelerated the hydrolysis of the ester and amidine groups.[4]

Lactose anhydrous is a reducing sugar with the potential to interact with primary[5] and secondary amines[6] (Maillard reaction) when stored under conditions of high humidity for extended periods.

See Lactose, Monohydrate.

13 Method of Manufacture

There are two anhydrous forms of lactose: α-lactose and β-lactose. The temperature of crystallization influences the ratio of α- and β-lactose. The anhydrous forms that are commercially available may exhibit hygroscopicity at high relative humidities. Anhydrous lactose is produced by roller drying a solution of lactose above 93.5°C. The resulting product is then milled and sieved. Two anhydrous α-lactoses can be prepared using special drying techniques: one is unstable and hygroscopic; the other exhibits good compaction properties.[7] However, these materials are not commercially available.

Table II: Particle size distribution of selected commercially available anhydrous lactose.

Supplier/grade	Percentage less than stated size			
	<45 μm	<53 μm	<150 μm	<250 μm
DMV-Fonterra Excipients				
SuperTab 21AN	⩽20	—	40–65	⩾80
SuperTab 22AN	⩽7	—	25–50	⩾65
Friesland Foods Domo				
Lactopress Anhydrous	—	⩽30	—	⩾80
Lactopress Anhydrous 250	⩽20	—	40–65	⩾80

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14 Safety

Lactose is widely used in pharmaceutical formulations as a diluent and filler-binder in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase, and is associated with oral ingestion of amounts well over those found in solid dosage forms.

See Lactose, Monohydrate.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of materials 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: powder for injection solution; IV and sublingual preparations; oral: capsules and tablets; powder for inhalation; vaginal). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lactose, inhalation; lactose, monohydrate; lactose, spray-dried.

18 Comments

Lactose anhydrous 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 6.5, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Lactose anhydrous has been used experimentally in hydrophilic matrix tablet formulations[8] and evaluated for dry powder inhalation applications.[9,10] Partial hydration of anhydrous lactose increases the specific surface area and reduces the flow properties of powders but has no effect on compactibility.[11] A specification for lactose is included in the Food Chemicals Codex (FCC[12]); *see* Lactose, Monohydrate.

The EINECS number for lactose anhydrous is 200-559-2. The PubChem Compound ID (CID) for lactose anhydrous includes 6134 and 84571.

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22 Date of Revision

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Lactose, Monohydrate

1 Nonproprietary Names

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

2 Synonyms

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

For grades, *see* Tables II and III.

3 Chemical Name and CAS Registry Number

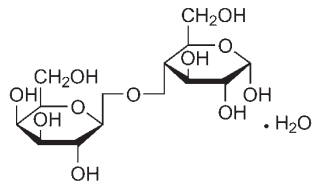
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [5989-81-1]; [10039-26-6]; [64044-51-5]

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

4 Empirical Formula and Molecular Weight

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

5 Structural Formula



α-Lactose monohydrate

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

6 Functional Category

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

7 Applications in Pharmaceutical Formulation or Technology

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

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

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

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

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

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

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

8 Description

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

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

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

10 Typical Properties

Brittle fracture index

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

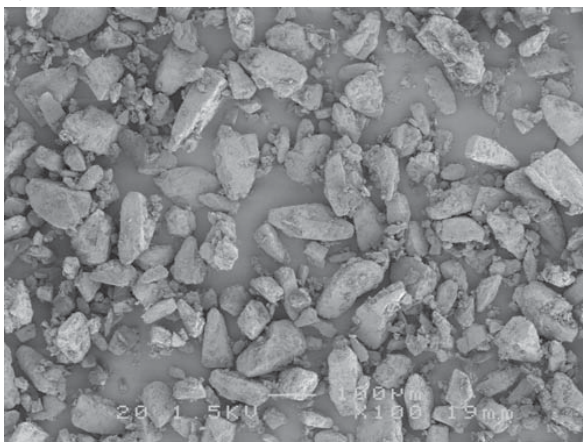
Bonding index

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

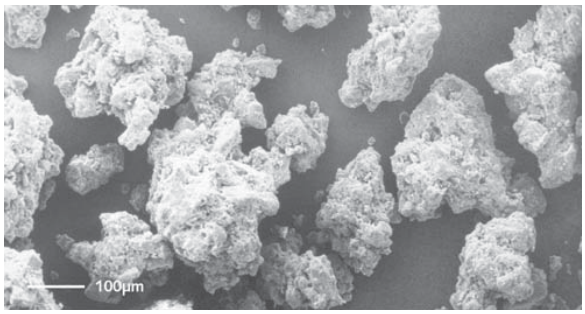
Density (true) 1.545 g/cm^3 (α-lactose monohydrate)

Density (bulk) *see* Table II.

