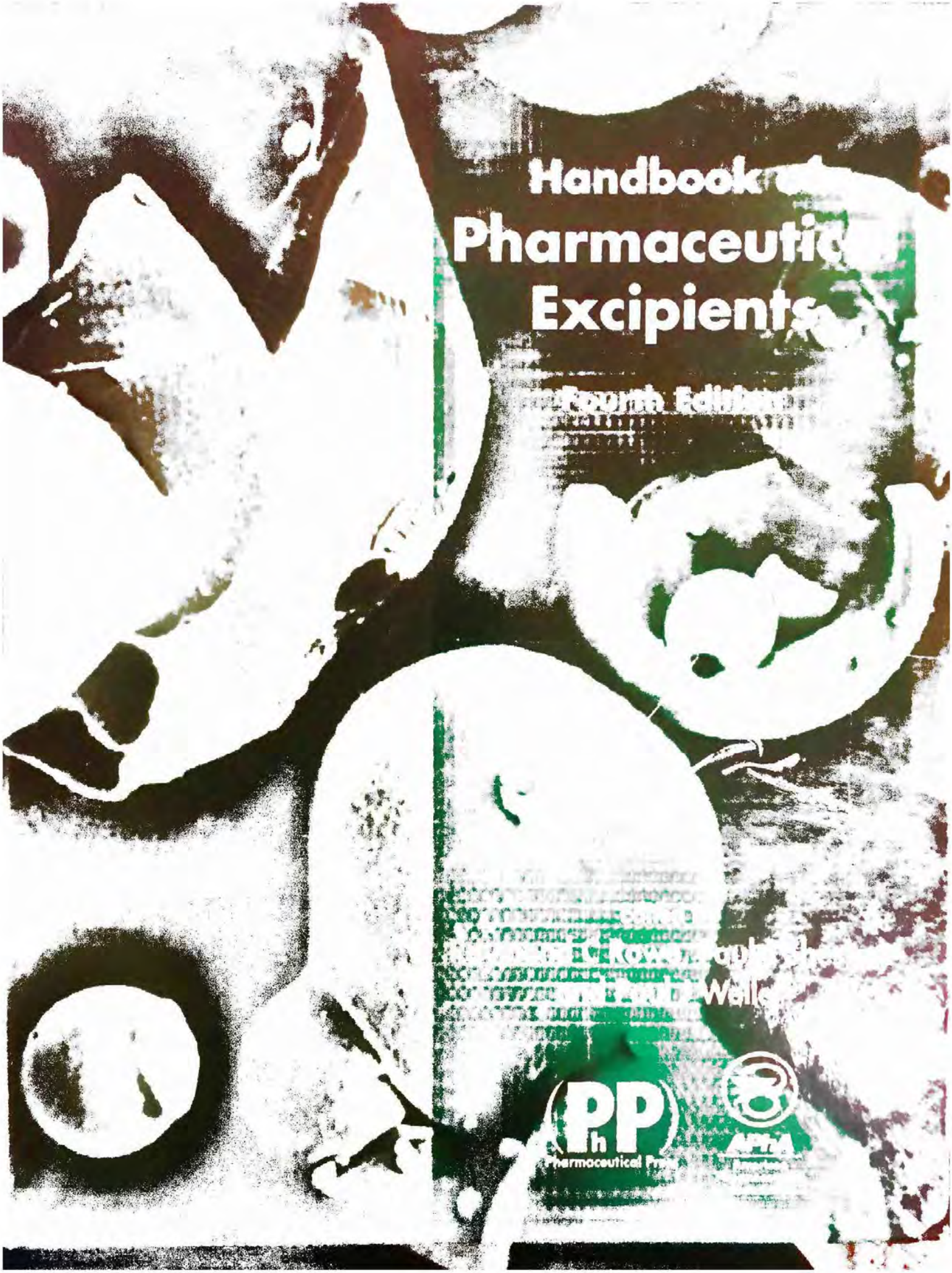
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Cellulose, Microcrystalline

1 Nonproprietary Names

BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcristallinum
USPNF: Microcrystalline cellulose

2 Synonyms

Avicel PH; *Celex*; cellulose gel; *Celphere*; *Ceolus KG*; crystalline cellulose; E460; *Emcocel*; *Ethispheres*; *Fibrocel*; *Pharmacel*; *Tabulose*; *Vivapur*.

3 Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

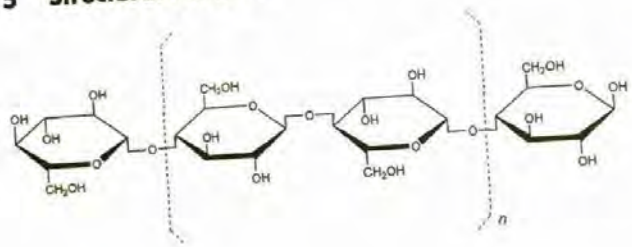
4 Empirical Formula

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

Molecular Weight

≈36 000

5 Structural Formula



6 Functional Category

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

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.

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

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

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.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2002 Suppl 4.2	USPNF 20
Identification	+	+	+
Characters	+	+	–
pH	5.0–7.0	5.0–7.5	5.0–7.0
Bulk density	+	–	+
Loss on drying	≤7.0%	≤6.0%	≤7.0%
Residue on ignition	≤0.05%	–	≤0.05%
Conductivity	+	–	+
Sulfated ash	–	≤0.1%	–
Ether-soluble substances	≤0.05%	≤0.05%	≤0.05%
Water-soluble substances	+	≤0.25%	≤0.24%
Heavy metals	≤10 ppm	≤10 ppm	≤0.001%
Starch	–	+	–
Organic volatile impurities	–	–	+
Microbial limits	+	+	+

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

Density (tapped):
0.478 g/cm^3
0.45 g/cm^3 for *Avicel PH-101*[10]
0.35 g/cm^3 for *Emcocel 90M*[9]

Density (true): 1.512–1.668 g/cm^3

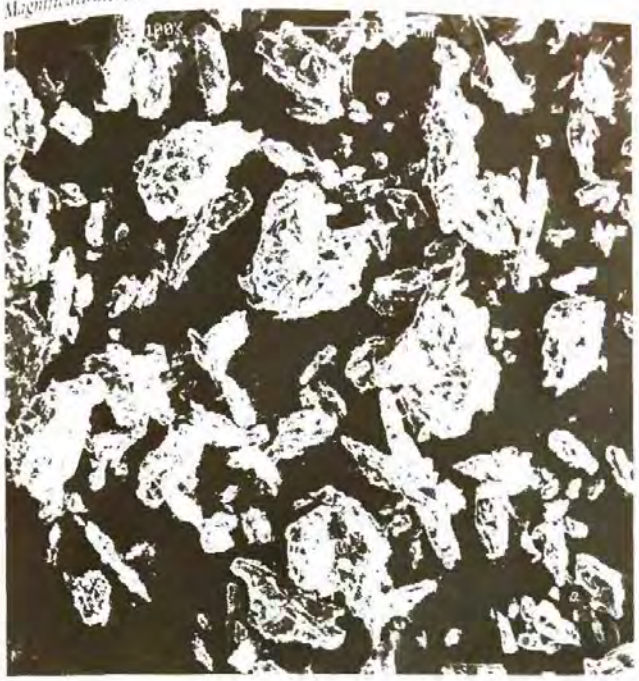
Flowability: 1.41 g/s for *Emcocel 90M*.[9]

Melting point: chars at 260–270°C.

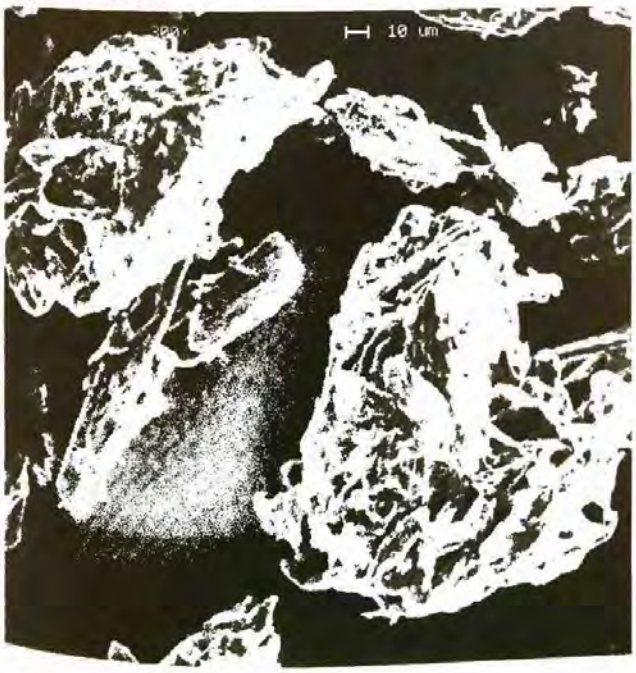
Moisture content: typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.[11] *See* Table III.

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

SEM: 1
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals Co.
Lot No.: 98662
Magnification: 100 ×



SEM: 2
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals Co.
Lot No.: 98662
Magnification: 300 ×



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.

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]	51	60	≤0.25	≤5.0
		200	≤30.0	
Emcocel 90M[d]	91	60	≤8.0	≤5.0
		200	≥45.0	
Vivapur 101[e]	50	60	≤1.0	≤5.0
		200	≤30.0	
Vivapur 102[e]	90	60	≤8.0	≤5.0
		200	≥45.0	
Vivapur 12[e]	160	38	≤1.0	≤5.0
		94	≤50.0	

Suppliers: [a]FMC Biopolymer; [b]International Specialty Products; [c]Asahi Kasei Corporation; [d]Penwest Pharmaceuticals Co.; [e]J Rettenmaier & Söhne GmbH.

SEM: 3
Excipient: Microcrystalline cellulose
Manufacturer: FMC Biopolymer
Magnification: 100 ×

13 Method of Manufacture

Microcrystalline cellulose is manufactured by the 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.[12]

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 occupational 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.[13]

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

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 carboxymethylcellulose sodium

Synonyms: *Avicel CL-611*; *Avicel RC-581*; *Avicel RC-591*; colloidal cellulose; dispersible cellulose.
Appearance: white, odorless and tasteless, hygroscopic powder.
Acidity/alkalinity: pH = 6–8 for a 1.2% w/v aqueous dispersion.
Moisture content: not more than 6.0% w/w.
Particle size distribution:
Avicel CL-611: ⩽0.1% retained on a #60 mesh sieve, ⩽50% retained on a #325 mesh
Avicel RC-581: ⩽0.1% retained on a #60 mesh sieve, ⩽35% retained on a #200 mesh
Avicel RC-591: ⩽0.1% retained on a #60 mesh sieve, ⩽45% retained on a #325 mesh
Solubility: practically insoluble in dilute acids and organic solvents. Partially soluble in dilute alkali and water (carboxymethylcellulose sodium fraction).
Viscosity (dynamic):
5–20 mPa s (5–20 cP) for a 1.2% w/v aqueous dispersion of *Avicel CL-611*
72–168 mPa s (72–168 cP) for *Avicel RC-581* at the same concentration
39–91 mPa s (39–91 cP) for *Avicel RC-591* at the same concentration
Comments: mixtures of microcrystalline cellulose and carboxymethylcellulose sodium that are dispersible in water and produce thixotropic gels are suitable as suspending vehicles in pharmaceutical formulations. The amount of carboxymethylcellulose present can vary between 8.5% and 18.8% w/w depending upon the grade of material.

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

Several different grades of microcrystalline cellulose are commercially available that differ in their method of manufacture,[14,15] particle size, moisture, flow, and other physical properties.[16–25] 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.

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PJ Weller.

22 Date of Revision

26 November 2002.

Cellulose, Powdered

1 Nonproprietary Names

BP: Powdered cellulose
JP: Powdered cellulose
PhEur: Cellulosi pulvis
USPNF: Powdered cellulose

2 Synonyms

Arbocel; E460; *Elcema*; *Sanacel*; *Solka-Floc*.

3 Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

4 Empirical Formula

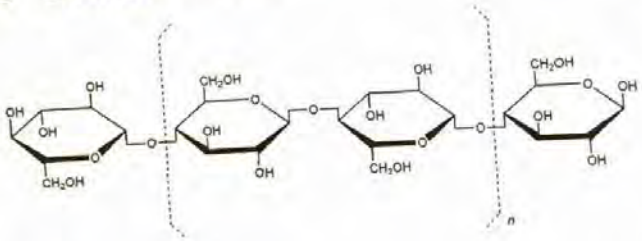
$(C_6H_{10}O_5)_n$
where $n \approx 500$.

Molecular Weight

≈243 000

Since cellulose is derived from a natural polymer, it has variable chain length and thus variable molecular weight. *See also Sections 8 and 13.*

5 Structural Formula



6 Functional Category

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

7 Applications in Pharmaceutical Formulation or Technology

Powdered cellulose is used as a tablet diluent and a hard gelatin capsule filler; *see* Table I. In both contexts it acts as a bulking agent to increase the physical size of the dosage form for formulations containing a small amount of active substance.

Powdered cellulose has acceptable compression properties, although its flow properties are poor. However, low-crystallinity powdered cellulose has exhibited properties that are different from standard powdered cellulose materials, and has shown potential as a direct-compression excipient.[1]

In soft gelatin capsules, powdered cellulose may be used to reduce the sedimentation rate of oily suspension fills. It is also used as the powder base material of powder dosage forms, and as a suspending agent in aqueous suspensions for peroral delivery. It may also be used to reduce sedimentation during the manufacture of suppositories.

Powdered cellulose has been investigated as an alternative to microcrystalline cellulose as an agent to assist the manufacture of pellets by extrusion/spheronization.[2]

Powdered cellulose is also used widely in cosmetics and food products.

Table I: Uses of powdered cellulose.

Use	Concentration (%)
Capsule filler	0–100
Tablet binder	5–25
Tablet disintegrant	5–15
Tablet glidant	1–2

8 Description

Powdered cellulose occurs as a white or almost white, odorless and tasteless powder of various particle sizes, ranging from a free-flowing fine or granular dense powder, to a coarse, fluffy, nonflowing material.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for powdered cellulose.

Test	JP 2001	PhEur 2002 (Suppl 4.2)	USPNF 20
Identification	+	+	+
Characters	+	+	–
Microbial limits			
Aerobic	≤1000/g	≤ 1000/g	≤1000/g
Fungi and yeast	≤100/g	≤100/g	–
Degree of polymerization	–	≥440	–
pH (10% w/w suspension)	5.0–7.5	5.0–7.5	+
Loss on drying	≤6.0%	≤6.5%	≤6.0%
Residue on ignition	≤0.3%	≤0.3%	≤0.3%
Solubility	–	+	–
Ether-soluble substances	≤0.15%	≤0.15%	≤0.15%
Water-soluble substances	≤1.5%	≤1.5%	≤1.5%
Heavy metals	≤10 ppm	≤10 ppm	≤0.001%
Organic volatile impurities	–	–	+
Starch	–	+	–

10 Typical Properties

Angle of repose:
<62° for *Arbocel M80*
<49° for *Arbocel P 290*
<36° for *Arbocel A 300* (J. Rettenmaier and Söhne)
Density (bulk): 0.139–0.391 g/cm^3, depending on the source.
Density (tapped): 0.210–0.481 g/cm^3, depending on the source.
Density (true): 1.5 g/cm^3

Moisture content: powdered cellulose is slightly hygroscopic;[3] *see* Figures 1 and 2.

Particle size distribution: powdered cellulose is commercially available in several different particle sizes.

Arbocel M80: average particle size 60 μm
Arbocel P 290: average particle size 70 μm
Arbocel A 300: average particle size 200 μm

Solubility: practically insoluble in water, dilute acids, and most organic solvents although it disperses in most liquids. Slightly soluble in 5% w/v sodium hydroxide solution. Powdered cellulose does not swell in water, but does so in dilute sodium hypochlorite (bleach).

11 Stability and Storage Conditions

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

12 Incompatibilities

Incompatible with strong oxidizing agents.

13 Method of Manufacture

Powdered cellulose is manufactured by the purification and mechanical size reduction of α-cellulose obtained as a pulp from fibrous plant materials.

14 Safety

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

Powdered cellulose is not absorbed systemically following peroral administration and thus has little toxic potential. Consumption of large quantities of cellulose may, however, 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.[4]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Powdered cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the occupational 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.[5]

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in nonparenteral medicines licensed in the UK.

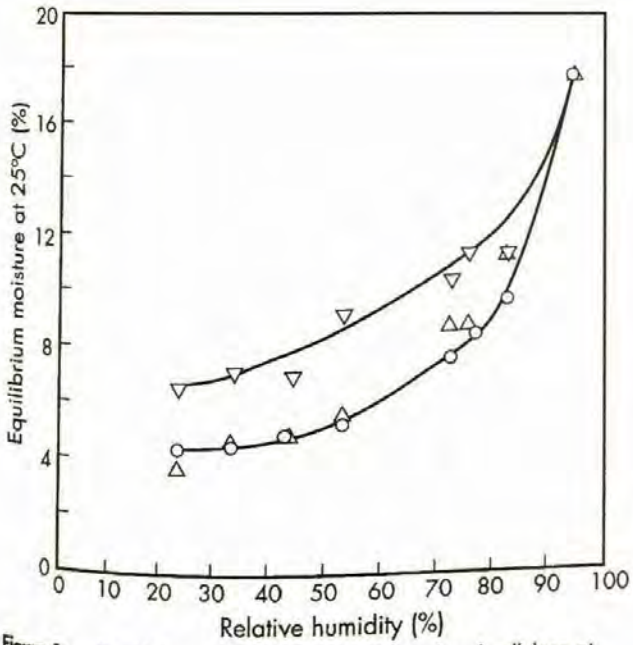


Figure 1: Equilibrium moisture content of powdered cellulose at 25°C.
○: Powdered cellulose (*Solka-Floc BW-40*, Lot no. 8-10-30A)
△: Powdered cellulose (*Solka-Floc BW-20*, Lot no. 22A-19)
▽: Powdered cellulose (*Solka-Floc Fine Granular*, Lot no. 9-10-8)

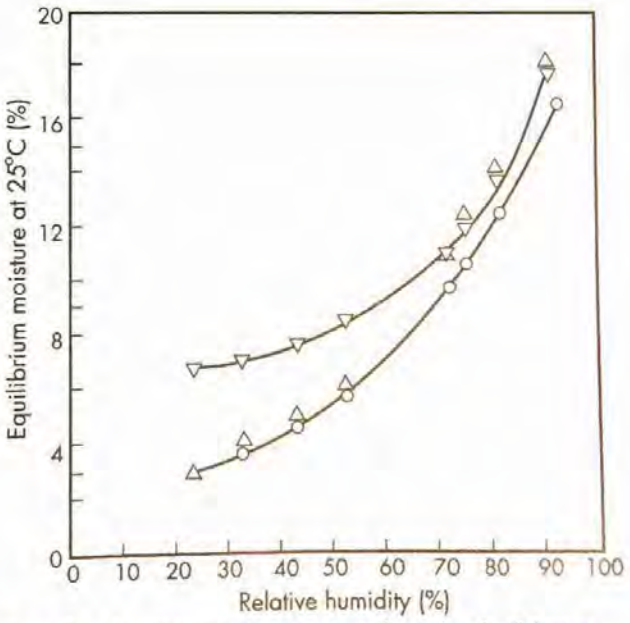


Figure 2: Equilibrium moisture content of powdered cellulose at 25°C.
○: Powdered cellulose (*Solka-Floc BW-100*, Lot no. 9-7-18B)
△: Powdered cellulose (*Solka-Floc BW-200*, Lot no. 22A-20)
▽: Powdered cellulose (*Solka-Floc Fine BW-2030*, Lot no. 240)

17 Related Substances

Cellulose, microcrystalline.

18 Comments

The EINECS number for powdered cellulose is 232-674-9.

19 Specific References

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See also Cellulose, microcrystalline.

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ME Aulton.

22 Date of Revision

21 October 2002.

Cellulose, Silicified Microcrystalline

1 Nonproprietary Names

None adopted.

2 Synonyms

ProSolv.

3 Chemical Name and CAS Registry Number

See Section 8.

4 Empirical Formula Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Silicified microcrystalline cellulose is used as a filler in the formulation of capsules and tablets. It has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose.[1–6] Silicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation.

8 Description

Silicified microcrystalline cellulose is a synergistic, intimate physical mixture of two components: microcrystalline cellulose and colloidal silicon dioxide (for further information see Cellulose, Microcrystalline and Colloidal Silicon Dioxide). Silicified microcrystalline cellulose contains 2% w/w colloidal silicon dioxide.

9 Pharmacopeial Specifications

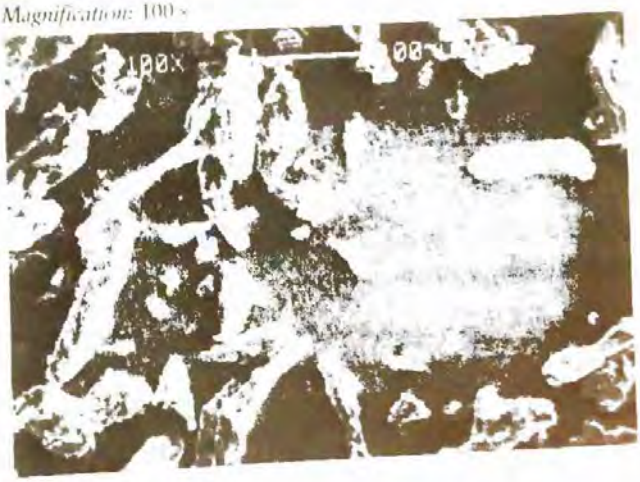
—

10 Typical properties

Acidity/alkalinity: pH = 5.0–7.5 (10% w/v suspension)
Density: 1.55 g/cm^3 [4]
Density (bulk.): 0.31 g/cm^3
Density (tapped): 0.39 g/cm^3 [4]
Melting point: the microcrystalline cellulose component chars at 260–270 °C.
Moisture content: typically less than 6% w/w.

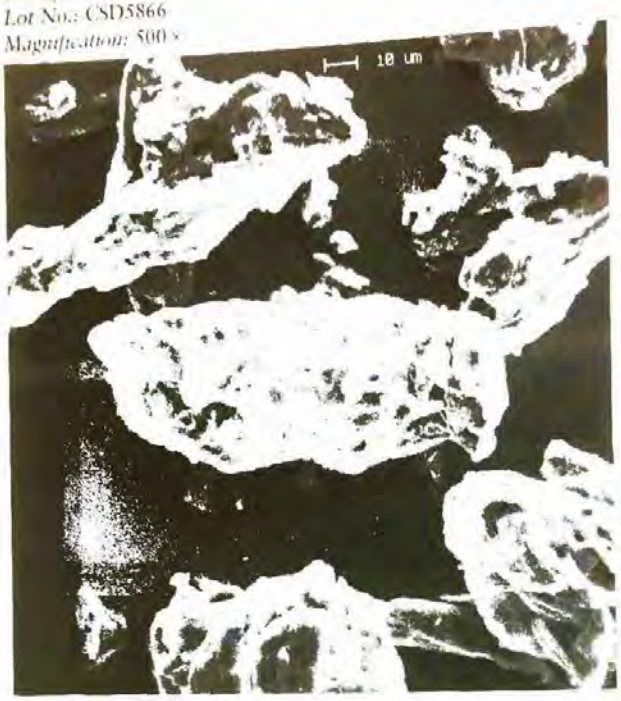
Particle size distribution: typical particle size is 20–200 µm. Different grades may have a different normal mean particle size.
Solubility: practically insoluble in water, dilute acids, and most organic solvents. The microcrystalline cellulose component is slightly soluble in 5% w/w sodium hydroxide solution.

SEM: 1
Excipient: Silicified microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals
Lot No.: CSD5866
Magnification: 100×



SEM: 2
Excipient: Silicified microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals
Lot No.: CSD5866
Magnification: 300×

SEM: 3
Excipient: Silicified microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals
Lot No.: CSD5866
Magnification: 500×



11 Stability and Storage Conditions

Silicified microcrystalline cellulose is stable when stored in a well-closed container in a cool, dry place.

12 Incompatibilities

See Cellulose, Microcrystalline and Colloidal Silicon Dioxide.

13 Method of Manufacture

Silicified microcrystalline cellulose is manufactured by co-drying a suspension of microcrystalline cellulose particles and colloidal silicon dioxide so that the dried finished product contains 2% w/w colloidal silicon dioxide.

The colloidal silicon dioxide appears physically bound onto the surface and inside the silicified microcrystalline cellulose particles. Extensive studies using different spectroscopic methods have failed to show any form of chemical interaction.[4]

14 Safety

See Cellulose, Microcrystalline and Colloidal Silicon Dioxide.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Handling of silicified microcrystalline cellulose can generate nuisance dusts and the use of a respirator or dust mask may be necessary.

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK the long-term occupational exposure limits (8-hour TWA) have been set at 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust; short-term limit for total inhalable dust has been set at 20 mg/m^3.[7]

Since the colloidal silicon dioxide is physically bound to the microcrystalline cellulose the general recommendations of gloves, eye protection, and a dust mask should be followed when handling silicified microcrystalline cellulose.

16 Regulatory Status

Silicified microcrystalline cellulose is a physical mixture of two materials both of which are generally regarded as nontoxic.

Microcrystalline cellulose: GRAS listed. Included in the FDA Inactive Ingredients Guide (inhalations, oral capsules, powders, suspensions, syrups, and tablets). Included in nonparenteral medicines licensed in Europe and the US.

Colloidal silicon dioxide: GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in Europe and the US.

17 Related Substances

Cellulose, microcrystalline; colloidal silicon dioxide.

