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

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

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

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

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

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

17 Related Substances
Castor oil; vegetable oil, hydrogenated.

18 Comments
Various different grades of hydrogenated castor oil are commercially available, the composition of which may vary considerably.

Sterotex K (Karlshamns Lipid Specialities), for example, is a mixture of hydrogenated castor oil and hydrogenated cottonseed oil. See Vegetable Oil, hydrogenated for further information.

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

19 Specific References
1 Kline CH. Thixcin R-thixotrope. Drug Cosmet Ind 1964; 95(6): 895-897.

20 General References

21 Author
RT Guest.

22 Date of Revision
11 February 2009.

Cellulose, Microcrystalline

1 Nonproprietary Names
BP: Microcrystalline Cellulose
JP: Microcrystalline Cellulose
PhEur: Cellulose, Microcrystalline
USP-NF: Microcrystalline Cellulose

2 Synonyms
Avicel PH; Celtex; Celex; cellulase gel; hedralum microcrystallinum; Celphree; Celclus KG; crystalline cellulose; E460; Emcocel; Ethiphosphes; Fibrocell; MCC Sanag; Pharmacel; Tabulose; Viaapur.

3 Chemical Name and CAS Registry Number
Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight
(C<sub>6</sub>H<sub>10</sub>O<sub>5</sub>)<sub>n</sub> ~ 36 000
where n ~ 220.

5 Structural Formula

6 Functional Category
Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
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.\footnote{1-7} In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant\footnote{8} and disintegrant properties that make it useful in tableting.
8 Description
Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

| Table I: Uses of microcrystalline cellulose. |
| Use | Concentration (%) |
| Adsorbent | 20-90 |
| Antioxidant | 5-20 |
| Capsule binder/diluent | 20-90 |
| Tablet disintegrant | 2-15 |
| Tablet binder/diluent | 20-90 |

9 Pharmacopeial Specifications
See Table II. See also Section 18.

| Table II: Pharmacopeial specifications for microcrystalline cellulose. |
| Test | JP XV | PhEur 6.3 | USP32-NF27 |
| Identification | + | + | + |
| Characters | + | + | - |
| pH | 5.0-7.5 | 5.0-7.5 | 5.0-7.5 |
| Bulk density | + | - | + |
| Loss on drying | ≤7.0% | ≤7.0% | ≤7.0% |
| Residue on ignition | ≤0.1% | - | ≤0.1% |
| Conductivity | + | + | - |
| Sulphated ash | - | ≤0.1% | - |
| Water-soluble substances | ≤0.05% | ≤0.05% | ≤0.05% |
| Heavy metals | ≤10 ppm | ≤10 ppm | ≤0.001% |
| Microbial limits | + | + | - |
| Aerobic | ≤10³ cfu/g | ≤10³ cfu/g | ≤10³ cfu/g |
| Molds and yeasts | ≤10³ cfu/g | ≤10³ cfu/g | ≤10³ cfu/g |
| Solubility | + | + | + |
| Particle size distribution | + | + | - |

10 Typical Properties

Angle of repose
49° for Cellulose KG;
34.4° for Emcocel 90M. (9)

Density (bulk)
0.337 g/cm³;
0.32 g/cm³ for Avicel PH-101; (10)
0.80 ± 5 g/cm³ for Cellots 100, 200, 350, 500, 700, 1000;
0.29 g/cm³ for Emcocel 90M; (9)
0.26-0.31 g/cm³ for MCC Sanag 101;
0.28-0.33 g/cm³ for MCC Sanag 102;
0.29-0.36 g/cm³ for MCC Sanag 200;
0.34-0.45 g/cm³ for MCC Sanag 301;
0.35-0.46 g/cm³ for MCC Sanag 302;
0.13-0.23 g/cm³ for MCC Sanag UL-002;
0.29 g/cm³ for Vivapur 101.

Density (tapped)
0.478 g/cm³;
0.45 g/cm³ for Avicel PH-101;
0.35 g/cm³ for Emcocel 90M; (9)

Density (true) 1.512-1.668 g/cm³;

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

1.420-1.460 g/cm³ for Avicel PH-102. (11)
Flowability 1.41 g/s for Emcocel 90M. (9)
Melting point Chars at 260-270°C.
Moisture content Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic. (11) See Table III.
NIR spectra See Figure 1.
Particle size distribution Typical mean particle size is 20-200 µm.
Different grades may have a different nominal mean particle size; see Table III.
Solubility Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
Specific surface area
1.05-1.31 m²/g for Avicel PH-101;
1.21-1.30 m²/g for Avicel PH-102;
0.78-1.18 m²/g for Avicel PH-200.

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

12 Incompatibilities
Microcrystalline cellulose is incompatible with strong oxidizing agents.

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

14 Safety
Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.
Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.
Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas. (11)
Table III: Properties of selected commercially available grades of microcrystalline cellulose.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nominal mean particle size (µm)</th>
<th>Particle size analysis</th>
<th>Moisture content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avisce/ PH-101</td>
<td>50</td>
<td>60</td>
<td>≤1.0 ≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-102</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-103</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-104</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-105</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-112</td>
<td>100</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-113</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-200</td>
<td>180</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-301</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Avisce/ PH-302</td>
<td>100</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Calex 101</td>
<td>75</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Celrose KG-802</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Emcocel 50M</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Emcocel 90M</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>MCC Sanaq 101</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>MCC Sanaq 102</td>
<td>100</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>MCC Sanaq 200</td>
<td>180</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>MCC Sanaq 301</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>MCC Sanaq 302</td>
<td>100</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>MCC Sanaq UL-002</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Vivapur 101</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Vivapur 102</td>
<td>50</td>
<td>60</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Vivapur 12</td>
<td>160</td>
<td>94</td>
<td>≤0.5</td>
</tr>
</tbody>
</table>

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

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritating to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the workplace exposure limits for cellulose have been set at 10 mg/m³ long-term (8-hour TWA) for total inhalable dust and 4 mg/m³ for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m³.54

16 Regulatory Status

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

17 Related Substances

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

Microcrystalline cellulose and carrageenan

Synonyms Lustre Clear.

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

Microcrystalline cellulose and guar gum

Synonyms Avisce CE-15.

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

18 Comments

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

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

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

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

According to PhEur 6.3, microcrystalline cellulose has certain functionality related characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient. Non-mandatory testing procedures have been described for particle size distribution (2.9.31 or 2.9.38) and powder flow (2.9.36). A specification for microcrystalline cellulose is contained in the Food Chemicals Codex (FCC).30 The PubChem Compound ID (CID) for microcrystalline cellulose is 14055602.

19 Specific References

20 General References

(accessed 6 November 2008).

Doelker E. Comparative compaction properties of various microcrystalline

European Directorate for the Quality of Medicines and Healthcare (EDQM).
nu/site/-614.html (accessed 5 February 2009).


(accessed 6 November 2008).

Pharmatrans Sanaq AG. Product literature: MCC Sanaq. http://www.pharma-

Smolinske SC. Handbook of Food, Drug, and Cosmetic Excipients. Boca

Staniforth JN et al. Effect of addition of water on the rheological and

21 Author

A Guy.

22 Date of Revision

5 February 2009.
It has been shown that the increased force required to expel coconut oil from plastic syringes was due to uptake of the oil into the rubber plunger; this resulted in swelling of the rubber plunger and an increased resistance to movement down the syringe barrel.\textsuperscript{124}

13 Method of Manufacture
Coconut oil is the fixed oil obtained from the seeds of Cocos nucifera Linn. (Palmace). This oil is then refined to produce refined coconut oil, which is referred to in the coconut industry as RBD (refined, bleached, and deodorized) coconut oil.

14 Safety
When administered orally, coconut oil is essentially nontoxic, although ingestion of large amounts may cause digestive or gastrointestinal irritation or upset. Coconut oil can act as an irritant when applied to the skin and when in contact with the eyes; it may be absorbed through the skin. Inhalation of mist or vapor may cause respiratory tract irritation.

15 Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of the material handled. Coconut oil should be kept away from heat and sources of ignition, and contact with oxidizing agents, acids, and alkalis should be avoided.

If in the solid form, large spillages of coconut oil should be dealt with by shoveling the material into a waste disposal container. For liquid spillages, the oil should be absorbed with an inert material before removal for disposal.

16 Regulatory Status
Included in the FDA Inactive Ingredients Database (oral capsules and tablets; topical creams, solutions, and ointments). Included in scalp ointments and therapeutic shampoos licensed in the UK.

17 Related Substances
Almond oil; canola oil; castor oil; castor oil, hydrogenated; corn oil; cottonseed oil; medium-chain triglycerides; olive oil; peanut oil; sesame oil; soybean oil; sunflower oil.

18 Comments
A specification for coconut oil (unhydrogenated) is contained in the Food Chemicals Codex (FCC).\textsuperscript{133}

19 Specific References

20 General References

21 Author
CG Cable.

22 Date of Revision
27 February 2009.

Colloidal Silicon Dioxide

1 Nonproprietary Names
BP: Colloidal Anhydrous Silica
JP: Light Anhydrous Silicic Acid
PhEur: Silica, Colloidal Anhydrous
USP-NF: Colloidal Silicon Dioxide

2 Synonyms
Aerosil; Cab-O-Sil; Cab-O-Sil M-SP; colloidal silica; fumed silica; fumed silicon dioxide; hochdisperse silicum dioxide; SAS; silica colloidalis anhydrica; silica sol; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica; Wacker HDK.

3 Chemical Name and CAS Registry Number
Silica [7631-86-9]

4 Empirical Formula and Molecular Weight
SiO\textsubscript{2} 60.08

5 Structural Formula
See Section 4.

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 tabletting and capsule filling.

Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. 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 a 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 hard 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. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres as a thickening agent for topical preparations and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

Table I: Uses of colloidal silicon dioxide.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerosols</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Emulsion stabilizer</td>
<td>1.0-5.0</td>
</tr>
<tr>
<td>Glidant</td>
<td>0.1-1.0</td>
</tr>
<tr>
<td>Suspending and thickening agent</td>
<td>2.0-10.0</td>
</tr>
</tbody>
</table>

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, amorphous powder.

SEM 1: Excipient: colloidal silicon dioxide (Aerosil A-200); manufacturer: Evonik Degussa Corp. lot no.: 87A-1 (04169C); magnification: 600x; voltage: 20kV.

9 Pharmacopeial Specifications

See Table II. See also Section 18.

Table II: Pharmacopeial specifications for colloidal silicon dioxide.

<table>
<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.0</th>
<th>USP32-NF27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pH (4% w/v dispersion)</td>
<td>-</td>
<td>3.5-5.5</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>Arsenic</td>
<td>≤5 ppm</td>
<td>≤5 µg/g</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>&lt;0.011%</td>
<td>≤250 ppm</td>
<td></td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤0.4 ppm</td>
<td>≤25 ppm</td>
<td></td>
</tr>
<tr>
<td>Aluminum</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcium</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Iron</td>
<td>≤500 ppm</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤7.0%</td>
<td>≤2.5%</td>
<td></td>
</tr>
<tr>
<td>Loss on ignition</td>
<td>≤12.0%</td>
<td>≤5.0%</td>
<td>≤2.0%</td>
</tr>
<tr>
<td>Volume test (5 g sample)</td>
<td>≥70 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay (on ignited sample)</td>
<td>≥98.0%</td>
<td>99.0-100.5%</td>
<td>99.0-100.5%</td>
</tr>
</tbody>
</table>

10 Typical Properties

Acidity/alkalinity pH = 3.8-4.2 (4% w/v aqueous dispersion) and 3.5-4.0 (10% w/v aqueous dispersion) for Cab-O-Sil M-SP

Density (bulk) 0.029-0.042 g/cm³

Density (tapped) see Tables III, IV, and V.

Melting point 1600°C

Moisture content see Figure 1 (12,13)

Particle size distribution Primary particle size is 7-16 nm. Aerosil forms loose agglomerates of 10-200 µm. 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. For Aerosil, solubility in water is 150 mg/L at 25°C (pH 7).

Specific gravity 2.2

Specific surface area 100-400 m²/g depending on grade. See also Tables III, IV, and 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 (Evonik Degussa Corp.), Cab-O-Sil (Cabot Corporation), and Wacker HDK (Wacker-Chemie GmbH) are shown in Tables III, IV and V, respectively.

11 Stability and Storage Conditions
Colloidal silicon dioxide is hygroscopic but adsorbs large 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 dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates.\(^{14}\) Colloidal silicon dioxide powder should be stored in a well-closed container.

12 Incompatibilities
Incompatible with diethylstilbestrol preparations.\(^{15}\)

13 Method of Manufacture
Colloidal silicon dioxide is prepared by the flame hydrolysis of chlorosilanes, such as silicon tetrachloride, at 1800°C using a hydrogen–oxygen flame. Rapid cooling from the molten state during manufacture causes the product to remain amorphous.

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.

\[ \text{LD}_{50} \text{ (rat, IV): } 0.015 \text{ g/kg} \]

\[ \text{LD}_{50} \text{ (rat, oral): } 3.16 \text{ g/kg} \]
15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Considered a nuisance dust, 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 Database (oral capsules, suspensions, and tablets; transdermal, rectal, and vaginal preparations). Also approved by the FDA as a food additive and for food contact. Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydrophobic colloidal silica.

18 Comments

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

The PhEur 6.0 also contains a specification for hydrated colloidal silicon dioxide. The incidence of microbial contamination of colloidal silicon dioxide is low due to the high production temperatures and inorganic precursor materials.

Note that porous silica gel particles may also be used as a glidant, thickener, dispersant and to adsorb moisture, which may be an advantage for some formulations. Syloid 244FP meets the USP-NF requirements for silicon dioxide, and Syloyd 244 FP-BU meets the PhEur and JP requirements for silicon dioxide.18

Another CAS number that is used for colloidal silicon dioxide is 112945-52-5.

The EINECS number for colloidal silicon dioxide is 231-545-4. The PubChem Compound ID (CID) for colloidal silicon dioxide is 24261.

19 Specific References

12 Ertlinger M et al. [Adsorption at the surface of fumed silica.] Arch Pharm 1987; 320: 1-15 (in German).

20 General References


21 Author

KP Hagood.

22 Date of Revision

3 February 2009.
Crospovidone

1 Nonproprietary Names
BP: Crospovidone
PhEur: Crospovidone
USP-NF: Crospovidone

2 Synonyms
Crospovidonum; Crospopharm; 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
(C6H9 NO)n > 1000,000

The USP32-NF27 describes crospovidone as 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. 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. 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. See also Section 18.

10 Typical Properties
Acidity/alkalinity pH = 5.0–8.0(1% w/v aqueous slurry)
Density 1.22 g/cm³
Density (bulk) see Table II.
Density (tapped) see Table II.
Particulate size distribution
Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Moisture content
Maximum moisture sorption is approximately 60%.

NIR spectra
See Figure 1.

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. The average particle size for Cospopham type A is 100 µm and for Cospopham type B it is 30 µm.

Solubility
Practically insoluble in water and most common organic solvents.

Specific surface area
See Table III.

Table I: Pharmacopeial specifications for crospovidone.

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 6.3</th>
<th>USP32-NF27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>pH (1% suspension)</td>
<td>-</td>
<td>5.0-8.0</td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>&gt; 0.1%</td>
<td>&lt; 0.4%</td>
</tr>
<tr>
<td>Water-soluble substances</td>
<td>&lt; 1.0%</td>
<td>&lt; 1.50%</td>
</tr>
<tr>
<td>Peroxides</td>
<td>&lt; 400 ppm</td>
<td>-</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>&lt; 10 ppm</td>
<td>&lt; 0.001%</td>
</tr>
<tr>
<td>VINylpyrrolidinone</td>
<td>&lt; 10 ppm</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>&lt;= 5.0%</td>
<td>-</td>
</tr>
<tr>
<td>Nitrogen content (anhydrous basis)</td>
<td>11.0-12.8%</td>
<td>+</td>
</tr>
</tbody>
</table>

Table II: Density values of commercial grades of crospovidone.