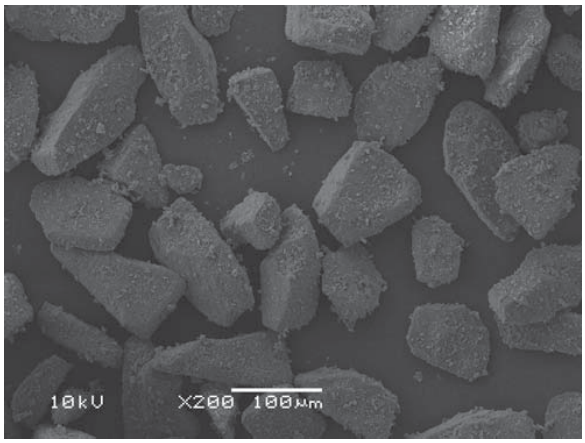
SEM 1: Excipient: *Pharmatose 125M*; manufacturer: DMV-Fonterra Excipients; magnification: 100×; voltage: 1.5 kV.



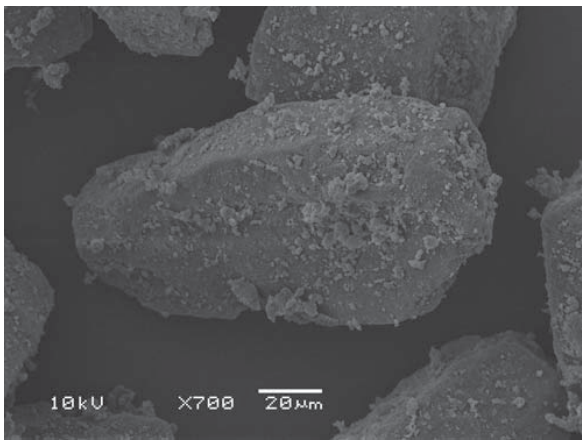
SEM 2: Excipient: *SuperTab 30GR*; manufacturer: DMV-Fonterra Excipients.



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



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



Density (tapped) *see* Table II.

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

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

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

NIR spectra *see* Figure 1.

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Table I: Pharmacopeial specifications for lactose, monohydrate.

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

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

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

370.0 MPa (at compression pressure 189.5 MPa);

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

Reduced modulus of elasticity

1472 (at compression pressure 189.5 MPa);

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

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

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

Table IV: Solubility of lactose.

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

11 Stability and Storage Conditions

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

Solutions show mutarotation; *see* Section 10.

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

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

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

12 Incompatibilities

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

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

13 Method of Manufacture

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

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

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

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

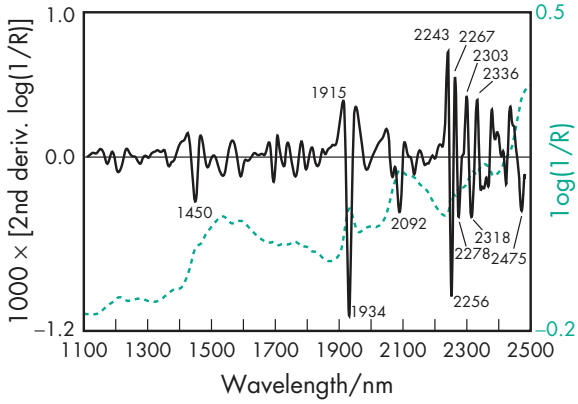

Figure 1: Near-infrared spectrum of lactose monohydrate measured by reflectance.

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

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

L

14 Safety

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

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

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

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

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

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

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

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

15 Handling Precautions

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

16 Regulatory Status

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

17 Related Substances

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

18 Comments

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

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

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

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

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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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Starch

1 Nonproprietary Names

BP: Maize starch
Potato starch
Rice Starch
Tapioca Starch
Wheat Starch

JP: Corn Starch
Potato Starch
Rice Starch
Wheat Starch

PhEur: Maize Starch
Pea Starch
Potato Starch
Rice Starch
Wheat Starch

USP-NF: Corn Starch
Potato Starch
Tapioca Starch
Wheat Starch

Note that the USP32–NF27 has individual monographs for corn (*Zea mays*), potato (*Solanum tuberosum*), tapioca (*Manihot utilissima* Pohl) and wheat starch (*Triticum aestivum*). The PhEur 6.3 has monographs for each of these starches, except tapioca starch, along with additional monographs for pea (*Pisi amylum*) and rice starch (*Oryza sativa*). The BP 2009 similarly describes corn (maize), potato, rice, tapioca, and wheat starch in individual monographs, tapioca starch being obtained from the rhizomes of *Manihot utilissima* Pohl. The JP XV similarly describes corn, potato, rice, and wheat starch in separate monographs. The USP 32 also includes a monograph for topical starch. *See also* Section 18.

2 Synonyms

Amido; amidon; amilo; amylum; *C*PharmGel*; *Eurylon*; fecule; *Hylon*; maydis amylum; *Melojel*; *Meritena*; oryzae amylum; *Pearl*; *Perfectamyl*; pisi amylum; *Pure-Dent*; *Purity 21*; *Purity 826*; solani amylum; tritici amylum; *Uni-Pure*.

See also Sections 1 and 18.