18 Comments

Silicified microcrystalline cellulose has greater tensile strength and requires lower compression pressures than regular grades of microcrystalline cellulose. Furthermore, silicified microcrystalline cellulose maintains its compactability when wet granulated; the compacts exhibit greater stiffness and they require considerably more energy for tensile failure to occur.[5,6]

19 Specific References

1 Sherwood BE, Hunter EA, Staniforth JN. Silicified microcrystalline cellulose (SMCC): a new class of high functionality binders for direct compression. *Pharm Res* 1996; 13(9): S197.
2 Staniforth JN, Sherwood BE, Hunter EA. Towards a new class of high functionality tablet binders. II: silicified microcrystalline cellulose (SMCC). *Pharm Res* 1996; 13(9): S197.
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21 Author

RC Moreton.

22 Date of Revision

8 July 2002.

Cellulose Acetate

1 Nonproprietary Names

BP: Cellulose acetate
PhEur: Cellulosi acetas
USPNF: Cellulose acetate

2 Synonyms

Acetyl cellulose; cellulose diacetate; cellulose triacetate.

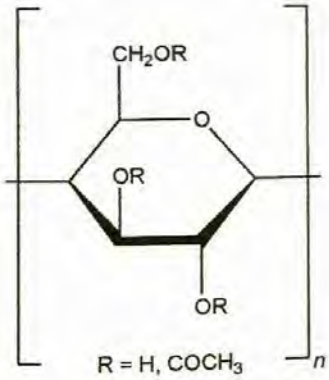
3 Chemical Name and CAS Registry Number

Cellulose acetate [9004-35-7]
Cellulose diacetate [9035-69-2]
Cellulose triacetate [9012-09-3]

4 Empirical Formula Molecular Weight

Cellulose acetate is cellulose in which a portion or all of the hydroxyl groups are acetylated. Cellulose acetate is available in a wide range of acetyl levels and chain lengths and thus molecular weights; *see* Table I

5 Structural Formula



6 Functional Category

Coating agent; extended release agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Cellulose acetate is widely used in pharmaceutical formulations both in sustained-release applications and for taste masking.

Cellulose acetate is used as a semipermeable coating on tablets, especially on osmotic pump-type tablets and implants. This allows for controlled, extended release of actives.[1–4] Cellulose acetate films, in conjunction with other materials, also offer sustained release without the necessity of drilling a hole in the coating as is typical with osmotic pump systems. Cellulose acetate and other cellulose esters have also been used to form drug-loaded microparticles with controlled-release characteristics.[5,6]

Cellulose acetate films are used in transdermal drug delivery systems[7,8] and also as film coatings on tablets or granules for taste masking. For example, acetaminophen granules have been coated with a cellulose acetate-based coating before being processed to provide chewable tablets. Extended-release tablets can also be formulated with cellulose acetate as a directly compressible matrix former.[9] The release profile can be modified by changing the ratio of active to cellulose acetate and by incorporation of plasticizer, but was shown to be insensitive to cellulose acetate molecular weight and particle size distribution.

Therapeutically, cellulose acetate has been used to treat cerebral aneurysms, and also for spinal perimedullary arteriovenous fistulas.[10]

8 Description

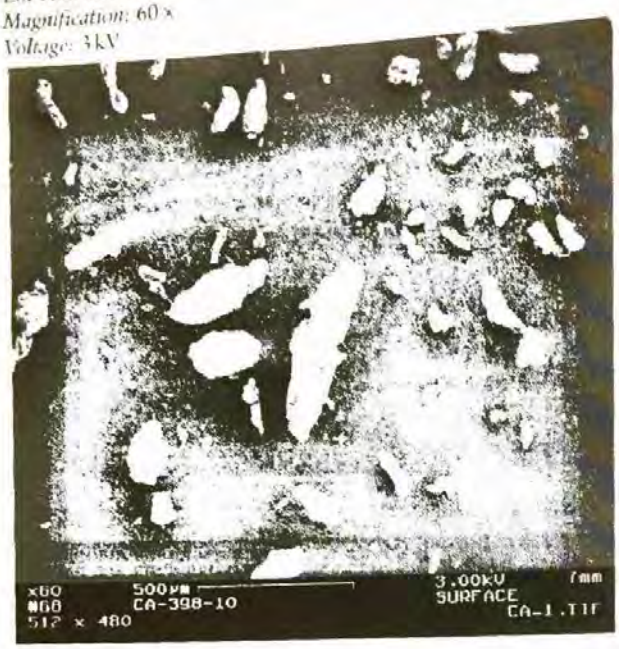
Cellulose acetate occurs as a white to off-white powder, free-flowing pellets, or flakes. It is tasteless and odorless, or may have a slight odor of acetic acid.

Table I: Comparison of different types of cellulose acetate.[1]

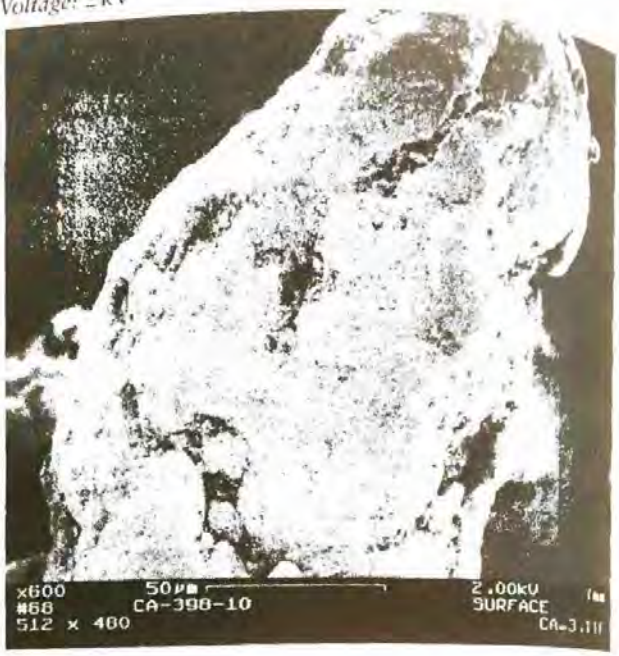
Type	Acetyl (%)	Viscosity (mPa s)	Hydroxyl (%)	Melting range (°C)	T_g[a] (°C)	Density[b] (g/cm³)	MWn[c]
CA-320S	32.0	210.0	8.7	230–250	180	0.4	38 000
CA-398-3	39.8	11.4	3.5	230–250	180	0.4	30 000
CA-398-6	39.8	22.8	3.5	230–250	182	0.4	35 000
CA-398-10NF	39.8	38.0	3.5	230–250	185	0.4	40 000
CA-398-30	39.7	114.0	3.5	230–250	189	0.4	50 000
CA-394-60S	39.5	228.0	4.0	240–260	186	–	60 000
CA-435-75	43.5	–	0.9	280–300	185	0.7	122 000

[a] Glass transition temperature.
[b] Tapped.
[c] Number average molecular weight in polystyrene equivalents.
Supplier: Eastman Chemical Company.

SEM: 1
Excipient: Cellulose acetate, CA-398-10NF
Manufacturer: Eastman Chemical Co.
Lot No.: AC65280NF
Magnification: 60×
Voltage: 3 kV



SEM 2
Excipient: Cellulose acetate, CA-398-10NF
Manufacturer: Eastman Chemical Co.
Lot No.: AC65280NF
Magnification: 600×
Voltage: 2 kV



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for cellulose acetate.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	—
Loss on drying	≤5.0%	≤5.0%
Residue on ignition	≤0.1%	≤0.1%
Free acid	+	≤0.1%
Heavy metals	≤10 ppm	≤0.001%
Microbial contamination	1000/g	—
Organic volatile impurities	—	+
Assay (of acetyl groups)	29.0–44.8%	29.0–44.8%

10 Typical Properties

Density (bulk): typically 0.4 g/cm^3 for powders
Glass transition temperature: 170–190°C
Melting point: melting range 230–300°C
Solubility: the solubility of cellulose acetate is greatly influenced by the level of acetyl groups present. In general, cellulose acetates are soluble in acetone–water blends of varying ratios, dichloromethane–ethanol blends, dimethyl formamide, and dioxane. The cellulose acetates of higher acetyl level are generally more limited in solvent choice than are the lower-acetyl materials.
Viscosity (dynamic): various grades of cellulose acetate are commercially available that differ in their acetyl content and degree of polymerization. They can be used to produce 10% w/v solutions in organic solvents with viscosities of 10–230 mPa s. Blends of cellulose acetates may also be prepared with intermediate viscosity values. *See also* Table I.

11 Stability and Storage Conditions

Cellulose acetate is stable if stored in a well-closed container in a cool, dry place. Cellulose acetate hydrolyzes slowly under prolonged adverse conditions such as high temperature and humidity, with a resultant increase in free acid content and odor of acetic acid.

12 Incompatibilities

Cellulose acetate is incompatible with strongly acidic or alkaline substances. Cellulose acetate is compatible with the following plasticizers: diethyl phthalate, polyethylene glycol, triacetin, and triethyl citrate.

13 Method of Manufacture

Cellulose acetate is prepared from highly purified cellulose by treatment with acid catalysis and acetic anhydride.

14 Safety

Cellulose acetate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic and nonirritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dust may be irritant to the eyes and eye protection should be worn. Like most organic materials in powder form, these materials are capable of creating dust explosions. Cellulose acetate is combustible.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral tablets).

17 Related Substances

Cellulose acetate phthalate.

18 Comments

When solutions are being prepared, cellulose acetate should always be added to the solvent, not the reverse. Various grades of cellulose acetate are available with varying physical properties; *see* Table I.

19 Specific References

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20 General References

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21 Author

RW Fengl.

22 Date of Revision

21 October 2002.

Cellulose Acetate Phthalate

1 Nonproprietary Names

BP: Cellacefate
JP: Cellulose acetate phthalate
PhEur: Cellulosi acetas phthalas
USPNF: Cellacefate

2 Synonyms

Acetyl phthalyl cellulose; *Aquacoat cPD*; CAP; cellacephate; cellulose acetate benzene-1,2-dicarboxylate; cellulose acetate hydrogen 1,2-benzenedicarboxylate; cellulose acetate hydrogen phthalate; cellulose acetate monophthalate; cellulose acetophthalate; cellulose acetylphthalate.

3 Chemical Name and CAS Registry Number

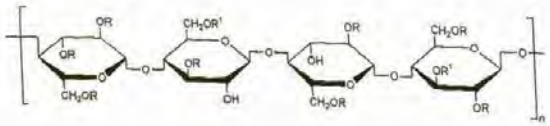
Cellulose, acetate, 1,2-benzenedicarboxylate [9004-38-0]

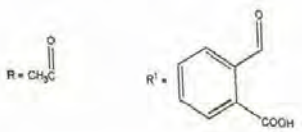
4 Empirical Formula Molecular Weight

Cellulose acetate phthalate is a cellulose in which about half the hydroxyl groups are acetylated, and about a quarter are esterified with one of two acid groups being phthalic acid, where the remaining acid group is free. *See* Section 5.

5 Structural Formula

The PhEur 2002 and USPNF 20 describe cellulose acetate phthalate as a reaction product of phthalic anhydride and a partial acetate ester of cellulose containing 21.5–26.0% of acetyl (C_2H_3O) groups, and 30.0–36.0% of phthalyl(*o*-carboxybenzoyl, $C_8H_5O_3$) groups.





6 Functional Category

Coating agent.

7 Applications in Pharmaceutical Formulation or Technology

Cellulose acetate phthalate (CAP) is used as an enteric film coating material, or as a matrix binder for tablets and capsules.[1–8] Such coatings resist prolonged contact with the strongly acidic gastric fluid, but dissolve in the mildly acidic or neutral intestinal environment.

Cellulose acetate phthalate is commonly applied to solid-dosage forms either by coating from organic or aqueous solvent systems or by direct compression. Concentrations generally used are 0.5–9.0% of the core weight. The addition of plasticizers improves the water resistance of this coating material, and formulations using such plasticizers are more effective than when cellulose acetate phthalate is used alone.

Cellulose acetate phthalate is compatible with many plasticizers, including acetylated monoglyceride; butyl phthalybutyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl phthalylethyl glycolate; glycerin; propylene glycol; triacetin; triacetin citrate; and tripropionin. It is also used in combination with other coating agents such as ethyl cellulose, in drug controlled-release preparations.

Therapeutically, cellulose acetate phthalate has recently been reported to exhibit experimental microbicidal activity against sexually transmitted disease pathogens, such as the HIV-1 retrovirus.[9,10]

8 Description

Cellulose acetate phthalate is a hygroscopic, white to off-white, free-flowing powder, granule, or flake. It is tasteless and odorless, or might have a slight odor of acetic acid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cellulose acetate phthalate.

Test	JP 2001	PhEur 2002 (Suppl 4.3)	USPNF 20
Identification	+	+	+
Characters	+	+	–
Free acid	⩽3.0%	⩽3.0%	⩽3.0%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Organic volatile impurities	–	–	+
Phthaloyl groups	–	+	+
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Viscosity (15% w/v solution)	45–90 mPa s	45.0–90.0 mPa s	45.0–90.0 mPa s
Water	⩽5.0%	⩽5.0%	⩽5.0%
Assay	+	+	+
Acetyl groups	21.5–26.0%	21.5–26.0%	21.5–26.0%
Carboxybenzoyl groups	30.0–40.0%	30.0–36.0%	30.0–36.0%

10 Typical Properties

Density (bulk): 0.260 g/cm^3
Density (tapped): 0.266 g/cm^3
Melting point: 192°C. Glass transition temperature is 163–170°C.[11]
Moisture content: 2.2%. Cellulose acetate phthalate is hygroscopic and precautions are necessary to avoid excessive absorption of moisture.[12] *See also* Figure 1.

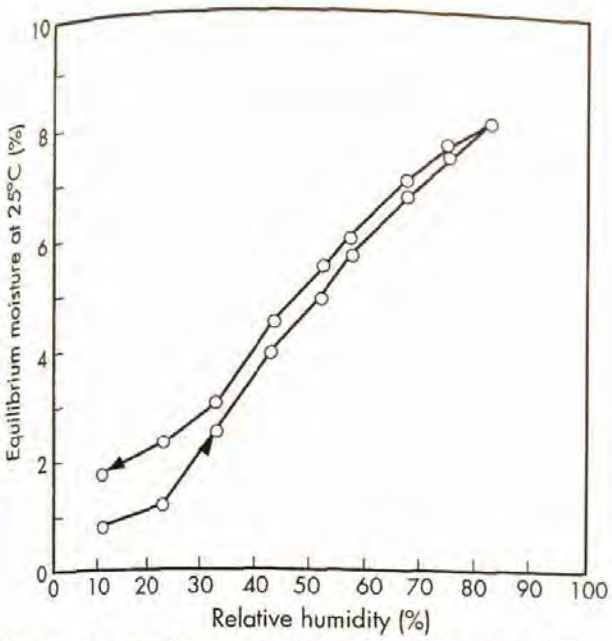


Figure 1: Sorption–desorption isotherm of cellulose acetate phthlate.

Table II: Examples of solvents with which cellulose acetate phthalate has ⩽10% w/w solubility.

Acetone
Diacetone alcohol
Dioxane
Ethoxyethyl acetate
Ethyl glycol monoacetate
Ethyl lactate
Methoxyethyl acetate
β-Methoxyethylene alcohol
Methyl acetate
Methyl ethyl ketone

Table III: Examples of solvent mixtures with which cellulose acetate phthalate has ⩽10% w/w solubility.

Acetone : ethanol (1 : 1)
Acetone : water (97 : 3)
Benzene : methanol (1 : 1)
Ethyl acetate : ethanol (1 : 1)
Methylene chloride : ethanol (3 : 1)

Solubility: practically insoluble in water, alcohols, and chlorinated and nonchlorinated hydrocarbons. Soluble in a number of ketones, esters, ether alcohols, cyclic ethers, and in certain solvent mixtures. It can be soluble in certain buffered aqueous solutions as low as pH 6.0. Cellulose acetate phthalate has a solubility of ⩽10% w/w in a wide range of solvents and solvent mixtures; Table II and Table III.

Viscosity (dynamic): a 15% w/w solution in acetone with a moisture content of 0.4% has a viscosity of 50–90 mPa s. This is a good coating solution with a honey-like consistency, but the viscosity is influenced by the purity of the solvent.

11 Stability and Storage Conditions

Slow hydrolysis of cellulose acetate phthalate will occur under prolonged adverse conditions such as high temperatures and high humidity, with a resultant increase in free acid content, viscosity, and odor of acetic acid. However, cellulose acetate phthalate is stable if stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Cellulose acetate phthalate is incompatible with ferrous sulfate, ferric chloride, silver nitrate, sodium citrate, aluminum sulfate, calcium chloride, mercuric chloride, barium nitrate, basic lead acetate, and strong oxidizing agents such as strong alkalis and acids.

13 Method of Manufacture

Cellulose acetate phthalate is produced by reacting the partial acetate ester of cellulose with phthalic anhydride in the presence of a tertiary organic base such as pyridine, or a strong acid such as sulfuric acid.

14 Safety

Cellulose acetate phthalate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic material, free of adverse effects.

Results of long-term feeding in rats and dogs have indicated a low oral toxicity. Rats survived daily feedings of up to 30% in the diet for up to 1 year without showing a depression in growth. Dogs fed 16 g daily in the diet for 1 year remained normal.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Cellulose acetate phthalate may be irritant to the eyes, mucous membranes, and upper respiratory tract. Eye protection and gloves are recommended. Cellulose acetate phthalate should be handled in a well-ventilated environment; use of a respirator is recommended when handling large quantities.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Cellulose acetate; hypromellose phthalate.

18 Comments

Any plasticizers that are used with cellulose acetate phthalate to improve performance should be chosen on the basis of experimental evidence. The same plasticizer used in a different tablet base coating may not yield a satisfactory product.

In using mixed solvents, it is important to dissolve the cellulose acetate phthalate in the solvent with the greater dissolving power, and then to add the second solvent. Cellulose acetate phthalate should always be added to the solvent, not the reverse.

Cellulose acetate phthalate films are permeable to certain ionic substances, such as potassium iodide and ammonium chloride. In such cases, an appropriate sealer subcoat should be used.

A reconstituted colloidal dispersion of latex particles rather than solvent solution coating material of cellulose acetate phthalate is also available. This white, water-insoluble powder is composed of solid or semisolid submicrometer-sized polymer spheres with an average particle size of 0.2 µm. A typical coating system made from this latex powder is a 10–30% solid-content aqueous dispersion with a viscosity in the 50–100 mPa s range.

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4 Stricker H, Kulke H. Rate of disintegration and passage of enteric-coated tablets in gastrointestinal tract [in German]. *Pharm Ind* 1981; **43**: 1018–1021.

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21 Author

RW Fengl.

22 Date of Revision

22 October 2002.

Lactose

1 Nonproprietary Names

BP: Lactose
JP: Lactose
PhEur: Lactosum monohydricum
USPNF: Lactose monohydrate
Note that the BP 2001, JP 2001, PhEur 2002, and USPNF 20 each also contain a monograph for anhydrous lactose.

2 Synonyms

Aero Flo 20; *Aero Flo 65*; *Aero Flo 95*; *Anhydrox*; *CapsuLac*; *Fast-Flo*; 4-(β-D-galactosido)-D-glucose; *FlowLac*; *GranuLac*; *InhaLac*; *HMS*; *Lactochem*; *Lactohale*; *Lactopress*; *Microfine*; *Microtose*; milk sugar; *Pharmatose*; *PrismaLac*; *Respitose*; saccharum lactis; *SacheLac*; *SorboLac*; *Super-Tab*; *Tablettose*; *Wyndale*; *Zeparox*.

3 Chemical Name and CAS Registry Number

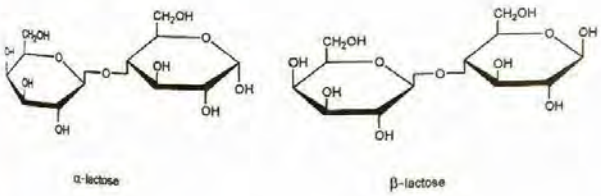
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous [63-42-3]

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [64044-51-5]

4 Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
$C_{12}H_{22}O_{11}$	342.30 (anhydrous)
$C_{12}H_{22}O_{11}\cdot H_2O$	360.31 (monohydrate)

5 Structural Formula



6 Functional Category

Diluent for dry-powder inhalers; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant feed formulas.[1–20] Lactose is also used as a diluent in dry-powder inhalations.[21]

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 upon 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 permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use as a carrier/diluent for inhalation products and in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid caking. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

The method for obtaining lactose from milk was patented in 1937. The process for making spray-dried lactose for use as direct-compression excipient was patented in 1958. Since that time, lactose has been used as the standard of comparison for all modern direct-compression excipients. Today, many other lactose grades are commercially available, including anhydrous α-lactose, α-lactose monohydrate, and, to a lesser extent, anhydrous β-lactose.

Generally, the grade of lactose chosen is dependent on the type of dosage form being developed. Direct-compression grades are often used to carry small quantities of drug and this permits tablets to be made without granulating.

Direct-compression grades of lactose are more fluid and more compressible than crystalline or powdered lactose and are generally composed of spray-dried lactoses that contain specially prepared pure α-lactose monohydrate along with a small amount of amorphous lactose. The amorphous lactose improves the compression force/hardness profile of the lactose. Other specially produced direct-compression grades of lactose do not contain amorphous material but may contain glassy or vitreous areas that impart improved compressibility. Direct-compression grades of lactose may also be combined with microcrystalline cellulose or starch, and usually require a tablet lubricant such as 0.5% w/w magnesium stearate. The use of direct-compression grades of lactose results in tablets of higher breaking strength than does use of standard lactose. Concentrations of lactose generally used in these formulations are from 65% to 85%. Lower amounts of spray-dried lactose can be used if additional direct-compression material such as pregelatinized starch is substituted.

8 Description

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 15% as sweet as sucrose, while β-lactose is sweeter than the α-form.

Several different forms of lactose are commercially available: anhydrous α-lactose, α-lactose monohydrate, and to a lesser extent, anhydrous β-lactose, which typically contains 70% anhydrous β-lactose and 30% anhydrous α-lactose, although grades containing a greater proportion of anhydrous β-lactose are also available, e.g., *Pharmatose DCL 21* (DMV Pharma). α-Lactose may also contain a small quantity of the β-form.

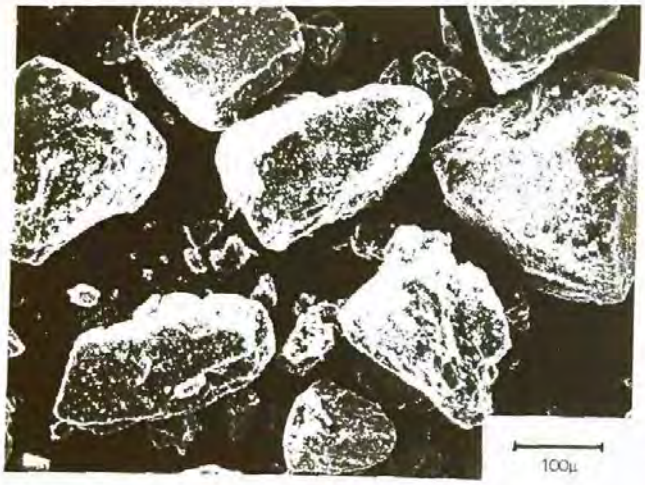
9 Pharmacopeial Specifications

See Table I.

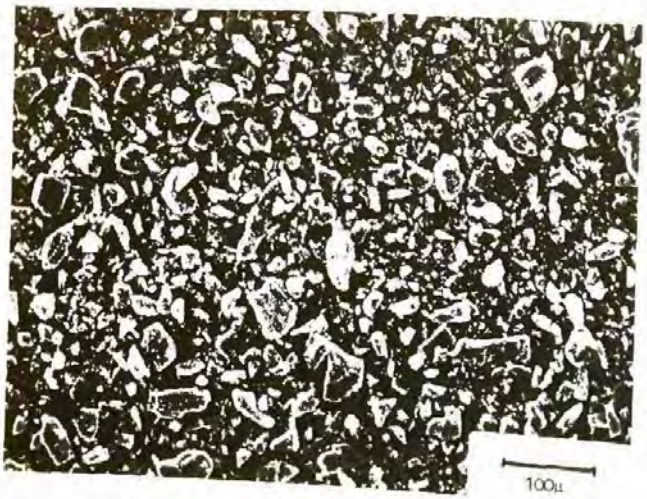
Table I: Pharmacopeial specifications for lactose.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	+
Specific rotation (anhydrous basis)	+54.4 to +55.9°	+54.4° to +55.9°	+54.4° to +55.9°
Microbial limits	100/g	100/g	100/g
Acidity or alkalinity	+	+	+
Loss on drying			
Anhydrous form	≤0.5%	—	≤0.5%
Monohydrate	≤0.5%	—	≤1.0%
Water			
Anhydrous form	≤1.0%	≤1.0%	≤1.0%
Monohydrate	4.5–5.5%	4.5–5.5%	4.5–5.5%
Residue on ignition	≤0.1%	≤0.1%	≤0.1%
Heavy metals	≤5 ppm	≤5 ppm	≤5 ppm
Protein and light-absorbing impurities	+	—	+

SEM: 1
Excipient: Lactose monohydrate (*Lactose D30*)
Manufacturer: Meggle GmbH

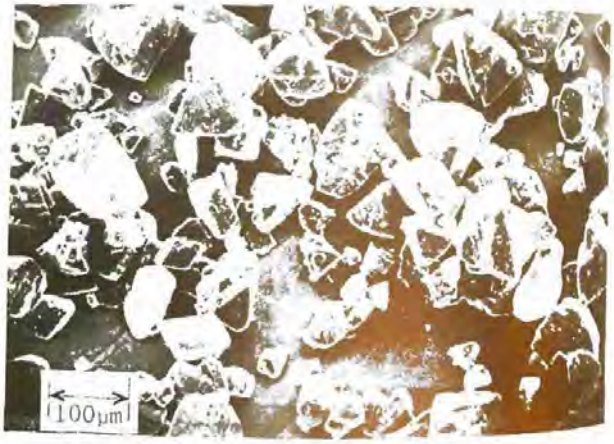


SEM: 2
Excipient: Lactose monohydrate (*Lactose G200*)
Manufacturer: Meggle GmbH



SEM: 3
Excipient: Lactose monohydrate (*Tablettose*)
Manufacturer: Meggle GmbH

SEM: 4
Excipient: Lactose monohydrate (*Lactose Monohydrate 60S*)
Manufacturer: Quest International Inc. (Sheffield Products)
Lot No.: 58A-13 (9 NJ 16)
Magnification: 120×
Voltage: 20 kV



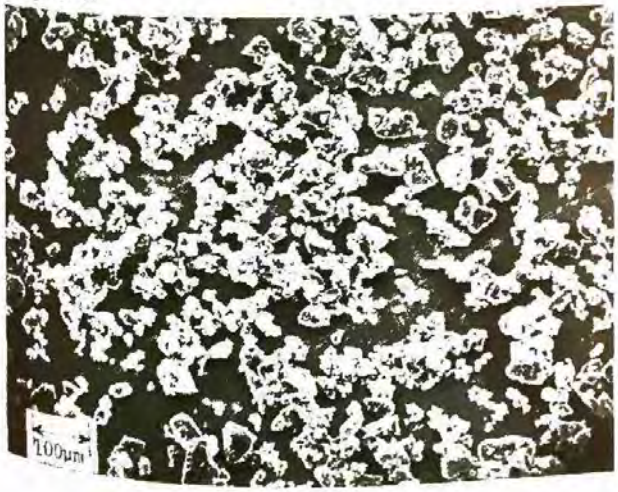
10 Typical Properties

Angle of repose: *see* Table II.
Compressibility: *see* Table III.
Density:
1.540 for α-lactose monohydrate
1.589 for anhydrous β-lactose
Density (bulk): 0.62 g/cm^3; *see also* Table II.
Density (tapped): 0.94 g/cm^3; *see also* Table II.
Density (true):
1.552 for α-lactose monohydrate
1.552 for anhydrous β-lactose
Flowability:
3.9 g/s (*Fast-Flo #316*, Foremost)
4.1 g/s (*Spray processed #315*, Foremost)
Hygroscopicity: lactose monohydrate is stable in air and is unaffected by humidity at room temperature. However, the amorphous form, depending upon how it is dried, may be affected by humidity and can be converted to the monohydrate.