<table>
<thead>
<tr>
<th>Commercial grade</th>
<th>Density (bulk) (g/cm³)</th>
<th>Density (tapped) (g/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon CL</td>
<td>0.3-0.4</td>
<td>0.4-0.5</td>
</tr>
<tr>
<td>Kollidon CL-M</td>
<td>0.15-0.25</td>
<td>0.3-0.5</td>
</tr>
<tr>
<td>Polyplasdone XL</td>
<td>0.213</td>
<td>0.273</td>
</tr>
<tr>
<td>Polyplasdone XL-10</td>
<td>0.323</td>
<td>0.461</td>
</tr>
</tbody>
</table>

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. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

LD₅₀ (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 Database (IM injections, oral capsules and tablets; topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.
Cyclodextrins

17 Related Substances
Copovidone; povidone.

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

Copovidone has been studied as a superdisintegrant. The ability of the compound to swell has been examined directly using scanning electron microscopy. The impact of copovidone on dissolution of poorly soluble drugs in tablets has also been investigated. Copovidone has been shown to be effective with highly hygroscopic drugs. It continues to be examined for its uses in a number of tablet formulations.

A specification for copovidone is contained in the Food Chemicals Codex (FCC). The PubChem Compound ID (CID) for copovidone is 6917.

19 Specific References
Dibutyl Sebacate

1 Nonproprietary Names
USP-NF: Dibutyl Sebacate

2 Synonyms
Bis(n-butyl)sebacate; butyl sebacate; DBS; decanedioic acid, dibutyl ester; dibutyl decanedioate; dibutyl 1,8-octanedicarboxylate; Kodal flex DBS, Morflex DBS.

3 Chemical Name and CAS Registry Number
Decanedioic acid, di-n-butyl ester [109-43-3]

4 Empirical Formula and Molecular Weight
C_{18}H_{34}O_{4} \text{ 314.47}
The USP32-NF27 describes dibutyl sebacate as consisting of the esters of n-butyl alcohol and saturated dibasic acids, principally sebacic acid.

5 Structural Formula

\[ \text{H}_2\text{C}-(\text{CH}_2)_{10}-\text{O}-(\text{CH}_2)_{8}-\text{C}-\text{O}-(\text{CH}_2)_{8}-\text{CH}_3 \]

6 Functional Category
Plasticizer.

7 Applications in Pharmaceutical Formulation or Technology
Dibutyl sebacate is used in oral pharmaceutical formulations as a plasticizer for film coatings on tablets, beads, and granules, at concentrations of 10–30% by weight of polymer.\(^{(1,2)}\) It is also used as a plasticizer in controlled-release tablets and microcapsule preparations.\(^{(3,4)}\)

Dibutyl sebacate is also used as a synthetic flavor and flavor adjuvant in food products;\(^{(3)}\) for example, up to 5 ppm is used in ice cream and nonalcoholic beverages.

8 Description
Dibutyl sebacate is a clear, colorless, oily liquid with a bland to slight butyl odor.

9 Pharmacopeial Specifications
See Table I.

<table>
<thead>
<tr>
<th>Test</th>
<th>USP32-NF27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific gravity</td>
<td>0.925-0.939</td>
</tr>
<tr>
<td>Refractive index</td>
<td>1.429-1.441</td>
</tr>
<tr>
<td>Acid value</td>
<td>≤0.1</td>
</tr>
<tr>
<td>Saponification value</td>
<td>352-360</td>
</tr>
<tr>
<td>Assay of C_{18}H_{34}O_{4}</td>
<td>≥92.0%</td>
</tr>
</tbody>
</table>

10 Typical Properties
Acid value 0.02
Boiling point 344–349°C; 180°C at 3 mmHg for Morflex DBS.
Flash point 193°C; 178°C (OC) for Morflex DBS.
Melting point -10°C
Refractive index \(n_D^2 = 1.4401\)
Solubility Soluble in ethanol (95%), ether, isopropanol, mineral oil, and toluene; practically insoluble in water.
Specific gravity 0.937 at 20°C
Vapor density (relative) 10.8 (air = 1)
Vapor pressure 0.4 kPa (3 mmHg) at 180°C

11 Stability and Storage Conditions
Dibutyl sebacate should be stored in a closed container in a cool, dry location. Dibutyl sebacate is stable under the recommended storage conditions and as used in specified applications under most conditions of use. As an ester, dibutyl sebacate may hydrolyze in the presence of water at high or low pH conditions.

12 Incompatibilities
Dibutyl sebacate is incompatible with strong oxidizing materials and strong alkalis.

13 Method of Manufacture
Dibutyl sebacate is manufactured by the esterification of n-butanol and sebacic acid in the presence of a suitable catalyst, and by the distillation of sebacic acid with n-butanol in the presence of concentrated acid.

14 Safety
Dibutyl sebacate is used in cosmetics, foods, and oral pharmaceutical formulations, and is generally regarded as a nontoxic and nonirritant material. Following oral administration, dibutyl sebacate is metabolized in the same way as fats. In humans, direct eye contact and prolonged or repeated contact with the skin may cause very mild irritation. Acute animal toxicity tests and long-term animal feeding studies have shown no serious adverse effects to be associated with orally administered dibutyl sebacate.

\(\text{LD}_{50} \text{ (rat, oral): } 16 \text{ g/kg}\)\(^{(6)}\)
228 Diethanolamine

15 Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. It is recommended that eye protection be used at all times. When heating this product, it is recommended to have a well-ventilated area, and the use of a respirator is advised.

16 Regulatory Status
Included in the FDA Inactive Ingredients Database (oral capsules, granules, film-coated, sustained action, and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

18 Comments
As dibutyl sebacate is an emollient ester, the personal care grade is recommended for use in cosmetics, hair products, lotions, and creams. The EINECS number for dibutyl sebacate is 203-672-5. The PubChem Compound ID (CID) for dibutyl sebacate is 7986.

19 Specific References
2 Iyer U et al. Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations. Pharm Technol 1990; 14(9): 68, 70, 72, 74, 76, 78, 80, 82, 84, 86.

20 General References

21 Author
T Farrell.

22 Date of Revision
14 January 2009.

Diethanolamine

1 Nonproprietary Names
USP-NF: Diethanolamine

2 Synonyms
Bis(hydroxyethyl)amine; DEA; diethylamine; 2,2'-dihydroxyethyldiethylamine; diolamine; 2,2'-iminodiethanol.

3 Chemical Name and CAS Registry Number
2,2'-Iminobis ethanol [111-42-2]

4 Empirical Formula and Molecular Weight
C₄H₁₁NO₂  105.14

5 Structural Formula

6 Functional Category
Alkalizing agent; emulsifying agent.

7 Applications in Pharmaceutical Formulation or Technology
Diethanolamine is primarily used in pharmaceutical formulations as a buffering agent, such as in the preparation of emulsions with fatty acids. In cosmetics and pharmaceuticals it is used as a pH adjuster and dispersant.

Diethanolamine has also been used to form the soluble salts of active compounds, such as iodinated organic acids that are used as contrast media. As a stabilizing agent, diethanolamine prevents the discoloration of aqueous formulations containing hexamethylenetetramine-1,3-dichloropropene salts.

Diethanolamine is also used in cosmetics.

8 Description
The USP32-NF27 describes diethanolamine as a mixture of ethanolamines consisting largely of diethanolamine. At about room temperature it is a white, deliquescent solid. Above room temperature diethanolamine is a clear, viscous liquid with a mildly ammoniacal odor.

9 Pharmacopeial Specifications
See Table I.
Isopropyl Alcohol

1 Nonproprietary Names
BP: Isopropyl Alcohol
JP: Isopropyl
PhEur: Isopropyl Alcohol
USP: Isopropyl Alcohol

2 Synonyms
Alcohol isopropyl; dimethyl carbinol; IPA; isopropanol; petrol; 2-propanol; sec-propyl alcohol; rubbing alcohol.

3 Chemical Name and CAS Registry Number
Propan-2-ol [67-63-0]

4 Empirical Formula and Molecular Weight
C₃H₈O 60.1

5 Structural Formula
\[
\text{CH}_3 \quad \text{CH}_3 \quad \text{O} \quad \text{H}
\]

6 Functional Category
Disinfectant; solvent.

7 Applications in Pharmaceutical Formulation or Technology
Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations.\(^1\) It is not recommended for oral use owing to its toxicity; see Section 14.

Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation,\(^2\) where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer 934.\(^3\)

Isopropyl alcohol has some antimicrobial activity (see Section 10) and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.\(^4\)

8 Description
Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

9 Pharmacopeial Specifications
See Table I.

<table>
<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.0</th>
<th>USP 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Absorbance</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Characters</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>0.785-0.788</td>
<td>0.785-0.789</td>
<td>0.783-0.787</td>
</tr>
<tr>
<td>Refractive index</td>
<td>-</td>
<td>1.376-1.379</td>
<td>1.376-1.378</td>
</tr>
<tr>
<td>Acidity or alkaliinity</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Water</td>
<td>≤0.75%</td>
<td>≤0.5%</td>
<td>-</td>
</tr>
<tr>
<td>Nonvolatile residue</td>
<td>≤1.0 mg</td>
<td>≤20 ppm</td>
<td>≤0.005%</td>
</tr>
<tr>
<td>Distillation range</td>
<td>81-83°C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Benzene</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Peroxides</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Assay</td>
<td>-</td>
<td>-</td>
<td>&gt;99.0%</td>
</tr>
</tbody>
</table>

10 Typical Properties

**Antimicrobial activity** Isopropyl alcohol is bactericidal; at concentrations greater than 70% v/v it is a more effective antibacterial preservative than ethanol (95%). The bactericidal effect of aqueous solutions increases steadily as the concentration approaches 100% v/v. Isopropyl alcohol is ineffective against bacterial spores.

**Autoignition temperature** 425°C

**Boiling point** 82.4°C

**Dielectric constant** \(D^2 = 18.62\)

**Explosive limits** 2.5-12.0% v/v in air

**Flammability** Flammable.

**Flash point** 11.7°C (closed cup); 13°C (open cup). The water azeotrope has a flash point of 16°C.

**Freezing point** -89.5°C

**Melting point** -88.5°C

**Moisture content** 0.1-13% w/w for commercial grades (13% w/w corresponds to the water azeotrope).

**Refractive index**

\[ n_D^{20} = 1.3776; \]

\[ n_P^{20} = 1.3749. \]

**Solubility** Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt.
solutions. Forms an azeotrope with water, containing 87.4% w/w isopropyl alcohol (boiling point 80.37°C).

**Specific gravity** 0.786

**Vapor density (relative)** 2.07 (air = 1)

**Vapor pressure**
- 133.3 Pa (1 mmHg) at -26.1°C;
- 4.32 kPa (32.4 mmHg) at 20°C;
- 5.33 kPa (40 mmHg) at 23.8°C;
- 13.33 kPa (100 mmHg) at 39.5°C.

**Viscosity (dynamic)** 2.43 mPa s (2.43 cP) at 20°C

### 11 Stability and Storage Conditions

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

### 12 Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate, and other salts, or by the addition of sodium hydroxide.

### 13 Method of Manufacture

Isopropyl alcohol may be prepared from propylene; by the catalytic reduction of acetone; or by fermentation of certain carbohydrates.

### 14 Safety

Isopropyl alcohol is widely used in cosmetics and topical pharmaceutical formulations. It is readily absorbed from the gastrointestinal tract and may be slowly absorbed through intact skin. Prolonged direct exposure of isopropyl alcohol to the skin may result in cardiac and neurological deficits. In neonates, isopropyl alcohol has been reported to cause chemical burns following topical application. Isopropyl alcohol is metabolized more slowly than ethanol, primarily to acetone. Metabolites and unchanged isopropyl alcohol are mainly excreted in the urine.

Isopropyl alcohol is about twice as toxic as ethanol and should therefore not be administered orally; isopropyl alcohol also has an unpleasant taste. Symptoms of isopropyl alcohol toxicity are similar to those for ethanol except that isopropyl alcohol has no initial euphoric action, and gastritis and vomiting are more prominent; see Alcohol. Delta osmolality may be useful as a rapid screen test to identify patients at risk of complications from ingestion of isopropyl alcohol. The lethal oral dose is estimated to be about 120-230 mL although toxic symptoms may be produced by 20 mL.

Adverse effects following parenteral administration of up to 20 mL of isopropyl alcohol diluted with water have included only a sensation of heat and a slight lowering of blood pressure. However, isopropyl alcohol is not commonly used in parenteral products.

Although inhalation can cause irritation and coma, the inhalation of isopropyl alcohol has been investigated in therapeutic applications. Isopropyl alcohol is most frequently used in topical pharmaceutical formulations where it may act as a local irritant. When applied to the eye it can cause corneal burns and eye damage.

**LD₅₀** (dog, oral): 4.80 g/kg
**LD₅₀** (mouse, oral): 3.6 g/kg
**LD₅₀** (mouse, IP): 4.48 g/kg
**LD₅₀** (mouse, IV): 1.51 g/kg
**LD₅₀** (rabbit, oral): 6.41 g/kg
**LD₅₀** (rabbit, skin): 12.8 g/kg
**LD₅₀** (rat, IP): 2.74 g/kg

**LD₅₀** (rat, IV): 1.09 g/kg
**LD₅₀** (rat, oral): 5.05 g/kg

### 15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Isopropyl alcohol may be irritant to the skin, eyes, and mucous membranes upon inhalation. Eye protection and gloves are recommended. Isopropyl alcohol should be handled in a well-ventilated environment. In the UK, the long-term (8-hour TWA) workplace exposure limit for isopropyl alcohol is 999 mg/m³ (400 ppm); the short-term (15-minute) workplace exposure limit is 1250 mg/m³ (500 ppm). OSHA standards state that IPA 8-hour time weighted average airborne level in the workplace cannot exceed 400 ppm. Isopropyl alcohol is flammable and produces toxic fumes on combustion.

### 16 Regulatory Status

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

### 17 Related Substances

**Propan-1-ol.**

**Empirical formula** C₃H₇O

**Molecular weight** 60.1

**CAS number** [71-23-8]

**Synonyms** Propanol; n-propanol; propyl alcohol; propionic alcohol.

**Autoignition temperature** 540°C

**Boiling point** 97.2°C

**Dielectric constant** D = 22.20

**Explosive limits** 2.15–13.15% v/v in air

**Flash point** 15°C (closed cup)

**Melting point** -127°C

**Refractive index** n D = 1.3862

**Solubility** Miscible with ethanol (95%), ether, and water.

**Specific gravity** 0.8053 at 20°C

**Viscosity (dynamic)** 2.3 mPa s (2.3 cP) at 20°C

**Comments** Propan-1-ol is more toxic than isopropyl alcohol. In the UK, the long-term (8-hour TWA) exposure limit for propan-1-ol is 500 mg/m³ (200 ppm); the short-term (15-minute) exposure limit is 625 mg/m³ (250 ppm).

### 18 Comments

A specification for isopropyl alcohol is contained in the Food Chemicals Codex (FCC).[11]

The EINECS number for isopropyl alcohol is 200-661-7. The PubChem Compound ID (CID) for isopropyl alcohol is 3776.

### 19 Specific References

Isopropyl Myristate

1 Nonproprietary Names
BP: Isopropyl Myristate
PhEur: Isopropyl Myristate
USP-NF: Isopropyl Myristate

2 Synonyms
Estol IPM; HallStar IPM-NF; isopropyl ester of myristic acid; Isopropylmyristate; isopropyl myristate; Kessco IPM 95; Lexol IPM-NF; myristic acid isopropyl ester; Rita IPM; Stepan IPM; Super Refined Crodamol IPM; Tegosoft M; tetradecanoic acid, 1-methylethyl ester; Waglinol 6014.

3 Chemical Name and CAS Registry Number
1-Methylethyl tetradecanoate [110-27-0]

4 Empirical Formula and Molecular Weight
$\text{C}_{17}\text{H}_{34}\text{O}_2$ 270.5

5 Structural Formula

6 Functional Category
Emollient; oleaginous vehicle; skin penetrant; solvent.

7 Applications in Pharmaceutical Formulation or Technology
Isopropyl myristate is a nongreasy emollient that is absorbed readily by the skin. It is used as a component of semisolid bases and as a solvent for many substances applied topically. Applications in topical pharmaceutical and cosmetic formulations include bath oils; make-up; hair and nail care products; creams; lotions; lip products; shaving products; skin lubricants; deodorants; otic suspensions; and vaginal creams; see Table I. For example, isopropyl myristate is a self-emulsifying component of a proposed cold cream formula, which is suitable for use as a vehicle for drugs or dermatological actives; it is also used cosmetically in stable mixtures of water and glycerol.

Isopropyl myristate is used as a penetration enhancer for transdermal formulations, and has been used in conjunction with therapeutic ultrasound and iontophoresis. It has been used in a water-oil gel prolonged-release emulsion and in various microemulsions. Such microemulsions may increase bioavailability in topical and transdermal applications. Isopropyl myristate has also been used in microspheres, and significantly increased the release of drug from etoposide-loaded microspheres.