3 Chemical Name and CAS Registry Number

Starch [9005-25-8]

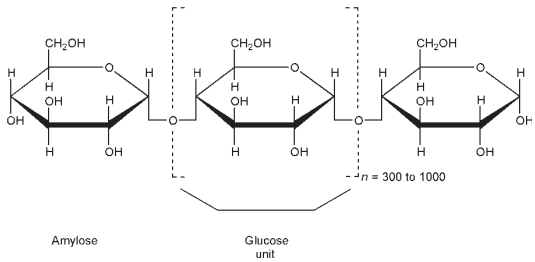
4 Empirical Formula and Molecular Weight

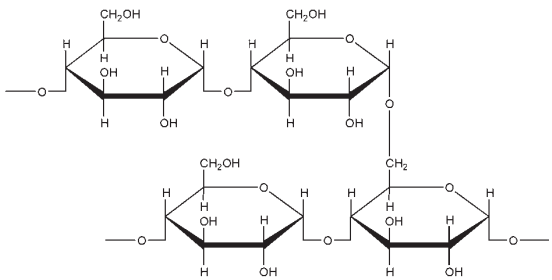
$(C_6H_{10}O_5)_n$ where n = 300–1000.

Starch consists of linear amylose and branched amylopectin, two polysaccharides based on α-(D)-glucose. Both polymers are organized in a semicrystalline structure, and in the starch granule, amylopectin forms the crystalline portion. The exact structure of starch is not yet fully understood. There is no specific distribution pattern of amylose and amylopectin molecules in the starch grain. Both molecules are organized in similar structures, probably as clusters according to the most recent scientifically recognized models. The different configurations of these molecules result in different behavior in cold aqueous solutions. Amylose (only linear 1,4 bonds) shows a high tendency for crystallization (retrogradation) resulting in insoluble adducts, whereas amylopectin (branched polymer) shows slow jellification, forming opaque and highly viscous preparations after some days. *See also* Sections 5 and 10.

The molecular weight depends on the origin and the nature of the starch. It can range between 50 and 500 million Da, with amylopectin having a higher molecular weight than amylose.

5 Structural Formula





Segment of amylopectin molecule

6 Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.

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7 Applications in Pharmaceutical Formulation or Technology

Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix,[1] and to improve powder flow, especially when using dried starches. Starch quantities of 3–10% w/w can act as an antiadherent and lubricant in tableting and capsule filling.

In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation. The required binder ratio should be determined by optimization studies, using parameters such as tablet friability and hardness, disintegration time, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w;[2–7] a typical concentration is 15%. When using starch, a prior granulation step is required in most cases to avoid problems with insufficient flow and segregation. A starch–lactose compound has been introduced enabling the use of granular starch in direct compression, improving the tableting process and the disintegration time of the tablets.[8,9] However, starch that is not pregelatinized does not compress well and tends to increase tablet friability and capping if used in high concentrations;[10] *see also* Table I. Balancing the elastic properties of starch with adapted excipients has been shown to improve the compaction properties in tableting.[8,11]

Starch, particularly the fine powders of rice and wheat starch, is also used in topical preparations for its absorbency of liquids. Starch paste is used in ointment formulations, usually in the presence of higher ratios of glycerin.

Starch has been investigated as an excipient in novel drug delivery systems for nasal,[12] and other site-specific delivery systems.[13,14] The retrogradation of starch can be used to modify the surface properties of drug particles.[15] Starches are useful carriers for amorphous drug preparations, such as pellets with immediate or delayed drug release obtained, for example, by melt extrusion,[16,17] and they can improve the bioavailability of poorly soluble drugs.

Starch, particularly rice starch, has also been used in the treatment of children's diarrheal diseases. Specific starch varieties with a high amylose content (resistant starches) are used as insoluble fiber in clinical nutrition, and also for colon-targeting applications.[18] Due to their very high gelatinization temperature, these starches are used in extrusion/spheronization processes.[19] Starches with a high amylopectin content (waxy starches) are used as the starting material for the synthesis of hydroxyethyl starch, a plasma volume expander.

Native starches conforming to pharmacopeial specifications are used as the raw materials for the production of starch-based excipients and active pharmaceutical ingredients, frequently covered with their own pharmacopeial monographs.