SEM: 5
Excipient: Lactose monohydrate (*Lactose Monohydrate 80S*)
Manufacturer: Quest International Inc. (Sheffield Products)
Lot No.: 58A-12 (9 NK 18)
Magnification: 120×
Voltage: 20 kV

SEM: 7
Excipient: Lactose monohydrate (*Lactose Monohydrate Capsulating*)
Manufacturer: Quest International Inc. (Sheffield Products)
Lot No.: 58A-10 (9 NL 20)
Magnification: 120×
Voltage: 20 kV

SEM: 6
Excipient: Lactose monohydrate (*Lactose Monohydrate 80M*)
Manufacturer: Quest International Inc. (Sheffield Products)
Lot No.: 58A-11 (9 NL 18)
Magnification: 120×
Voltage: 20 kV



SEM: 8
Excipient: Lactose monohydrate (*Lactose Monohydrate Impalpable*)
Manufacturer: Quest International Inc. (Sheffield Products)
Lot No.: 58A-14 (9 NH 22)
Magnification: 120×
Voltage: 20 kV

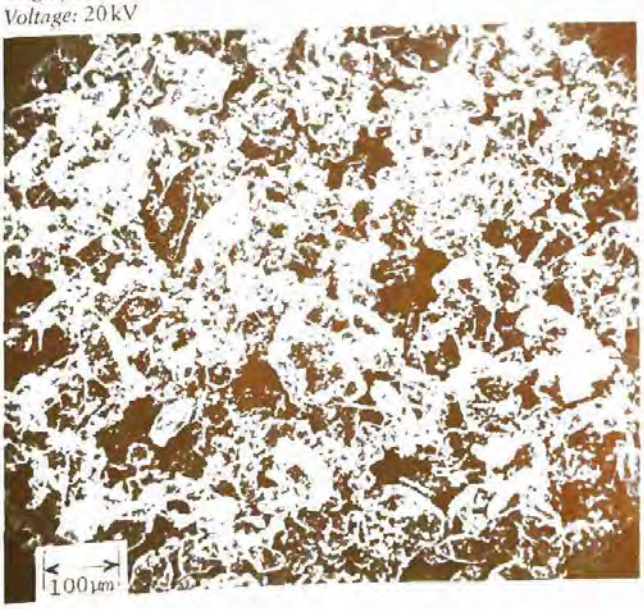


Table II: Typical physical properties of selected commercially available lactoses.

Supplier/grade	Angle of repose (°)	Density bulk (g/cm³)	Density tapped (g/cm³)	Specific surface area (m²/g)	Water content (%)
Borculo Domo Ingredients					
Microfine	–	–	–	–	5.5
Zeparox[a]	–	0.6–0.7	–	–	5.5
DMV Pharma					
Pharmatose 50M	36	0.80	0.95	–	5.2
Pharmatose 80M	38	0.76	0.91	–	5.2
Pharmatose 90M	39	0.76	0.91	–	5.2
Pharmatose 100M	39	0.75	0.90	–	5.2
Pharmatose 110M	40	0.73	0.89	–	5.2
Pharmatose 125M	44	0.68	0.87	–	5.2
Pharmatose 150M	–	0.58	0.89	0.45	5.2
Pharmatose 200M	–	0.55	0.85	0.50	5.2
Pharmatose 325M	40	0.67	0.84	–	5.2
Pharmatose 350M	–	0.50	0.82	0.60	5.2
Pharmatose 450M	–	0.47	0.77	1.0	5.2
Pharmatose DCL 11[b]	31	0.61	0.73	–	4.8
Pharmatose DCL 21[c]	39	0.67	0.85	0.35	0.5
Foremost Farms USA					
Regular 310A	45	0.66	0.95	–	4.8–5.2
Regular 310B	47	0.66	0.92	–	4.8–5.2
Impalpable 312	–	0.53	0.81	–	4.8–5.2
Impalpable 313	–	0.48	0.78	–	4.8–5.2
Spray Process 315[b]	33	0.67	0.78	–	4.8–5.2
Fast-Flo 316[b]	33	0.58	0.67	–	4.8–5.2
Hollandse Melksuikerfabriek					
HMS Lactose DT	33	0.53	0.66	–	4.8
Meggle GmbH					
Capsulac 60	–	0.56	0.67	–	5.2
Flowlac 100[a]	32.2	0.60	0.71	–	5.2
Granulac 70	–	0.72	0.91	–	5.2
Granulac 140	–	0.66	0.85	–	5.2
Granulac 200	–	0.53	0.77	–	5.2
Granulac 230	–	0.45	0.72	–	5.2
Prismalac 40	–	0.45	0.54	–	5.2
Sachelac 80	–	0.64	0.82	–	5.2
Sorbolac 400	–	0.37	0.67	–	5.2
Spherolac 100	–	0.68	0.85	–	5.2
Tablettose 70[a]	31.9	0.52	0.64	–	5.2
Tablettose 80[a]	32.2	0.55	0.69	–	5.2
Quest International Inc. (Sheffield Products)					
Monohydrate 60S	–	–	–	–	≤5.5
Monohydrate 80S	–	–	–	–	≤5.5
Monohydrate 80M	–	–	–	–	≤5.5
Monohydrate Capsulating	–	–	–	–	≤5.5
Monohydrate Impalpable	–	–	–	–	≤5.5
Anhydrous Direct Tableting	–	–	–	–	≤1.0
Anhydrous 60M	–	–	–	–	≤1.0
Anhydrous 80M	–	–	–	–	≤1.0
Anhydrous Impalpable	–	–	–	–	≤1.0

[a] Direct compression grade of lactose.
[b] Spray-dried lactose monohydrate.
[c] Anhydrous lactose containing 82% β-lactose.
Unless otherwise stated all of the above grades are α-lactose monohydrate.

Melting point:
201–202°C for α-lactose monohydrate
223°C for anhydrous α-lactose
252.2°C for anhydrous β-lactose

Moisture content: anhydrous lactose normally contains up to 1% w/w water. Lactose monohydrate contains approximately 5% w/w water of crystallization and normally ranges between 4.5% and 5.5% w/w water content. *See also* Table II and Figures 1–3.

Osmolarity: a 9.75% w/v aqueous solution is isoosmotic with serum.

Particle size distribution: *see* Table IV.

Table III: Summary of mechanical properties of lactose.

Lactose type	Compression pressure (kN/cm²)	Tensile strength (kN/cm²)	Permanent deformation pressure (kN/cm²)	Brittle fracture index	Bonding index	Reduced modulus of elasticity
Lactose anhydrous (EM Industries)	17.78	0.2577	52.1	0.0362	0.0049	5315
Lactose monohydrate	19.10	0.2517	48.5	0.0883	0.0052	5155
Lactose monohydrate (EM Industries)	18.95	0.2987	37.0	0.0749	0.0081	1472
Lactose spray process	15.49	0.2368	54.3	0.1671	0.0044	5648

Solubility: see Table V.

Specific rotation $[\alpha]_D^{20}$: +54.8° to +55.5° for anhydrous lactose, as a 10% w/v aqueous solution.

Specific rotation $[\alpha]_D^{25}$: +52° to +52.6° for lactose monohydrate, as a 10% w/v aqueous 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.

Specific surface area:
0.24–0.25 m²/g for lactose, regular
0.55–0.56 m²/g for lactose, 170 mesh

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 also* Section 12. The purities of different lactoses can vary and color evaluation may thus be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also differ.

Saturated solutions of β-lactose may precipitate crystals of α-lactose on standing. Solutions also 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-colored products.[22] This reaction occurs more readily with the amorphous material than with crystalline lactose. The spray-dried material, which contains about 10% amorphous lactose, is also prone to discoloration. The 'browning reaction' is base-catalyzed and may therefore be accelerated if alkaline lubricants are used. Lactose may also develop a yellow-brown color, in the absence of amines, with browning again occurring most rapidly in the spray-dried material, possibly owing to the formation of 5-hydroxymethyl-2-furfural.

Lactose is incompatible with amino acids, aminophylline,[23] amfetamines,[24] and lisinopril.[25]

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

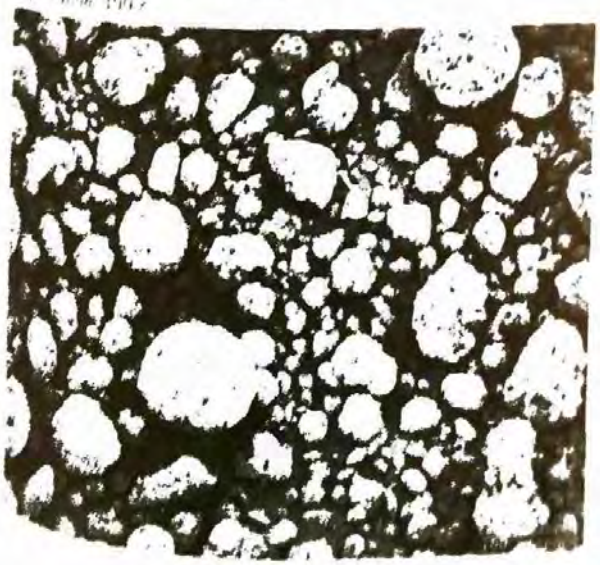
Lactose exists as two anomeric forms, α and β, which are normally handled as, respectively, the monohydrate and the anhydrous material. α-Lactose is prepared by crystallization from supersaturated solutions below 93.5°C, whereas β-lactose is prepared from solutions above this temperature. The commercially available β-lactose typically contains 70% of the β-form and 30% of the α-form and is prepared by roller drying. Other grades containing greater amounts of the β-form are also available.

SEM: 9

Excipient: Spray dried lactose monohydrate (*Super-Tab*)

Manufacturer: Lactose New Zealand

Magnification: 100×



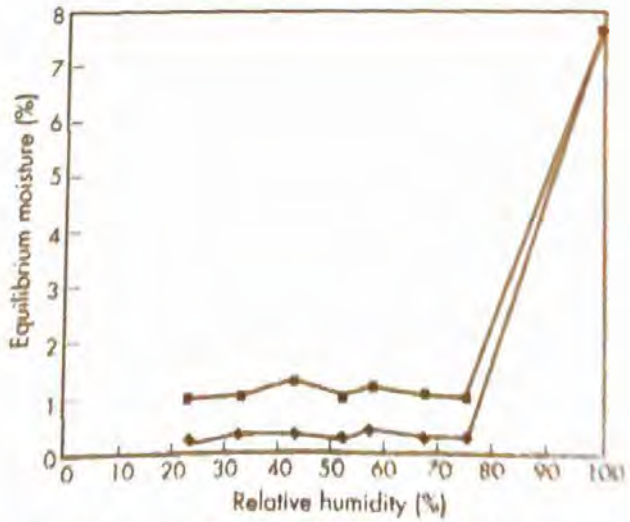


Figure 1: Moisture sorption–desorption isotherm for lactose monohydrate
■ sorption
◆ desorption

Table IV: Particle size distribution of selected commercially available lactoses.

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
Borculo Domo Ingredients													
Microfine	99.9	–	–	–	–	–	–	–	–	–	–	–	–
Zeparox[a]	–	–	–	–	10–20	40–65	70–95	95–100	–	–	–	–	–
DMV Pharma													
Pharmatose 50M	–	–	–	–	–	–	–	10	–	–	92	–	–
Pharmatose 80M	–	–	–	–	–	10	–	–	84	99	–	–	–
Pharmatose 90M	–	–	–	6	–	21	65	–	–	100	–	–	–
Pharmatose 100M	–	–	–	9	–	–	68	–	99.7	–	–	–	–
Pharmatose 110M	–	–	–	15	–	40	85	–	–	100	–	–	–
Pharmatose 125M	–	–	25	55	–	97	–	–	–	100	–	–	–
Pharmatose 150M	–	–	45	–	–	75	90	–	–	100	–	–	–
Pharmatose 200M	–	–	60	–	83	92	98	–	100	–	–	–	–
Pharmatose 325M	–	8	–	78	–	100	–	–	–	–	–	–	–
Pharmatose 350M	–	–	75	–	–	98	–	–	100	–	–	–	–
Pharmatose 450M	–	–	95	99	–	–	100	–	–	–	–	–	–
Pharmatose DCL 11[b]	–	–	10	–	–	45	–	–	100	–	–	–	–
Pharmatose DCL 15	–	–	–	–	25	–	60	–	–	–	–	–	–
Pharmatose DCL 21[c]	–	–	15	–	–	–	50	–	85	–	–	–	–
Foremost Farms USA													
Regular 310A	–	24	30	–	53	–	73	–	100	–	–	–	–
Regular 310B	–	29	37	–	66	–	86	–	100	–	–	–	–
Impalpable 312	–	65	77	–	97	99	–	–	–	–	–	–	–
Impalpable 313	–	83	93	–	99	–	–	–	–	–	–	–	–
Spray Process 315[b]	–	5	10	–	33	–	57	–	100	–	–	–	–
Fast-Flo 316[b]	–	6	9	–	32	–	62	–	100	–	–	–	–
Hollandse Melksuikerfabriek													
HMS Lactose DT	–	–	–	–	25	–	60	–	–	–	–	100	–
Meggle GmbH													
CapsuLac 60	–	–	–	–	–	<10	–	–	40–70	–	–	>97	–
FlowLac 100[a]	–	<10	–	–	–	25–40	–	>85	–	–	–	–	–
GranuLac 70	–	–	–	–	–	40–60	–	–	–	–	>95	–	–
GranuLac 140	–	<40	–	–	–	>80	–	–	–	–	–	–	–
GranuLac 200	–	45–75	–	–	–	>90	–	–	–	–	–	–	–
GranuLac 230	–	>90	–	>90	–	–	–	–	–	–	–	–	–
PrismaLac 40	–	–	–	–	–	–	–	<10	–	–	–	–	>97
SacheLac 80	–	–	–	–	–	<20	–	–	–	–	>98	–	–
SorboLac 400	–	>90	–	–	–	–	–	–	–	–	–	–	–
SpheroLac 100	–	–	–	<20	–	–	–	>75	–	–	–	–	–
Tablettose 70[a]	–	–	–	<6	–	–	–	40–75	–	–	>85	>97	–
Tablettose 80[a]	–	–	–	–	–	–	–	–	–	–	–	–	–

Continued

Quest International Inc. (Sheffield Products)												
Monohydrate 60S	—	—	—	—	15–35	70–85	80–90	—	97–100	—	—	—
Monohydrate 80S	—	—	—	—	20–35	—	80–95	—	99.3–100	—	—	—
Monohydrate 80M	—	—	—	—	65–90	95–98	95–99.5	—	99.5–100	—	—	—
Monohydrate Capsulating	—	—	—	—	58–70	—	94–100	—	—	—	—	—
Monohydrate Impalpable	—	—	—	—	90	97–99	98.5–100	—	—	—	—	—
Anhydrous Direct Tableting	—	—	—	—	15–30	75–90	85–93	—	—	—	—	—
Anhydrous 60M	—	—	—	—	20–40	75–90	85–93	—	95–98	—	—	—
Anhydrous 80M	—	—	—	—	70	—	—	—	—	—	—	—
Anhydrous Impalpable	—	—	—	—	90	—	—	—	—	—	—	—

[a] Direct compression grade of lactose

[b] Spray-dried lactose monohydrate

[c] Anhydrous lactose containing 82% β-lactose

Unless otherwise stated all of the above grades are α-lactose monohydrate.

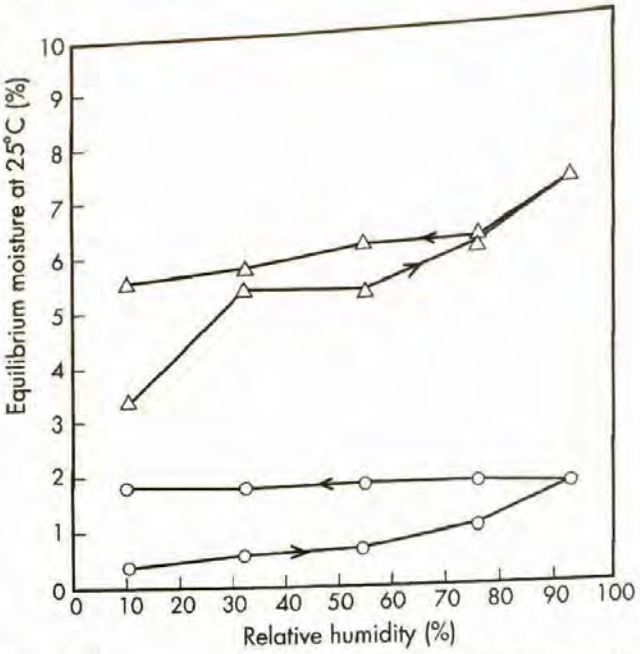


Figure 2: Moisture sorption–desorption isotherms of different grades of lactose.
○: Anhydrous lactose, *Anhydrous Impalpable* (Lot no. 7N4868)
△: Lactose, *Spray Process #315* (Lot no. RH914)

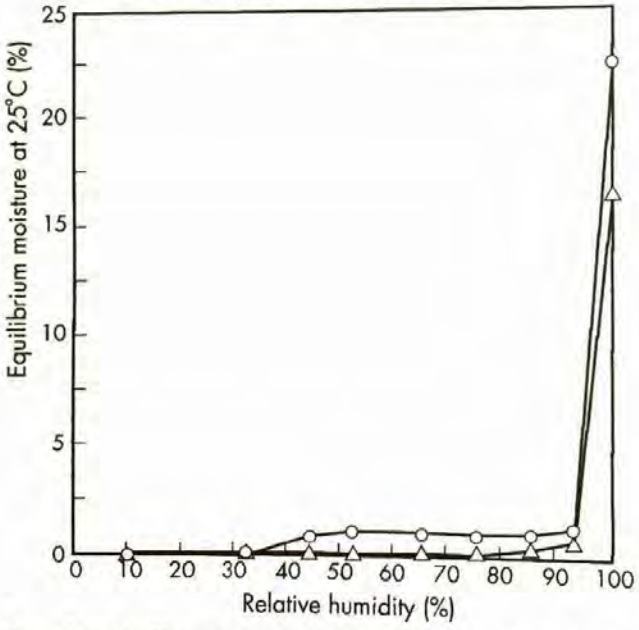


Figure 3: Equilibrium moisture content of different grades of lactose.
○: Lactose, *Spray Process #315* (Lot no. 56165)
△: Lactose, *Fast-Flo #316* (Lot no. RB806)

α-Lactose is available primarily as the monohydrate, but two anhydrous forms also exist. Anhydrous forms that are commercially available may exhibit hygroscopicity. An unstable hygroscopic form can also be prepared using special drying techniques; however, this material is not used or available in normal practice.

An amorphous or glassy form of lactose is present in lactose when it is either spray-dried from a suspension or lyophilized. This noncrystalline portion is responsible for the improved compressibility of spray-dried lactose.

Table V: Solubility of lactose.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Ether	Practically insoluble
Water	1 in 4.63
	1 in 3.14 at 40°C
	1 in 2.04 at 50°C
	1 in 1.68 at 60°C
	1 in 1.07 at 80°C

α-Lactose monohydrate has also been prepared by special commercial crystallization procedures that improve compressibility over the normally prepared material. These special grades may be readily identified by microscopic examination. Various crystalline shapes are prism, pyramidal, and tomahawk; these are dependent on the method of precipitation and crystallization.

14 Safety

Lactose is widely used in pharmaceutical formulations as a diluent 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 persons with a deficiency of the intestinal enzyme lactase.[26–28] This results in lactose being undigested and may lead to clinical symptoms including abdominal cramps, diarrhea, distension, and flatulence. In lactose-tolerant individuals, the enzyme lactase hydrolyzes lactose in the small intestine to glucose and galactose, which are then absorbed. Lactose is excreted unchanged when administered intravenously. Lactase is normally high at birth but declines rapidly in early childhood. Malabsorption of lactose (hypolactasia) may thus occur at an early age, e.g., at 4–8 years, and varies among different ethnic groups.

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, thus causing abdominal distension and discomfort.

A lactase tolerance test has been developed based upon the measurement of the 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.[26,27] In one of these studies,[26] 75% of the subjects had symptoms with 12 g of lactose (equivalent to 250 ml of milk). In the other study,[27] 8 out of 13 individuals developed diarrhea after the administration of 20 g of lactose, and 9 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 can still ingest normal amounts of lactose, such as that in milk, without the development of significant adverse effects.

Most adults consume about 25 g of lactose per day (500 ml of milk) without symptoms.[29,30] 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 actose intolerant. However, anecdotal reports of drug-nduced diarrhea due to lactose intolerance have been made ollowing administration of pharmaceutical preparations con-aining lactose.

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 dust inhalation, should be avoided.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections; oral capsules and tablets). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

–

18 Comments

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.[7–9,13]

A number of excipient mixtures intended for direct compression use are commercially available, e.g., *Cellactose* (Meggle GmbH) is a mixture of lactose and cellulose.[31,32]

Lactose, depending on its form, 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.[33] For example, α-lactose monohydrate becomes anhydrous at 120°C and has a melting point of 201–202°C; endothermic peaks occur at approximately 150°C and vary depending upon the particle size of the material.

Coprocessed lactose and starch (*Starlac*, Roquette Corp.) is commercially available for direct compression.

The EINECS number for lactose is 200-559-2.

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21 Authors

AH Kibbe, PJ Weller.

22 Date of Revision

26 November 2002.

Mannitol

1 Nonproprietary Names

BP: Mannitol
JP: D-Mannitol
PhEur: Mannitolum
USP: Mannitol

2 Synonyms

Cordycepic acid; E421; manna sugar; D-mannite; mannite; *Mannogem*; *Pearlitol*.

3 Chemical Name and CAS Registry Number

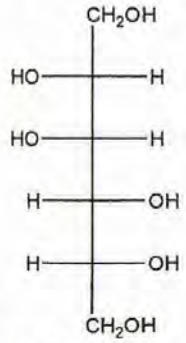
D-Mannitol [69-65-8]

4 Empirical Formula and Molecular Weight

$C_6H_{14}O_6$

182.17

5 Structural Formula



6 Functional Category

Sweetening agent; tablet and capsule diluent; tonicity agent; vehicle (bulking agent) for lyophilized preparations.

7 Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.[1]

Mannitol may be used in direct-compression tablet applications,[2–6] for which the granular and spray-dried forms are available, or in wet granulations.[7] Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.[8,9]

In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.[10–17] A pyrogen-free form is available specifically for this use.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,[18] and as a carrier in dry powder inhalers.[19] It is also used in food applications as a bulking agent.

Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the GI tract, but in large doses it can cause osmotic diarrhea; *see* Section 14.

8 Description

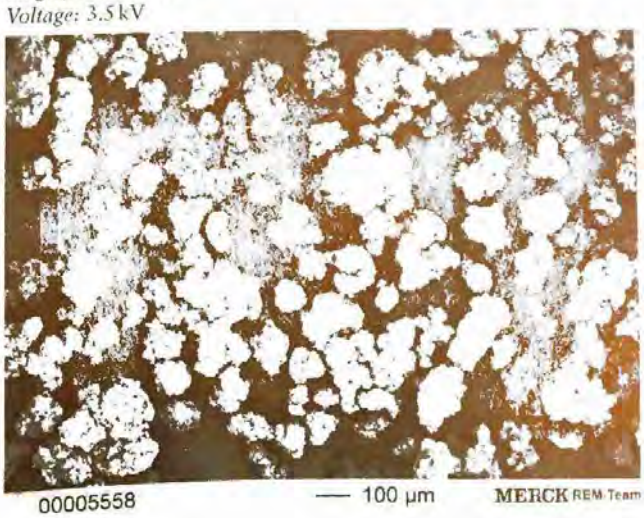
Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.

Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.[20]

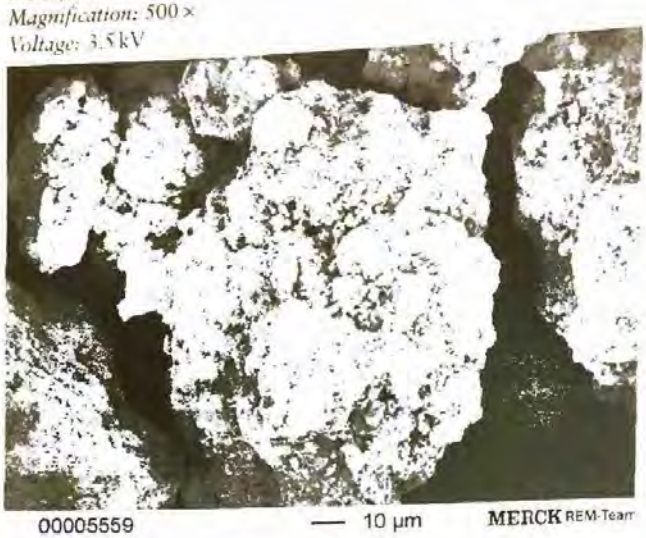
9 Pharmacopeial Specifications

See Table I.

SEM: 1
Excipient: Mannitol
Manufacturer: Merck
Magnification: 50×
Voltage: 3.5 kV



SEM: 2
Excipient: Mannitol
Manufacturer: Merck
Magnification: 500×
Voltage: 3.5 kV



SEM: 3
Excipient: Mannitol powder
Manufacturer: SPI Polyols Inc.
Lot No: 3140G8
Magnification: 100×

10 Typical Properties

Compressibility: *see* Figure 1.
Density (bulk):
0.430 g/cm^3 for powder
0.7 g/cm^3 for granules
Density (tapped):
0.734 g/cm^3 for powder
0.8 g/cm^3 for granules
Density (true): 1.514 g/cm^3
Dissociation constant: pK_a = 13.5 at 18°C
Flash point: <150°C
Flowability: powder is cohesive, granules are free flowing.
Heat of combustion: 16.57 kJ/g (3.96 Kcal/g)
Heat of solution: −120.9 J/g (−28.9 cal/g) at 25°C
Melting point: 166–168°C
Moisture content: *see* Figure 2.

SEM: 4
Excipient: Mannitol granular
Manufacturer: SPI Polyols Inc.
Lot No: 2034F8
Magnification: 100×

Osmolarity: a 5.07% w/v aqueous solution is isoosmotic with serum.
Particle size distribution:
Pearlitol 300 DC: maximum of 0.1% greater than 500 µm and minimum of 90% greater than 200 µm in size
Pearlitol 400 DC: maximum of 20% greater than 500 µm and minimum of 85% greater than 100 µm in size
Pearlitol 500 DC: maximum of 0.5% greater than 841 µm and minimum of 90% greater than 150 µm in size
Average particle diameter is 250 µm for *Pearlitol 300 DC*, 360 µm for *Pearlitol 400 DC* and 520 µm for *Pearlitol 500 DC*.[21] *See also* Figure 3.
Refractive index: n_D^{20} = 1.333
Solubility: *see* Table II.
Specific surface area: 0.37–0.39 m^2/g

Table I: Pharmacopeial specifications for mannitol.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	–	+	–
Solution appearance	+	+	–
Melting range	166–169°C	165–170°C	164–169°C
Specific rotation	+137° to +145°	+23° to +25°	+137° to +145°
Conductivity	–	+	–
Acidity	+	–	+
Loss on drying	≤0.3%	≤0.5%	≤0.3%
Chloride	≤0.007%	–	≤0.007%
Sulfate	≤0.01%	–	≤0.01%
Arsenic	≤1.3 ppm	–	≤1 ppm
Lead	–	≤0.5 ppm	–
Nickel	+	≤1 ppm	–
Heavy metals	≤5 ppm	–	–
Reducing sugars	+	≤0.2%	+
Residue on ignition	≤0.10%	–	–
Related substances	–	≤0.1%	–
Bacterial endotoxins	–	≤4 IU/g[a]	–
Microbial contamination	–	≤100/g	–
Assay (dried basis)	≥ 98.0%	98.0–102.0%	96.0–101.5%

[a] Test applied only if the mannitol is to be used in the manufacture of parenteral dosage forms.

Table II: Solubility of mannitol.

Solvent	Solubility at 20°C
Alkalis	Soluble
Ethanol (95%)	1 in 83
Ether	Practically insoluble
Glycerin	1 in 18
Propan-2-ol	1 in 100
Water	1 in 5.5

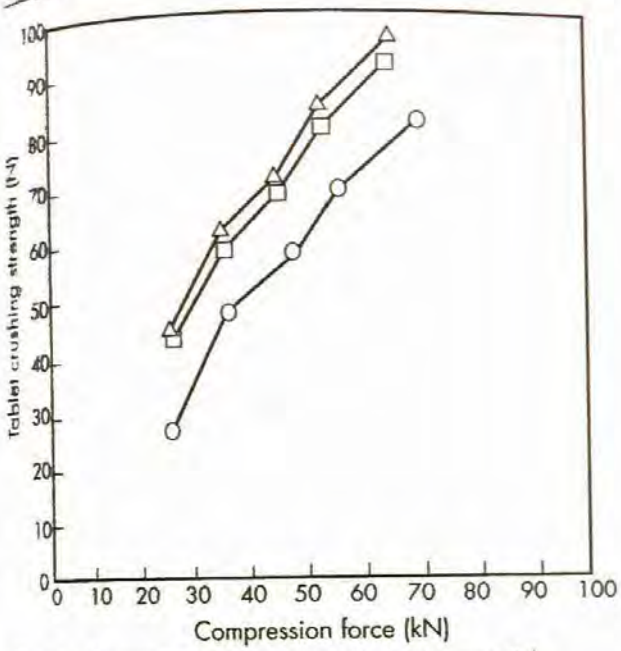


Figure 1: Compression characteristics of granular mannitol (*Pearlitol*, Roquette Frères).
○: *Pearlitol 300DC*
□: *Pearlitol 400DC*
△: *Pearlitol 500DC*
Tablet diameter: 20 mm
Lubricant: magnesium stearate 0.7% w/w for *Pearlitol 400DC* and *Pearlitol 500DC*; magnesium stearate 1% w/w for *Pearlitol 300DC*.

11 Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects.[22] In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.[23] Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.[24] Sodium cephapirin at 2 mg/mL and 30 mg/mL is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.[25] Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.[26]

13 Method of Manufacture

Mannitol may be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.

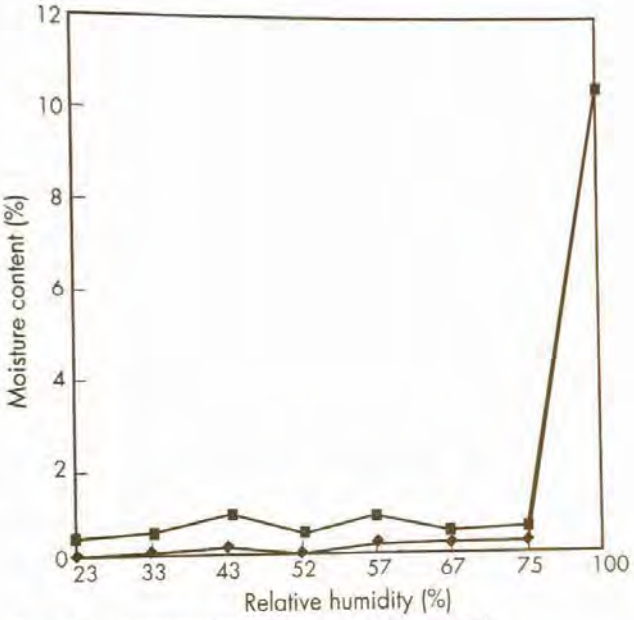


Figure 2: Sorption–desorption isotherm for mannitol.
◆: Sorption equilibrium moisture
■: Desorption equilibrium moisture

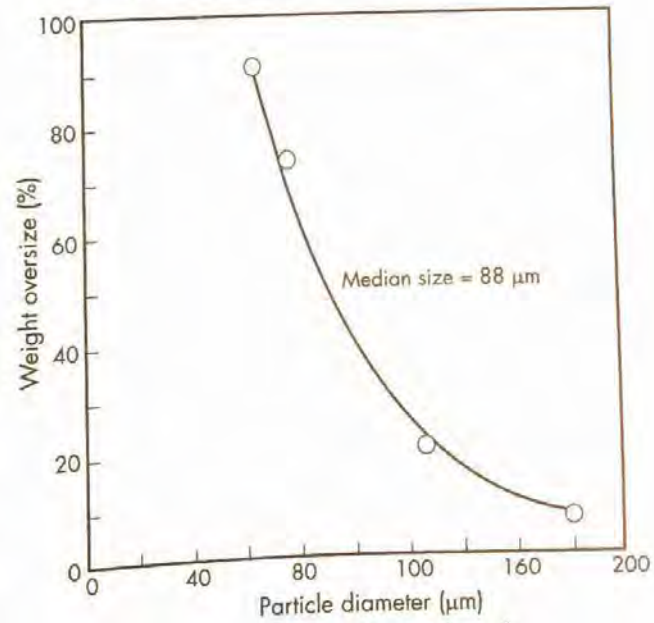


Figure 3: Particle size distribution of mannitol powder.

14 Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities.[27] If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement 'excessive consumption may have a laxative effect'. After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.[28]

A number of adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions.[29] The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitive-type reactions may occur when mannitol is used as an excipient.

An acceptable daily intake of mannitol has not been specified by the WHO since the amount consumed as a sweetening agent was not considered to represent a hazard to health.[30]

LD_{50} (mouse, IP): 14 g/kg[31]
LD_{50} (mouse, IV): 7.47 g/kg
LD_{50} (mouse, oral): 22 g/kg
LD_{50} (rat, IV): 9.69 g/kg
LD_{50} (rat, oral): 13.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IP, IM, IV, and SC injections; infusions; buccal, oral and sublingual tablets and capsules). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Sorbitol.

18 Comments

Mannitol is an isomer of sorbitol, the difference between the two polyols occurring in the planar orientation of the OH group on the second carbon atom. Each isomer is characterized by its own individual set of properties, the most important difference being the response to moisture. Sorbitol is hygroscopic, while mannitol resists moisture sorption, even at high relative humidities.

Granular mannitol flows well and imparts improved flow properties to other materials. However, it usually cannot be used with concentrations of other materials exceeding 25% by weight. Recommended levels of lubricant are 1% w/w calcium stearate or 1–2% w/w magnesium stearate. Suitable binders for preparing granulations of powdered mannitol are gelatin, methylcellulose 400, starch paste, povidone, and sorbitol. Usually, 3–6 times as much magnesium stearate or 1.5–3 times as much calcium stearate is needed for lubrication of mannitol granulations than is needed for other excipients.

Mannitol has been reported to sublime at 130°C.[32]

The EINECS number for mannitol is 200-711-8.

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21 Author

NA Armstrong.

22 Date of Revision

22 October 2002.

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: Maydis amylum (maize starch)
Solani amylum (potato starch)
Oryzae amylum (rice starch)
Tritici amylum (wheat starch)

USPNF: Starch

Note that the USPNF 20 describes starch, in a single monograph, as being obtained from either the mature grain of corn, *Zea mays*, or of wheat, *Triticum aestivum*, or from tubers of the potato, *Solanum tuberosum*, or of tapioca, *Manihot utilissima*. The PhEur 2002 has individual monographs for each of these starches, except for tapioca starch, along with an additional monograph for rice starch, *Oryza sativa*. The BP 2001 similarly describes maize, potato, rice, tapioca (cassava), and wheat starch in individual monographs, tapioca starch being obtained from the rhizomes of *Manihot utilissima* Pohl. The JP 2001 similarly describes corn (maize), rice, potato and wheat starch in separate monographs. *See also* Section 18.

2 Synonyms

Amido; amidon; amilo; amylum; *Aytex P*; *Fluftex W*; *Instant Pure-Cote*; *Melojel*; *Meritena*; *Paygel 55*; *Perfectamyl D6PH*; *Pure-Bind*; *Pure-Cote*; *Pure-Dent*; *Pure-Gel*; *Pure-Set*; *Purity 21*; *Purity 826*; *Tablet White*.

See also Sections 1 and 18.

3 Chemical Name and CAS Registry Number

Starch [9005-25-8]

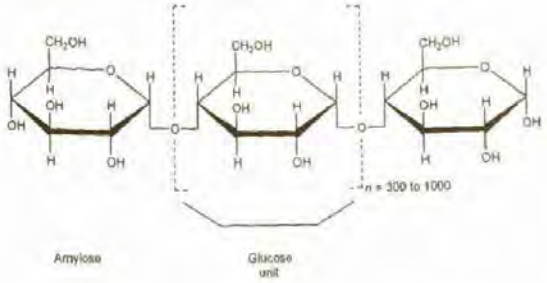
4 Empirical Formula and Molecular Weight

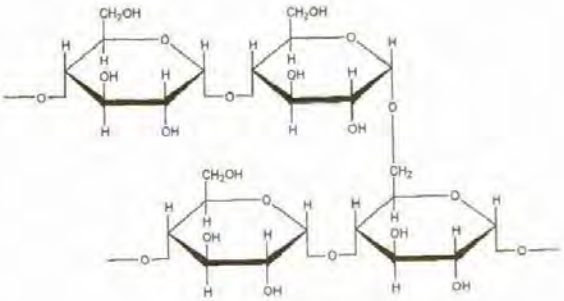
$(C_6H_{10}O_5)_n$
where n = 300–1000.

50 000–160 000

Starch consists of amylose and amylopectin, two polysaccharides based on α-glucose. *See also* Sections 5 and 17.

5 Structural Formula





Segment of amylopectin molecule

6 Functional Category

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

7 Applications in Pharmaceutical Formulation or Technology

Starch is used as an excipient 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 or potent drugs to facilitate 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]

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w.[2–9] However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In

granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also starch when used as a disintegrant exhibits type II isotherms and has a high specific surface for water sorption.[10]

Starch has been investigated as an excipient in novel drug delivery systems for nasal,[11] oral,[12,13] peridontal,[14] and other site-specific delivery systems.[15]

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

Therapeutically, rice starch-based solutions have been used in the prevention and treatment of dehydration due to acute diarrheal diseases.

8 Description

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–6.5 for a 2% w/v aqueous dispersion of corn starch, at 25°C.

Compressibility: *see* Figure 1.

Density (bulk): 0.462 g/cm^3 for corn starch.

Density (tapped): 0.658 g/cm^3 for corn starch.

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

Flowability: 10.8–11.7 g/s for corn starch;[9] 30% for corn starch (Carr compressibility index).[16] Corn starch is cohesive and has poor flow characteristics.

Gelatinization temperature: 73°C for corn starch; 72°C for potato starch; 63°C for wheat starch.

Moisture content: all starches are hygroscopic and rapidly absorb atmospheric moisture.[17,18] Approximate equilibrium moisture content values at 50% relative humidity are 11% for corn starch; 18% for potato starch; 14% for rice starch; and 13% for wheat starch. Between 30% and 80% relative humidity, corn starch is the least hygroscopic starch and potato starch is the most hygroscopic. Commercially available grades of corn starch usually contain 10–14% water. *See also* Figures 2 and 3.

Particle size distribution:
- Corn starch: 2–32 μm
- Potato starch: 10–100 μm
- Rice starch: 2–20 μm
- Tapioca starch: 5–35 μm
- Wheat starch: 2–45 μm

Median diameter for corn starch is 17 μm and for wheat starch is 23 μm.

Solubility: practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about 5–10% at 37°C.[2,18] Polyvalent cations produce more swelling than monovalent ions, but pH has little effect.

Specific surface area:
- 0.41–0.43 m^2/g for corn starch
- 0.12 m^2/g for potato starch
- 0.27–0.31 m^2/g for wheat starch

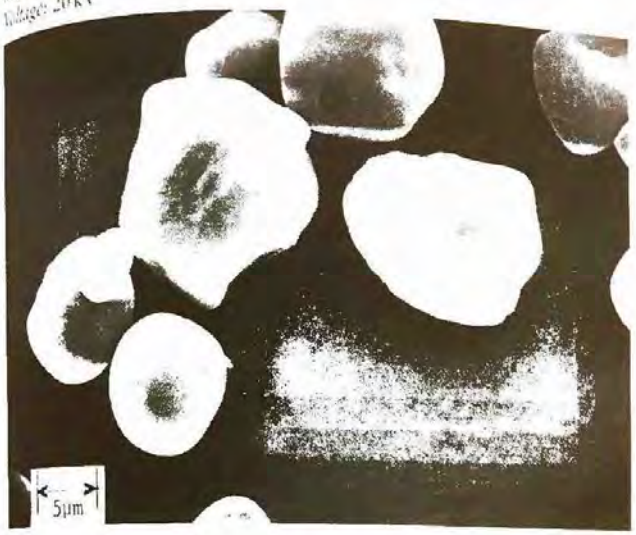
Swelling temperature:
- 65°C for corn starch
- 64°C for potato starch
- 55°C for wheat starch

Viscosity (dynamic): 13.0 mPa s (13.0 cP) for a 2% w/v aqueous dispersion of corn starch at 25°C.

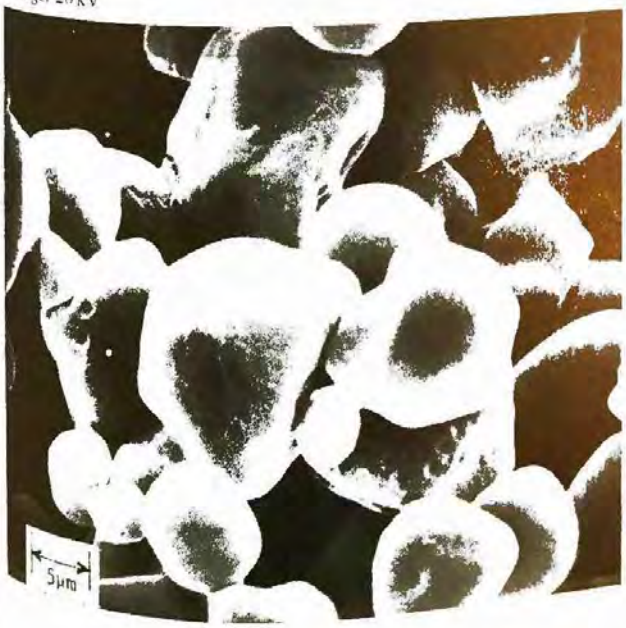
Table I: Pharmacopeial specifications for starch.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Botanic characteristics	–	+	+
Microbial limits	–	+	+
pH			
Corn starch	–	–	4.5–7.0
Potato starch	–	5.0–8.0	5.0–8.0
Tapioca	–	–	4.5–7.0
Wheat starch	–	5.0–8.0	4.5–7.0
Acidity	–	+	–
Loss on drying			
Corn starch	≤15.0%	≤15.0%	≤14.0%
Rice starch	≤15.0%	≤15.0%	–
Potato starch	≤18.0%	≤20.0%	≤14.0%
Tapioca	–	–	≤14.0%
Wheat starch	≤15.0%	≤15.0%	≤14.0%
Residue on ignition	–	–	≤0.5%
Sulfated ash			
Corn starch	≤0.5%	≤0.6%	–
Rice starch	≤1.0%	≤1.0%	–
Potato starch	≤0.5%	≤0.6%	–
Wheat starch	≤1.0%	≤0.6%	–
Iron			
Corn starch	–	–	≤0.002%
Potato starch	–	≤10 ppm	≤0.002%
Tapioca starch	–	–	≤0.002%
Wheat starch	–	≤10 ppm	≤0.002%
Organic volatile impurities	–	–	+
Oxidizing substances			
Corn starch	–	–	≤0.002%
Potato starch	–	+	≤0.002%
Tapioca starch	–	–	≤0.002%
Wheat starch	–	+	≤0.002%
Sulfur dioxide			
Corn starch	–	–	≤0.008%
Potato starch	–	≤50 ppm	≤0.008%
Wheat starch	–	≤50 ppm	≤0.008%
Total protein			
Corn starch	–	–	–
Rice starch	–	–	–
Potato starch	–	≤0.1%	–
Wheat starch	–	≤0.3%	–
Foreign matter	–	+	–

SEM: 1
Excipient: Corn starch
Manufacturer: Anheuser Busch
Lot No.: 96A-3 (67)
Magnification: 2400×
Voltage: 20 kV

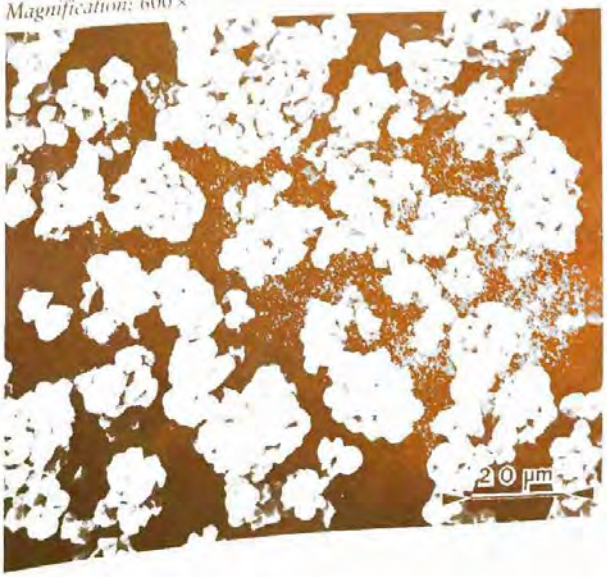


SEM: 2
Excipient: Corn starch
Manufacturer: AE Staley Mfg. Co.
Lot No.: 96A-4 (G77912)
Magnification: 2400×
Voltage: 20 kV



SEM: 3
Excipient: Potato starch
Manufacturer: Starchem
Lot No.: 96A-5 (1179)
Magnification: 2400×
Voltage: 20 kV

SEM: 4
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 600×



SEM: 5
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 3000×

SEM: 7
Excipient: Wheat starch (*Aytex P*)
Manufacturer: Henkel Corp.
Lot No.: 96A-2 (2919D)
Magnification: 2400×
Voltage: 20 kV

11 Stability and Storage Conditions

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties.

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

SEM: 6
Excipient: Wheat starch (*Paygel 55*)
Manufacturer: Henkel Corp.
Lot No.: 96A-1 (2917D)
Magnification: 2400×
Voltage: 20 kV

12 Incompatibilities

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13 Method of Manufacture

Starch is extracted from plant sources through a sequence of processing steps involving coarse milling, repeated water washing, wet sieving, and centrifugal separation. The wet starch obtained from these processes is dried and milled before use in pharmaceutical formulations.

14 Safety

Starch is widely used as an excipient in pharmaceutical formulations, particularly oral tablets.

Starch is an edible food substance and is generally regarded as an essentially nontoxic and nonirritant material.[19] However, oral consumption of massive doses can be harmful owing the formation of starch calculi, which cause bowel obstruction.[20] Starch may also cause granulomatous reactions when applied to the peritoneum or the meninges. Contamination of surgical wounds with the starch glove powder used by surgeons has also resulted in the development of granulomatous lesions.[21]

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.

LD_{50} (mouse, IP): 6.6 g/kg[22]

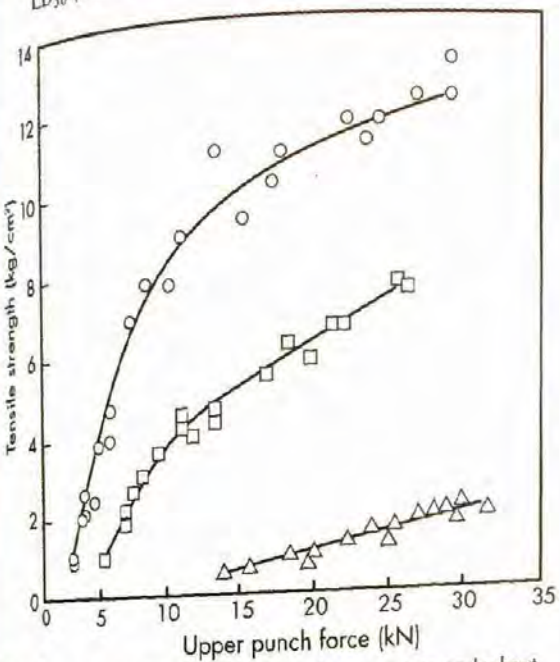

Figure 1: Compression characteristics of corn, potato and wheat starches.
□: Corn starch
○: Potato starch
△: Wheat starch
Tablet machine: Manesty F; speed: 50 per min; weight: 490–510 mg. Strength test: Diametral compression between flat-faced rams. Upper ram stationary, lower moving at 66 μm/s.

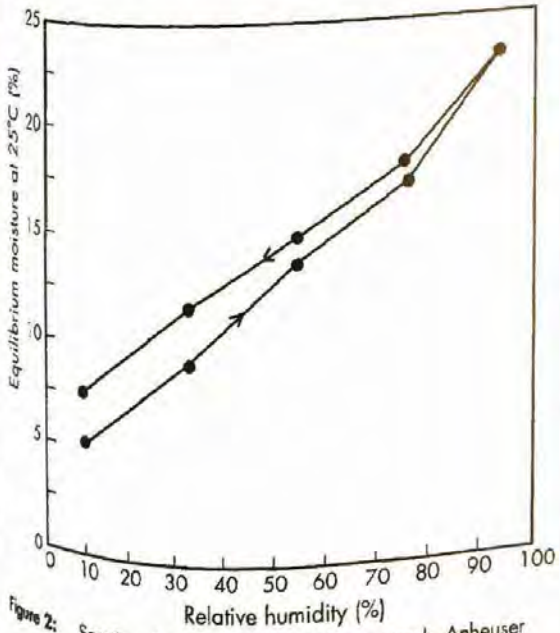

Figure 2: Sorption–desorption isotherm of corn starch. Anheuser Busch; Lot #67.