Isopropyl myristate is used in soft adhesives for pressure-sensitive adhesive tapes.

Table I: Uses of isopropyl myristate.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detergent</td>
<td>0.003-0.03</td>
</tr>
<tr>
<td>Otic suspension</td>
<td>0.024</td>
</tr>
<tr>
<td>Perfumes</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Microemulsions</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Soap</td>
<td>0.03-0.3</td>
</tr>
<tr>
<td>Topical aerosols</td>
<td>2.0-98.0</td>
</tr>
<tr>
<td>Topical creams and lotions</td>
<td>1.0-10.0</td>
</tr>
</tbody>
</table>

8 Description
Isopropyl myristate is a clear, colorless, practically odorless liquid of low viscosity that congeals at about 5°C. It consists of esters of propan-2-ol and saturated high molecular weight fatty acids, principally myristic acid.

9 Pharmacopeial Specifications
See Table II.

10 Typical Properties
Boiling point 140.2°C at 266 Pa (2 mmHg)
Flash point 153.5°C (closed cup)
Freezing point $\approx$5°C
Solubility Soluble in acetone, chloroform, ethanol (95%), ethyl acetate, fats, fatty alcohols, fixed oils, liquid hydrocarbons, toluene, and waxes. Dissolves many waxes, cholesterol, or lanolin. Practically insoluble in glycerin, glycols, and water.
Viscosity (dynamic) 5-7 mPa s (5-7 cP) at 25°C
11 Stability and Storage Conditions
Isopropyl myristate is resistant to oxidation and hydrolysis, and does not become rancid. It should be stored in a well-closed container in a cool, dry place and protected from light.

12 Incompatibilities
When isopropyl myristate comes into contact with rubber, there is a drop in viscosity with concomitant swelling and partial dissolution of the rubber; contact with plastics, e.g. nylon and polyethylene, results in swelling. Isopropyl myristate is incompatible with hard paraffin, producing a granular mixture. It is also incompatible with strong oxidizing agents.

13 Method of Manufacture
Isopropyl myristate may be prepared either by the esterification of myristic acid with propan-2-ol or by the reaction of myristoyl chloride and propan-2-ol with the aid of a suitable dehydrochlorinating agent. A high-purity material is also commercially available, produced by enzymatic esterification at low temperature.

14 Safety
Isopropyl myristate is widely used in cosmetics and topical pharmaceutical formulations, and is generally regarded as a nontoxic and nonirritant material.\(^{(7-9)}\)

LD\(_{50}\) (mouse, oral): 49.7 g/kg\(^{(10)}\)
LD\(_{50}\) (rabbit, skin): 5 g/kg

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

16 Regulatory Status
Included in the FDA Inactive Ingredients Database (otic, topical, transdermal, and vaginal preparations). Used in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances
Isopropyl palmitate.

18 Comments
Isopropyl myristate has been used in microemulsion templates to produce nanoparticles as potential drug delivery vehicles for proteins and peptides.\(^{(11,12)}\)

Isopropyl myristate 50% has been shown to be an effective pediculicide for the control of head lice.\(^{(13)}\)
The EINECS number for isopropyl myristate is 203-751-4. The PubChem Compound ID (CID) for isopropyl myristate is 8042.

19 Specific References

20 General References

21 Author
AK Taylor

22 Date of Revision
Lactose, Anhydrous

1 Nonproprietary Names
BP: Anhydrous Lactose
JP: Anhydrous Lactose
PhEur: Lactose, Anhydrous
USP-NF: Anhydrous Lactose

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

3 Chemical Name and CAS Registry Number
O-β-D-Galactopyranosyl-(1→4)-β-D-glucopyranose [63-42-3]

4 Empirical Formula and Molecular Weight
C₁₂H₂₂O₁₁ 342.30

5 Structural Formula

- Anhydrous α-lactose
- Anhydrous β-lactose

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

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

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

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

9 Pharmacopeial Specifications
See Table I. See also Section 18.

10 Typical Properties
Brittle fracture index 0.0362
Bonding index 0.0049 (at compression pressure 177.8 MPa)¹
Density (true) 1.589 g/cm³ for anhydrous β-lactose
Density (bulk) 0.71 g/cm³ for SuperTab 21AN; 0.66 g/cm³ for SuperTab 22AN.

SEM 1: Excipient: SuperTab 21AN; manufacturer: DMV-Fonterra
Exipients; magnification: 200 x; voltage: 1.5 kV.

SEM 2: Excipient: SuperTab 22AN; manufacturer: DMV-Fonterra
Exipients; magnification: 55 x; voltage: 1.5 kV.
Table I: Pharmacopeial specifications for lactose anhydrous.

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<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.5</th>
<th>USP32-NF27</th>
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<tr>
<td>Identification</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Appearance/color of solution</td>
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<td>+</td>
<td>-</td>
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<td>Characters</td>
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<td>-</td>
<td>+</td>
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<tr>
<td>Optical rotation</td>
<td>+54.4° to +55.9°</td>
<td>+54.4° to +55.9°</td>
<td>+54.4° to +55.9°</td>
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<tr>
<td>Acidity or alkalinity</td>
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<td>Heavy metals</td>
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<td>-</td>
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</tr>
<tr>
<td>Protein and light absorbing</td>
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</tr>
<tr>
<td>Impurities/substances</td>
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<td>Absorbance</td>
<td>≤0.25</td>
<td>≤0.25</td>
<td>≤0.25</td>
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<tr>
<td>210-220 nm</td>
<td>≤0.07</td>
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<tr>
<td>270-300 nm</td>
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<td>Water</td>
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<td>≤1.0%</td>
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<tr>
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<td>≤0.1%</td>
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<td>Sulfated ash</td>
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<td>≤10000 cfu/g</td>
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<td>≤5000 cfu/g</td>
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<tr>
<td>Absence of Salmonella</td>
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<td>-</td>
<td>+</td>
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<tr>
<td>Isomer ratio</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

(a) Not a mandatory test.

Density (tap) 0.88 g/cm³ for Super Tab 21AN; 0.78 g/cm³ for Super-Tab 22AN.

Melting point
- 223.0°C for anhydrous α-lactose;
- 252.2°C for anhydrous β-lactose;
- 232.0°C for commercial anhydrous lactose.

NIR spectra see Figure 1.

Particle size distribution see Table II.

Permanent deformation pressure 521.0 MPa (at compression pressure 177.8 MPa)

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

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

Specific rotation [α]D = 54.4° to 55.9°

Tensile strength 2.577 MPa (at compression pressure 177.8 MPa)

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

11 Stability and Storage Conditions

Mold growth may occur under humid conditions (80% RH and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; see Section 12 Incompatibilities

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

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

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

See Lactose, Monohydrate.

13 Method of Manufacture

There are two anhydrous forms of lactose: α-lactose and β-lactose. The temperature of crystallization influences the ratio of α- and β-lactose. The anhydrous forms that are commercially available may exhibit hygroscopicity at high relative humidities. Anhydrous lactose is produced by roller drying a solution of lactose above 93.5°C. The resulting product is then milled and sieved. Two anhydrous α-lactoses can be prepared using special drying techniques: one is unstable and hygroscopic; the other exhibits good compaction properties. However, these materials are not commercially available.
14 Safety
Lactose is widely used in pharmaceutical formulations as a diluent and filler-binder in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase, and is associated with oral ingestion of amounts well over those found in solid dosage forms.

See Lactose, Monohydrate.

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

16 Regulatory Status
GRAS listed. Included in the FDA Inactive Ingredients Database (IM, IV: powder for injection solution; IV and sublingual preparations; oral: capsules and tablets; powder for inhalation; vaginal). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances
Lactose, inhalation; lactose, monohydrate; lactose, spray-dried.

18 Comments
Lactose anhydrous is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.5, along with the ‘State of Work’ document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Lactose anhydrous has been used experimentally in hydrophilic matrix tablet formulations[6] and evaluated for dry powder inhalation applications.[9,10] Partial hydration of anhydrous lactose increases the specific surface area and reduces the flow properties of powders but has no effect on compactibility.[11] A specification for lactose is included in the Food Chemicals Codex (FCC)[12]; see Lactose, Monohydrate.

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

19 Specific References

20 General References

21 Authors
S Edge, AH Kibbe, J Shur.

22 Date of Revision
27 February 2009.
Lactose, Inhalation

1 Nonproprietary Names
None adopted.

2 Synonyms
Inhalac; inhalation lactose; Lactohale; Respitose.
For grades, see Tables I and II.

3 Chemical Name and CAS Registry Number
Inhalation lactose is lactose monohydrate, O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [5989-81-1]; [10039-26-6]; [64044-51-5] (see Lactose, Monohydrate), anhydrous lactose, O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose [63-42-3], or a mixture of O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose and O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose (see Lactose, Anhydrous).
CAS numbers for lactose monohydrate are [5989-81-1] (lactose monohydrate); [10039-26-6] (lactose monohydrate, cyclic); [64044-51-5] (lactose monohydrate, open form).

4 Empirical Formula and Molecular Weight
C_{12}H_{22}O_{11} 342.30 (for anhydrous)
C_{12}H_{22}O_{11}·H_{2}O 360.31 (for monohydrate)

5 Structural Formula
See Lactose, Anhydrous; Lactose, Monohydrate.

6 Functional Category
Diluent; dry powder inhaler carrier.

7 Applications in Pharmaceutical Formulation or Technology
Inhalation lactose is widely used as a carrier, diluent, and flow aid in dry powder inhalation formulations. Inhalation lactose of suitable particle size can also be used to prepare soft pellets of dry powder inhaler formulations.
See also Lactose, Anhydrous; Lactose, Monohydrate.

8 Description
Lactose occurs as white to off-white crystalline particles or powder. It is odorless and slightly sweet-tasting.

9 Pharmacopeial Specifications
See Lactose, Anhydrous; Lactose, Monohydrate.

10 Typical Properties
Density (bulk) see Table I.
Density (tapped) see Table I.
Loss on drying see Table I.
Particle size distribution see Table II.
Surface area see Table I.

11 Stability and Storage Conditions
Inhalation lactose should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities
Lactose is a reducing sugar. Typical reactions include the Maillard reaction with either primary or secondary amines.
See also Lactose, Anhydrous; Lactose, Monohydrate.

13 Method of Manufacture
Inhalation lactose is manufactured by milling, sieving, air classifying, micronizing and/or blending pharmaceutical grade lactose, typically in dedicated facilities. Although off-the-shelf grades are available, the manufacturing processes can be tailored to produce lactose with properties for a specific application.

14 Safety
Lactose is widely used in pharmaceutical formulations as a diluent in oral capsule and tablet formulations, and has a history of being used in dry powder inhaler formulations.
meggle GmbH

Inhalation preparations. Included in nonparenteral and parenteral medicines licensed in the UK, which refer to lactose monohydrate in general.

See also Lactose, Anhydrous; Lactose, Monohydrate.

17 Related Substances
See Lactose, Anhydrous; Lactose, Monohydrate.

18 Comments
Lactose is one of a very small number of excipients that are used in marketed dry powder inhaler products. Specific grades of inhalation lactose can be produced from the readily available wide range of pharmaceutical lactose grades using standard pharmaceutical manufacturing processes. Lactose is found in capsule, blister, and reservoir-based dry powder inhaler products. The relatively low mass per dose of lactose used means that, compared with conventional oral solid dosage forms, the levels of inhalation lactose ingested during inhalation are relatively small.

In view of the importance of particle characteristics for powder blending and drug product performance, it has been suggested that pharmacopeial monograph acceptance criteria are not adequate for controlling key physicochemical characteristics for inhalation applications of this excipient. Accordingly, further material controls may be required to ensure consistent drug product pharmaceutical performance, such as control of surface properties.

The effect of modifying the surfaces of lactose particles by particle smoothing, crystallization, and co-processing with other excipients on the aerosolization performance has been reported.

See also Lactose, Anhydrous; Lactose, Monohydrate.

19 Specific References
Lactose, Monohydrate

1 Nonproprietary Names
BP: Lactose
PhEur: Lactose Monohydrate
JP: Lactose Hydrate
USP-NF: Lactose Monohydrate

2 Synonyms
CapsaLac; GranuLac; Lactochem; lactosum monohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose.
For grades, see Tables II and III.

3 Chemical Name and CAS Registry Number
O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [5989-81-1]; [10039-26-6]; [64044-51-5]
CAS Registry numbers for lactose monohydrate are [5989-81-1] (lactose monohydrate), [10039-26-6] (lactose monohydrate, cyclic), and [64044-51-5] (lactose monohydrate, open form).

4 Empirical Formula and Molecular Weight
C_{12}H_{22}O_{11}·H_{2}O 360.31

5 Structural Formula

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

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

7 Applications in Pharmaceutical Formulation or Technology
Lactose is widely used as a filler and diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation; see Lactose, Inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used.
Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently.

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

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

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

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

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

8 Description

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

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

9 Pharmacopeial Specifications

See Table I. See also Section 18.

10 Typical Properties

Brittle fracture index:

0.0749 (at compression pressure 189.5 MPa);
0.0883 (at compression pressure 191.0 MPa).\(^{(10)}\)

Bonding index:

0.0081 (at compression pressure 189.5 MPa);
0.0052 (at compression pressure 191.0 MPa).\(^{(10)}\)

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

Density (bulk) see Table II.

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

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

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

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

SEM figures show excipients at different magnifications and voltages.

Density (tapped) see Table II.

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

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

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

NIR spectra see Figure 1.
Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; see Section 12. The purities of different lactoses can vary and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also differ. Solutions show mutarotation; see Section 10.

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

12 Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products.\(^{[13]}\) The Maillard interaction has also been shown to occur between lactose and secondary amine. However, the reaction sequence stops with the formation of the imine, and no yellow-brown coloration develops.\(^{[13]}\)

Lactose is also incompatible with amino acids, amphetamines,\(^{[12]}\) and lisinopril.\(^{[12]}\)

13 Method of Manufacture

Lactose is a natural disaccharide consisting of galactose and glucose, and is present in the milk of most mammals. Commercially, lactose is produced from the whey of cows' milk; whey being the
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<thead>
<tr>
<th>Supplier/grade</th>
<th>Typical particle size distribution (%)</th>
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<tr>
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<td>&lt;10 µm</td>
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<td>DMV-Fonterra Excipients</td>
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(a) <180 µm.
(b) <355 µm.
(c) <500 µm.
(d) <425 µm.
(e) <33 µm.
(f) <212 µm.
(g) <106 µm.
(h) <125 µm.
(i) <500 µm.
residual liquid of the milk following cheese and casein production. Cows’ milk contains 4.4–5.2% lactose; lactose constitutes 38% of the total solid content of milk.

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

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

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

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

Lower doses of lactose produce fewer adverse effects, and lactose is better tolerated if taken with other foods. As a result, there is a significant population with lactose malabsorption who are still able to ingest normal amounts of lactose, such as that in milk, without the development of adverse side effects. Most adults consume about 25 g of lactose per day (500 mL of milk) without symptoms. When symptoms appear, they are usually mild and dose-related. The dose of lactose in most pharmaceuticals seldom exceeds 2 g per day. It is unlikely that severe gastrointestinal symptoms can be attributed to the lactose in a conventional oral solid-dosage form, especially in adults who have not previously been diagnosed as severely lactose-intolerant. However, anecdotal reports of drug-induced diarrhea due to lactose intolerance have been made following administration of pharmaceutical preparations containing lactose.

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

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

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

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

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

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

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

A number of different grades of lactose are commercially available that vary in their physical properties, and many studies have been reported in the literature comparing the behavior of these various materials in different formulations. A number of co-processed excipients which contain lactose are available for direct-compression applications: co-processed lactose and starch (Starlac, Meggle/Roquette Frères); lactose and microcrystalline cellulose (Microcel, Meggle); lactose and cellulose powder (Cellactose, Meggle); lactose, povidone, and crospovidone (Ludipress, Ludipress LCE, BASEF).

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

A specification for lactose is included in the Food Chemicals Codex (FCC).
The EINECS number for lactose is 200-559-2. The PubChem Compound ID (CID) for lactose monohydrate includes 62223 and 104938.

19 Specific References

20 General References

21 Authors
S Edge, AH Kibbe, J Shur.

22 Date of Revision
10 March 2009.
**Lactose, Monohydrate and Corn Starch**

1. **Nonproprietary Names**
   None adopted.