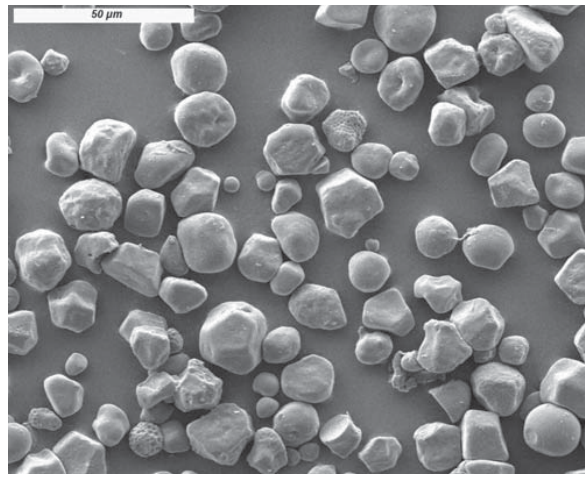
8 Description

Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

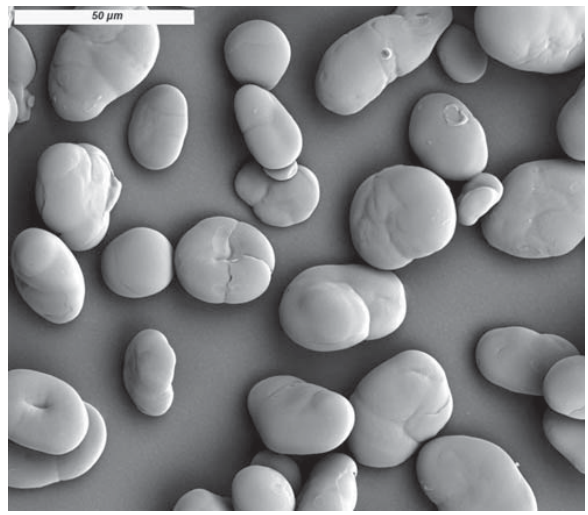
9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

SEM 1: Excipient: corn starch; manufacturer: Roquette Frères; magnification: 750×; voltage: 5 kV.



SEM 2: Excipient: pea starch; manufacturer: Roquette Frères; magnification: 750×; voltage: 5 kV.



10 Typical Properties

Acidity/alkalinity Aqueous dispersions of starch usually have a pH in the range 4.0–8.0. Starch does not exhibit a significant self-buffering capacity.

Amylose content

24–28% for corn starch;
35–39% for pea starch;
20–23% for potato starch;
17–20% for tapioca starch;
24–28% for wheat starch.

Compactability *see* Figure 1.

Density (bulk) (depending on the industrial process and humidity)

0.45–0.58 g/cm^3 for corn starch;[20,30]
0.56–0.82 g/cm^3 for potato starch;[20]
≈0.50 g/cm^3 for wheat starch.

Density (tapped) (depending on the industrial process and humidity)

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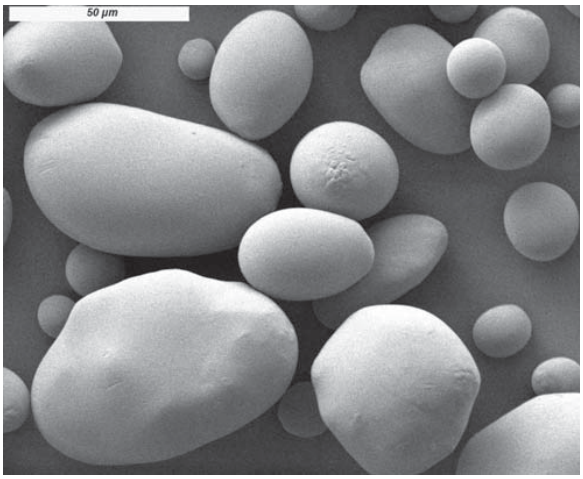
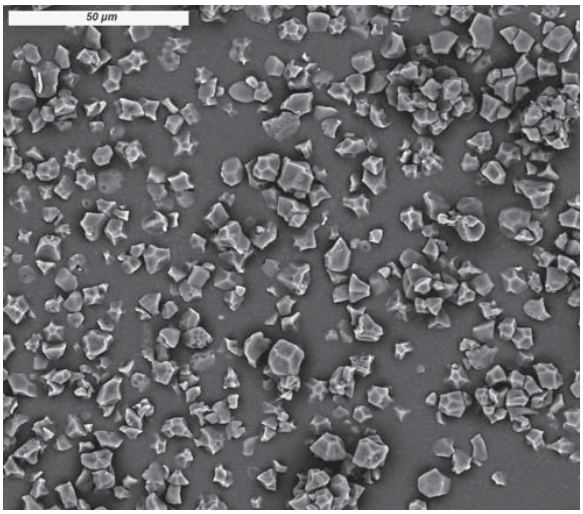
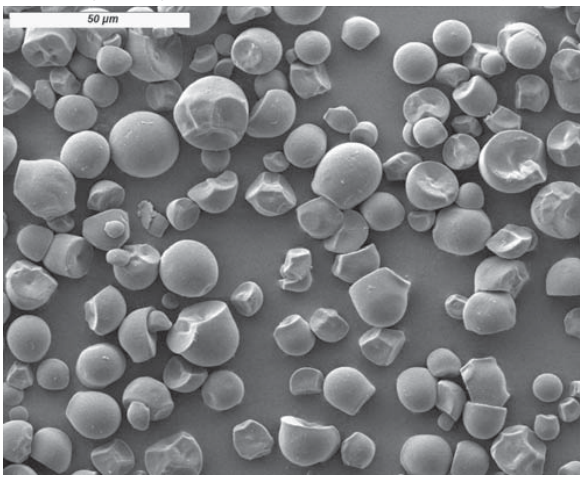
SEM 3: Excipient: potato starch; manufacturer: Roquette Frères; magnification: 750×; voltage: 5 kV.