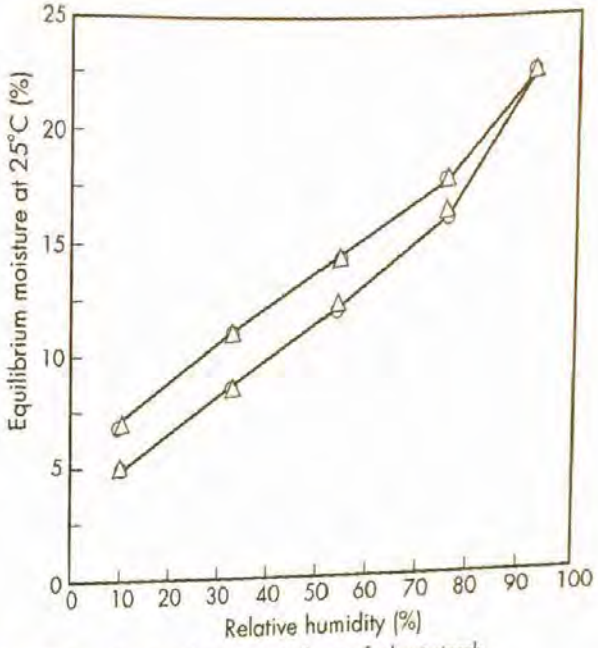

Figure 3: Sorption–desorption isotherm of wheat starch.
○: *Paygel 55* (Henkel Corp.; Lot #2917D)
△: *Aytex P* (Henkel Corp.; Lot #2919D)

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.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[23]

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Amylopectin; α-amylose; starch, pregelatinized; starch, sterilizable maize.

Amylopectin

CAS number: [9037-22-3]
Comments: amylopectin is a branched D-glucan with mostly α-D-(1→4) and approximately 4% α-D-(1→6) linkages.
The EINECS number for amylopectin is 232-911-6.

α-Amylose

CAS number: [9005-82-7]
Comments: amylose is a linear (1→4)-α-D-glucan.

18 Comments

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

Whereas the USPNF 20 specifies that starch should be produced from corn, potato, tapioca, or wheat, the BP 2001

also permits starch to be produced from rice. In tropical and subtropical countries where these starches may not be readily available, the BP 2001 additionally permits the use of tapioca starch, subject to additional requirements.

Starches from different plant sources differ in their amylose/amylopectin ratio. For example, corn starch contains about 27% amylose, potato starch about 22%, and tapioca starch about 17%. In contrast, waxy corn starch contains almost entirely amylopectin, with no amylose. These differences modify the physical properties of the starches such that the various types may not be interchangeable in a given pharmaceutical application.

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20 General References

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21 Author

G Rowley.

22 Date of Revision

10 March 2002.

Starch, Pregelatinized

1 Nonproprietary Names

BP: Pregelatinised starch
PhEur: Amylum pregelificatum
USPNF: Pregelatinized starch

2 Synonyms

Compressible starch; *Instastarch*; *Lycatab C*; *Lycatab PGS*; Merigel; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST 200*; *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 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 and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. The USPNF 20 does not specify the botanical origin of the original starch, but the PhEur 2002 (Suppl 4.1) specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch. *See also* Starch and Section 13.

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

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,[1,2] and disintegrant.[3]

In comparison to starch, grades of 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 processes.[4–14] 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.[15]

Pregelatinized starch may also be used in wet granulation processes.[16] See Table I.

Table I: Uses of pregelatinized starch.

Use	Concentration (%)
Diluent (hard gelatin capsules)	5–75
Tablet binder (direct compression)	5–20
Tablet binder (wet granulation)	5–10
Tablet disintegrant	5–10

8 Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e., no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin show characteristic forms depending upon the method of drying used during manufacture: either irregular chunks from drum drying or thin plates. Partially pregelatinized starch (e.g., *Starch 1500G* and *Sepistab ST200*) show retention of birefringence patterns typical of unmodified starch granules.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for pregelatinized starch.

Test	PhEur 2002 (Suppl 4.1)	USPNF 20
Identification	+	+
pH (10% w/v slurry)	4.5–7.0	4.5–7.0
Iron	≤ 20 ppm	≤ 0.002%
Oxidizing substances	+	+
Sulfur dioxide	≤ 50 ppm	≤ 0.008%
Microbial limits	+	+
Loss on drying	≤ 15.0%	≤ 14.0%
Residue on ignition	—	≤ 0.5%
Foreign matter	+	—
Sulfated ash	≤ 0.6%	—
Organic volatile impurities	—	+

10 Typical Properties

Acidity/alkalinity: pH = 4.5–7.0 for a 10% w/v aqueous dispersion
Angle of repose: 40.7°[6]
Compressibility: *see* Starch.
Density (bulk): 0.586 g/cm³
Density (tapped): 0.879 g/cm³
Density (true): 1.516 g/cm³
Flowability: 18–23% (Carr compressibility index)[17]
Moisture content: pregelatinized maize starch is hygroscopic.[14,18,19] *See also* Figure 1.

Particle size distribution: 30–150 μm, median diameter 52 μm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 μm); and less than 0.5% retained on a US #40 mesh (420 μm).

Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold-water-soluble matter for partially pregelatinized starch is 10–20%.

Specific surface area:
0.26 m^2/g (Colorcon)
0.18–0.28 m^2/g (Roquette Ltd)

Viscosity (dynamic): 8–10 mPa s (8–10 cP) for a 2% w/v aqueous dispersion at 25 °C.

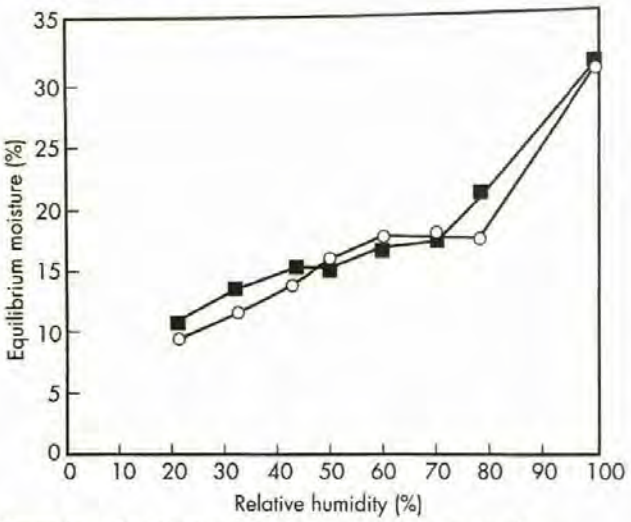

Figure 1: Pregelatinized starch sorption–desorption isotherm. ○: Sorption. ■: Desorption.

11 Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

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13 Method of Manufacture

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–72 °C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the last case, the dried material may be processed to produce a desired particle size range.

Pharmaceutical grades of fully pregelatinized starch use no additives and are prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where gelatinization and subsequent drying takes place. Partially pregelatinized starch is produced by subjecting moistened starch to mechanical pressure. The resultant material is ground and the moisture content is adjusted to specifications.

14 Safety

Pregelatinized starch and starch are widely used in oral solid dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of pregelatinized starch may be harmful.

See Starch for further information.

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 explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[20]

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Starch; starch, sterilizable maize.

18 Comments

A low-moisture grade of pregelatinized starch, *Starch 1500 LM* (Colorcon), containing less than 7% of water, specifically intended for use as a diluent in capsule formulations is commercially available.[15]

Sepistab ST200 is described as an agglomerate of starch granules consisting of native and pregelatinized corn starch.[21]

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21 Author

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22 Date of Revision

13 June 2002.

Crospovidone

1 Nonproprietary Names

BP: Crospovidone
PhEur: Crospovidonum
USPNF: Crospovidone

2 Synonyms

Crosslinked povidone; E1202; *Kollidon CL*; *Kollidon CL-M*; *Polyplasdone XL*; *Polyplasdone XL-10*; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ >1 000 000

Crospovidone is a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5 Structural Formula

See Povidone.

6 Functional Category

Tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods.[1–4] It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets.[5] Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

8 Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for crospovidone.

Test	PhEur 2002	USPNF 20 (Suppl 1)
Identification	+	+
Characters	+	–
pH (1% suspension)	–	5.0–8.0
Water	–	≤5.0%
Residue on ignition	≤0.1%	≤0.4%
Water-soluble substances	≤1.0%	≤1.5%
Peroxides	≤400 ppm	–
Heavy metals	≤10 ppm	≤0.001%
Vinylpyrrolidinone	–	≤0.1%
Loss on drying	≤5.0%	–
Nitrogen content (anhydrous basis)	11.0–12.8%	11.0–12.8%

10 Typical Properties

Acidity/alkalinity: pH = 5.0–8.0 (1% w/v aqueous slurry)
Density: 1.22 g/cm^3
Density (bulk): *see* Table II.
Density (tapped): *see* Table II.

Table II: Density values of commercial grades of crospovidone.

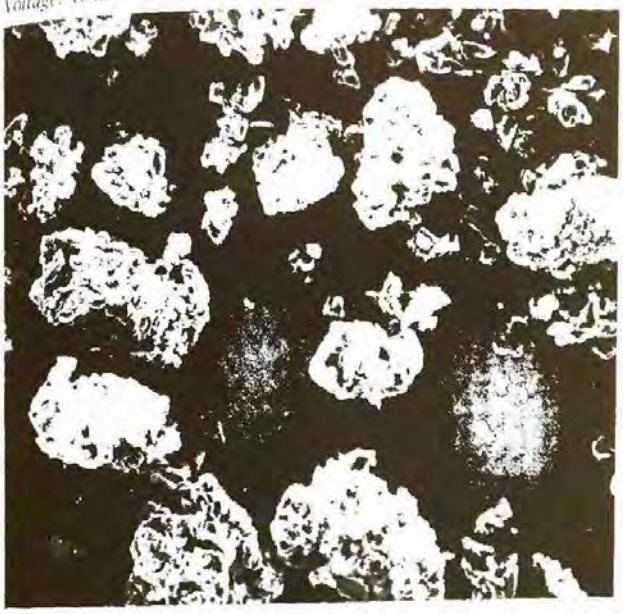
Commercial grade	Density (bulk) g/cm^3	Density (tapped) g/cm^3
Kollidon CL	0.3–0.4	0.4–0.5
Kollidon CL-M	0.15–0.25	0.3–0.5
Polyplasdone XL	0.213	0.273
Polyplasdone XL-10	0.323	0.461

Moisture content: maximum moisture sorption is approximately 60%.
Particle size distribution: less than 400 µm for *Polyplasdone XL*; less than 74 µm for *Polyplasdone XL-10*. Approximately 50% greater than 50 µm and maximum of 3% greater than 250 µm in size for *Kollidon CL*. Minimum of 90% of particles are below 15 µm for *Kollidon CL-M*.
Solubility: practically insoluble in water and most common organic solvents.
Specific surface area: *see* Table III.

Table III: Specific surface areas for commercial grades of crospovidone.

Commercial grade	Surface area (m^2/g)
Kollidon CL	1.0
Kollidon CL-M	3.0–6.0
Polyplasdone XL	0.6–0.8
Polyplasdone XL-10	1.2–1.4

SEM 1
Excipient: Crospovidone (*Polyplasdone XL-10*)
Manufacturer: ISP Corp.
Lot No.: S81031
Magnification: 400×
Voltage: 10 kV



11 Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials; *see* Povidone.

13 Method of Manufacture

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a 'popcorn polymerization' process.

14 Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone.[6] However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.[6]

LD_{50} (mouse, IP): 12 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Povidone.

18 Comments

Crospovidone has been studied as a superdisintegrant. The ability of the compound to swell has been examined directly using scanning electron microscopy.[7] The impact of crospovidone on percolation has also been examined.[8] The impact of crospovidone on dissolution of poorly soluble drugs in tablets has also been investigated.[9]

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21 Authors

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22 Date of Revision

25 October 2002.

Croscarmellose Sodium

1 Nonproprietary Names

BP: Croscarmellose sodium
PhEur: Carmellosum natricum conexum
USPNF: Croscarmellose sodium

2 Synonyms

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; *Explocel*; modified cellulose gum; *Nymcel ZSX*; *Pharmacel XL*; *Primellose*; *Solutab*; *Vivasol*.

3 Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

4 Empirical Formula Molecular Weight

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

See Carboxymethylcellulose sodium.

5 Structural Formula

See Carboxymethylcellulose sodium.

6 Functional Category

Tablet and capsule disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules,[1,2] tablets,[3–13] and granules.

In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.[11,12] Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process. *See* Table I.

Table I: Uses of croscarmellose sodium.

Use	Concentration (%)
Disintegrant in capsules	10–25
Disintegrant in tablets	0.5–5.0

SEM: 1
Excipient: Croscarmellose sodium (*Ac-Di-Sol*)
Manufacturer: FMC Biopolymer
Magnification: 100 ×

SEM: 2
Excipient: Croscarmellose sodium (*Ac-Di-Sol*)
Manufacturer: FMC Biopolymer
Magnification: 1000 ×

8 Description

Croscarmellose sodium occurs as an odorless, white or greyish-white powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for croscarmellose sodium.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	–
pH (1% w/v dispersion)	5.0–7.0	5.0–7.0
Loss on drying	≤10.0%	≤10.0%
Heavy metals	≤10 ppm	≤0.001%
Sodium chloride and sodium glycolate	≤0.5%	≤0.5%
Sulfated ash	14.0–28.0%	–
Degree of substitution	0.60–0.85	0.60–0.85
Content of water-soluble material	≤10.0%	1.0–10.0%
Settling volume	+	+
Microbial contamination	+	–
Organic volatile impurities	–	+

10 Typical Properties

Bonding index: 0.0456
Brittle fracture index: 0.1000
Density (bulk): 0.529 g/cm^3 for *Ac-Di-Sol*[7]
Density (tapped): 0.819 g/cm^3 for *Ac-Di-Sol*[7]
Density (true): 1.543 g/cm^3 for *Ac-Di-Sol*[7]
Particle size distribution:
Ac-Di-Sol: not more than 2% retained on a #200 (73.7 µm) mesh and not more than 10% retained on a #325 (44.5 µm) mesh
Pharmacel XL: more than 90% less than 45 µm, and more than 98% less than 100 µm in size
Solubility: insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water.
Specific surface area: 0.81–0.83 m^2/g

11 Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material.

A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months.[9]

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

12 Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol.[10]

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

13 Method of Manufacture

Alkali cellulose is prepared by steeping cellulose, obtained from wood pulp or cotton fibers, in sodium hydroxide solution. The alkali cellulose is then reacted with sodium monochloroacetate to obtain carboxymethylcellulose sodium. After the substitution reaction is completed and all of the sodium hydroxide has been used, the excess sodium monochloroacetate slowly hydrolyzes to glycolic acid. The glycolic acid changes a few of the sodium carboxymethyl groups to the free acid and catalyzes the formation of crosslinks to produce croscarmellose sodium. The croscarmellose sodium is then extracted with aqueous alcohol and any remaining sodium chloride or sodium glycolate is removed. After purification, croscarmellose sodium of purity greater than 99.5% is obtained.[4] The croscarmellose sodium may be milled to break the polymer fibers into shorter lengths and hence improve its flow properties.

14 Safety

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

In the UK, croscarmellose sodium is accepted for use in dietary supplements.

The WHO has not specified an acceptable daily intake for the related substance carboxymethylcellulose sodium, used as a food additive, since the levels necessary to achieve a desired effect were not considered sufficient to be a hazard to health.[14]

See also Carboxymethylcellulose sodium.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Croscarmellose sodium may be irritant to the eyes; eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Carboxymethylcellulose calcium; carboxymethylcellulose sodium.

18 Comments

Typically, the degree of substitution (DS) for croscarmellose sodium is 0.7.

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21 Author

RT Guest.

22 Date of Revision

14 October 2002.

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidonum
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2- pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula Molecular Weight

$(C_6H_9NO)_n$ 2500–3 000 000

The USP 25 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, ranging from 10 to 120. The *K*-value is calculated using Fikentscher's equation:[1]

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value $\times 10^{-3}$, and c is the concentration in % w/v.

Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value} \sqrt{\frac{300c\log z(c+1.5c\log z)^2+1.5}{0.15c+0.003c^2}}$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value $\times 10^{-3}$, and c is the concentration in % w/v.

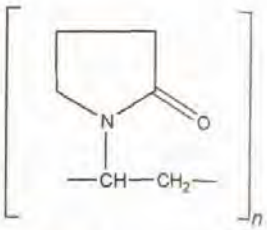
Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[4–6] Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. *See* Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; *see* Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for povidone.

Test	JP 2001	PhEur 2002 (Suppl 4.3)	USP 25
Identification	+	+	+
Characters	—	+	—
pH	—	—	3.0–7.0
K ≤ 30	3.0–5.0	3.0–5.0	—
K > 30	4.0–7.0	4.0–7.0	—
Appearance of solution	+	+	—
Viscosity	—	+	—
Water	≤5.0%	≤5.0%	≤5.0%
Residue on ignition	≤0.1%	≤0.1%	≤0.1%
Iron	—	—	≤10 ppm
Aldehydes	≤500 ppm[a]	≤500 ppm[a]	≤0.05%
Hydrazine	≤1 ppm	≤1 ppm	≤1 ppm
1-Vinylpyrrolidinone	≤10 ppm	≤10 ppm	≤0.2%
Peroxides	≤400 ppm[b]	≤400 ppm[b]	—
K-value	25–90	—	10–120
≤15	90.0–108.0%	85.0–115.0%	85.0–115.0%
>15	90.0–108.0%	90.0–108.0%	90.0–108.0%
Heavy metals	≤10 ppm	≤10 ppm	—
Assay (nitrogen content)	11.5–12.8%	11.5–12.8%	11.5–12.8%

[a] Expressed as acetaldehyde.
[b] Expressed as hydrogen peroxide.

10 Typical Properties

Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution).
Density (bulk): 0.29–0.39 g/cm^3 for *Plasdone*.
Density (tapped): 0.39–0.54 g/cm^3 for *Plasdone*.
Density (true): 1.180 g/cm^3
Flowability:
10 g/s for povidone K-15
16 g/s for povidone K-29/32
Melting point: softens at 150°C.
Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. *See* Figures 1 and 2.

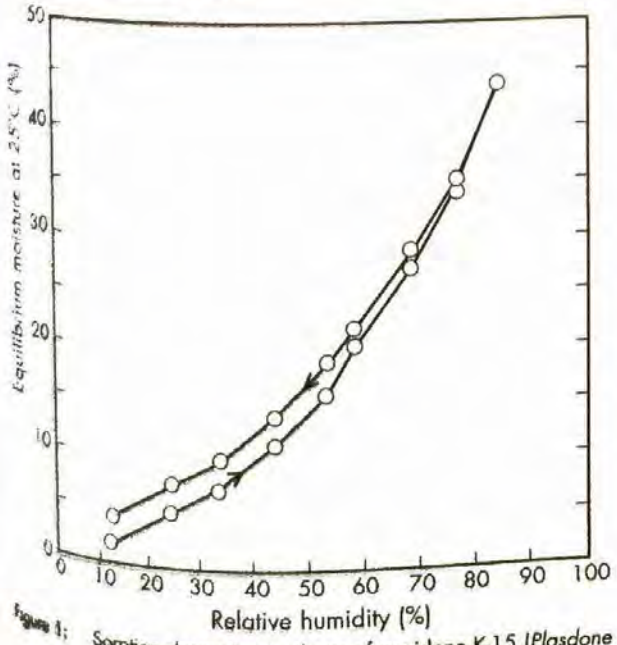


Figure 1: Sorption–desorption isotherm of povidone K-15 (*Plasdone K-15*).

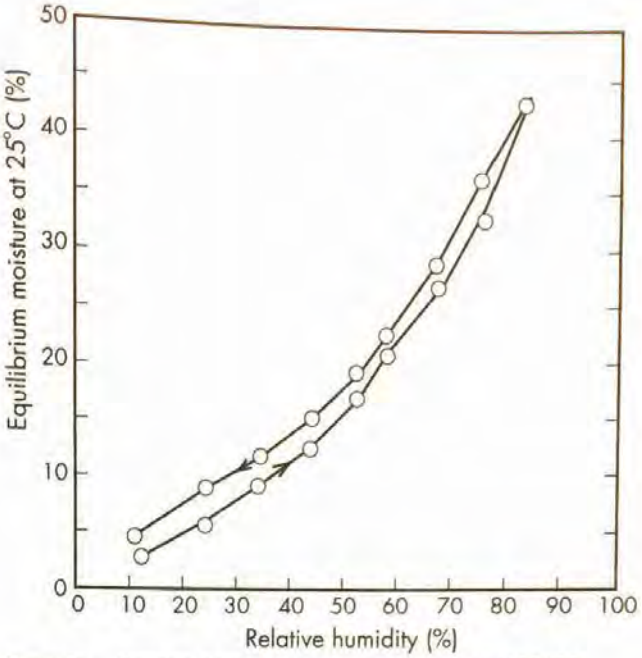


Figure 2: Sorption–desorption isotherm of povidone K-29/32 (*Plasdone K-29/32*).

Particle size distribution:
Kollidon 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm
Kollidon 90: 90% >200 μm, 95% >250 μm[7]

Solubility: freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.

Viscosity (dynamic): the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. *See* Tables IV and V.[7]

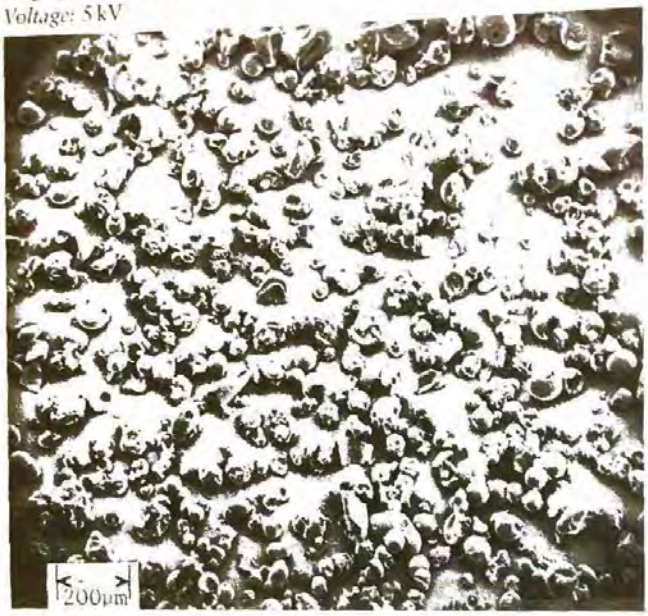
Table IV: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.[7]

Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

Table V: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol and propan-2-ol at 25°C.[7]

Grade	Dynamic viscosity (mPa s)	
	Ethanol	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

SEM: 1
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 60×
Voltage: 5 kV

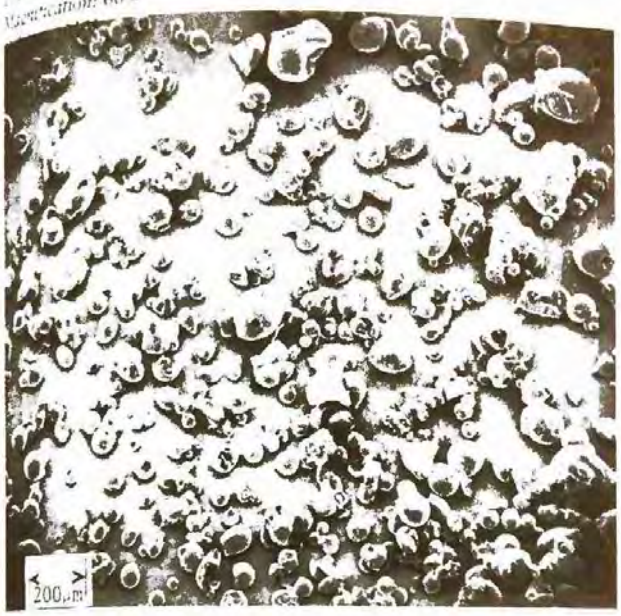


SEM: 2
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 600×
Voltage: 5 kV

SEM: 3
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 60×
Voltage: 5 kV

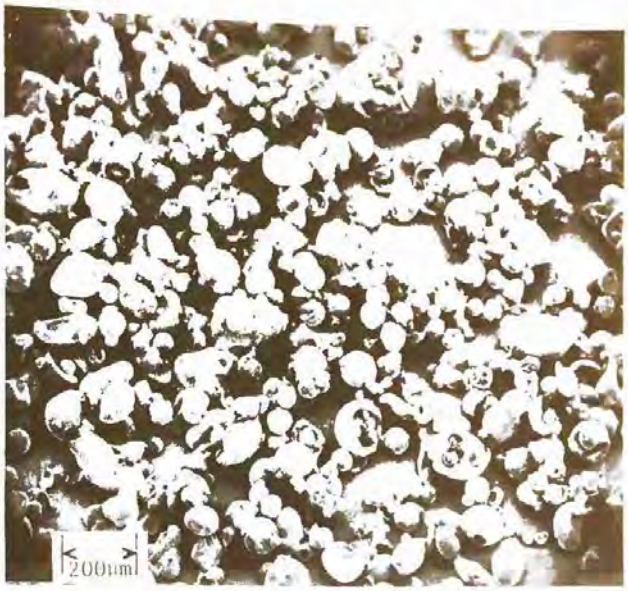
SEM: 4
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 600×
Voltage: 10 kV

SEM: 5
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 60 ×



SEM: 6
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 600 ×
Voltage: 10 kV

SEM: 7
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 60 ×
Voltage: 5 kV



SEM: 8
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 600 ×
Voltage: 10 kV

11 Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous

solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; *see* Section 18. The efficacy of some preservatives, e.g., thimerosal, may be adversely affected by the formation of complexes with povidone.