2. **Synonyms**
   StarLac.

3. **Chemical Name and CAS Registry Number**
   See Section 8.

4. **Empirical Formula and Molecular Weight**
   See Section 8.

5. **Structural Formula**
   See Section 8.

6. **Functional Category**
   Directly compressible tablet excipient; disintegrant; tablet and capsule diluent.

7. **Applications in Pharmaceutical Formulation or Technology**
   Lactose monohydrate and corn starch can be used in tablets to improve compressibility, flowability and disintegration properties. It is used in homeopathic and low-dose to mid-dose formulations.

8. **Description**
   α-Lactose monohydrate and corn starch occurs as a white or almost white odorless powder containing 82–88% of lactose monohydrate and 12–18% of corn (maize) starch. It is a free-flowing powder owing to its spherical structure.

9. **Pharmacopeial Specifications**
   Both lactose monohydrate and corn (maize) starch are listed as separate monographs in the JP, PhEur, and USP-NF, but the combination is not listed. See Lactose, Monohydrate, and Starch. See also Section 18.

10. **Typical Properties**
    - Angle of repose: ≤29° for StarLac
    - Density (bulk): 0.57 g/cm³ for StarLac
    - Density (tapped): 0.68 g/cm³ for StarLac
    - Hausner ratio: 1.19 for StarLac
    - Heavy metals: 5 ppm for StarLac
    - Loss on drying: ≤3.0% for StarLac
    - Microbial content: Total viable aerobic count ≤100 cfu/g, molds <10 cfu/g, yeasts <10 cfu/g (Escherichia coli and Salmonella species absent) for StarLac.
    - Particle size distribution: ≤15% <32 μm, 35–65% <160 μm, >80% <250 μm for StarLac.
    - Sulfated ash: ≤0.25% for StarLac
    - Solubility: Partially soluble in cold water for StarLac.

11. **Stability and Storage Conditions**
    Store in well-closed containers under dry and odor-free conditions.

12. **Incompatibilities**
    See Lactose, Monohydrate, and Starch.

13. **Method of Manufacture**
    Lactose monohydrate and corn starch is prepared by spray-drying a mixture of the two ingredients.

14. **Safety**
    See Lactose, Monohydrate, and Starch.

15. **Handling Precautions**
    Observe normal precautions appropriate to the circumstances and quantity of material handled.

16. **Regulatory Status**
    Lactose monohydrate and corn starch is a mixture of two materials both of which are generally regarded as nontoxic:
    - **Lactose monohydrate** GRAS listed. Included in the FDA Inactive Ingredients Database (IM, IV, and SC: powder for injections; oral: capsules and tablets; inhalation preparations; vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.
    - **Starch** GRAS listed. Included in the FDA Inactive Ingredients Database (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17. **Related Substances**
    Lactose, monohydrate; starch.
Lactose, Monohydrate and Microcrystalline Cellulose

18 Comments
Lactose monohydrate and corn starch are two of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General Chapter 5.8 in PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

StarLac has been designed for direct compression, combining good flowability and compressibility with fast disintegration properties. Excipients or formulations containing a variety of drugs, namely ascorbic acid, paracetamol [acetaminophen] and theophylline monohydrate show it to be superior to a simple mixture of its components in terms of flowability, tablet strength, friability and disintegration time.\(^{1,2}\) Starch particles are embedded in a matrix mainly consisting of crystalline lactose monohydrate, and very low quantities of amorphous lactose are detectable. Its balanced elastic and brittle properties make it suitable for roller compaction. Specific quantitative, analytical methods for the assay of starch and lactose in StarLac have been developed and validated.\(^{(3)}\)

19 Specific References
1 Wagner KG, Dressler JA. A corn starch/alpha-lactose monohydrate compound as a new directly compressible excipient. Pharm Ind 2002; 64(9): 992-999.

20 General References
Haediker O. A star is born. Pharmaceutical Formulation and Quality 2002; 54-57.
Nachegari SK, Bansal AK. Coprocessed excipients for solid dosage forms. Pharm Tech 2004; (Jan): 52-64.

21 Authors
ME Quinn, RC Rowe.

22 Date of Revision
3 March 2009.

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Lactose, Monohydrate and Microcrystalline Cellulose

1 Nonproprietary Names
None adopted.

2 Synonyms
MicroLac 100.

3 Chemical Name and CAS Registry Number
See Section 8.

4 Empirical Formula and 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
Lactose monohydrate and microcrystalline cellulose can be used in tablets for direct compression.

8 Description
Lactose monohydrate and microcrystalline cellulose occurs as a white or almost white odorless powder containing 73-77% of lactose monohydrate and 23-27% of microcrystalline cellulose.

9 Pharmacopeial Specifications
Both lactose monohydrate and microcrystalline cellulose are listed as separate monographs in the JP, PhEur, and USP-NF, but the combination is not listed. See Lactose, Monohydrate, and Cellulose, Microcrystalline. See also Section 18.

10 Typical Properties
Acidity/alkalinity \( \text{pH} = 4.0-7.0 \) for MicroLac 100
Angle of repose \( 34^\circ \) for MicroLac 100
Density (bulk) \( 0.5 \text{ g/cm}^3 \) for MicroLac 100
Density (tapped) \( 0.61 \text{ g/cm}^3 \) for MicroLac 100
Hausner ratio \( 1.16 \) for MicroLac 100
Heavy metals \( \leq 5 \text{ ppm} \) for MicroLac 100
Loss on drying \( < 1.5 \% \) for MicroLac 100
Microbial content Total viable aerobic count \( \leq 100 \text{ cfu/g} \), molds\( < 10 \text{ cfu/g} \), yeasts \( < 10 \text{ cfu/g} \) (Escherichia coli and Salmonella species absent) for MicroLac 100
Particle size distribution \( \leq 15 \% < 32 \mu \text{m}, 45-70 \% < 160 \mu \text{m} \), \( > 90 \% < 250 \mu \text{m} \) for MicroLac 100
Solubility Partially soluble in water for MicroLac 100
Sulfated ash \( < 0.1 \% \) for MicroLac 100
Water content 4-6\% for MicroLac 100
372  Lactose, Monohydrate and Microcrystalline Cellulose

Excipient: Microcelac 100; manufacturer: Meggie; magnification: 200x; voltage: 3 kV.

SEM 2: Excipient: Microcelac 100; manufacturer: Meggie; magnification: 500x; voltage: 3 kV.

11 Stability and Storage Conditions
Store at room temperature in well-closed containers under dry and odor-free conditions.

12 Incompatibilities
See Lactose, Monohydrate, and Cellulose, Microcrystalline.

13 Method of Manufacture
Lactose monohydrate and microcrystalline cellulose is prepared by spray-drying a mixture of the two ingredients.

14 Safety
See Lactose, Monohydrate, and Cellulose, Microcrystalline.

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

16 Regulatory Status
Lactose monohydrate and microcrystalline cellulose is a mixture of two materials both of which are generally regarded as nontoxic:
Lactose monohydrate  GRAS listed. Included in the FDA Inactive Ingredients Database (IM, IV, and SC: powder for injections; oral: capsules and tablets; inhalation preparations; vaginal preparations). Included in nonparenteral and parenteral medi-
cines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.
Microcrystalline cellulose  GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances
Cellulose, microcrystalline; lactose, monohydrate.

18 Comments
Lactose monohydrate and microcrystalline cellulose are two of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General Chapter 5.8 in PhEur 6.0, along with the ‘State of Work’ document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Microcelac 100 has been designed for formulating high-dose small tablets with a poorly flowable active ingredient. It showed superior flow and binding properties compared to simple mixtures of its components. Differences between Microcelac 100 and Cellactose 80 have recently been evaluated.

A specification for lactose and microcrystalline cellulose spheres is contained in the Japanese Pharmaceutical Excipients (JPE), see Table I.

Table I: JPE specification for lactose and microcrystalline cellulose spheres.

<table>
<thead>
<tr>
<th>Test</th>
<th>JPE 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>+</td>
</tr>
<tr>
<td>Identification</td>
<td>+</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤5 ppm</td>
</tr>
<tr>
<td>Arsenic</td>
<td>≤2 ppm</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤3.0%</td>
</tr>
<tr>
<td>Water</td>
<td>≤9.0%</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>≤0.1%</td>
</tr>
<tr>
<td>Assay (dried basis)</td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>60-80%</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>20-40%</td>
</tr>
</tbody>
</table>

19 Specific References

20 General References
Lactose, Monohydrate and Povidone

1 Nonproprietary Names
None adopted.

2 Synonyms
Ludipress LCE.

3 Chemical Name and CAS Registry Number
See Section 8.

4 Empirical Formula and 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
Lactose monohydrate and povidone can be used to formulate chewable tablets, lozenges, effervescent tablets, and controlled-release tablets by direct compression. It is suitable for low-dose drugs.

8 Description
Lactose monohydrate and povidone occurs as white free-flowing granules, odorless with a neutral taste, containing 96.5% ± 1.8% of lactose monohydrate and 3.5% ± 0.5% of povidone K30.

9 Pharmacopeial Specifications
Both lactose monohydrate and povidone are listed as separate monographs in the JP, PhEur, and USP-NF, but the combination is not listed. See Lactose, Monohydrate, and Povidone. See also Section 18.

10 Typical Properties
Angle of repose 29.5° for Ludipress LCE
Density (bulk) 0.56 ± 0.6 g/cm³ for Ludipress LCE
Haussner ratio 1.20 ± 0.10 for Ludipress LCE
Heavy metals ≤10 ppm for Ludipress LCE
Loss on drying 5.75% for Ludipress LCE
Microbial content Mesophilic aerobes ≤1000 cfu/g, yeasts and fungi ≤100 cfu/g (Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Salmonella species absent), other Enterobacteriaceae ≤100 cfu/g for Ludipress LCE

11 Stability and Storage Conditions
Store at room temperature in tightly closed containers.

12 Incompatibilities
See Lactose, Monohydrate, and Povidone.

13 Method of Manufacture
Lactose monohydrate and povidone is manufactured by a proprietary agglomeration process.

14 Safety
See Lactose, Monohydrate, and Povidone.

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

16 Regulatory Status
Lactose monohydrate and povidone is a mixture of two materials both of which are generally regarded as nontoxic:
Lactose monohydrate GRAS listed. Included in the FDA Inactive Ingredients Database (IM, IV, and SC: powder for injections; oral: capsules and tablets; inhalation preparations; vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.
Povidone Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Database (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. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances
Lactose, monohydrate; povidone.

18 Comments
Lactose monohydrate and povidone are two of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General
text
Lactose, Monohydrate and Powdered Cellulose

1 Nonproprietary Names
None adopted.

2 Synonyms
Cellactose 80.

3 Chemical Name and CAS Registry Number
See Section 8.

4 Empirical Formula and 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
Lactose monohydrate and powdered cellulose can be used in tablets for direct compression to improve compressibility and mouthfeel.

8 Description
Lactose monohydrate and powdered cellulose occurs as a white or almost white odorless powder containing 73–77% of lactose monohydrate and 23–27% of cellulose powder.

9 Pharmacopeial Specifications
Both lactose monohydrate and powdered cellulose are listed as separate monographs in the JP, PhEur, and USP-NF, but the combination is not listed. See Lactose, Monohydrate, and Cellulose, Powdered. See also Section 18.

10 Typical Properties
- **Acidity/alkalinity**: pH = 4.0–7.0 for Cellactose 80
- **Angle of repose**: 32–35° for Cellactose 80
- **Density (bulk)**: 0.38 g/cm³ for Cellactose 80
- **Density (tapped)**: 0.5 g/cm³ for Cellactose 80
- **Hausner ratio**: 1.24 for Cellactose 80
- **Heavy metals**: ≤ 5 ppm for Cellactose 80
- **Loss on drying**: ≤ 3.5% for Cellactose 80
- **Microbial content**: Total viable aerobic count ≤ 100 cfu/g, molds and yeasts ≤ 10 cfu/g (Escherichia coli and Salmonella species absent) for Cellactose 80
- **Particle size distribution**: ≤ 20% < 32 µm, 35–65% < 160 µm, ≥ 80% < 230 µm for Cellactose 80
- **Sulfated ash**: ≤ 0.2% for Cellactose 80
- **Solubility**: Partially soluble in water for Cellactose 80
- **Water content**: 4–7% for Cellactose 80
Lactose, Monohydrate and Powdered Cellulose

11 Stability and Storage Conditions
Store at room temperature in well-closed containers under dry and odor-free conditions.

12 Incompatibilities
See Lactose, Monohydrate, and Cellulose, Powdered.

13 Method of Manufacture
Lactose monohydrate and powdered cellulose is prepared by spray-drying a mixture of the two ingredients.

14 Safety
See Lactose, Monohydrate, and Cellulose, Powdered.

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

16 Regulatory Status
Lactose monohydrate and powdered cellulose is a mixture of two materials both of which are generally regarded as nontoxic:

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

Powdered cellulose—GRAS listed. Accepted for use as a food additive in Europe (except for infant food in the UK). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances
Lactose, monohydrate; cellulose, powdered.

18 Comments
Lactose monohydrate and powdered cellulose are two of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General Chapter 5.8 in PhEur 6.0, along with the ‘State of Work’ document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Cellactose 80 has been designed especially for direct compression. It has been shown to be superior to a simple mixture of its components in terms of dilution potential, compressibility, tensile strength, lubricant susceptibility, and subsequent table properties for a range of drugs.

19 Specific References

20 General References

21 Authors
ME Quinn, RC Rowe.

22 Date of Revision
3 March 2009.
Lactose, Spray-Dried

1 Nonproprietary Names
None adopted.

2 Synonyms
FlowLac 90; FlowLac 100; Lactopress Spray-Dried; Lactopress Spray-Dried 250; NF Lactose-315; NF Lactose-316 Fast Flo; SuperTab 11SD; SuperTab 14SD.

3 Chemical Name and CAS Registry Number
Spray-dried lactose is a mixture of amorphous lactose, which is a 1:1 mixture of α-and β-lactose, and O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [5989-81-1]; [10039-26-6]; [64044-51-5].
CAS numbers for lactose monohydrate are [5989-81-1] (lactose monohydrate); [10039-26-6] (lactose monohydrate, cyclic); [64044-51-5] (lactose monohydrate, open form).

4 Empirical Formula and Molecular Weight
C₁₂H₂₂O₁₁  342.30 (for amorphous)
C₁₂H₂₂O₁₁·H₂O  360.31 (for monohydrate)

5 Structural Formula
See Lactose, Anhydrous and Lactose, Monohydrate.

6 Functional Category
Directly compressible tablet excipient; tablet and capsule diluent; tablet and capsule filler.

7 Applications in Pharmaceutical Formulation or Technology
Spray-dried lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting.
See also Lactose, Monohydrate; Lactose, Anhydrous.

8 Description
Lactose occurs as white to off-white crystalline particles or powder. It is odorless and slightly sweet-tasting. Spray-dried direct-compression grades of lactose are generally composed of 80-90% specially prepared pure α-lactose monohydrate along with 10-20% of amorphous lactose.

9 Pharmacopeial Specifications
See Section 18. See also Lactose, Monohydrate.

10 Typical Properties
Angle of repose  29° for FlowLac 90; 28° for FlowLac 100.
Bonding index  0.0044 for NF Lactose-315 (at compression pressure 54.90 MPa)¹
Brittle fracture index  0.1671 for NF Lactose-315 (at compression pressure 54.90 MPa)²
Density bulk  see Table I.
Loss on drying  0.3% for NF Lactose-315; 0.6% for NF Lactose-316.
Particle size distribution  see Table II.
Reduced modulus of elasticity  5648 for NF Lactose-315 (at compression pressure 54.90 MPa)³
Tensile strength  2.368 MPa for NF Lactose-315 (at compression pressure 54.90 MPa)³
Water content  see Table I.
Methods for characterizing the mechanical properties of compacts of pharmaceutical ingredients are specified in the Handbook of Pharmaceutical Excipients, 3rd edn.\textsuperscript{(1)}

11 Stability and Storage Conditions
Spray-dried lactose should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities
Lactose is a reducing sugar. The amorphous lactose, which is the most reactive form of lactose present in spray-dried lactose, will interact more readily than conventional crystalline grades.\textsuperscript{(2)} Typical reactions include the Maillard reaction with either primary\textsuperscript{(3)} or secondary\textsuperscript{(4)} amines.

See Lactose, Anhydrous and Lactose, Monohydrate.