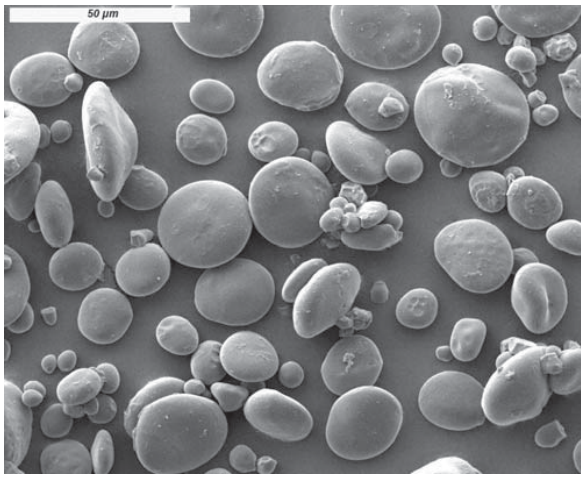
SEM 4: Excipient: rice starch; manufacturer: Remy Industries NV; magnification: 750×; voltage: 5 kV.



SEM 5: Excipient: tapioca starch; magnification: 750×; voltage: 5 kV.



SEM 6: Excipient: wheat starch; manufacturer: Roquette Frères; magnification: 750×; voltage: 5 kV.



0.69–0.77 g/cm^3 for corn starch;[20]
0.80–0.90 g/cm^3 for potato starch;[20]
≈0.76 g/cm^3 for wheat starch.

Density (true) 1.478 g/cm^3 for corn starch.

Flowability Commercial starch is generally cohesive and has poor flow characteristics. The flow properties depend strictly on the moisture content,[20,21] and drying can result in a free-flowing material.

Gelatinization temperature (measured at 20% w/w in water with differential scanning colorimetry (peak))

71°C for corn starch;
62°C for pea starch,
64°C for potato starch;
68°C for rice starch;
59°C for wheat starch.

Gelatinization causes the rupture of the starch grains and is an irreversible loss of the structure of the starch particle.[22]

Moisture content All starches are hygroscopic and absorb atmospheric moisture to reach the equilibrium humidity.[23,24] The approximate equilibrium moisture is characteristic for each starch. At 50% relative humidity:

12% for corn starch;
14% for pea starch,
18% for potato starch;
14% for rice starch;
13% for wheat starch.

Excessively dried starches with a humidity lower than the equilibrium humidity, are commercially available. These products should be stored in hermetically sealed containers to maintain their low moisture content. *See also* Figures 2 and 3.

NIR spectra *see* Figures 4, 5, 6, and 7.

Particle size distribution

Corn starch: 2–32 µm; average particle diameter 13 µm;
Pea starch: 5–90 µm; average particle diameter 30 µm;
Potato starch: 10–100 µm; average particle diameter 46 µm;
Rice starch: 2–20 µm; average particle diameter 5 µm;
Tapioca starch: 5–35 µm; average particle diameter 13 µm;
Wheat starch: 2–45 µm; bimodal particle size distribution, peak values approx. 2 µm and 20 µm.

See also Figure 8.

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Table I: Pharmacopeial specifications for starch.

Test	JP XV	PhEur 6.3	USP32–NF27
Identification	+	+	+
Characters	—	+	—
Microbial limits	—	+	+
pH			
Corn starch	4.0–7.0	4.0–7.0	4.0–7.0
Pea starch	—	5.0–8.0	—
Potato starch	—	5.0–8.0	—
Rice starch	—	5.0–8.0	—
Tapioca starch	—	—	4.5–7.0
Wheat starch	4.5–7.0	4.5–7.0	4.5–7.0
Loss on drying			
Corn starch	⩽15.0%	⩽15.0%	⩽15.0%
Pea starch	—	⩽16.0%	—
Potato starch	⩽20.0%	⩽20.0%	⩽20.0%
Rice starch	⩽15.0%	⩽15.0%	—
Tapioca starch	—	—	⩽16.0%
Wheat starch	⩽15.0%	⩽15.0%	⩽15.0%
Residue on ignition			
Corn starch	⩽0.6%	—	⩽0.6%
Potato starch	⩽0.6%	—	⩽0.6%
Rice starch	⩽0.1%	—	—
Tapioca starch	—	—	⩽0.6%
Wheat starch	⩽0.6%	—	⩽0.6%
Sulfated ash			
Corn starch	—	⩽0.6%	—
Pea starch	—	⩽0.6%	—
Potato starch	—	⩽0.6%	—
Rice starch	—	⩽0.6%	—
Wheat starch	—	⩽0.6%	—
Iron			
Corn starch	⩽10 ppm	⩽10 ppm	⩽10 μg/g
Pea starch	—	⩽50 ppm	—
Potato starch	⩽10 ppm	⩽10 ppm	⩽10 μg/g
Rice starch	—	⩽10 ppm	—
Tapioca starch	—	—	⩽0.002%
Wheat starch	⩽10 ppm	⩽10 ppm	⩽10 μg/g
Oxidizing substances			
Corn starch	⩽20 ppm	⩽20 ppm	⩽20 μg/g
Pea starch	—	⩽20 ppm	—
Potato starch	⩽20 ppm	⩽20 ppm	⩽20 μg/g
Rice starch	—	⩽0.002%	—
Tapioca starch	—	—	⩽0.002%
Wheat starch	⩽20 ppm	⩽20 ppm	⩽20 μg/g
Sulfur dioxide			
Corn starch	⩽50 ppm	⩽50 ppm	⩽50 μg/g
Pea starch	—	⩽50 ppm	—
Potato starch	⩽50 ppm	⩽50 ppm	⩽50 μg/g
Rice starch	—	⩽50 ppm	—
Tapioca starch	—	—	⩽0.005%
Wheat starch	⩽50 ppm	⩽50 ppm	⩽50 μg/g
Total protein			
Wheat starch	—	⩽0.3%	⩽0.3%
Foreign matter			
Corn starch	—	+	—
Pea starch	—	+	—
Potato starch	—	+	—
Rice starch	+	+	—
Wheat starch	—	+	—