13 Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14 Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.[8]

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.[8] Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.[9] Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.[10]

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.[11]

LD_{50} (mouse, IP): 12 g/kg[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Crospovidone.

18 Comments

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms, and parenteral formulations. Perhaps the best-known example of povidone complex formation is povidone–iodine, which is used as a topical disinfectant.

For accurate standardization of solutions, the water content of the solid povidone must be determined before use and taken into account for any calculations.

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21 Author

AH Kibbe.

22 Date of Revision

30 October 2002.

Sodium Starch Glycolate

1 Nonproprietary Names

BP: Sodium starch glycollate
PhEur: Carboxymethylamylum natricum
USPNF: Sodium starch glycolate

2 Synonyms

Carboxymethyl starch, sodium salt; *Explotab*; *Primojel*; *Vivastar P*.

3 Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

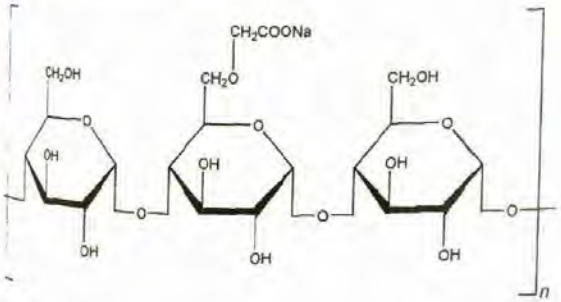
4 Empirical Formula Molecular Weight

The USPNF 20 states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch. The molecular weight is typically 5×10^5–1×10^6.

The PhEur 2002 describes three types of material; Type A, equivalent to the USPNF 20 material, containing 2.8–4.2% of sodium; Type B containing 2.0–3.4% of sodium; and Type C containing 2.8–5.0% of sodium.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking.

5 Structural Formula



6 Functional Category

Tablet and capsule disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule[1–6] and tablet formulations.[7–10] It is commonly used in tablets prepared by either direct-compression[11–13] or wet-granulation processes.[14–16] The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.[17–20]

Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.[10–14]

Sodium starch glycolate has also been investigated for use as a suspending vehicle.[21,22]

8 Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. It consists of oval or spherical granules, 30–100 μm in diameter, with some less-spherical granules ranging from 10–35 μm in diameter.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium starch glycolate.

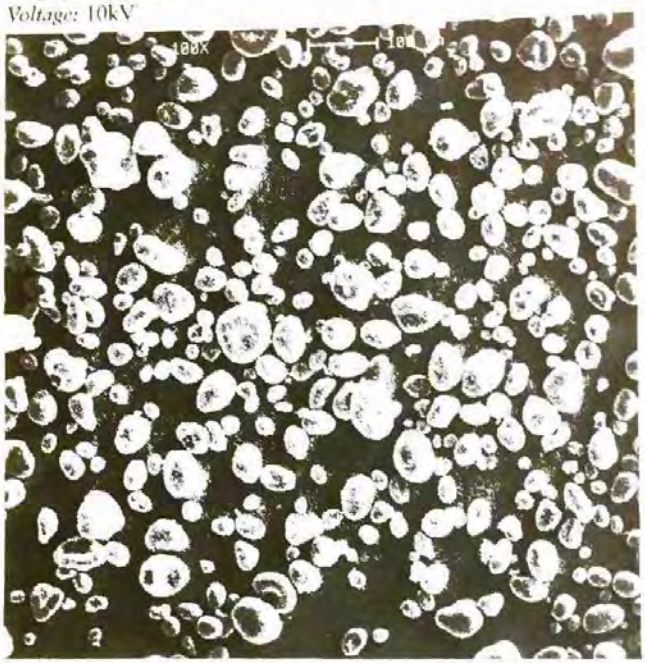
Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	–
Appearance of solution	+	–
pH	+	3.0–5.0 or 5.5–7.5
Type A	5.5–7.5	–
Type B	3.0–5.9	–
Heavy metals	≤20 ppm	≤0.002%
Iron	≤20 ppm	≤0.002%
Loss on drying	+	+
Type A	≤10.0%	≤10.0%
Type B	≤10.0%	≤10.0%
Type C	≤7.0%	–
Microbial limits	+	+
Sodium chloride	+	+
Type A	≤7.0%	≤7.0%
Type B	≤7.0%	≤7.0%
Type C	≤1.0%	–
Sodium glycolate	+	–
Assay (of Na)	+	–
Type A	2.8–4.2%	–
Type B	2.0–3.4%	–
Type C	2.8–5.0%	–

10 Typical Properties

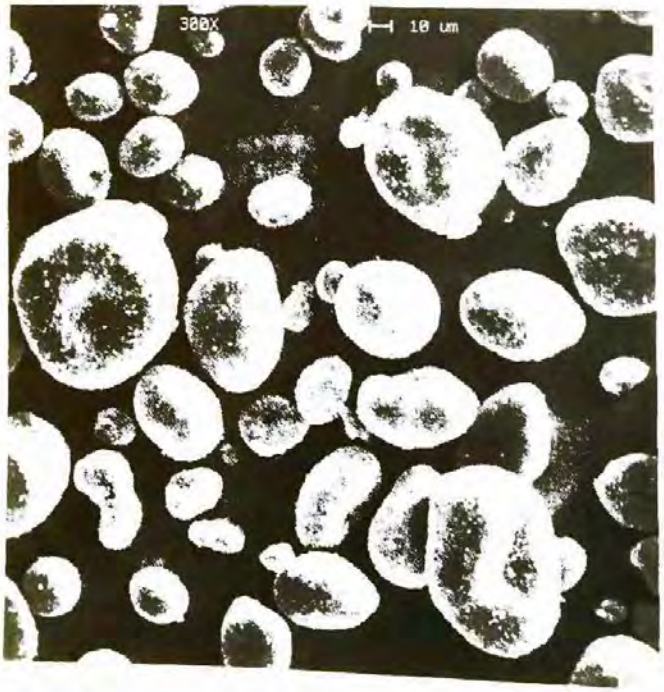
Acidity/alkalinity: pH = 3.0–5.0 or pH = 5.5–7.5 for a 3.3% w/v aqueous dispersion. *See* Section 18.
Ash: ≤15%
Density (bulk): 0.756 g/cm^3
Density (tapped): 0.945 g/cm^3
Density (true): 1.443 g/cm^3
Melting point: does not melt, but chars at approximately 200°C.
Particle size distribution: 100% of particles less than 104 μm in size. Average particle size is 42 μm for *Explotab*.
Solubility: sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer.
Specific surface area: 0.24 m^2/g
Swelling capacity: in water, sodium starch glycolate swells to up to 300 times its volume.

Viscosity (dynamic): ≤200 mPa s (200 cP) for a 4% w/v aqueous dispersion. Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

SEM 1
Excipient: Sodium starch glycolate
Manufacturer: Penwest Pharmaceuticals
Lot No.: E7834
Magnification: 100 ×
Voltage: 10kV



SEM 2
Excipient: Sodium starch glycolate
Manufacturer: Penwest Pharmaceuticals
Lot No.: E7834
Magnification: 300 ×
Voltage: 10kV



SEM 3
Excipient: Sodium starch glycolate
Manufacturer: Penwest Pharmaceuticals
Lot No.: E7834
Magnification: 500 ×
Voltage: 10kV

11 Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties.[23–25] Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 4 years if it is stored at moderate temperatures and humidity.

12 Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.[26]

13 Method of Manufacture

Sodium starch glycolate is a substituted and crosslinked derivative of potato starch.

Starch is carboxymethylated by reacting it with sodium chloroacetate in an alkaline medium followed by neutralization with citric acid or some other acid. Crosslinking may be achieved either by physical methods or chemically by using reagents such as phosphorus oxytrichloride or sodium trimetaphosphate.[27]

14 Safety

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Pregelatinized starch; starch.

18 Comments

The physical properties of sodium starch glycolate, and hence its effectiveness as a disintegrant, are affected by the degree of crosslinkage and extent of carboxymethylation.

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21 Author

RW Miller.

22 Date of Revision

15 October 2002.

Talc

1 Nonproprietary Names

BP: Purified talc
JP: Talc
PhEur: Talcum
USP: Talc

2 Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; *Luzenac*; *Luzenac Pharma*; magnesium hydrogen metasilicate; *Magsil Osmanthus*; *Magsil Star*; powdered talc; purified French chalk; *Purtalc*; soapstone; steatite; *Superiore*.

3 Chemical Name and CAS Registry Number

Talc [14807-96-6]

4 Empirical Formula Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

5 Structural Formula

See Section 4.

6 Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, *see* Table I,[1–3] although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.[4–6]

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; *see* Section 14. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder; *see* Section 11.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Table I: Uses of talc.

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluent	5.0–30.0

8 Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

SEM: 1
Excipient: Talc (*Purtalc*)
Manufacturer: Charles B Chrystal Co., Inc.
Lot No.: 1102A-2
Magnification: 1200×
Voltage: 10 kV

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.
Hardness (Mohs): 1.0–1.5
Moisture content: talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.
Particle size distribution: varies with the source and grade of material. Two typical grades are ≥99% through a 74 μm (#200 mesh) or ≥99% through a 44 μm (#325 mesh).
Refractive index: $n_D^{20} = 1.54–1.59$
Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.
Specific gravity: 2.7–2.8
Specific surface area: 2.41–2.42 m^2/g

Table II: Pharmacopeial specifications for talc.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	+	+	–
Acid-soluble substances	≤2.0%	–	≤2.0%
Production	–	+	–
pH	–	7.0–9.0	–
Water-soluble substances	–	≤0.2%	≤0.1%
Aluminum	–	≤2.0%	–
Calcium	–	≤0.9%	–
Iron	–	≤0.25%	–
Lead	–	≤10 ppm	–
Magnesium	–	17.0–19.5	–
Loss on ignition	≤5.0%	≤7.0%	≤6.5%
Microbial contamination	–	+	≤500/g
Aerobic bacteria	–	100/g	–
Fungi	–	100/g	–
Acid and alkali-soluble substances	≤4.0 mg	–	–
Water-soluble iron	+	–	+
Arsenic	≤4 ppm	–	≤3 ppm
Heavy metals	–	–	≤0.004%
Lead	–	–	≤0.001%

11 Stability and Storage Conditions

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.[7]

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

12 Incompatibilities

Incompatible with quaternary ammonium compounds.

13 Method of Manufacture

Talc is a naturally occurring hydropolysilicate mineral found in many parts of the world including Australia, China, Italy, India, France, and the USA.[8]

The purity of talc varies depending on the country of origin. For example, Italian types are reported to contain calcium silicate as the contaminant; Indian types contain aluminum and iron oxides; French types contain aluminum oxide; and American types contain calcium carbonate (California), iron oxide (Montana), aluminum and iron oxides (North Carolina), or aluminum oxide (Alabama).[9]

Naturally occurring talc is mined and pulverized before being subjected to flotation processes to remove various impurities such as asbestos (tremolite); carbon; dolomite; iron oxide; and various other magnesium and carbonate minerals. Following this process, the talc is finely powdered, treated with dilute hydrochloric acid, washed with water, and then dried. The processing variables of agglomerated talc strongly influence its physical characteristics.[10–12]

14 Safety

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs.[13–15] Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants;[16] *see also* Section 15.

Although talc has been extensively investigated for its carcinogenic potential, and it has been suggested that there is an increased risk of ovarian cancer in women using talc, the evidence is inconclusive.[17,18] However, talc contaminated with asbestos has been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products.[19]

Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.[20]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis.

In the UK, the occupational exposure limit for talc is 1 mg/m^3 of respirable dust long-term (8-hour TWA).[21] Eye protection, gloves, and a respirator are recommended.

16 Regulatory Status

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (buccal tablets; oral capsules and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

Various different grades of talc are commercially available that vary in their chemical composition depending upon their source and method of preparation.[8,22,23]

Talc derived from deposits that are known to contain associated asbestos is not suitable for pharmaceutical use. Tests for amphiboles and serpentines should be carried out to ensure that the product is free of asbestos.

The EINECS number for talc is 238-877-9.

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21 Author

AH Kibbe.

22 Date of Revision

28 October 2002.

Colloidal Silicon Dioxide

1 Nonproprietary Names

BP: Colloidal anhydrous silica
PhEur: Silicii colloidalis anhydrica
USPNF: Colloidal silicon dioxide

2 Synonyms

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica, light; anhydrous silicic acid; silicic anhydride; silicon dioxide; fumed; Wacker HDK.

3 Chemical Name and CAS Registry Number

Silica [7631-86-9]

4 Empirical Formula and Molecular Weight

SiO_2

60.08

5 Structural Formula

SiO_2

6 Functional Category

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics and food products; *see* Table I. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting.[1–3]

Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.[4] With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of the system may affect the viscosity; *see* Section 11.

In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate caking, settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.[5]

Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate.[6,7]

Table I: Uses of colloidal silicon dioxide.

Use	Concentration (%)
Aerosols	0.5–2.0
Emulsion stabilizer	1.0–5.0
Glidant	0.1–0.5
Suspending and thickening agent	2.0–10.0

8 Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for colloidal silicon dioxide.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	–
pH [4% w/v dispersion]	3.5–5.5	3.5–5.5
Arsenic	–	≤8 ppm
Chloride	≤250 ppm	–
Heavy metals	≤25 ppm	–
Loss on drying	–	≤2.5%
Loss on ignition	≤5.0%	≤2.0%
Organic volatile impurities	–	+
Assay [on ignited sample]	99.0–100.5%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 3.5–4.4 (4% w/v aqueous dispersion)
Density (bulk): 0.029–0.042 g/cm^3
Density (tapped): *See* Tables III to V.
Flowability: 35.52% (Carr compressibility index)
Moisture content: *See* Figure 1.[8,9]
Particle size distribution: 7–16 nm. *See also Figure 2.*
Refractive index: 1.46
Solubility: practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.
Specific gravity: 2.2

Specific surface area: 200–400 m^2/g (Stroehlein apparatus, single point); 50–380 m^2/g (BET method). *See also* Tables III to V.

Several grades of colloidal silicon dioxide are commercially available, which are produced by modifying the manufacturing process. The modifications do not affect the silica content, specific gravity, refractive index, color, or amorphous form. However, particle size, surface areas, and densities are affected. The physical properties of three commercially available colloidal silicon dioxides, *Aerosil* (Degussa), *Cab-O-Sil* (Cabot Corporation), and *Wacker HDK* (Wacker-Chemie GmbH) are shown in Tables III to V, respectively.

Table III: Physical properties of *Aerosil*.

Grade	Specific surface area[a] (m^2/g)	Density (tapped) (g/cm^3)
130	130 ± 25	0.05
130vs	130 ± 25	0.12
200	200 ± 25	0.05
200vs	200 ± 25	0.12
300	300 ± 30	0.05
380	380 ± 30	0.05

[a] BET method.

Table IV: Physical properties of *Cab-O-Sil*.[10]

Grade	Specific surface area[a] (m^2/g)	Density (tapped) (g/cm^3)
LM-5	130 ± 25	0.04
LM-50	150 ± 25	0.04
M-5	200 ± 25	0.04
H-5	325 ± 25	0.04
EH-5	390 ± 40	0.04
M-7D	200 ± 25	0.10

[a] BET method.

Table V: Physical properties of *Wacker HDK*.[11]

Grade	Specific surface area[a] (m^2/g)	Density (tapped) (g/cm^3)
S13	125 ± 15	0.05
V15	150 ± 20	0.05
N20	200 ± 30	0.04
T30	300 ± 30	0.04
T40	400 ± 40	0.04
H15	120 ± 20	0.04
H20	170 ± 30	0.04
H30	250 ± 30	0.04
H2000	140 ± 30	0.04
H3004	210 ± 30	0.22
H2015	110 ± 30	0.08
H2050	110 ± 30	0.20
		0.20

[a] BET method.

SEM: 1
Excipient: Colloidal silicon dioxide (*Aerosil A-200*)
Manufacturer: Degussa
Lot No.: 87A-1 (04169C)
Magnification: 600×
Voltage: 20 kV

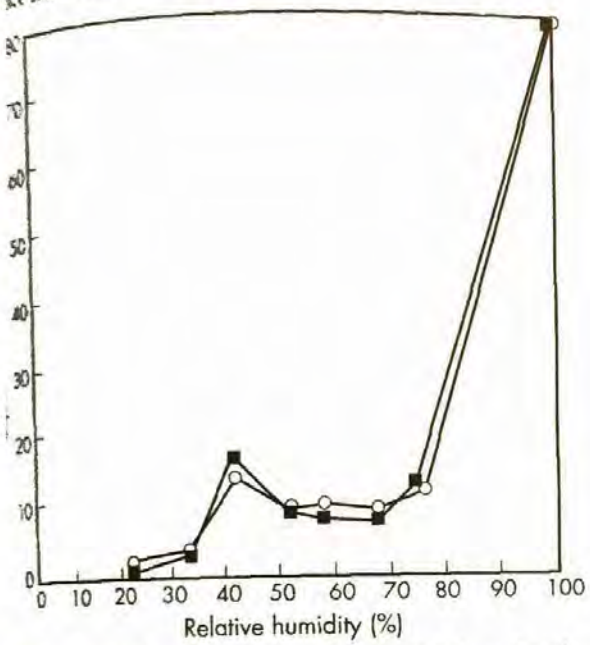
SEM: 2
Excipient: Colloidal silicon dioxide (*Aerosil A-200*)
Manufacturer: Degussa
Lot No.: 87A-1 (04169C)
Magnification: 2400×
Voltage: 20 kV

11 Stability and Storage Conditions

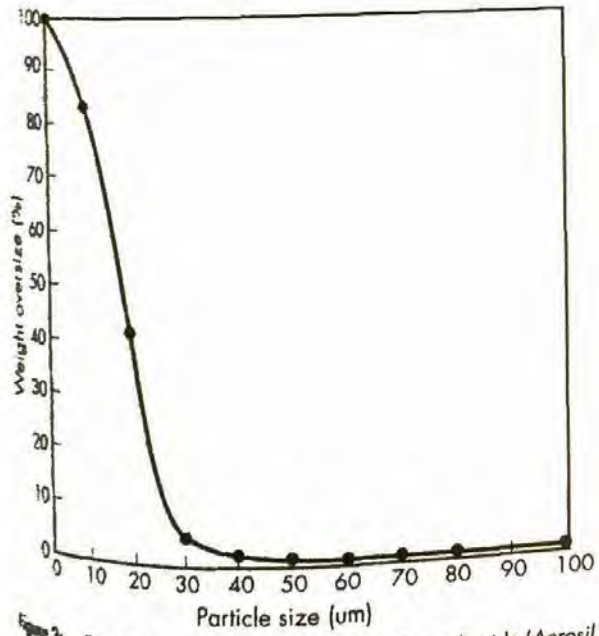
Colloidal silicon dioxide is hygroscopic but adsorbs [illegible] quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon

...ble are reduced; and at a pH greater than 10.7 this ability ...e entirely since the silicon dioxide dissolves to form ...s.[1] Colloidal silicon dioxide powder should be stored ... well-closed container.

...me grades of colloidal silicon dioxide have hydrophobic ...ce treatments that greatly minimize their hygroscopicity.



...gure 1: Sorption–desorption isotherm for colloidal silicon dioxide.
○: Sorption
■: Desorption



...Figure 2: Particle size distribution of colloidal silicon dioxide (*Aerosil* A-200).

12 Incompatibilities

...incompatible with diethylstilbestrol preparations.[12]

13 Method of Manufacture

Colloidal silicon dioxide is prepared by the vapor hydrolysis of chlorosilanes, such as silicon tetrachloride, at 1800°C using a hydrogen–oxygen flame.

14 Safety

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

LD_{50} (rat, IV): 15 mg/kg[13]
LD_{50} (rat, oral): 3.16 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Precautions should be taken to avoid inhalation of colloidal silicon dioxide. In the absence of suitable containment facilities, a dust mask should be worn when handling small quantities of material. For larger quantities, a dust respirator is recommended.

Inhalation of colloidal silicon dioxide dust may cause irritation to the respiratory tract but it is not associated with fibrosis of the lungs (silicosis), which can occur upon exposure to crystalline silica.

16 Regulatory Acceptance

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets; transdermal and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

The incidence of microbial contamination of colloidal silicon dioxide is low.

The EINECS number for colloidal silicon dioxide is 231-545-4.

19 Specific References

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21 Authors

E Morefield, J Seyer.

22 Date of Revision

22 October 2002.

Calcium Stearate

1 Nonproprietary Names

BP: Calcium stearate
JP: Calcium stearate
PhEur: Calcii stearas
USPNF: Calcium stearate

2 Synonyms

Calcium distearate; *HyQual*; stearic acid, calcium salt.

3 Chemical Name and CAS Registry Number

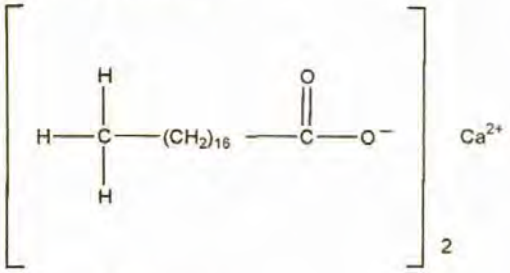
Octadecanoic acid calcium salt [1592-23-0]

4 Empirical Formula Molecular Weight

$C_{36}H_{70}CaO_4$ 607.03 (for pure material)

The PhEur 2002 describes calcium stearate as a mixture of calcium salts of different fatty acids consisting mainly of stearic acid $[(C_{17}H_{35}COO)_2Ca]$ and palmitic acid $[(C_{15}H_{31}COO)_2Ca]$ with minor proportions of other fatty acids. It contains the equivalent of 9.0–10.5% of calcium oxide.

5 Structural Formula



6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

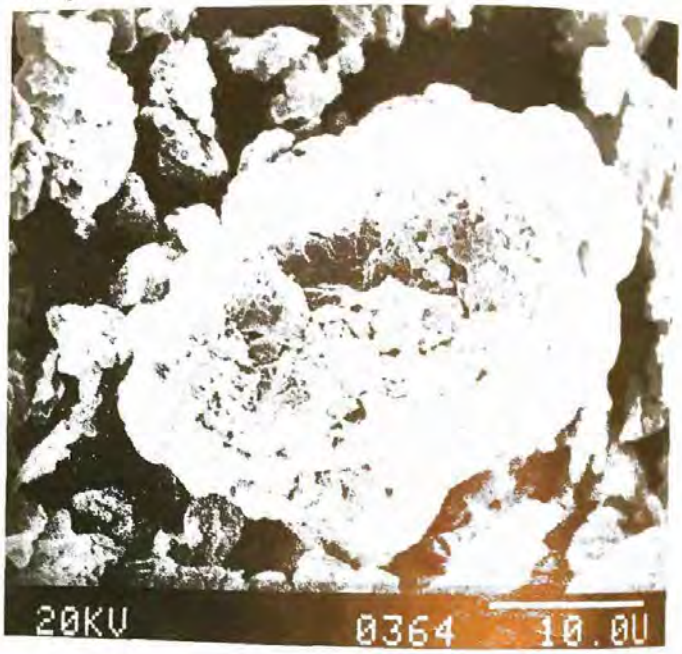
Calcium stearate is primarily used in pharmaceutical formulations as a lubricant in tablet and capsule manufacture at concentrations up to 1.0% w/w. Although it has good anti-adherent and lubricant properties, calcium stearate has poor glidant properties.

Calcium stearate is also employed as an emulsifier, stabilizing agent, and suspending agent, and is also used in cosmetics and food products.

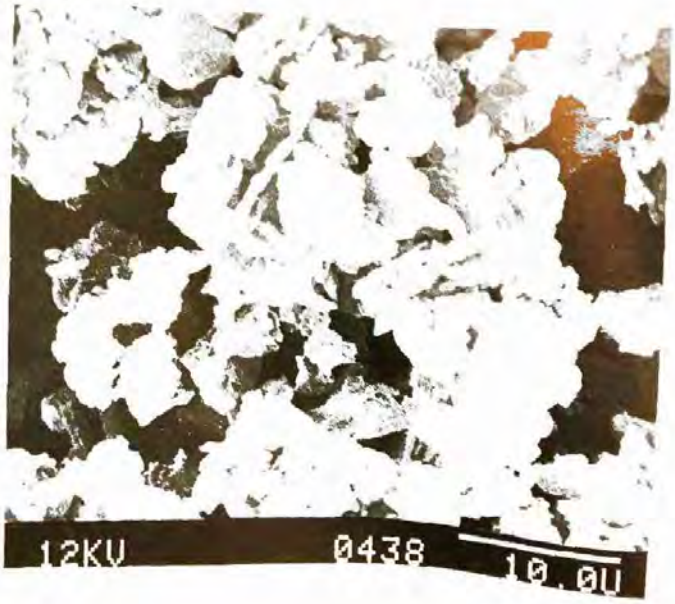
8 Description

Calcium stearate occurs as a fine, white to yellowish-white, bulky powder having a slight, characteristic odor. It is unctuous and free from grittiness.