13 Method of Manufacture
A suspension of α-lactose monohydrate crystals in a lactose solution is atomized and dried in a spray drier.\textsuperscript{(5,6)} Approximately 10–20% of the total amount of lactose is in solution and the remaining 80–90% is present in the crystalline form. The spray-drying process predominantly produces spherical particles. The compactibility of the material and its flow characteristics are a function of the primary particle size of the lactose monohydrate and the amount of amorphous lactose.\textsuperscript{(7)}

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 due to lactose intolerance, which occurs in individuals with a deficiency of the enzyme lactase.

See Lactose, Monohydrate.

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

16 Regulatory Status
See Lactose, Monohydrate.

17 Related Substances
Lactose, anhydrous; lactose, inhalation; lactose, monohydrate.

18 Comments
Spray-dried lactose was one of the first direct-compression excipients. Spray-dried lactose typically comprises lactose monohydrate and amorphous lactose (see Section 8); see Lactose, Monohydrate for the relevant pharmacopeial information.

It has been shown that during the spray-drying process the effects of nozzle orifice diameter and atomization air flow control the droplet size during atomization; however, it has also been demonstrated that increasing feed concentration results in increased shell thickness of hollow particles that are formed.\textsuperscript{(8)} The physical properties of spray-dried lactose produced from alcoholic media are directly affected by the ethanol-to-water ratio in the feed solution. Lactose spray-dried from pure ethanol was shown to be 100% crystalline, whereas lactose spray-dried from pure water was 100% amorphous. Furthermore, the surface area of the spray-dried lactose increased as a function of amorphous content.\textsuperscript{(9)} Spray-dried lactoses exhibit good flow properties.\textsuperscript{(10)}

Polyethylene glycol (PEG) 4000, when spray-dried with lactose, has been shown to accelerate the rate and extent of crystallization of lactose.\textsuperscript{(11)} It has also been shown that spray-dried lactose composite particles containing an ion complex of chitosan are suitable for the dry-coating of tablets.\textsuperscript{(12)} Spray-dried lactose and crystallized spray-dried lactose have been evaluated for dry powder
inhalation application.\textsuperscript{[13,14]} Amorphous spray-dried lactose has also been studied in composites with PVP.\textsuperscript{[15]}

See also Lactose, Anhydrous, Lactose, Inhalation and Lactose, Monohydrate.

19 Specific References

1 Nonproprietary Names
BP: Wool Fat
JP: Purified Lanolin
PhEur: Wool Fat
USP: Lanolin

2 Synonyms
Adeps lanae; cera lanae; E913; lanolina; lanolin anhydrous; Protalan anhydrous; purified lanolin; refined wool fat.

3 Chemical Name and CAS Registry Number
Anhydrous lanolin [8006-54-0]

4 Empirical Formula and Molecular Weight
The USP 32 describes lanolin as the purified wax-like substance obtained from the wool of the sheep, Ovis aries Linné (Bovidae), that has been cleaned, decolorized, and deodorized. It contains not more than 0.25% w/w of water and may contain up to 0.02% w/w of a suitable antioxidant; the PhEur 6.0 specifies up to 200 ppm of butylated hydroxytoluene as an antioxidant.

See also Section 18.

5 Structural Formulas
See Section 4.

6 Functional Category
Emulsifying agent; ointment base.
Magnesium Stearate

1 Nonproprietary Names
BP: Magnesium Stearate
JP: Magnesium Stearate
PhEur: Magnesium Stearate
USP-NF: Magnesium Stearate

2 Synonyms
Dibasic magnesium stearate; magnesium distearate; magnesium stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

3 Chemical Name and CAS Registry Number
Octadecanoic acid magnesium salt [557-04-0]

4 Empirical Formula and Molecular Weight
\[ \text{C}_{32}\text{H}_{62}\text{MgO}_4 \]
591.24

The USP32 - NF27 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 \((\text{C}_{32}\text{H}_{62}\text{MgO}_4)\). The PhEur 6.5 describes magnesium stearate as a mixture of solid organic acids consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin.

5 Structural Formula
\[ \text{CH}_3\text{(CH}_2\text){}_{16}\text{COO}_2\text{Mg} \]

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 very fine, light 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. See also Section 18.

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/cm³
Density (tapped) 0.286 g/cm³
Density (true) 1.092 g/cm³
Flash point 250°C
Flowability Poorly flowing, cohesive powder.
Melting range 117-150°C (commercial samples);
126-130°C (high purity magnesium stearate).
NIR spectra see Figure 1.
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 m²/g

11 Stability and Storage Conditions
Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Table 1: Pharmacopeial specifications for magnesium stearate.

<table>
<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.5</th>
<th>USP32-NF27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Microbial limits</td>
<td>Aerobic microbes</td>
<td>≤10⁰ chU/g</td>
<td>≤10² chU/g</td>
</tr>
<tr>
<td></td>
<td>Fungi and yeasts</td>
<td>≤500 chU/g</td>
<td>≤10⁵ chU/g</td>
</tr>
<tr>
<td>Acid or alkalinity</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acid value of the fatty acid</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤6.0%</td>
<td>≤6.0%</td>
<td>≤6.0%</td>
</tr>
<tr>
<td>Chloride</td>
<td>≤0.1%</td>
<td>≤0.1%</td>
<td>≤0.1%</td>
</tr>
<tr>
<td>Sulfate</td>
<td>≤1.0%</td>
<td>≤1.0%</td>
<td>≤1.0%</td>
</tr>
<tr>
<td>Lead</td>
<td>≤10 ppm</td>
<td>≤10 ppm</td>
<td>≤0.001%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤20 ppm</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Relative stearic/palmitic content</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Assay (dried, as Mg)</td>
<td>4.0-5.0%</td>
<td>4.0-5.0%</td>
<td>4.0-5.0%</td>
</tr>
</tbody>
</table>

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 alkoloidal salts.

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)

LD₅₀ (rat, inhalation): >2 mg/L.(2)

LD₅₀ (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. In the USA, the OSHA limit is 10 mg/m³ TWA for magnesium stearate.

16 Regulatory Acceptance
GRAS listed. Accepted as a food additive in the USA and UK. Included in the FDA Inactive Ingredients Database (oral capsules, powders, and tablets; buccal and vaginal tablets; topical preparations; intravitreal implants and injections). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients. Listed on the US TSIA inventory.

17 Related Substances
Calcium stearate; magnesium aluminum silicate; stearic acid; zinc stearate.

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

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.(13-29) A variety of online analytical techniques have been investigated to monitor magnesium stearate in powder blends and tablets.(30-32) Inverse gas chromatography has been used to examine the surface coverage of magnesium stearate on powder blends.(33) Magnesium stearate also affects the flow properties of blends.(34)

The existence of various crystalline forms of magnesium stearate has been established.(35-39) A trihydrate, a dihydrate, and an anhydride have been isolated,(35,37,39,40) and an amorphous form has been observed.(41) While the hydrated forms are stable in the presence of moisture, the anhydrous form absorbs moisture at relative humidity up to 30%, and at higher humidities it dehydrates to form the trihydrate. The anhydride may be formed by drying either of the hydrates at 105°C.(38)

It has not been conclusively established which form of pure magnesium stearate possesses the best lubricating properties.(36,37,41-43) Commercial lots of magnesium stearate generally...
Magnesium Stearate

consist of mixtures of crystalline forms. 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.

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

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. Due to variations in the specific surface area, the labeling states that specific area and the method specified for its determination should be listed on the label. 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.

The impact of magnesium stearate levels on tablet compaction properties and performance of roller compacted granulations has been examined. In other compaction studies performed with granules, magnesium stearate has been shown to exert an influence on granule relaxation and may help to prevent capping.

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.

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. However, other studies have indicated that fatty acid composition has no influence on lubricant activity and high-purity magnesium stearate was as effective a lubricant as the commercial material.

Moisture sorption at different relative humidities can result in morphological changes in the magnesium stearate. Magnesium stearate has been investigated for use in inhalation powders to control their performance.

A specification for magnesium stearate is included in the Food Chemicals Codex (FCC). The EINECS number for magnesium stearate is 209-150-3.

19 Specific References


Billany MR, Richards JH. Batch variation of magnesium stearate and its effect on the dissolution rate of salicylic acid from solid dosage forms. Drug Dev Ind Pharm 1982; 8: 497-511.

Frattoni C, Simioni L. Should magnesium stearate be assessed in the formulation of solid dosage forms by weight or by surface area? Drug Dev Ind Pharm 1984; 10: 1117-1130.


20 General References


Butcher AE, Jones TM. Some physical characteristics of magnesium stearate. J Pharm Pharmacol 1972; 24: 1P-9P.


21 Authors

LV Allen Jr, PE Luner.

22 Date of Revision

3 February 2009.
gloves, and a dust respirator are recommended. When heated to decomposition, maltose emits acrid smoke and irritating fumes.

16 Regulatory Status
In the USA, maltose is considered as a food by the FDA and is therefore not subject to food additive and GRAS regulations. Included in the FDA Inactive Ingredients Database (oral solutions). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in parenteral products available in a number of countries worldwide.

17 Related Substances
Glucose, liquid.

18 Comments
Crystalline maltose, e.g. Advantose 100 (SPI Pharma Group), is spray-dried to produce spherical particles with good flow properties. The material is also nonhygroscopic and is highly compressible. A specification for maltose syrup powder is contained in the Japanese Pharmaceutical Excipients (JPE). The EINECS number for maltose is 200-716-5. The PubChem Compound ID (CID) for maltose includes 6235 and 23724983.

19 Specific References
3 Mulder KB. Placebo evaluation of selected sugar-based excipients in pharmaceutical and nutraceutical tableting. Pharm Technol 2000; 24(5): 34, 36, 38, 40, 42, 44.

20 General References

21 Author
CK Tye.

22 Date of Revision
19 February 2009.
It is 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 gastrointestinal tract, but in large doses it can cause osmotic diarrhea; see Section 14.

8 Description
Mannitol is D-mannitol. It is a hexahydrated 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.

9 Pharmacopeial Specifications
See Table I. See also Section 18.

10 Typical Properties
Compressibility see Figure 1.
Density (bulk) 0.430 g/cm³ for powder; 0.7 g/cm³ for granules.
Density (tapped) 0.734 g/cm³ for powder; 0.8 g/cm³ for granules.
Density (true) 1.514 g/cm³
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.
NIR spectra see Figure 3.
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;
Table I: Pharmacopeial specifications for mannitol.

<table>
<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.4</th>
<th>USP 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Melting range</td>
<td>166-169°C</td>
<td>165-170°C</td>
<td>164-169°C</td>
</tr>
<tr>
<td>Specific rotation</td>
<td>+137° to +145°</td>
<td>+23° to +25°</td>
<td>+137° to +145°</td>
</tr>
<tr>
<td>Conductivity</td>
<td></td>
<td>≤ 20 µS·cm⁻¹</td>
<td>-</td>
</tr>
<tr>
<td>Acidity</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤ 0.3%</td>
<td>≤ 0.5%</td>
<td>≤ 0.3%</td>
</tr>
<tr>
<td>Chloride</td>
<td>≤ 0.007%</td>
<td>-</td>
<td>≤ 0.007%</td>
</tr>
<tr>
<td>Sulfate</td>
<td>≤ 1.3 ppm</td>
<td>-</td>
<td>≤ 1 ppm</td>
</tr>
<tr>
<td>Arsenic</td>
<td></td>
<td>≤ 0.1%</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td></td>
<td>≤ 0.5 ppm</td>
<td>-</td>
</tr>
<tr>
<td>Nickel</td>
<td>+</td>
<td>≤ 1 ppm</td>
<td>-</td>
</tr>
<tr>
<td>Heavy metals</td>
<td></td>
<td>≤ 5 ppm</td>
<td>-</td>
</tr>
<tr>
<td>Reducing sugars</td>
<td>+</td>
<td>≤ 0.2%</td>
<td>+</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td></td>
<td>≤ 0.10%</td>
<td></td>
</tr>
<tr>
<td>Related substances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial endotoxins</td>
<td></td>
<td>≤ 4 IU/g</td>
<td>-</td>
</tr>
<tr>
<td>Microbial contamination</td>
<td></td>
<td>≤ 100 cfu/g</td>
<td>-</td>
</tr>
<tr>
<td>Assay (dried basis)</td>
<td></td>
<td>≥ 98.0%</td>
<td>98.0-102.0%</td>
</tr>
<tr>
<td>(a) Test applied only if the mannitol is to be used in the manufacture of parenteral dosage forms.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) For parenteral preparations having a concentration of 100 g/L or less of mannitol.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) For parenteral preparations having a concentration of more than 100 g/L of mannitol.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. See also Figure 4.
Refractive index: nD²⁰ = 1.333
Solubility see Table II.
Specific surface area: 0.37-0.39 m²/g

Table II: Solubility of mannitol.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility at 20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkalies</td>
<td>Soluble</td>
</tr>
<tr>
<td>Ethanol (95%)</td>
<td>1 in 83</td>
</tr>
<tr>
<td>Ether</td>
<td>Practically insoluble</td>
</tr>
<tr>
<td>Glycerin</td>
<td>1 in 18</td>
</tr>
<tr>
<td>Propan-2-ol</td>
<td>1 in 100</td>
</tr>
<tr>
<td>Water</td>
<td>1 in 5.5</td>
</tr>
</tbody>
</table>

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. In solution, mannitol is not attacked by cold, dilute acids or alkalies, 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. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephalirin at 2 mg/mL and 30 mg/mL concentration 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 formulation. Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.
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.

**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. 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 excrated in the urine in 3 hours.

A number of adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions. 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.

- \( \text{LD}_{50} \) (mouse, IP): 14 g/kg
- \( \text{LD}_{50} \) (mouse, IV): 7.47 g/kg
- \( \text{LD}_{50} \) (mouse, oral): 22 g/kg
- \( \text{LD}_{50} \) (rat, IV): 9.69 g/kg
- \( \text{LD}_{50} \) (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 USPNF, NF, and the Genera Information Chapters in the JP XV. Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

**17 Related Substances**

Sorbitol.

**18 Comments**

Mannitol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter in the USP 32-NF27, the General Chapters of the PhEur 6.0, and the State of Work document on the PhEur EDQM website, and also the General Information Chapters in the JP XV.

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.

A study has examined the influence of common excipients such as sucrose and trehalose, on the crystallization of mannitol in freeze-drying.

Mannitol has been reported to sublime at 130°C. "Ludiflash" (BASF) is a coprocessed excipient used as a tablet filler, binder, and disintegrant, and contains mainly mannitol, and also crospovidone and polyvinyl acetate.

A specification for mannitol is contained in the Food Chemicals Codex (FCC).

The EINECS number for mannitol is 200-711-8. The PubChem Compound ID (CID) for mannitol includes 6251 and 453.

**19 Specific References**

Mannitol


20 General References

21 Author
NA Armstrong.

22 Date of Revision
3 February 2009.
Polymethacrylates

1 Nonproprietary Names

BP:  Ammonio Methacrylate Copolymer (Type A)
     Basic Butylated Methacrylate Copolymer
     Methacrylic Acid-Ethyl Acrylate Copolymer
     Dispersion 30 per cent
     Methacrylic Acid-Methyl Methacrylate Copolymer (1:1)
     Polyacrylate Dispersion 30 per cent

PhEur: Ammonio Methacrylate Copolymer (Type A)
       Ammonio Methacrylate Copolymer (Type B)
       Basic Butylated Methacrylate Copolymer
       Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)
       Methacrylic Acid-Ethyl Acrylate Acryl Acryl (1:1)
       Dispersion 30 per cent
       Methacrylic Acid-Methyl Methacrylate Copolymer (1:1)
       Methacrylic Acid-Methyl Methacrylate Copolymer (1:2)
       Polyacrylate Dispersion 30 per cent

USP-NF: Ammonio Methacrylate Copolymer
         Ammonio Methacrylate Copolymer Dispersion
         Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion
         Methacrylic Acid Copolymer
         Methacrylic Acid Copolymer Dispersion

Note that six separate monographs applicable to polymethacrylates are contained in the USP32-NF27. Several different types of material are defined in the same monographs. The PhEur (6.0, 6.2, and 6.3) contains eight separate monographs applicable to polymethacrylates. See also Section 9.

2 Synonyms

Acryl-EZE; acidi methacrylici et ethylis acrylatis polymerisatum; acidi methacrylici et methylis methacrylatis polymerisatum; ammonio methacrylatis copolymerum; copolymerum methacrylatis butylatis basicum; Eastacryl; Eudragit; Kollicoat MAE; polyacrylatis dispersio 30 per centum; polymeric methacrylates. See also Table I.