Solubility Practically insoluble in cold ethanol (96%) and in cold water. Starch swells instantaneously in water by about 5–10% at 37°C.[3] Starch becomes soluble in hot water at temperatures above the gelatinization temperature. Starches are partially soluble in dimethylsulfoxide and dimethylformamide.

Specific surface area 0.40–0.54 m^2/g for corn starch.[8]

Swelling temperature Swelling is a reversible process.[22]

64°C for corn starch;

63°C for potato starch;

72°C for rice starch;

55°C for wheat starch.

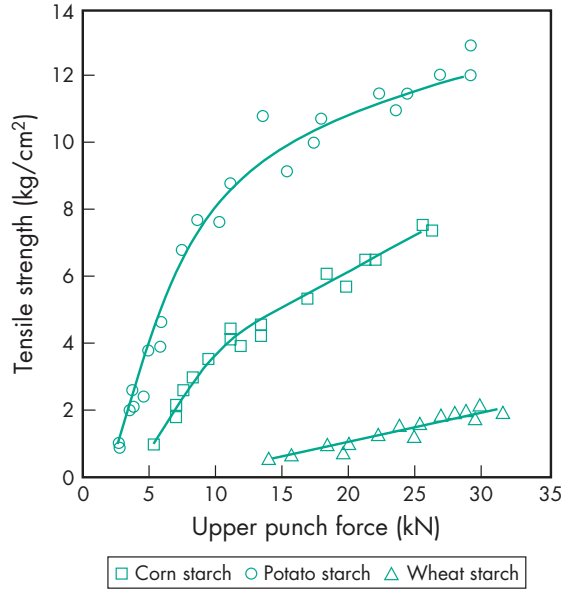

Figure 1: Compaction characteristics of corn, potato and wheat starches. Tablet machine: Manesty F; speed: 50 per min; weight: 490–510 mg. Strength test: Diametral compression between flat-faced rams. Upper ram stationary, lower moving at 66 μm/s.

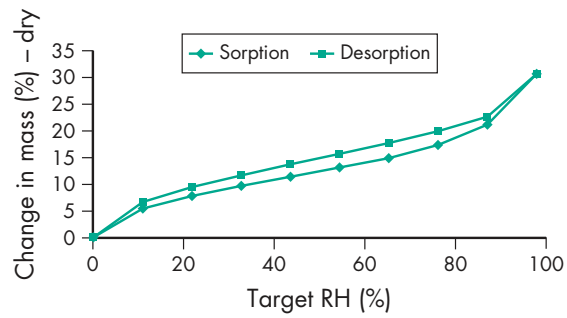

Figure 2: Sorption–desorption isotherm of wheat starch at 20°C.

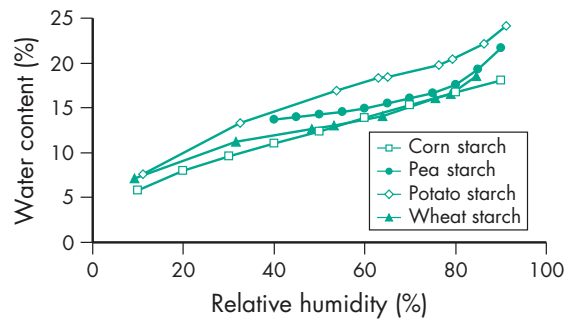

Figure 3: Sorption isotherm of various granular starches at 20°C, measured with dynamic vapor sorption equipment.