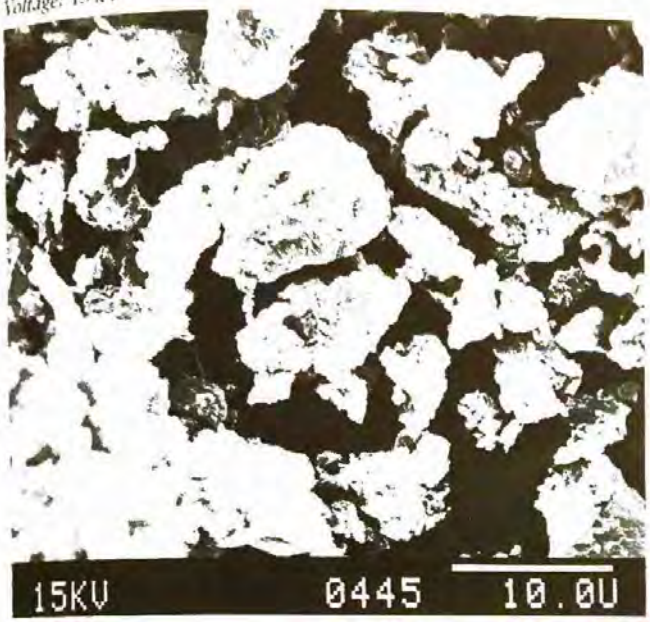
SEM: 1
Excipient: Calcium stearate (Standard)
Manufacturer: Durham Chemicals
Lot No.: 0364
Voltage: 20 kV



SEM: 2
Excipient: Calcium stearate (Precipitated)
Manufacturer: Witco Corporation
Lot No.: 0438
Voltage: 12 kV



SEM: 3
Excipient: Calcium stearate (Fused)
Manufacturer: Witco Corporation
Voltage: 15 kV



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for calcium stearate.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Microbial limit	—	1000/g	—
Acidity or alkalinity	—	+	—
Loss on drying	≤4.0%	≤6.0%	≤4.0%
Arsenic	≤2 ppm	—	—
Heavy metals	≤20 ppm	—	≤10 ppm
Chlorides	—	≤0.1%	—
Sulfates	—	≤0.3%	—
Cadmium	—	≤3 ppm	—
Lead	—	≤10 ppm	—
Nickel	—	≤5 ppm	—
Organic volatile impurities	—	—	+
Assay (as CaO)	—	—	9.0–10.5%
Assay (as Ca)	6.4–7.1%	6.4–7.4%	—

10 Typical Properties

Acid value: 191–203
Ash: 9.9–10.3%
Chloride: <200 ppm
Density (bulk and tapped): *see* Table II.
Density (true): 1.064–1.096 g/cm^3
Flowability: 21.2–22.6% (Carr compressibility index)
Free fatty acid: 0.3–0.5%
Melting point: 149–160°C
Moisture content: 2.96%
Particle size distribution: 1.7–60 μm; 100% through a 73.7 μm (#200 mesh); 99.5% through a 44.5 μm (#325 mesh).
Shear strength: 14.71 MPa

Table II: Density (bulk and tapped) of calcium stearate.

	Bulk density (g/cm^3)	Tapped density (g/cm^3)
Durham Chemicals		
Standard	—	0.26
A	—	0.45
AM	—	0.33
Witco Corporation		
EA	0.21	0.27
Fused	0.38	0.48
Precipitated	0.16	0.20

Solubility: practically insoluble in ethanol (95%), ether, and water.
Specific surface area: 4.73–8.03 m^2/g
Sulfate: <0.25%

11 Stability and Storage Conditions

Calcium stearate is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Calcium stearate is prepared by the reaction of calcium chloride with a mixture of the sodium salts of stearic and palmitic acids. The calcium stearate formed is collected and washed with water to remove any sodium chloride.

14 Safety

Calcium stearate is used in oral pharmaceutical formulations and is generally regarded as a relatively nontoxic and non-irritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Calcium stearate should be used in a well-ventilated environment; eye protection, gloves, and a respirator are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Magnesium stearate; stearic acid; zinc stearate.

18 Comments

See Magnesium stearate for further information and references.

The EINECS number for calcium stearate is 216-472-8.

19 Specific References

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20 General References

Büsch G, Neuwald F. Metallic soaps as water-in-oil emulsifiers [in German]. *J Soc Cosmet Chem* 1973; **24**: 763–769.

Phadke DS, Sack MJ. Evaluation of batch-to-batch and manufacturer-to-manufacturer variability in the physical and lubricant properties of calcium stearate. *Pharm Technol* 1996; **20**(Mar): 126–140.

21 Author

LV Allen.

22 Date of Revision

17 October 2002.

Magnesium Stearate

1 Nonproprietary Names

BP: Magnesium stearate
JP: Magnesium stearate
PhEur: Magnesii stearas
USPNF: Magnesium stearate

2 Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

3 Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4 Empirical Formula Molecular Weight

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 20 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2002 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

5 Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. *See also* Section 18.

8 Description

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for magnesium stearate

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Microbial limits	+	+	+
Aerobic microbes	≤1000/g	—	—
Fungi and yeasts	≤500/g	—	—
Acidity or alkalinity	+	+	+
Acid value of the fatty acid	—	195–210	—
Freezing point	—	≥53°C	—
Nickel	—	≤5 ppm	—
Cadmium	—	≤3 ppm	—
Specific surface area	—	—	+
Loss on drying	≤6.0%	≤6.0%	≤6.0%
Chloride	≤0.1%	≤0.1%	≤0.1%
Sulfate	≤1.0%	≤0.5%	≤1.0%
Lead	—	≤10 ppm	≤0.001%
Heavy metals	≤20 ppm	—	—
Relative stearic/palmitic content	+	+	+
Organic volatile impurities	—	—	+
Assay (dried, as Mg)	4.0–5.0%	4.0–5.0%	4.0–5.0%

10 Typical Properties

Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.
Density (bulk): 0.159 g/cm^3
Density (tapped): 0.286 g/cm^3
Density (true): 1.092 g/cm^3
Flash point: 250°C
Flowability: poorly flowing, cohesive powder.
Melting range:
117–150°C (commercial samples)
126–130°C (high purity magnesium stearate)
Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Specific surface area: 1.6–14.8 m^2/g

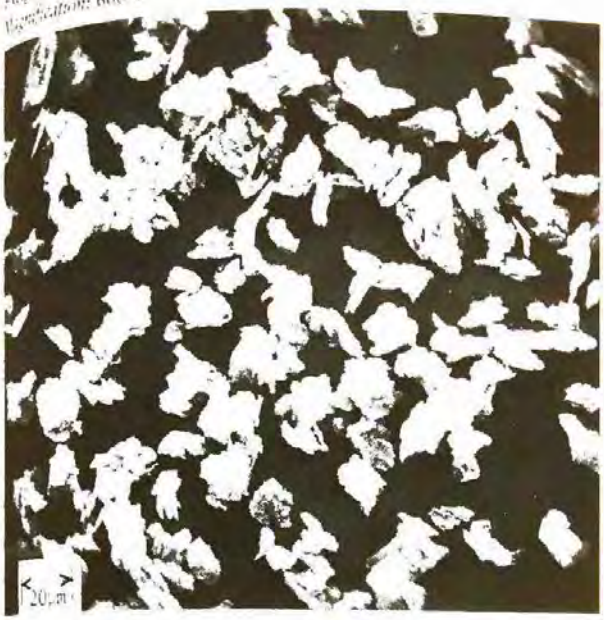
11 Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

SEM: 1
Excipient: Magnesium stearate
Magnification: 600 ×



SEM: 2
Excipient: Magnesium stearate
Magnification: 2400 ×

13 Method of Manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

14 Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worst-case daily intake and heavy metal composition.[1]

Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled.[2,3]

Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice.[4]

LD_{50} (rat, inhalation): >2 mg/L[2]
LD_{50} (rat, oral): >10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

16 Regulatory Acceptance

GRAS listed. Accepted as a food additive in the UK. Included in the FDA Inactive Ingredients Guide (oral capsules, powders, and tablets; buccal and vaginal tablets; topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Calcium stearate; stearic acid; zinc stearate.

18 Comments

Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations.[5–10] Capsule dissolution is also sensitive to both the amount of magnesium stearate in the formulation and the mixing time; higher levels of magnesium stearate and long mixing times can result in the formation of hydrophobic powder beds that do not disperse after the capsule shell dissolves.[11,12]

An increase in the coefficient of variation of mixing and a decrease in the dissolution rate have been observed following blending of magnesium stearate with a tablet granulation. Tablet dissolution rate and crushing strength decreased as the time of blending increased; and magnesium stearate may also increase tablet friability. Blending times with magnesium stearate should therefore be carefully controlled.[13–27]

The existence of various crystalline forms of magnesium stearate has been established.[28–32] A trihydrate, a dihydrate, and an anhydrate have been isolated,[5,30,31,33] and an amorphous form has been observed.[34] While the hydrate forms are stable in the presence of moisture, the anhydrous form adsorbs moisture at relative humidity up to 50%, and at higher humidities rehydrates to form the trihydrate. The anhydrate can be formed by drying either of the hydrates at 105°C.[31]

It has not been conclusively established which form of pure magnesium stearate possesses the best lubricating properties.[29,30,34,35] Commercial lots of magnesium stearate generally consist of mixtures of crystalline forms.[30,32,36–38] Because of the possibility of conversion of crystalline forms during heating, consideration should be given to the pretreatment

conditions employed when determining physical properties of magnesium stearate powders such as surface area.[39]

Physical properties of magnesium stearate can vary among batches from different manufacturers[38] because the solid-state characteristics of the powder are influenced by manufacturing variables.[29] Variations in the physical properties of different lots of magnesium stearate from the same vendor have also been observed.[38] Presumably because of these variations, it has not been possible to conclusively correlate the dissolution rate retardation with observed lubricity.[40]

However, various physical properties of different batches of magnesium stearate such as specific surface area, particle size, crystalline structure, moisture content, and fatty acid composition have been correlated with lubricant efficacy.[30,34,37,38,41–45] Reduction in dissolution caused by the effects of magnesium stearate in some cases can be overcome by including a highly swelling disintegrant in the formulation.[46]

There is evidence to suggest that the hydrophobic nature of magnesium stearate can vary from batch to batch owing to the presence of water-soluble, surface-active impurities such as sodium stearate. Batches containing very low concentrations of these impurities have been shown to retard the dissolution of a drug to a greater extent than when using batches that contain higher levels of impurities.[40] One study related lubricity to the fatty acid composition (stearate : palmitate) of lubricant lots for tablet formulations based on compaction data and tablet material properties.[45] However, other studies have indicated that fatty acid composition has no influence on lubricant activity[30] and high-purity magnesium stearate was as effective a lubricant as the commercial material.[10]

The EINECS number for magnesium stearate is 209-150-3.

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21 Authors

LV Allen, PE Luner.

22 Date of Revision

5 November 2002.

Polyethylene Glycol

1 Nonproprietary Names

BP: Macrogols
JP: Macrogol 400
Macrogol 1500
Macrogol 4000
Macrogol 6000
Macrogol 20000
PhEur: Macrogola
USPNF: Polyethylene glycol

2 Synonyms

Carbowax; *Carbowax Sentry*; *Lipo*; *Lipoxol*; *Lutrol E*; PEG; *Pluriol E*; polyoxyethylene glycol.

3 Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

4 Empirical Formula Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$ where m represents the average number of oxyethylene groups.

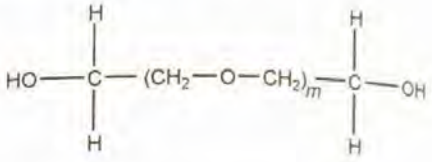
Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where n is a number m in the previous formula + 1.

See Table I for the average molecular weights of typical polyethylene glycols. Note that the number that follows PEG indicates the average molecular weight of the polymer.

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	m	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1 050
PEG 1450	32.5	1 300–1 600
PEG 1540	28.0–36.0	1 300–1 600
PEG 2000	40.0–50.0	1 800–2 200
PEG 3000	60.0–75.0	2 700–3 300
PEG 3350	75.7	3 000–3 700
PEG 4000	69.0–84.0	3 000–4 800
PEG 4600	104.1	4 400–4 800
PEG 8000	181.4	7 000–9 000

5 Structural Formula



6 Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; *see* Section 14. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.[1] Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases,[2] for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.[3] However, they have only limited binding action when used alone, and can

prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations,[4–6] a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes pastelike and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.[7] Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.[8] The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

In addition, polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents.

8 Description

The USPNF 20 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Density:
1.11–1.14 g/cm^3 at 25°C for liquid PEGs
1.15–1.21 g/cm^3 at 25°C for solid PEGs

Flash point:
182°C for PEG 200
213°C for PEG 300
238°C for PEG 400
250°C for PEG 600

Freezing point:
≤ −65°C PEG 200 sets to a glass
−15 to −8°C for PEG 300
4–8°C for PEG 400
15–25°C for PEG 600

Melting point:
37–40°C for PEG 1000
44–48°C for PEG 1500
40–48°C for PEG 1540
45–50°C for PEG 2000
48–54°C for PEG 3000
50–58°C for PEG 4000
55–63°C for PEG 6000
60–63°C for PEG 8000
60–63°C for PEG 20000

Moisture content: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g., PEG 4000 and above, are not hygroscopic. *See* Figures 1–3.

Particle size distribution: *see* Figures 4 and 5.

Refractive index:
n_D^{25} = 1.459 for PEG 200
n_D^{25} = 1.463 for PEG 300
n_D^{25} = 1.465 for PEG 400
n_D^{25} = 1.467 for PEG 600

Table II: Pharmacopeial specifications for polyethylene glycol.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	–
Characters	–	+	–
Appearance of solution	–	+	+
Density	–	See Table IV	–
Freezing point	See Table III	See Table IV	–
Viscosity	–	See Table IV	See Table V
Average molecular weight	See Table III	–	See Table V
pH (5% w/v solution)	See Table III	–	4.5–7.5
Hydroxyl value	–	See Table IV	–
Reducing substances	–	+	–
Residue on ignition	See Table III	–	≤0.1%
Sulfated ash	–	≤0.2%	–
Limit of ethylene glycol and diethylene glycol	≤0.25%	≤0.4%	≤0.25%
Ethylene oxide	–	≤1 ppm	≤10 ppm
1,4-Dioxane	–	≤10 ppm	≤10 ppm
Heavy metals	–	≤20 ppm	≤5 ppm
Organic volatile impurities	–	–	+
Water	≤1.0%	≤2.0%	–
Formaldehyde	–	≤15 ppm	–

Table III: Specifications from JP 2001.

Type of PEG	Average molecular weight	Freezing point (°C)	pH (5% w/v solution)	Residue on ignition
400	380–420	4–8	4.0–7.0	≤0.1%
1500	–	37–41	4.0–7.0	≤0.1%
4000	2 600–3 800	53–57	4.0–7.5	≤0.25%
6000	7 300–9 300	56–61	4.5–7.5	≤0.25%
20000	15 000–25 000	56–64	4.5–7.5	≤0.25%

Table IV: Specifications from PhEur 2002.

Type of PEG	Density (g/cm³)	Freezing point (°C)	Hydroxyl value	Viscosity (dynamic) [mPa s (cP)]	Viscosity (kinematic) [mm²/s (cSt)]
300	1.120	–	340–394	80–105	71–94
400	1.120	–	264–300	105–130	94–116
600	1.080	15–25	178–197	15–20	13.9–18.5
1000	1.080	35–40	107–118	22–30	20.4–27.7
1500	1.080	42–48	70–80	34–50	31–46
3000	1.080	50–56	34–42	75–100	69–93
3350	1.080	53–57	30–38	83–120	76–110
4000	1.080	53–59	25–32	110–170	102–158
6000	1.080	55–61	16–22	200–270	185–250
8000	1.080	55–62	12–16	260–510	240–472
20000	1.080	⩾57	–	2 700–3 500	2 500–3 200
35000	1.080	⩾57	–	11 000–14 000	10 000–13 000

Solubility: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol, and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Surface tension: approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (kinematic): *see* Tables IV, V, and VI.

11 Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.[9] Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain normally solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

12 Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.

The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

13 Method of Manufacture

Polyethylene glycols are condensation polymers formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

14 Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.[10–12]

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols are relatively low.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically have also been reported, including urticaria and delayed allergic reactions.[13]

The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.[14] Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 l of an aqueous mixture of electrolytes and high-molecular-weight polyethylene glycol is consumed by patients undergoing bowel cleansing.[15]

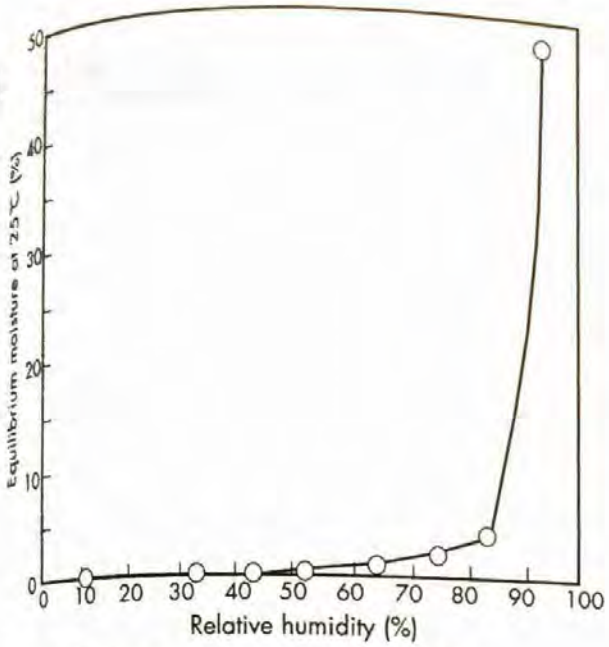


Figure 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot No. B192–8209) at 25°C.

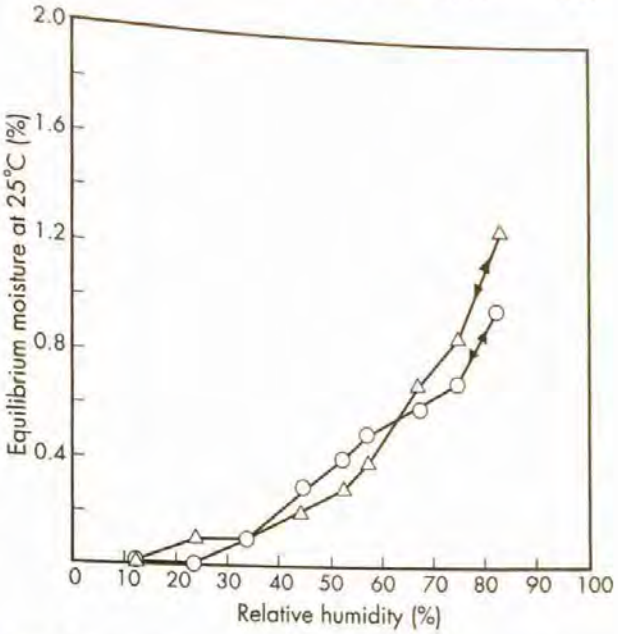


Figure 3: Equilibrium moisture content of PEG 6000 at 25°C.
○: PEG 6000 powder (Union Carbide Corp., Lot no. B–507)
△: PEG E-6000 (BASF, Lot no.WPNA–124B)

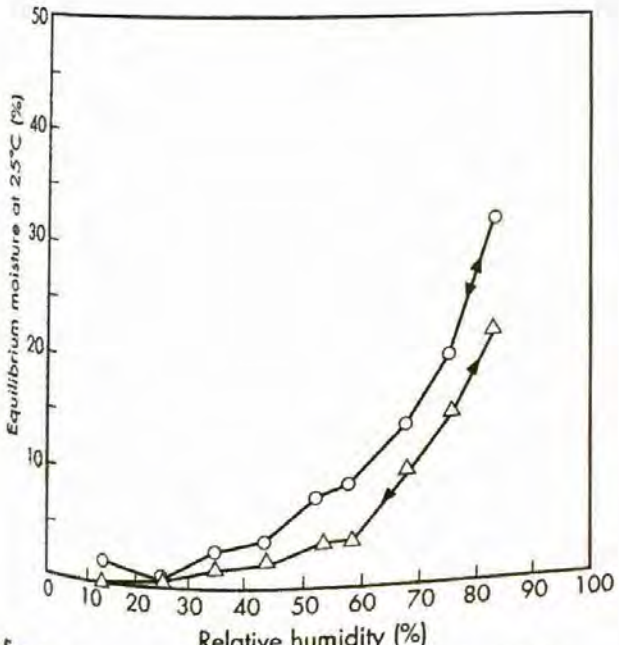


Figure 2: Equilibrium moisture content of PEG 4000 at 25°C.
○: PEG 4000 powder (Union Carbide Corp, Lot no. B-251)
△: PEG E–4000 (BASF, Lot no. WPYA–575B)

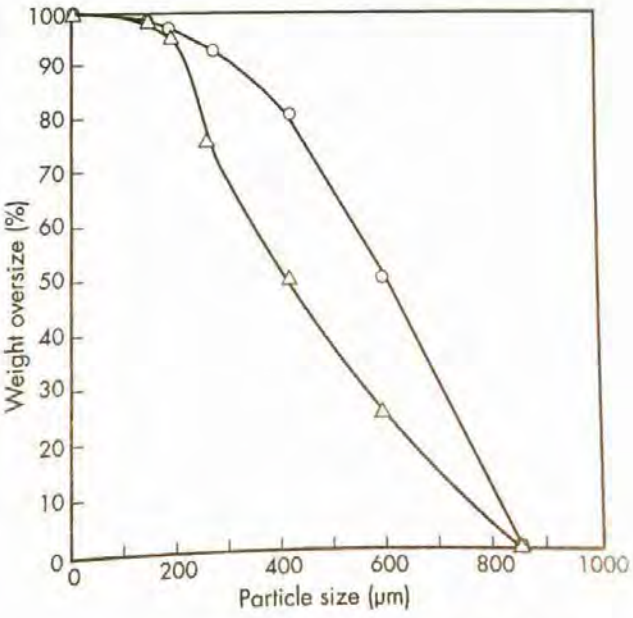


Figure 4: Particle size distribution of PEG 4000 and PEG 6000 flakes.
○: PEG 4000 flakes
△: PEG 6000 flakes

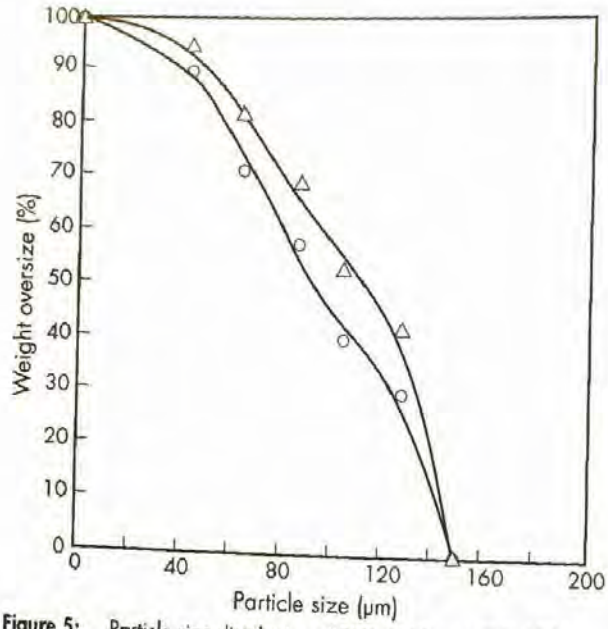


Figure 5: Particle size distribution of PEG 4000 and PEG 6000 powder.
○: PEG 4000 powder
△: PEG 6000 powder

Liquid polyethylene glycols may be absorbed when taken orally, but the higher-molecular-weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine, although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.[16]

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v as hemolytic effects have been observed at concentrations greater than about 40% v/v.

For animal toxicity data, *see* Table VII.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Polyoxyethylene alkyl ethers; polyoxyethylene sorbitan fatty acid esters; suppository bases.

18 Comments

—

Table V: Specification for viscosity of polyethylene glycol of the given nominal molecular weight at 98.9 °C ± 0.3 °C from the USPNF 20.

Type of PEG (nominal average molecular weight)	Viscosity (kinematic) [mm^2/s (cSt)]
200	3.9–4.8
300	5.4–6.4
400	6.8–8.0
500	8.3–9.6
600	9.9–11.3
700	11.5–13.0
800	12.5–14.5
900	15.0–17.0
1000	16.0–19.0
1100	18.0–22.0
1200	20.0–24.5
1300	22.0–27.5
1400	24–30
1450	25–32
1500	26–33
1600	28–36
1700	31–39
1800	33–42
1900	35–45
2000	38–49
2100	40–53
2200	43–56
2300	46–60
2400	49–65
2500	51–70
2600	54–74
2700	57–78
2800	60–83
2900	64–88
3000	67–93
3250	73–105
3350	76–110
3500	87–123
3750	99–140
4000	110–158
4250	123–177
4500	140–200
4750	155–228
5000	170–250
5500	206–315
6000	250–390
6500	295–480
7000	350–590
7500	405–735
8000	470–900

Table VI: Viscosity of selected polyethylene glycols at 25 °C and 99 °C.

Type of PEG	Viscosity [mm^2/s (cSt)]	
	25 °C	99 °C
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000 solid	19.5	—
PEG 2000 solid	47	—
PEG 4000 solid	180	—
PEG 6000 solid	580	—
PEG 20000 solid	6900	—

Table VII: Animal toxicity data (LD_{50}) for various grades of polyethylene glycol.[17]

PEG grade	LD_{50} (g/kg)								
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (IV)	Rat (IP)	Rat (IV)	Rat (oral)
PEG 200	–	7.5	–	34	19.9	–	–	–	28.0
PEG 300	19.6	–	–	–	17.3	–	–	–	27.5
PEG 400	15.7	10.0	8.6	28.9	26.8	–	9.7	7.3	–
PEG 600	–	–	–	47	–	–	–	–	38.1
PEG 1000	–	20	–	–	–	–	15.6	–	32
PEG 1500	28.9	–	–	–	28.9	8	17.7	–	44.2
PEG 4000	50.9	–	16	–	76	–	11.6	–	50
PEG 6000	50	–	–	–	–	–	6.8	–	–

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21 Author

JC Price.