3 Chemical Name and CAS Registry Number

See Table I.

4 Empirical Formula and Molecular Weight

The PhEur 6.2 describes methacrylic acid-ethyl acrylate copolymer (1:1) as a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1:1. It may contain suitable surfactants such as sodium dodecyl sulfate or polysorbate 80. An aqueous 30% w/w dispersion of this material is also defined in a separate monograph. Methacrylic acid-methyl methacrylate copolymer (1:1) is described in the PhEur 6.0 as a copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic acid to ester groups is about 1:1. A further monograph in the PhEur 6.0 describes methacrylic acid-methyl methacrylate copolymer (1:2), where the ratio of carboxylic acid to ester groups is about 1:2. The PhEur 6.0 describes basic butylated methacrylate copolymer as a copolymer of (2-dimethylaminoethyl) methacrylate, butyl methacrylate, and methyl methacrylate having a mean relative molecular mass of about 150 000. The ratio of (2-dimethylaminoethyl) methacrylate groups to butyl methacrylate and methyl methacrylate groups is about 2:1:1. The PhEur 6.0 describes ammonio methacrylate copolymer as a poly(ethyl propenoate-co-methyl 2-methylpropenoate-co-2-(trimethylammonio)ethyl 2-methylpropenoate) chloride having a mean relative molecular mass of about 150 000. The ratio of ethyl propenoate to methyl 2-methylpropenoate to 2-(trimethylammonio)ethyl 2-methylpropenoate is about 1:2:0.2 for Type A and 1:2:0.1 for Type B. Polyacrylate dispersion (30 per cent) is described in the PhEur 6.3 as a dispersion in water of a copolymer of ethyl acrylate and methyl methacrylate having a mean relative molecular mass of about 800 000. It may contain a suitable emulsifier.

The USP32-NF27 describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types of copolymers, namely Type A, Type B, and Type C, are defined in the monograph. They vary in their methacrylic acid content and solution viscosity. Type C may contain suitable surfactants and also ethyl acrylate and methyl methacrylate. See Sections 9 and 18. Further monographs for aqueous dispersions of Type C methacrylic acid copolymer, ammonio methacrylate copolymer, and also ethyl acrylate and methyl methacrylate copolymer are also defined; see Section 9.

Typically, the molecular weight of the polymer is \( \geq 100 000 \).

5 Structural Formula

For Eudragit E:

\[
R_1, R_3 = \text{CH}_3 \\
R_2 = \text{CH}_3\text{CH}_2\text{N(CH}_3)_2 \\
R_4 = \text{CH}_3, \text{C}_6\text{H}_9
\]

For Eudragit L and Eudragit S:

\[
R_1, R_3 = \text{CH}_3 \\
R_2 = \text{H} \\
R_4 = \text{CH}_3
\]

For Eudragit FS:

\[
R_1 = \text{H} \\
R_2 = \text{H}, \text{CH}_3 \\
R_3 = \text{CH}_3 \\
R_4 = \text{CH}_3
\]

For Eudragit RL and Eudragit RS:

\[
R_1 = \text{H}, \text{CH}_3 \\
R_2 = \text{CH}_3, \text{C}_2\text{H}_5 \\
R_3 = \text{CH}_3
\]
types to get her. Then neutral Eudragit RL and films of varying permeability can be obtained by mixing the two polymers used, films of different solubility characteristics can be produced; see Table II.

For Eudragit NE 30 D and Eudragit NE 40 D:
R¹, R² = H, CH₃
R³, R⁴ = CH₃, C₂H₅

For Acryl-EZE and Acryl-EZE MP; Eudragit L 30 D-55 and Eudragit L 100-55, Eastacryl 30 D, Kollicoat MAE 100 P, and Kollicoat MAE 30 DP:
R¹ = H, CH₃
R² = H
R³ = CH₃, C₂H₅

6 Functional Category
Film-forming agent; tablet binder; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology
Poly(methacrylate) are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced; see Table II.

Eudragit E is used as a plain or insolubilizing film former. It is soluble in gastric fluid below pH 5. In contrast, Eudragit L, S and FS types are used as enteric coating agents because they are resistant to gastric fluid. Different types of enteric coatings are soluble at different pH values: e.g. Eudragit L is soluble at pH > 6 whereas Eudragit S and FS are soluble at pH > 7. The S grade is generally used for coating tablets, while the flexible FS 30 D dispersion is preferred for coating particles.

Eudragit RL, RS, NE 30 D, NE 40 D, and NM 30 D are used to form water-insoluble film coats for sustained-release products. Eudragit RI films are more permeable than those of Eudragit RS, and films of varying permeability can be obtained by mixing the two types together. The neutral Eudragit NE/NM grades do not have functional ionic groups. They swell in aqueous media independently of pH without dissolving.

Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5. Eudragit L 100-55 is an alternative to Eudragit L 30 D-55. It is commercially available as a dispersible powder. Kollicoat MAE 100 P, Acryl-EZE and Acryl-EZE MP are also commercially available as dispersible powder forms, which are designed for enteric coating of tablets or beads.

Eastacryl 30 D and Kollicoat MAE 30 DP are aqueous dispersions of methacrylic acid-ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms.

Poly(methacrylates) are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5-20%) of dry polymer are used to control the release of a active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10-50%.

Poly(methacrylates) polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration. See also Section 18.

8 Description
Poly(methacrylates) are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60:40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. See Tables I and III.

Eudragit E is a cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to pH
### Table II: Summary of properties and uses of commercially available polymethacrylates.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Supply form</th>
<th>Polymer dry weight content</th>
<th>Recommended solvents or diluents</th>
<th>Solubility/permeability</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit E 12.5</td>
<td>Organic solution</td>
<td>12.5%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid to pH 5</td>
<td>Film coating</td>
</tr>
<tr>
<td>Eudragit E 100</td>
<td>Granules</td>
<td>98%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid to pH 5</td>
<td>Film coating</td>
</tr>
<tr>
<td>Eudragit E PO</td>
<td>Powder</td>
<td>98%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid to pH 5</td>
<td>Film coating</td>
</tr>
<tr>
<td>Eudragit L 12.5 P</td>
<td>Organic solution</td>
<td>12.5%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit L 12.5</td>
<td>Organic solution</td>
<td>12.5%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit L 100</td>
<td>Powder</td>
<td>95%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit L 100-55</td>
<td>Powder</td>
<td>95%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit L 30 D-55</td>
<td>Aqueous dispersion</td>
<td>30%</td>
<td>Water</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit S 12.5 P</td>
<td>Organic solution</td>
<td>12.5%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit S 12.5</td>
<td>Organic solution</td>
<td>12.5%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>Powder</td>
<td>95%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit FS 30 D</td>
<td>Aqueous dispersion</td>
<td>30%</td>
<td>Water</td>
<td>Soluble in gastric fluid from pH 6</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit RL 12.5</td>
<td>Organic solution</td>
<td>12.5%</td>
<td>Acetone, alcohols</td>
<td>High permeability</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Eudragit RL 100</td>
<td>Granules</td>
<td>97%</td>
<td>Acetone, alcohols</td>
<td>High permeability</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Eudragit RL PO</td>
<td>Powder</td>
<td>97%</td>
<td>Acetone, alcohols</td>
<td>High permeability</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Eudragit RS 12.5</td>
<td>Organic solution</td>
<td>12.5%</td>
<td>Water</td>
<td>Low permeability</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Eudragit RS 100</td>
<td>Granules</td>
<td>97%</td>
<td>Acetone, alcohols</td>
<td>Low permeability</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Eudragit RS 30 D</td>
<td>Aqueous dispersion</td>
<td>30%</td>
<td>Water</td>
<td>Low permeability</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Eudragit NE 30 D</td>
<td>Aqueous dispersion</td>
<td>30%</td>
<td>Water</td>
<td>Swellable, permeable</td>
<td>Sustained release, tablet matrix</td>
</tr>
<tr>
<td>Eudragit NE 40 D</td>
<td>Aqueous dispersion</td>
<td>40%</td>
<td>Water</td>
<td>Swellable, permeable</td>
<td>Sustained release, tablet matrix</td>
</tr>
<tr>
<td>Eudragit NM 30 D</td>
<td>Aqueous dispersion</td>
<td>30%</td>
<td>Water</td>
<td>Soluble in gastric fluid from pH 5</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eostacryl 30 D</td>
<td>Aqueous dispersion</td>
<td>30%</td>
<td>Water</td>
<td>Soluble in gastric fluid from pH 5</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Kollidac MAE 30 DP</td>
<td>Aqueous dispersion</td>
<td>30%</td>
<td>Water</td>
<td>Soluble in gastric fluid from pH 5</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Kollidac MAE 100 P</td>
<td>Powder</td>
<td>95%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 5</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Acryl-EZE 93 A</td>
<td>Powder</td>
<td>95%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 5</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Acryl-EZE MP</td>
<td>Powder</td>
<td>95%</td>
<td>Acetone, alcohols</td>
<td>Soluble in gastric fluid from pH 5</td>
<td>Enteric coatings</td>
</tr>
</tbody>
</table>

Note: Recommended plasticizers for the above polymers include dibutyl phthalate, polyethylene glycols, triethyl citrate, triacetin, and 1,2-propylene glycol. The recommended concentration of the plasticizer is approximately 10-25% plasticizer (based on the dry polymer weight). A plasticizer is not necessary with Eudragit E 12.5, Eudragit E 100, and Eudragit NE 30 D.

≈ 5). Eudragit E is available as a 12.5% ready-to-use solution in propan-2-ol-acetone (60:40). It is light yellow in color with the characteristic odor of the solvents. Solvent-free granules contain ≈98% dried weight content of Eudragit E. Eudragit E PO is a white free-flowing powder with at least 95% of dry polymer.

Eudragit L and S, also referred to as methacrylic acid copolymers in the USP32-NF27 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in Eudragit L (Type A) and approximately 1:2 in Eudragit S (Type B). Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alcalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer (Eudragit L 12.5 and S 12.5); and as a 12.5% ready-to-use solution in propan-2-ol with 1.25% dibutyl phthalate as plasticizer (Eudragit L 12.5 P and S 12.5 P). Solutions are colorless, with the characteristic odor of the solvent. Eudragit L 100 and Eudragit S 100 are white free-flowing powders with at least 95% of dry polymers.

Eudragit ES 30 D is the aqueous dispersion of an anionic copolymer based on methyl acrylate, methyl methacrylate, and methacrylic acid. The ratio of free carboxyl groups to ester groups is approximately 1:10. It is a highly flexible polymer, designed for use in enteric-coated solid-dosage forms, and dissolves in aqueous systems at pH >7.

Eudragit RL and Eudragit RS, also referred to as ammonio methacrylate copolymers in the USP32–NF27 monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters, with Eudragit RL (Type A) having 10% of functional...
quaternary ammonium groups and Eudragit RS (Type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from Eudragit RL are freely permeable to water, whereas, films prepared from Eudragit RS are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol-acetone (60:40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (Eudragit RL 100 and Eudragit RS 100) contain ≥97% of the dried weight content of the polymer.

Eudragit RL PO and Eudragit RS PO are fine, white powders with a slight amine-like odor. They are characteristically the same polymers as Eudragit RL and RS. They contain ≥97% of dry polymer.

Eudragit RL 30 D and Eudragit RS 30 D are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from Eudragit RL 30 D are readily permeable to water and to dissolved active substances, whereas films prepared from Eudragit RS 30 D are less permeable to water. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.

Eudragit NE 30 D and Eudragit NE 40 D are aqueous dispersions of a neutral copolymer consisting of polymeric acrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

Eudragit NM 30 D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate, and is of identical monomer composition to Eudragit NE 30 D.

Eudragit L 30 D-55 is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer corresponds to USP32-NF27 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1:1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine.

Eastacryl 30 D and Kollcoat MAE 30 DP are also aqueous dispersions of the anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer also corresponds to USP32-NF27 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1:1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying Eudragit L 30 D-55) is a white, free-flowing powder that is dispersible in water to form a latex that has properties similar to those of Eudragit L 30 D-55.

Acryl-EZE and Acryl-EZE MP are also commercially available as dispersible powder forms, which are designed for enteric coating of tablets and beads, respectively.

### Table III: Solubility of commercially available polymethacrylates in various solvents.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Solvent</th>
<th>Acetone and alcohols&lt;sup&gt;(a)&lt;/sup&gt;</th>
<th>Dichloromethane</th>
<th>Ethyl acetate</th>
<th>1 N HCl</th>
<th>1 N NaOH</th>
<th>Petroleum ether</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit E 12.5</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit E 100</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>M</td>
<td>P</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit L 12.5 P</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>M</td>
<td>-</td>
<td>M</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit L 12.5</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>M</td>
<td>-</td>
<td>M</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit L 100-55</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit L 100</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit L 30 D-55&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit S 12.5 P</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit S 12.5</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit S 12.5</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit S 100</td>
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<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>I</td>
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<tr>
<td>Eudragit L 12.5</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit L 100</td>
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<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Eudragit L 30 D</td>
<td>M</td>
<td>M</td>
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<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
<td>-</td>
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<tr>
<td>Eudragit RS 12.5</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
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<td>Eudragit RS 100</td>
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<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit RS PO</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Eudragit RS 30 D&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
<td>-</td>
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<tr>
<td>Eastacryl 30 DP</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>Kollcoat MAE 30 DP&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>M</td>
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<tr>
<td>Kollcoat MAE 100 P</td>
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<td>S</td>
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<td>-</td>
<td>M</td>
<td>-</td>
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<td>I</td>
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<td>I</td>
<td>M</td>
<td>P</td>
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<td>-</td>
<td>-</td>
<td>M</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>(a)</sup> Alcohols including ethanol (95%), methanol, and propan-2-ol.
<sup>(b)</sup> Supplied as a milky-white aqueous dispersion.
<sup>(c)</sup> A 1:5 mixture forms a clear, viscous, solution.

S = soluble; M = miscible; I = insoluble or immiscible; P = precipitates.

1 part of Eudragit RL 30 D or of Eudragit RS 30 D dissolves completely in 5 parts acetone, ethanol (95%), or propan-2-ol to form a clear or slightly turbid solution. However, when mixed in a ratio of 1:5 with methanol, Eudragit RL 30 D dissolves completely, whereas Eudragit RS 30 D dissolves only partially.