Viscosity (dynamic) Nonmodified starches are not the preferred polymer for regulating the viscosity of pharmaceutical preparations, except for clinical nutrition products. This is due to the

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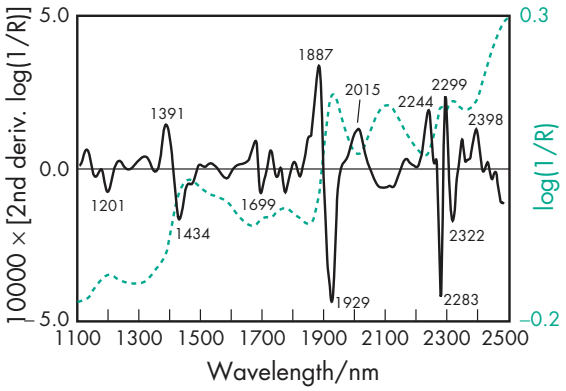

Figure 4: Near-infrared spectrum of starch measured by reflectance.

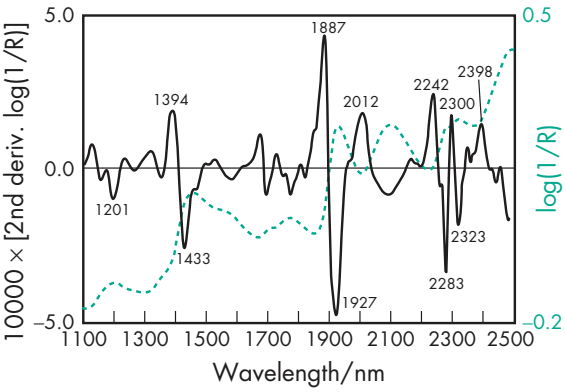

Figure 5: Near-infrared spectrum of corn starch measured by reflectance.

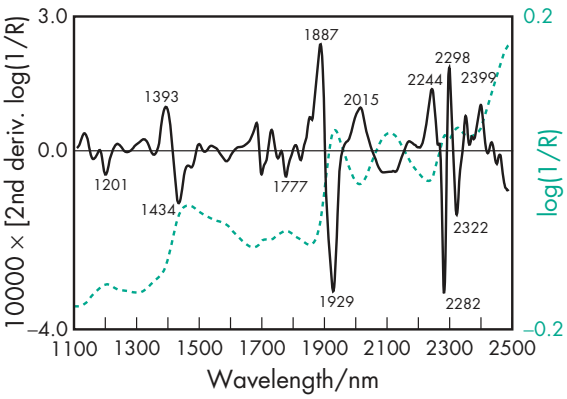

Figure 6: Near-infrared spectrum of rice starch measured by reflectance.

physical and microbial instability of starch paste. In food applications, starch contributes to higher viscosity via the volume effect of the swollen particles and not with its dynamic viscosity. The viscosities of starch paste, obtained and measured under similar conditions may be ranked as follows: potato starch >> tapioca starch > corn starch. Note that aqueous starch dispersions show significant rheopexy, especially at concentrations above 40% w/w.

11 Stability and Storage Conditions

Dry starch is stable if protected from high humidity. Starch is considered to be chemically and microbiologically inert under

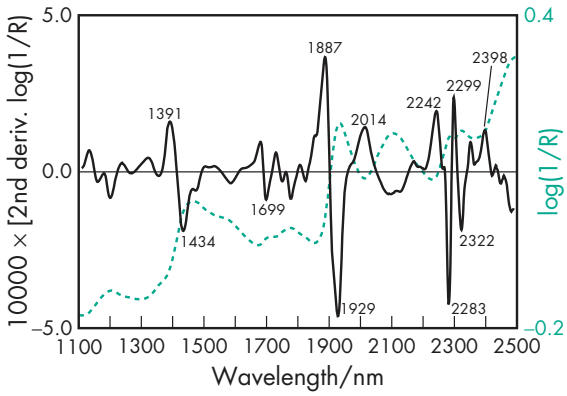

Figure 7: Near-infrared spectrum of wheat starch measured by reflectance.

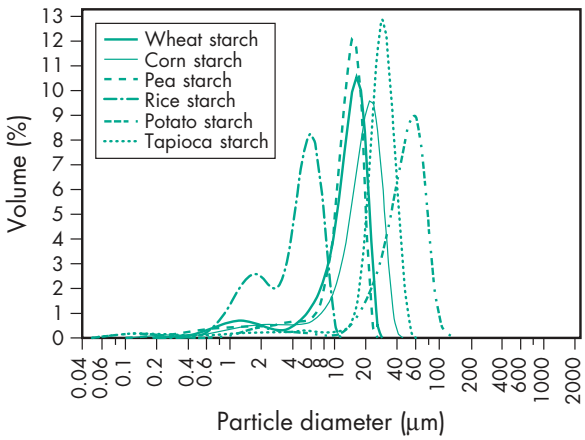

Figure 8: Particle size distribution of commercial starches (laser method, volume distribution).

normal storage conditions. Starch solutions or pastes are physically unstable and are readily metabolized by microorganisms; they should therefore be freshly prepared when used for wet granulation.