22 Date of Revision

29 October 2002.

Sodium Stearyl Fumarate

1 Nonproprietary Names

BP: Sodium stearyl fumarate
PhEur: Natrii stearylis fumaras
USPNF: Sodium stearyl fumarate

2 Synonyms

Fumaric acid, octadecyl ester, sodium salt; *Pruv*; sodium monostearyl fumarate.

3 Chemical Name and CAS Registry Number

2-Butenedioic acid , monooctadecyl ester, sodium salt [4070-80-8]

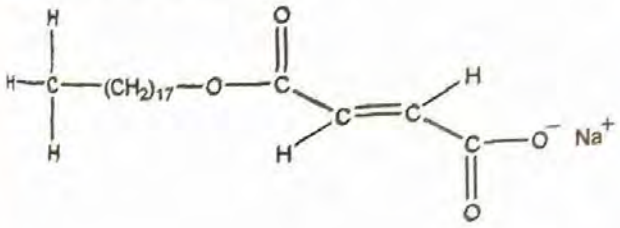
4 Empirical Formula

$C_{22}H_{39}NaO_4$

Molecular Weight

390.5

5 Structural Formula



6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration.[1–9] It is also used in certain food applications; *see* Section 16.

8 Description

Sodium stearyl fumarate is a fine, white powder with agglomerates of flat, circular-shaped particles.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium stearyl fumarate.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	–
Water	≤5.0%	≤5.0%
Lead	–	≤0.001%
Heavy metals	–	≤0.002%
Related substances	+	–
Sodium stearyl maleate	–	≤0.25%
Stearyl alcohol	–	≤0.5%
Saponification value (anhydrous basis)	–	142.2–146.0
Organic volatile impurities	–	+
Assay (anhydrous basis)	99.0–101.5%	99.0–101.5%

10 Typical Properties

Acidity/alkalinity: pH = 8.3 for a 5% w/v aqueous solution at 90 °C.
Density: 1.107 g/cm^3.
Density (bulk): 0.2–0.35 g/cm^3
Density (tapped): 0.3–0.5 g/cm^3
Melting point: 224–245 °C (with decomposition)
Solubility: *see* Table II.

Table II: Solubility of sodium stearyl fumarate.

Solvent	Solubility at 20 °C unless otherwise stated
Acetone	Practically insoluble
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Methanol	Slightly soluble
Water	1 in 20 000 at 25 °C
	1 in 10 at 80 °C
	1 in 5 at 90 °C

Specific surface area: 1.2–2.0 m^2/g.

11 Stability and Storage Conditions

At ambient temperature, sodium stearyl fumarate is stable for up to 3 years when stored in amber glass bottles with polyethylene screw caps.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.[10]

13 Method of Manufacture

Stearyl alcohol is reacted with maleic anhydride. The product of this reaction then undergoes an isomerization step followed by salt formation to produce sodium stearyl fumarate.

SEM: 1
Excipient: Sodium stearyl fumarate
Manufacturer: Penwest Pharmaceuticals
Lot No.: 255-01
Magnification: 300 ×

SEM: 2
Excipient: Sodium stearyl fumarate
Manufacturer: Penwest Pharmaceuticals
Lot No.: 255-01
Magnification: 500 ×

SEM: 3
Excipient: Sodium stearyl fumarate
Manufacturer: Penwest Pharmaceuticals
Lot No.: 255-01
Magnification: 1000 ×

14 Safety

Sodium stearyl fumarate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

Metabolic studies of sodium stearyl fumarate in the rat and dog indicated that approximately 80% was absorbed and 35% was rapidly metabolized. The fraction absorbed was hydrolyzed to stearyl alcohol and fumaric acid, with the stearyl alcohol further oxidized to stearic acid. In the dog, sodium stearyl fumarate that was not absorbed was excreted unchanged in the feces within 24 hours.[11]

Stearyl alcohol and stearic acid are naturally occurring constituents in various food products, while fumaric acid is a normal constituent of body tissue. Stearates and stearyl citrate have been reviewed by the WHO and an acceptable daily intake for stearyl citrate has been set at up to 50 mg/kg bodyweight.[12] The establishment of an acceptable daily intake for stearates[12] and fumaric acid[13] was thought unnecessary.

Disodium fumarate has been reported to have a toxicity not greatly exceeding that of sodium chloride.[14,15]

See Fumaric Acid, Stearic Acid, and Stearyl Alcohol for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium stearyl fumarate should be handled in a well-ventilated environment; eye protection is recommended.

16 Regulatory Status

GRAS listed. Permitted by the FDA for direct addition to food for human consumption as a conditioning or stabilizing agent

in various bakery products, flour-thickened foods, dehydrated potatoes, and processed cereals up to 0.2–1.0% by weight of the food. Included in nonparenteral medicines licensed in the UK. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets).

17 Related Substances

–

18 Comments

Sodium stearyl fumarate is supplied in a pure form and is often of value when the less pure stearate-type lubricants are unsuitable owing to chemical incompatibility. Sodium stearyl fumarate is less hydrophobic than magnesium stearate or stearic acid and has a less retardant effect on tablet dissolution than magnesium stearate.

The EINECS number for sodium stearyl fumarate is 203-743-0.

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21 Author

PJ Weller.

22 Date of Revision

30 May 2002.

Stearic Acid

1 Nonproprietary Names

BP: Stearic acid
JP: Stearic acid
PhEur: Acidum stearicum
USPNF: Stearic acid

2 Synonyms

Crodacid; E570; *Emersol*; *Hystrene*; *Industrene*; *Kortacid 1895*; *Pristerene*.

3 Chemical Name and CAS Registry Number

Octadecanoic acid [57-11-4]

4 Empirical Formula — Molecular Weight

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

The USPNF 20 describe 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 USPNF 20, 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 USPNF 20 also contains a monograph for purified stearic acid; *see* Section 17. The PhEur 2002 contains a single monograph for stearic acid but defines stearic acid 50, stearic acid 70, and stearic acid 95 as containing specific amounts of stearic acid ($C_{18}H_{36}O_2$); *see* Section 9.

5 Structural Formula

6 Functional Category

Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

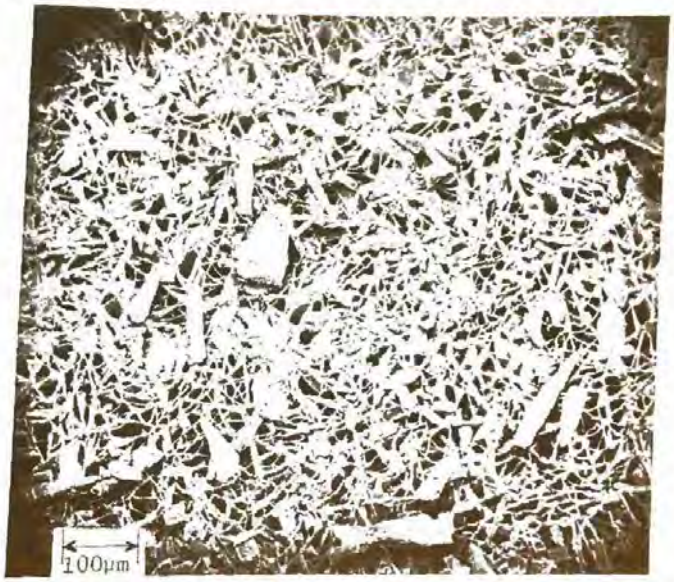
Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant;[1–3] *see* Table I, although it may also be used as a binder[4] or in combination with shellac as a tablet coating. It has also been suggested that stearic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

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

SEM: 1
Excipient: Stearic acid, 95% (*Emersol 153*)
Manufacturer: Emery Industries
Lot No.: 18895
Magnification: 120×
Voltage: 10 kV



SEM: 2
Excipient: Stearic acid, food grade (*Emersol 6332*)
Manufacturer: Emery Industries
Lot No.: 18895
Magnification: 120×
Voltage: 10 kV

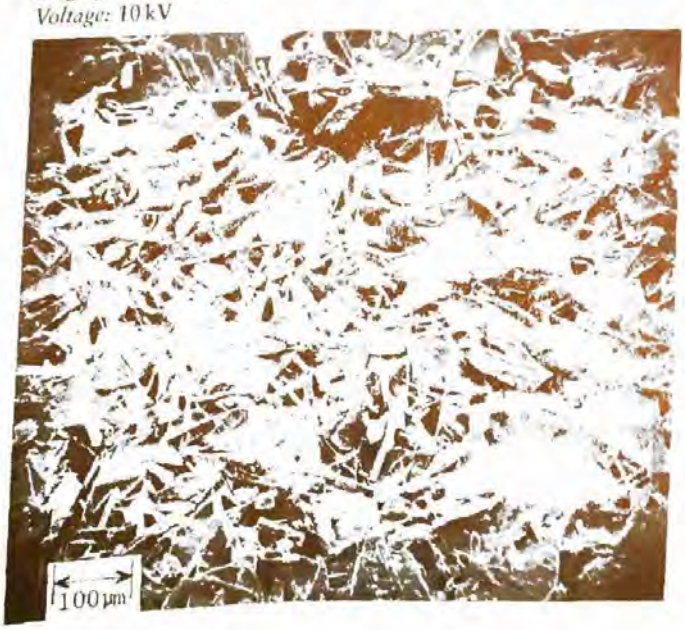


Table I: Uses of stearic acid.

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 and taste suggesting tallow.

See also Section 13.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for stearic acid.

Test	JP 2001	PhEur 2002 (Suppl 4.1)	USPNF 20
Acidity	–	+	–
Acid value	194–210	194–212	–
Appearance	–	+	–
Characters	–	+	–
Content of stearic acid	–	–	≥40.0%
Stearic acid 50	–	40–60%	–
Stearic acid 70	–	60–80%	–
Stearic acid 95	–	≥90.0%	–
Content of stearic and palmitic acids	–	–	≥90.0%
Stearic acid 50	–	≥90.0%	–
Stearic acid 70	–	≥90.0%	–
Stearic acid 95	–	≥96.0%	–
Congealing temperature	56.0–72.0°C	–	≥54°C
Freezing point		+	
Stearic acid 50	–	53–59°C	–
Stearic acid 70	–	57–64°C	–
Stearic acid 95	–	64–69°C	–
Iodine value	≤4.0	+	≤4.0
Stearic acid 50	–	≤4.0%	–
Stearic acid 70	–	≤4.0%	–
Stearic acid 95	–	≤1.5%	–
Nickel	–	≤1 ppm	–
Residue on ignition	≤0.1%	–	≤0.1%
Heavy metals	≤20 ppm	–	≤0.001%
Neutral fat or paraffin	+	–	+
Mineral acid	+	–	+
Organic volatile impurities	–	–	+

10 Typical Properties

Acid value: 200–212
Density (bulk): ≈0.537 g/cm^3
Density (tapped): 0.571 g/cm^3
Density (true): 0.980 g/cm^3
Melting point: ≥54°C
Moisture content: contains practically no water.
Saponification value: 200–220
Solubility: freely soluble in benzene, carbon tetrachloride, chloroform, and ether; soluble in ethanol, hexane, and propylene glycol; practically insoluble in water.
Specific surface area: 0.51–0.53 m^2/g
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 oxidizing agents.

Insoluble stearates are formed with many metals; 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,[8] they may not necessarily be applicable to formulated products.

Stearic acid has been reported to cause pitting in the film coating of tablets coated using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid.[9]

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. Stearic acid may contain a suitable antioxidant such as 0.005% w/w butylated hydroxytoluene.

14 Safety

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

LD_{50} (mouse, IV): 23 mg/kg[10]
LD_{50} (rat, IV): 21.5 mg/kg

15 Handling Precautions

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

Table III: Specifications of different stearic acid grades.

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

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe (fatty acids). Included in the FDA Inactive Ingredients Guide (sublingual tablets; oral capsules, solutions, suspensions, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Calcium stearate; magnesium stearate; palmitic acid; purified stearic acid; zinc stearate.

Palmitic acid

Empirical formula: $C_{16}H_{32}O_2$
Molecular weight: 256.42
CAS number: [57-10-3]
Synonyms: cetylic acid; hexadecanoic acid; hexadecylic acid.
Appearance: the pure material is a white, crystalline powder.
Boiling point: 215°C
Density: 0.853 g/cm^3 at 62°C
Melting point: 63–64°C
Refractive index: $n_D^{80} = 1.4273$
Solubility: freely soluble in chloroform, ether, propan-2-ol, and hot ethanol (95%); sparingly soluble in ethanol (95%); practically insoluble in water.
Comments: the EINECS number for palmitic acid is 200-312-9.

Purified stearic acid

Empirical formula: $C_{18}H_{36}O_2$
Molecular weight: 284.47
CAS number: [57-11-4]
Synonyms: octadecanoic acid.
Acid value: 195–200
Boiling point: 361°C
Density: 0.847 g/cm^3 at 70°C
Flash point: 196°C
Iodine number: ≤1.5
Melting point: 66–69°C
Refractive index: $n_D^{80} = 1.4299$
Solubility: soluble 1 in 5 parts benzene, 1 in 6 parts carbon tetrachloride, 1 in 2 parts chloroform, 1 in 15 parts ethanol, 1 in 3 parts ether; practically insoluble in water.
Vapor density (relative): 9.80 (air = 1)
Comments: purified stearic acid contains not less than 96.0% of stearic and palmitic acid, of which stearic acid constitutes not less than 90.0% of the total.

18 Comments

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.[11]

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

19 Specific References

1 Iranloye TA, Parrott EL. Effects of compression force, particle size, and lubricants on dissolution rate. *J Pharm Sci* 1978; 67: 535–539.
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8 Botha SA, Lötter AP. Comparibility study between naproxen and tablet excipients using differential scanning calorimetry. *Drug Dev Ind Pharm* 1990; 16: 673–683.
9 Rowe RC, Forse SF. Pitting: a defect on film-coated tablets. *Int J Pharm* 1983; 17: 347–349.
10 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 3298.
11 Phadke DS, Keeney MP, Norris DA. Evaluation of batch-to-batch and manufacturer-to-manufacturer variability in the physical properties of talc and stearic acid. *Drug Dev Ind Pharm* 1994; 20: 859–871.

20 General References

Allen LV. Featured excipient: capsule and tablet lubricants. *Int J Pharm Compound* 2000; 4(5): 390–392, 404–405.
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21 Author

LV Allen.

22 Date of Revision

15 October 2002.

Sugar, Compressible

1 Nonproprietary Names

USPNF: Compressible sugar

2 Synonyms

Di-Pac; direct compacting sucrose.

3 Chemical name and CAS Registry Number

See Section 4 and Section 18.

4 Empirical Formula Molecular Weight

The USPNF 20 states that compressible sugar contains not less than 95.0% and not more than 98.0% of sucrose ($C_{12}H_{22}O_{11}$). It may contain starch, maltodextrin, or invert sugar, and may contain a suitable lubricant.

5 Structural Formula

See Section 4.

6 Functional Category

Sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Compressible sugar is used primarily in the preparation of direct-compression chewable tablets. Its tableting properties can be influenced by small changes in moisture level;[1,2] *see* Table I.

Table I: Uses of compressible sugar.

Use	Concentration (%)
Dry binder in tablet formulations	5–20
Filler in chewable tablets	20–60
Filler in tablets	20–60
Sweetener in chewable tablets	10–50

8 Description

Compressible sugar is a sweet-tasting, white, crystalline powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for compressible sugar.

Test	USPNF 20
Identification	+
Calcium	+
Chloride	≤0.014%
Heavy metals	≤5 ppm
Loss on drying	0.25–1.0%
Residue on ignition	≤0.1%
Microbial limits	+
Organic volatile impurities	+
Sulfate	≤0.010%
Assay	95.0–98.0%

10 Typical Properties

Density (bulk): 0.492 g/cm^3
Density (tapped): 0.6 g/cm^3
Moisture content: 0.57%
Particle size distribution: for *Di-Pac*, 3% maximum retained on a #40 (425 µm) mesh; 75% minimum through a #100 (150 µm) mesh; 5% maximum through #200 (75 µm) mesh.
Solubility: the sucrose portion is water-soluble.
Specific surface area: 0.13–0.14 m^2/g

11 Stability and Storage Conditions

Compressible sugar is stable in air under normal storage conditions of room temperature and low relative humidity. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with dilute acids, which cause hydrolysis of sucrose to invert sugar, and with alkaline earth hydroxides, which react with sucrose to form sucrates.

13 Method of Manufacture

Compressible sugar is prepared by cocrystallization of sucrose with other excipients such as maltodextrin.[1] Compressible sugar may also be prepared using a dry granulation process.

14 Safety

Compressible sugar is generally regarded as a relatively nontoxic and nonirritant material. *See also* Sucrose.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. *See also* Sucrose.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Confectioner's sugar; sucrose; sugar spheres; Sugartab.

Sugartab

Appearance: *Sugartab* (Penwest Pharmaceuticals Co.) is a compressible sugar that does not conform to the USPNF 20 specification. It is an agglomerated sugar product containing approximately 90–93% sucrose, the balance being invert sugar.

Density (bulk): 0.60 g/cm^3

Density (tapped): 0.69 g/cm^3

EINECS number: [64333-34-2]

Flowability: 42.7 g/s

Moisture content: 0.20–0.57%.

Particle size distribution: 30% through a #20 (850 μm) mesh; 3% through a #30 (600 μm) mesh.

18 Comments

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19 Specific References

1 Rizzuto AB, Chen AC, Veiga MF. Modification of the sucrose crystal structure to enhance pharmaceutical properties of excipient and drug substances. *Pharm Technol* 1984; 8(9): 32, 34, 36, 38–39.

2 Tabibi SE, Hollenbeck RG. Interaction of water vapor and compressible sugar. *Int J Pharm* 1984; 18: 169–183.

20 General References

Mendes RW, Gupta MR, Katz IA, O'Neil JA. Nu-tab as a chewable direct compression carrier. *Drug Cosmet Ind* 1974; 115(6): 42–46,130–133.

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Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients for direct compression. *Pharm Technol* 1981; 5: 69–78.

21 Author

AW Wood.

22 Date of Revision

8 October 2002.

Sugar, Confectioner's

1 Nonproprietary Names

USPNF: Confectioner's sugar

2 Synonyms

Icing sugar; powdered sugar.

3 Chemical Name and CAS Registry Number

See Section 4.

4 Empirical Formula Molecular Weight

The USPNF 20 describes confectioner's sugar as a mixture of sucrose ($C_{12}H_{22}O_{11}$) and corn starch that has been ground to a fine powder; it contains not less than 95.0% sucrose.

5 Structural Formula

See Section 4 and Sucrose.

6 Functional Category

Sugar coating adjunct; sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Confectioner's sugar is used in pharmaceutical formulations when a rapidly dissolving form of sugar is required for flavoring or sweetening. It is used as a diluent in solid-dosage formulations when a small particle size is necessary to achieve content uniformity in blends with finely divided active ingredients. In solutions, at high concentrations (70% w/v), confectioner's sugar provides increased viscosity along with some preservative effects. Confectioner's sugar is also used in the preparation of sugar-coating solutions and in wet granulations as a binder/diluent. *See* Table I.

Table I: Uses of confectioner's sugar.

Use	Concentration (%)
Sweetening agent in tablets	10–20
Tablet diluent	10–50

See also Section 18.

8 Description

Confectioner's sugar occurs as a sweet-tasting, fine, white, odorless powder.

SEM: 1
Excipient: Confectioner's sugar
Manufacturer: Frost
Lot No.: 101A-1
Magnification: 60×
Voltage: 20 kV

SEM: 2
Excipient: Confectioner's sugar
Manufacturer: Frost
Lot No.: 101A-1
Magnification: 600×
Voltage: 20 kV

Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for confectioner's sugar.

Test	USPNF 20
Identification	+
Chloride	≤0.014%
Calcium	+
Heavy metals	≤5 ppm
Loss on drying	≤1.0%
Microbial limits	+
Organic volatile impurities	+
Residue on ignition	≤0.08%
Specific rotation	≥62.6°
Sulfate	≤0.006%
Assay	≤95.0%

10 Typical Properties

Density (bulk): 0.465 g/cm^3
Density (tapped): 0.824 g/cm^3
Moisture content: 0.1–0.31%
Particle size distribution: various grades with different particle sizes are commercially available, e.g., 6X, 10X, and 12X grades of confectioner's sugar from the Domino Sugar Corp. Mean particle size is 14.3 μm.
For 6X, 94% through a #200 (75 μm) mesh
For 10X, 99.9% through a #100 (150 μm) mesh and 97.5% through a #200 (75 μm) mesh
For 12X, 99% through a #200 (75 μm) mesh and 96% through a #325 (45 μm) mesh.
Solubility: the sucrose portion is water-soluble while the starch portion is insoluble in water, although it forms a cloudy solution.

11 Stability and Storage Conditions

Confectioner's sugar is stable in air at moderate temperatures but may caramelize and decompose above 160°C. It is more hygroscopic than granular sucrose. Microbial growth may occur on dry storage if adsorbed moisture is present or in dilute aqueous solutions.

Confectioner's sugar should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Confectioner's sugar is incompatible with dilute acids, which cause the hydrolysis of sucrose to invert sugar. It is also incompatible with alkaline earth hydroxides, which react with sucrose to form sucrates.

13 Method of Manufacture

Confectioner's sugar is usually manufactured by grinding refined granulated sucrose with corn starch to produce a fine powder. Other anticaking agents, such as tricalcium phosphate and various silicates, have also been used but are less common.

14 Safety

Confectioner's sugar is used in confectionery and oral pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material. *See also* Sucrose.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. *See also* Sucrose.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (capsules and tablets).

17 Related Substances

Compressible sugar; sucrose; sugar spheres.

18 Comments

Confectioner's sugar is not widely used in pharmaceutical formulations because the poor-flow characteristics prevent its use in direct-compression blends. However, confectioner's sugar is used when a smooth mouth feel or a rapidly dissolving sweetener is required, and when a milled/micronized active ingredient must be blended with a diluent of similar particle size for powders or wet granulations.

Low-starch grades of confectioner's sugar containing 0.01% w/w starch are also commercially available.

19 Specific References

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20 General References

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21 Author

AH Kibbe.

22 Date of Revision

8 October 2002.

Sugar Spheres

1 Nonproprietary Names

BP: Sugar spheres
PhEur: Sacchari spheri
USPNF: Sugar spheres

2 Synonyms

Non-pareil; non-pareil seeds; *NPTAB*; *Nu-Core*; *Nu-Pareil PG*; sugar seeds; *Suglets*.

3 Chemical Name and CAS Registry Number

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4 Empirical Formula Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained-release formulations.[1–4] They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating.

Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or through to the controlled erosion of the polymer coating.

Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

Sugar spheres are also used in confectionery products.

8 Description

The USPNF 20 describes sugar spheres as approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch.

The PhEur 2002 states that sugar spheres contain not more than 92% of sucrose calculated on the dried basis. The remainder consists of corn (maize) starch and may also contain starch hydrolysates and color additives. The diameter of sugar spheres varies from 200 to 2000 µm and the upper and lower limits of the size of the sugar spheres are stated on the label.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sugar spheres.

Test	PhEur 2002	USPNF 20
Identification	+	+
Heavy metals	≤5 ppm	≤5 ppm
Loss on drying	≤5.0%	≤4.0%
Microbial limits	+	+
Organic volatile impurities	—	+
Particle size distribution	+	+
Residue on ignition	≤0.2%	≤0.25%
Specific rotation	—	+41° to +61°
Sucrose (dried basis)	≤92%	62.5–91.5%

10 Typical properties

Density:
1.57–1.59 g/cm^3 for *Suglets* less than 500 µm in size
1.55–1.58 g/cm^3 for *Suglets* more than 500 µm in size

Flowability: <10 seconds, free flowing.

Particle size distribution: sugar spheres are of a uniform diameter. The following sizes are commercially available from various suppliers (US standard sieves):

45–60 mesh (250–355 µm)
40–50 mesh (300–425 µm)
35–45 mesh (355–500 µm)
35–40 mesh (420–500 µm)
30–35 mesh (500–600 µm)
25–30 mesh (610–710 µm)
20–25 mesh (710–850 µm)
18–20 mesh (850–1000 µm)
16–20 mesh (850–1180 µm)
14–18 mesh (1000–1400 µm)

Solubility: solubility in water varies according to the sucrose-to-starch ratio. The sucrose component is freely soluble in water, whereas the starch component is practically insoluble in cold water.

Specific surface area:
0.1–0.2 m^2/g for *Suglets* less than 500 µm in size
>0.2 m^2/g for *Suglets* more than 500 µm in size

11 Stability and Storage Conditions

Sugar spheres are stable when stored in a well-closed container in a cool, dry place.

12 Incompatibilities

See Starch and Sucrose for information concerning the incompatibilities of the component materials of sugar spheres.

13 Method of Manufacture

Sugar spheres are prepared from crystalline sucrose, which is coated using sugar syrup and a starch dusting powder.

14 Safety

Sugar spheres are used in oral pharmaceutical formulations. The sucrose and starch components of sugar spheres are widely used in edible food products and oral pharmaceutical formulations.

The adverse reactions and precautions necessary with the starch and sucrose components should be considered in any product containing sugar spheres. For example, sucrose is generally regarded as more cariogenic than other carbohydrates, and in higher doses is also contraindicated in diabetic patients.

See Starch and Sucrose for further information.

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK and Europe. The sucrose and starch components of sugar spheres are individually approved for use as food additives in Europe and the USA.

17 Related Substances

Compressible sugar; confectioner's sugar; starch; sucrose.

18 Comments

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19 Specific References

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2 Bansal AK, Kakkar AP. Solvent deposition of diazepam over sucrose pellets. *Indian J Pharm Sci* 1990; 52: 186–187.

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4 Miller RA, Leung EM, Oates RJ. The compression of spheres coated with an aqueous ethylcellulose dispersion. *Drug Devel Ind Pharm* 1999; 25(4): 503–511.

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RC Moreton.

22 Date of Revision

7 October 2002.