### 9 Pharmacopeial Specifications

Specifications for polymethacrylates from PhEur 6.0, 6.2, and 6.3 are shown in Table IV, and those from the USP32-NF27 in Table V. See also Section 18.
<table>
<thead>
<tr>
<th>Test</th>
<th>Ammonia methacrylate copolymer (PhEur 6.0)</th>
<th>Methacrylic acid-ethyl acrylate copolymer (1:1) (PhEur 6.2)</th>
<th>Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30% (PhEur 6.3)</th>
<th>Methacrylic acid-methyl methacrylate copolymer (1:1) (PhEur 6.0)</th>
<th>Methacrylic acid-methyl methacrylate copolymer (1:2) (PhEur 6.0)</th>
<th>Basic butylated methacrylate copolymer (PhEur 6.0)</th>
<th>Polyacrylate dispersion 30% (PhEur 6.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Appearance of a film</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Relative density</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Apparent viscosity</td>
<td>≤ 1.5 mPa s</td>
<td>≤ 15 mPa s</td>
<td>50-200 mPa s</td>
<td>3-6 mPa s</td>
<td>≤ 0.3</td>
<td>1.037-1.047</td>
<td>-</td>
</tr>
<tr>
<td>Absorbance at 420 nm</td>
<td>&lt; 1.0%</td>
<td>≤ 0.1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Particulate matter</td>
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<td>-</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Limit of monomers</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Ethyl acrylate and methacrylic acid</td>
<td>≤ 100 ppm</td>
<td>≤ 0.1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methyl methacrylate and methacrylic acid</td>
<td>≤ 50 ppm</td>
<td>≤ 0.1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Residue on evaporation</td>
<td>&lt; 5.0%</td>
<td>28.5-31.5%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28.5-31.5%</td>
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<tr>
<td>Loss on drying</td>
<td>&lt; 3.0%</td>
<td>≤ 5.0%</td>
<td>-</td>
<td>&lt; 5.0%</td>
<td>≤ 5.0%</td>
<td>≤ 2.0%</td>
<td>-</td>
</tr>
<tr>
<td>Methanol</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 20 ppm</td>
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<td>Sulfated ash</td>
<td>-</td>
<td>≥ 0.2%</td>
<td>≤ 0.1%</td>
<td>≤ 0.1%</td>
<td>≤ 0.1%</td>
<td>≤ 0.1%</td>
<td>-</td>
</tr>
<tr>
<td>Type A</td>
<td>-</td>
<td>0.4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
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<td>Type B</td>
<td>-</td>
<td>0.5-3.0%</td>
<td>-</td>
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<td>Microbial contamination</td>
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<td>≤ 10^3 cfu/g</td>
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<td>-</td>
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<td>Assay</td>
<td>Ammonia methacrylate units</td>
<td>Methacrylic acid units</td>
<td>Methacrylic acid units</td>
<td>Methacrylic acid units</td>
<td>Dimethylaminoethyl units</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Assay</td>
<td>Methacrylic acid units</td>
<td>Methacrylic acid units</td>
<td>Methacrylic acid units</td>
<td>Methacrylic acid units</td>
<td>Residue on evaporation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type A</td>
<td>8.9-12.3%</td>
<td>46.0-50.6%</td>
<td>46.0-50.6%</td>
<td>27.6-30.7%</td>
<td>20.8-25.5%</td>
<td>28.5%-31.5%</td>
<td></td>
</tr>
<tr>
<td>Type B</td>
<td>4.5-7.0%</td>
<td>43.0-48.0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) Corresponds to Eudragit RL/RS.
(b) Corresponds to Eudragit L100-55.
(c) Corresponds to Eudragit L30 D-55.
(d) Corresponds to Eudragit L.
(e) Corresponds to Eudragit S.
(f) Corresponds to Eudragit E.
(g) Corresponds to Eudragit NE 30 D.
<table>
<thead>
<tr>
<th>Test</th>
<th>Amino methacrylate copolymer&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ammonio methacrylate copolymer&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ammonio methacrylate copolymer dispersion&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Ethyl acrylate and methyl methacrylate copolymer dispersion&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Methacrylic acid copolymer&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Methacrylic acid copolymer dispersion&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Color of solution</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Viscosity</td>
<td>3.6 mPa s</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Type B</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤2.0%</td>
<td>≤3.0%</td>
<td>68.5–71.5%&lt;sup&gt;g&lt;/sup&gt;</td>
<td>68.5–71.5%&lt;sup&gt;g&lt;/sup&gt;</td>
<td>≤50 mPa s</td>
<td>50–200 mPa s</td>
</tr>
<tr>
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<td>-</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>≤0.1%</td>
<td>≤0.1%</td>
<td>≤0.5%</td>
<td>&lt;0.4%</td>
<td>≤0.1%</td>
<td>-</td>
</tr>
<tr>
<td>Type A</td>
<td>-</td>
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<td>Type B</td>
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<td>Heavy metals</td>
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<td>-</td>
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<td>Limit of total monomers</td>
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<td>≤0.002%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Limit of methyl methacrylate</td>
<td>-</td>
<td>≤0.005%</td>
<td>≤0.002%</td>
<td>≤0.01%</td>
<td>≤0.1%</td>
<td>-</td>
</tr>
<tr>
<td>Limit of butyl methacrylate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Limit of 2-dimethylaminomethyl methacrylate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Limit of allyl acrylate</td>
<td>-</td>
<td>≤0.025%</td>
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<td>-</td>
</tr>
<tr>
<td>Coagulum content</td>
<td>-</td>
<td>≤1.0%&lt;sup&gt;h&lt;/sup&gt;</td>
<td>≤1.0%&lt;sup&gt;h&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>≤1%&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Microbial contamination</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aerobic bacteria</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yeast and mold</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Assay (dried basis)</td>
<td>Dimethylaminoethyl units 20.8–25.5%</td>
<td>Ammonio methacrylate units 8.85–11.96%</td>
<td>Ammonio methacrylate units 10.18–13.73%</td>
<td>-</td>
<td>46.0–50.6%</td>
<td>-</td>
</tr>
<tr>
<td>Type A</td>
<td>-</td>
<td>8.85–11.96%</td>
<td>10.18–13.73%</td>
<td>-</td>
<td>46.0–50.6%</td>
<td>-</td>
</tr>
<tr>
<td>Type B</td>
<td>-</td>
<td>4.48–6.77%</td>
<td>6.11–8.26%</td>
<td>-</td>
<td>46.0–50.6%</td>
<td>-</td>
</tr>
<tr>
<td>Type C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>46.0–50.6%</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Corresponds to Eudragit E 100.
<sup>b</sup> Corresponds to Eudragit RL and RS.
<sup>c</sup> Corresponds to Eudragit RL 30 D and RS 30 D.
<sup>d</sup> Corresponds to Eudragit NE 30 D.
<sup>e</sup> Corresponds to Eudragit L, S and L100–55.
<sup>f</sup> Corresponds to Eudragit L 30 D–55.
<sup>g</sup> Calculated based on undried dispersion basis.
10 Typical Properties

Acid value

Alkal value
162–198 for Eudragit E 12.5 and E 100;
23.9–32.3 for Eudragit RL 12.5, RL 100, and RL PO;
27.5–31.7 for Eudragit RL 30 D;
12.1–18.3 for Eudragit RS 12.5, RS 100, and RS PO;
16.5–22.3 for Eudragit RS 30 D.

Density (bulk) 0.390 g/cm³
Density (tapped) 0.424 g/cm³

Near-infrared spectrum of polymethacrylates

Refractive index:
\[ n^D = 1.38–1.385 \text{ for Eudragit E;} \]
\[ n^S = 1.39–1.395 \text{ for Eudragit L and S;} \]
\[ n^L = 1.387–1.392 \text{ for Eudragit L 100-55;} \]
\[ n^RL = 1.38–1.385 \text{ for Eudragit RL and RS.} \]

Solubility see Table III.

Viscosity (dynamic)
3–12 mPa s for Eudragit E;
\[ \leq 50 \text{ mPa s for Eudragit NE 30 D;} \]
50–200 mPa s for Eudragit L and S;
\[ \leq 20 \text{ mPa s for Eudragit FS 30 D;} \]
\[ \leq 15 \text{ mPa s for Eudragit L 30 D-55;} \]
100–200 mPa s for Eudragit L 100-55;
\[ \leq 15 \text{ mPa s for Eudragit RL and RS;} \]
\[ \leq 200 \text{ mPa s for Eudragit RL and RS 30 D;} \]
\[ \leq 15 \text{ mPa s for Kollicoat MAE 100 P and Kollicoat MAE 30 DP;} \]
145 mPa s for Eastacryl 30 D.

11 Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can be readily broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5 and 25°C and are stable for at least 18 months after shipping from the manufacturer’s warehouse if stored in a tightly closed container at the above conditions.

12 Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; see Table II. For example, dispersions of Eudragit L 30 D, RL 30 D, L 100-55, and RS 30 D are incompatible with magnesium stearate. Eastacryl 30 D, Kollicoat MAE 100 P, and Kollicoat MAE 30 DP are also incompatible with magnesium stearate.
Prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g. butyl ester or dimethylaminoethyl ester.

Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

13 Method of Manufacture
Prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g. butyl ester or dimethylaminoethyl ester.

14 Safety
Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials.

Based on relevant chronic oral toxicity studies in rats and conventionally calculated with a safety factor of 100, a daily intake of 2–200 mg/kg body-weight depending on the grade of Eudragit may be regarded as essentially safe in humans.

See also Section 15.

15 Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves, and a dust mask or respirator are recommended. Polymethacrylates should be handled in a well-ventilated environment and measures should be taken to prevent dust formation.

Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly(methyl methacrylate) (PMMA). In the UK, the workplace exposure limit for methyl methacrylate has been set at 208 mg/m³ (50 ppm) long-term (8-hour TWA), and 416 mg/m³ (100 ppm) short-term.

See also Section 17.

16 Regulatory Status
Included in the FDA Inactive Ingredients Database (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances
Methyl methacrylate; poly(methyl methacrylate).

Methyl methacrylate

Empirical formula \( \text{C}_5\text{H}_8\text{O}_2 \)

Molecular weight 100.13

CAS number [80-62-6]

Synonyms Methacrylic acid, methyl ester; methyl 2-methacrylate; methyl 2-methylpropenoate; MME.

Safety

LD₅₀ (dog, SC): 4.5 g/kg
LD₅₀ (mouse, IP): 1 g/kg
LD₅₀ (mouse, oral): 5.2 g/kg
LD₅₀ (mouse, SC): 6.3 g/kg
LD₃₀ (rat, IP): 1.33 g/kg
LD₃₀ (rat, SC): 7.5 g/kg

**Coments** Methyl methacrylate forms the basis of acrylic bone cements used in orthopedic surgery.

**Poly(methyl methacrylate)**

**Empirical formula** \((C₅H₈O₂)ₙ\)

**Synonyms** Methyl methacrylate polymer; PMMA.

**Comments** Poly(methyl methacrylate) has been used as a material for intracocular lenses, for denture bases, and as a cement for dental prostheses.

**18 Comments**
A number of different poly(methyl methacrylates) are commercially available that have different applications and properties; see Table II.

For spray coating, polymer solutions and dispersions should be diluted with suitable solvents. Some products need the addition of a plasticizer such as dibutyl sebacate, dibutyl phthalate, glycerol, or polyethylene glycol. Different types of plasticizer may be mixed to optimize the polymer properties for special requirements.

The *Japanese Pharmaceutical Excipients* (JPE) 2004 includes specifications for aminooalkyl methacrylate copolymer RS, aminooalkyl methacrylate copolymer E, dried methacrylic acid copolymer LD, ethyl acrylate and methacrylic acid copolymer dispersion, methacrylic acid copolymer L, methacrylic acid copolymer S, and methacrylic acid copolymer LD.

**19 Specific References**


**20 General References**


**21 Authors**

RK Chang, Y Peng, N Trivedi, AJ Shukla.

**22 Date of Revision**

4 March 2009.
Povidone

1 Nonproprietary Names
BP: Povidone
JP: Povidone
PhEur: Povidone
USP: Povidone

2 Synonyms
E1201; Kollidon; Plasdone; poly(1-(2-oxo-1-pyrrolidinyl)ethylene); polyvidone; polyvinylpyrrolidone; povidonum; Povipharma; PVP; 1-vinyl-2-pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number
1-Ethyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula and Molecular Weight
(C₆H₉NO)n, 2300–3 000 000
The USP 32 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, in the range 10–120. The K-value is calculated using Fikentscher’s equation:\(^1\)

\[
\log \eta = c \left( \frac{75k^2}{1 + 1.5kc} \right) + k
\]

where \(\eta\) is the relative viscosity of the solution of concentration \(c\) (in % w/v), and \(k\) is the K-value \(\times 10^{-3}\). Alternatively, the K-value may be determined from the following equation:

\[
K-values = \frac{300c \log \eta (c + 1.5c \log \eta^2 + 1.5)}{0.15c + 0.003c^2}
\]

where \(\eta\) is the relative viscosity of the solution of concentration \(c\) (in % w/v). Approximate molecular weights for different povidone grades are shown in Table I.

<table>
<thead>
<tr>
<th>K-value</th>
<th>Approximate molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>2 500</td>
</tr>
<tr>
<td>15</td>
<td>8 000</td>
</tr>
<tr>
<td>17</td>
<td>10 000</td>
</tr>
<tr>
<td>25</td>
<td>30 000</td>
</tr>
<tr>
<td>30</td>
<td>50 000</td>
</tr>
<tr>
<td>60</td>
<td>400 000</td>
</tr>
<tr>
<td>90</td>
<td>1 000 000</td>
</tr>
<tr>
<td>120</td>
<td>3 000 000</td>
</tr>
</tbody>
</table>

See also Section 8.

5 Structural Formula

6 Functional Category
Disintegrant; dissolution enhancer; 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.\(^4,5\) Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads.

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.**

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier for drugs</td>
<td>10–25</td>
</tr>
<tr>
<td>Dispersing agent</td>
<td>Up to 5</td>
</tr>
<tr>
<td>Eye drops</td>
<td>2–10</td>
</tr>
<tr>
<td>Suspending agent</td>
<td>Up to 5</td>
</tr>
<tr>
<td>Tablet binder, tablet diluent, or coating agent</td>
<td>0.5–5</td>
</tr>
</tbody>
</table>

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. See also Section 18.

10 **Typical Properties**

**Acidity/alkalinity**  
$pH = 3.0-7.0$ (5% w/v aqueous solution); $pH = 4.0-7.0$ (5% w/v aqueous solution) for Povipharm K90.

**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**  
20 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.

**NIR spectra** see Figure 3.

**SEM 1:** Excipient: povidone K-15 (Plasdone K-15); manufacturer: ISP; lot no.: 82A-1; magnification: 60x; voltage: 5 kV.

**SEM 2:** Excipient: povidone K-15 (Plasdone K-15); manufacturer: ISP; lot no.: 82A-1; magnification: 600x; voltage: 5 kV.

**SEM 3:** Excipient: povidone K-26/28 (Plasdone K-26/28); manufacturer: ISP; lot no.: 82A-2; magnification: 60x; voltage: 5 kV.

**Particle size distribution**

Kollidon 25/30: 90% >50 µm, 50% >100 µm, 5% >200 µm;  
Kollidon 90: 90% >200 µm, 95% >250 µm. 

**Solubility** Freely soluble in acids, chloroform, ethanol (95%), 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.

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.
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. 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. Evidence also...
exists that povidone may accumulate in the organs of the body following intramuscular injection. A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.

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 in Europe as a food additive. Included in the INAC database (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topicals and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Crospovidone.

18 Comments

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

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. Many excipients such as povidone may contain peroxides as trace contaminants. This can lead to degradation of an active pharmaceutical ingredient that is sensitive to oxidation.

A specification for povidone is contained in the Food Chemicals Codex (FCC).

19 Specific References


20 General References


21 Author

AH Kibble.

22 Date of Revision

3 February 2009.
The therapeutic use of sodium propionate in topical antifungal preparations has largely been superseded by a new generation of antifungal drugs.

A specification for sodium propionate is contained in the Food Chemicals Codex (FCC). The EINECS number for sodium propionate is 205-290-4. The PubChem Compound ID (CID) for sodium propionate is 23663426.

### Specific References


### Sodium Starch Glycolate

#### Nonproprietary Names

BP: Sodium Starch Glycolate  
PhEur: Sodium Starch Glycolate  
USP-NF: Sodium Starch Glycolate

#### Synonyms

Carboxymethyl starch, sodium salt; carboxymethylamyllum natrium; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

#### Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

#### Empirical Formula and Molecular Weight

The USP32-NF27 describes two types of sodium starch glycolate, Type A and Type B, and states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch or of a crosslinked carboxymethyl ether of starch.

The PhEur 6.0 describes three types of material: Type A and Type B are described as the sodium salt of a crosslinked partly O-carboxymethylated potato starch. Type C is described as the sodium salt of a partly O-carboxymethylated starch, crosslinked by physical dehydration. Types A, B, and C are differentiated by their pH, sodium, and sodium chloride content.

The PhEur and USP-NF monographs have been harmonized for Type A and Type B variants.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically $5 \times 10^5 - 1 \times 10^6$.

#### Structural Formula

![Structural Formula](image)

#### Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration around 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

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.

Sodium starch glycolate has also been investigated for use as a suspending vehicle.

#### Date of Revision

5 February 2009.

#### Author

T Sakurai.
Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 states that when examined under a microscope it is seen to consist of granules, irregularly shaped, ovoid or pear-shaped, 30-100 µm in size, or rounded, 10-35 µm in size; compound granules consisting of 2–4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules show considerable swelling in contact with water.

9 Pharmacopeial Specifications
See Table I. See also Section 18.

10 Typical Properties

Acidity/alkalinity  See Section 9.
Density (bulk)

SEM 1: Excipient: sodium starch glycolate (Explotab); manufacturer: JRS Pharma; magnification: 300x; voltage: 5 kV.

SEM 2: Excipient: sodium starch glycolate (Glycolys); manufacturer: Roquettes Frères.

SEM 3: Excipient: sodium starch glycolate (Primojet); manufacturer: DMV-Fonterra Excipients; magnification: 200x; voltage: 1.5 kV.

SEM 4: Excipient: sodium starch glycolate (Vivastar P); manufacturer: JRS Pharma; magnification: 300x; voltage: 5 kV.