Starch should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

13 Method of Manufacture

Starch is extracted from plant sources with specific processes according to the botanical origin. Typical production steps are steeping (corn), wet milling (corn, potato), dry milling (wheat), or sieving and physical separation with hydrocyclones. The last production step is usually a centrifugal separation from the starch slurry followed by drying with hot air. The starch separation process may use sulfur dioxide or peroxides as a processing aid, improving the separation process and the microbial quality of the final product.

14 Safety

Starch is an edible food substance, considered a food ingredient and not a food additive. It is regarded as an essentially nontoxic and nonirritant material.[25] Starch is therefore widely used as an excipient in pharmaceutical formulations.

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Both amylose and amylopectin have been evaluated as safe and without limitation for daily intake.[26] Allergic reactions to starch are extremely rare and individuals apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical source. The wheat proteins (gluten) are problematic for conditions such as celiac disease.

Contamination of surgical wounds with the starch glove powder used by surgeons has resulted in the development of granulomatous lesions.[27]

LD_{50} (mouse, IP): 6.6 g/kg[28]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion. The minimal explosive concentration of corn starch is 30–60 g/m^3 air.

In the UK, the long-term (8-hour TWA) workplace exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[29]

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrin; hydroxypropyl starch; maltodextrin; sodium starch glycolate; starch, pregelatinized; starch, sterilizable maize.

18 Comments

Note that corn starch is also known as maize starch and that tapioca starch is also known as cassava or manioc starch.

Corn starch, potato starch, rice starch, and wheat starch 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.

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Starch is isolated from vegetable sources. Pure starch should only contain traces of foreign matter (e.g. tissue fragments) and no traces of starches other than from the declared botanical origin. Inside their crystalline structure, starch particles contain smaller quantities of lipids (0–0.8%) and proteins (0–0.5%). The contents are relatively stable and typical for each starch variety. Starches from different plant sources differ in their amylose/amylopectin ratio (*see also* Section 10). Differences in the physical properties of the various starches mean that they are not automatically interchangeable in a given pharmaceutical application.

Corn starch is also available in a naturally white variety (extra white corn starch), containing low levels of carotenoids (especially lutein and zeaxanthin). This starch variety is extracted from specific and nongenetically modified organism hybrids of *Zea mays* L. Bleached starches are considered as modified (oxidized) starches. They are not interchangeable with nontreated starches for regulatory and technical reasons.[30]

The pharmacopeial monographs for starch do not include an assay for starch content. Possible analytical methods for quantification are polarimetric[31] or enzymatic tests.[32]

Modified starch and modified pregelatinized starch are listed in USP32–NF27. Waxy corn starch derivatives are used to increase the viscosity of liquid products such as syrups and nutritional preparations. Modified and pregelatinized starches are valuable excipients in hydrophilic matrix systems for controlled drug release.[33,34] Gelatin-free hard and soft capsules and caplets are made in some cases with specific modified starches, especially the hydroxypropylated grades. Amphiphilic starch derivatives improve the solubility of drugs[35,36] and may be used to make microcapsules and nanoparticles. Hydrophobic starch derivatives serve as ingredients in creams and ointments to reduce the stickiness on the skin. Modified starches exhibit excellent film-forming properties and are therefore valuable excipients in the film-coating of tablets and capsules, and in the production of oral edible films.[37] *Instant Pure-Cote*, *Pure-Bind*, *Pure-Coat*, *Pure-Gel* and *Pure-Set* (Grain Processing Corp.) are tradenames for modified starches.

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Starch, Pregelatinized

1 Nonproprietary Names

BP: Pregelatinised Starch
PhEur: Starch, Pregelatinised
USP-NF: Pregelatinized Starch

2 Synonyms

Amylum pregelificatum; compressible starch; *C*PharmGel*; *Instastarch*; *Lycatab C*; *Lycatab PGS*; *Merigel*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST200*; *Spress B820*; *Starch 1500 G*; *Tablitz*; *Unipure LD*; *Unipure WG220*.

3 Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules. Both fully and partially pregelatinized grades are commercially available. Partial pregelatinization renders the starch flowable and directly compressible. Full pregelatinization produces a cold-water soluble starch that can be used as a wet granulation binder. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. The USP32–NF27 does not specify the botanical origin of the original starch, but the PhEur 6.3 specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch. *See also* Starch and Section 13. Normally the fully pregelatinized starch contains 20–30% amylose and the rest amylopectin, which is about the same ratio (1 : 3) as for the partially pregelatinized form. There are ways to increase the amylose portion.[1]

5 Structural Formula

See Starch.

6 Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Partially pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,[2,3] and disintegrant.[4]

In comparison to starch, partially pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression or direct compression processes.[5–15] In such processes, pregelatinized starch is self-lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.[16]

Partially pregelatinized starch is used in oral dry powder hard capsule formulations.

Both partially and fully pregelatinized starch may also be used in wet granulation processes.[17] *See* Table I.

Fully pregelatinized starches can be used to make soft capsules, shells, and coatings as well as binders in tablets.

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