Density (tapped)
0.756 g/cm³ for Glycolys;
0.81 g/cm³ for Primojet;
0.67 g/cm³ for Tablo.

Density (true)
1.56 g/cm³ for Primojet;
1.49 g/cm³ for Tablo.

Melting point  Does not melt, but chars at approximately 200°C.
NIR spectra  see Figure 1.

Particle size distribution  100% of particles less than 106 µm in size. Average particle size (d50) is 38 µm and 42 µm for Primojet by microscopy and sieving, respectively.

Solubility  Practically insoluble in methylene chloride. It gives a translucent suspension in water.

Specific surface area
0.24 m²/g for Glycolys;
0.185 m²/g for Primojet;
0.335 m²/g for Tablo.
Sodium starch glycolate is incompatible with ascorbic acid.

Viscosity (dynamic) citric acid, acetic acid, or some other acid. Typically, commercial products are also crosslinked using either denatured ethanol or methanol, followed by neutralization with sodium chlorate.

Starch is carboxymethylated by reacting it with sodium glutarate in an alkaline, nonaqueous medium, typically denatured ethanol or methanol, followed by neutralization with citric acid, acetic acid, or some other acid. Vivastar P is manufactured in methanolic medium, and Explotab in ethanolic medium.

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 Database (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances
Pregelatinized starch; starch.

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

The physical properties of sodium starch glycolate, and hence its effectiveness as a disintegrant, are affected by the degree of crosslinkage, extent of carboxymethylation, and purity. The solubility of the formulation matrix and mode of incorporation in wet granulation can affect the disintegration time; disintegration times can be slower in tablets containing high levels of soluble excipients.

Commercially, sodium starch glycolate is available in a number of specialty grades, e.g., low pH (Explotab Low pH, Glycoyls Low pH); low viscosity (Explotab CLV, Glycoyls LV); low solvent (Vivastar PSF); and low moisture Glycoyls LM.

A specification for sodium starch glycolate is included in the Japanese Pharmaceutical Excipients (JPE).

19 Specific References

### Table 1: Pharmacopeial specifications for sodium starch glycolate.

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 6.0</th>
<th>USP32-NF27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>5.5-7.5</td>
<td>5.5-7.5</td>
</tr>
<tr>
<td>Type B</td>
<td>3.0-5.0</td>
<td>3.0-5.0</td>
</tr>
<tr>
<td>Type C</td>
<td>5.5-7.5</td>
<td>-</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>&lt;20 ppm</td>
<td>&lt;0.002%</td>
</tr>
<tr>
<td>Iron</td>
<td>&lt;20 ppm</td>
<td>&lt;0.002%</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Type A</td>
<td>≤10.0%</td>
<td>-</td>
</tr>
<tr>
<td>Type B</td>
<td>≤10.0%</td>
<td>-</td>
</tr>
<tr>
<td>Type C</td>
<td>≤7.0%</td>
<td>-</td>
</tr>
<tr>
<td>Microbial limits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Type A</td>
<td>≤7.0%</td>
<td>-</td>
</tr>
<tr>
<td>Type B</td>
<td>≤7.0%</td>
<td>-</td>
</tr>
<tr>
<td>Type C</td>
<td>≤1.0%</td>
<td>-</td>
</tr>
<tr>
<td>Sodium glycolate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>≤2.0%</td>
<td>-</td>
</tr>
<tr>
<td>Type B</td>
<td>≤2.0%</td>
<td>-</td>
</tr>
<tr>
<td>Type C</td>
<td>≤2.0%</td>
<td>-</td>
</tr>
<tr>
<td>Assay (of No)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>2.8-4.2%</td>
<td>2.8-4.2%</td>
</tr>
<tr>
<td>Type B</td>
<td>2.0-3.4%</td>
<td>2.0-3.4%</td>
</tr>
<tr>
<td>Type C</td>
<td>2.8-5.0%</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) Complies with tests for Salmonella and Escherichia coli.

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 (depending on source and grade).

11 Stability and Storage Conditions
Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, 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 3 years if it is stored at moderate temperatures and humidity.

12 Incompatibilities
Sodium starch glycolate is incompatible with ascorbic acid.

13 Method of Manufacture
Sodium starch glycolate is a substituted derivative of potato starch. Typically, commercial products are also crosslinked using either sodium trimetaphosphate (Types A and B) or dehydration (Type C).

Starch is carboxymethylated by reacting it with sodium chloroacetate in an alkaline, nonaqueous medium, typically denatured ethanol or methanol, followed by neutralization with citric acid, acetic acid, or some other acid. Vivastar P is manufactured in methanolic medium, and Explotab in ethanolic medium.

Figure 1: Near-infrared spectrum of sodium starch glycolate measured by reflectance.

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 Database (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances
Pregelatinized starch; starch.

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

The physical properties of sodium starch glycolate, and hence its effectiveness as a disintegrant, are affected by the degree of crosslinkage, extent of carboxymethylation, and purity. The solubility of the formulation matrix and mode of incorporation in wet granulation can affect the disintegration time; disintegration times can be slower in tablets containing high levels of soluble excipients.

Commercially, sodium starch glycolate is available in a number of specialty grades, e.g., low pH (Explotab Low pH, Glycoyls Low pH); low viscosity (Explotab CLV, Glycoyls LV); low solvent (Vivastar PSF); and low moisture Glycoyls LM.

A specification for sodium starch glycolate is included in the Japanese Pharmaceutical Excipients (JPE).

19 Specific References


20 General References


21 Author

PM Young.

22 Date of Revision

3 February 2009.
**Synonyms** l-Tartaric acid

**Empirical formula** C\textsubscript{6}H\textsubscript{12}O\textsubscript{6}

**CAS number** 17598-82-2

**Melting point** 134-135°C

**Specific rotation** $[\alpha]_D^\text{20} = +1^\circ$ (2% aqueous solution)

**Comments** Sweetening agent for pharmaceutical and personal aid products.

**18 Comments**

The EINECS number for tagatose is 201-772-3. The PubChem Compound ID (CID) for tagatose is 92092.

**19 Specific References**


**20 General References**

**21 Author**

GE Amidon.

**22 Date of Revision**

28 February 2009.

---

**Talc**

**1 Nonproprietary Names**

BP: Purified Talc
JP: Talc
PhEur: Talc
USP: Talc

**2 Synonyms**

Altaic; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Pertal; soapstone; steatite; Superior; talcum.

**3 Chemical Name and CAS Registry Number**

Talc [14807-96-6]

**4 Empirical Formula and Molecular Weight**

Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg\textsubscript{6}(Si\textsubscript{2}O\textsubscript{5})(OH)\textsubscript{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, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.

**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.

**9 Pharmacopeial Specifications**

See Table II. See also Section 18.

**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%.

NIR spectra see Figure 1.

Particle size distribution Varies with the source and grade of material. Two typical grades are $\geq 99\%$ through a 74 µm (#200 mesh) or $\geq 99\%$ through a 44 µm (#325 mesh).
Table II: Pharmacopeial specifications for talc.

<table>
<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.3</th>
<th>USP 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acidsoluble substances</td>
<td>≤2.0%</td>
<td>≤2.0%</td>
<td>≤2.0%</td>
</tr>
<tr>
<td>Acidity or alkalinity</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Production</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pH</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Water-soluble substances</td>
<td>-</td>
<td>&lt;0.2%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Aluminum</td>
<td>-</td>
<td>≤2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Calcium</td>
<td>-</td>
<td>≤0.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Iron</td>
<td>-</td>
<td>0.25%</td>
<td>0.25%</td>
</tr>
<tr>
<td>Lead</td>
<td>-</td>
<td>≤10 ppm</td>
<td>≤0.001%</td>
</tr>
<tr>
<td>Magnesium</td>
<td>-</td>
<td>17.0-19.5%</td>
<td>17.0-19.5%</td>
</tr>
<tr>
<td>Loss on ignition</td>
<td>≤5.0%</td>
<td>≤7.0%</td>
<td>≤7.0%</td>
</tr>
<tr>
<td>Microbial contamination</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Aerobic bacteria</td>
<td>-</td>
<td>≤10² cfu/g</td>
<td>10⁶ cfu/g³</td>
</tr>
<tr>
<td>Fungi</td>
<td>-</td>
<td>≤10² cfu/g</td>
<td>50 cfu/g³</td>
</tr>
<tr>
<td>Acid and alkali-soluble substances</td>
<td>≤4.0 mg</td>
<td>-</td>
<td>≤2.0%</td>
</tr>
<tr>
<td>Water-soluble iron</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arsenic</td>
<td>-</td>
<td>≤4 ppm</td>
<td>≤3 ppm</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>-</td>
<td>-</td>
<td>≤0.004%</td>
</tr>
<tr>
<td>Absence of asbestos</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

(a) If intended for topical administration.
(b) If intended for oral administration.

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

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.

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 hydrosilicate mineral found in many parts of the world including Australia, China, Italy, India, France, and the USA.

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).\(^{12}\)

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.\(^{13-15}\)

## 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 non-toxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs.\(^{16-18}\) 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.\(^{19}\) 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.\(^{20,21}\) However, talc contaminated with asbestos has been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products.\(^{22}\)

Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidently exposed to the substance.\(^{23}\)

## 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 workplace exposure limit for talc is 1 mg/m\(^3\) of respirable dust long-term (8-hour TWA).\(^{24}\) Eye protection, gloves, and a respirator are recommended.

## 16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (buccal tablets; oral capsules and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

## 17 Related Substances

Bentonite; magnesium aluminum silicate; magnesium silicate; magnesium trisilicate.

## 18 Comments

Talc is one of the materials that have been selected for harmonization by the Pharmacopoeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General Chapter S.8 in PhEur 6.0, along with the ‘State of Work’ document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Various grades of talc are commercially available that vary in their chemical composition depending upon their source and method of preparation.\(^{11,12,25}\)

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

A specification for talc is contained in the Food Chemicals Codex (FCC).\(^{27}\)

The EINECS number for talc is 238-877-9. The PubChem Compound ID (CID) for talc includes 26924, 443754 and 16211421.

## 19 Specific References

Tartaric Acid

1 Nonproprietary Names
BP: Tartaric Acid
JP: Tartaric Acid
PhEur: Tartaric Acid
USP-NF: Tartaric Acid

2 Synonyms
Acidum tartaricum; L-(+)-2,3-dihydroxybutanedioic acid; (2R,3R)-2,3-dihydroxybutane-1,4-dioic acid; 2,3-dihydroxysuccinic acid; E334; d-tartaric acid; L-(+)-tartaric acid.

3 Chemical Name and CAS Registry Number
[R-(R*,R*)]-2,3-Dihydroxybutanedioic acid [87-69-4]

4 Empirical Formula and Molecular Weight
C₄H₆O₆ 150.09

5 Structural Formula

6 Functional Category
Acidifying agent; flavoring agent; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology
Tartaric acid is used in beverages, confectionery, food products, and pharmaceutical formulations as an acidulant. It may also be used as a sequestering agent and as an antioxidant synergist. In pharmaceutical formulations, it is widely used in combination with bicarbonates, as the acid component of effervescent granules, powders, and tablets.

Tartaric acid is also used to form molecular compounds (salts and cocrystals) with active pharmaceutical ingredients to improve physicochemical properties such as dissolution rate and solubility.¹²

8 Description
Tartaric acid occurs as colorless monoclinic crystals, or a white or almost white crystalline powder. It is odorless, with an extremely tart taste.

9 Pharmacopeial Specifications
See Table I.

<table>
<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.0</th>
<th>USP32-NF27</th>
</tr>
</thead>
<tbody>
<tr>
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10 Typical Properties
Acidity/alkalinity  pH = 2.2 (1.5% w/v aqueous solution)
Density  1.76 g/cm³
Dissociation constant
pKₐ₁ = 2.93 at 25°C;
pKₐ₂ = 4.23 at 25°C.
Heat of combustion  1151 kJ/mol (275.1 kcal/mol)
Melting point  168-170°C
NIR spectra see Figure 1.
Osmolarity  A 3.9% w/v aqueous solution is isoosmotic with serum.
Solubility see Table II.
Specific heat  1.20 J/g (0.288 cal/g) at 20°C.
Specific rotation  [α]D₀ = +12.0° (20% w/v aqueous solution).
The term 'water' is used to describe potable water that is freshly drawn direct from the public supply and is suitable for drinking. Water used in the pharmaceutical industry and related disciplines is classified as either drinking (potable) water, purified water, sterile water, for injection (WFI), sterile water for injection, bacteriostatic water for injection, sterile water for irrigation, or sterile water for inhalation. Validation is required for all systems producing the water indicated, with the exception of potable water.

The chemical composition of potable water is variable, and the nature and concentrations of the impurities in it depend upon the source from which it is drawn. Water classified as potable water for applications such as some initial rinsing and API manufacturing operations, must meet the US Environmental Protection Agency's National Primary Drinking Water Regulations, or comparable regulations of the EU or Japan. For most pharmaceutical applications, potable water is purified by distillation, ion exchange treatment, reverse osmosis (RO), or some other suitable process to produce 'purified water'. For certain applications, water with pharmacopeial specifications differing from those of purified water should be used, e.g. WFI; see Sections 9 and 18.

Water is a clear, colorless, odorless, and tasteless liquid.

### 9 Pharmacopeial Specifications

See Table II. See also Section 17.

### 10 Typical Properties

**Boiling point** 100°C

**Critical pressure** 22.1 MPa (218.3 atm)

**Critical temperature** 374.2°C

**Dielectric constant** $D = 82.7$

**Dipole moment** 1.76 in benzene at 25°C;

1.86 in dioxane at 25°C.

**Ionization constant** $1.008 \times 10^{-14}$ at 25°C.

**Latent heat of fusion** 6.146 kJ/mol (1.436 kcal/mol)

**Latent heat of vaporization** 40.7 kJ/mol (9.717 kcal/mol)

**Melting point** 0°C

**Refractive index** $n_0^2 = 1.3330$

**Solubility** Miscible with most polar solvents.

**Specific gravity** 0.9971 at 25°C

**Specific heat (liquid)** $4.184 \text{ J/g}^\circ \text{C} (1.00 \text{ cal/g}^\circ \text{C})$ at 14°C

**Surface tension** 71.97 mN/m (71.97 dynes/cm) at 25°C

**Vapor pressure** 3.17 kPa (23.76 mmHg) at 25°C

**Viscosity (dynamic)** 0.89 mPa s (0.89 cP) at 25°C

### 11 Stability and Storage Conditions

Water is chemically stable in all physical states (ice, liquid, and vapor). Water leaving the pharmaceutical purification system and entering the storage tank must meet specific requirements. The goal when designing and operating the storage and distribution system is to keep the water from exceeding allowable limits during storage. In particular, the storage and distribution system must ensure that water is protected against ionic and organic contamination, which would lead to an increase in conductivity and total organic carbon, respectively. The system must also be protected against physical entry of foreign particles and microorganisms so that microbial growth is prevented or minimized. Water for specific purposes should be stored in appropriate containers; see Table III.
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</tr>
<tr>
<td>Biological activity</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
</tbody>
</table>

(a) For water for injection preserved in containers and sterilized, the JP XV provides separate tests for acid or alkali, chloride, ammonium, and residue on evaporation within the monograph.

(b) For water for injection prepared by reverse osmosis-ultrafiltration.
supply of the appropriate quality, but permits distillation, ion exchange, RO or any other suitable method that complies with regulations on water intended for human consumption laid down by the competent authority. The USP 32 and the JP XV permit the use of RO in addition to distillation and ultrafiltration. In the past 10–15 years, RO has become the most common way to produce pharmaceutical purified water, either as a final treatment step or as a pretreatment step for the distillation stills.

**Distillation** Distillation is a process that involves the evaporation of water followed by the condensation of the resulting steam. While expensive, it allows removal of almost all organic and inorganic impurities and achieves very high quality water. It is also considered the safest method to avoid microbial and endotoxin contamination. To improve energy efficiency, distillation is usually conducted in multiple-effects stills designed to recover most of the energy spent on evaporating the water. A typical design consists of an evaporator, vapor separator, and compressor. The distillate (raw feed water) is heated in the evaporator to boiling and the vapor produced is separated from entrained distilland in the separator. The vapor then enters a compressor where the temperature of the vapors is raised to 107°C. Superheated vapors are then condensed on the outer surface of the tubes of the evaporator containing cool distillate circulating within.

Vapor compression stills of various sizes are commercially available and can be used to produce water of high purity when properly constructed. A high-quality distillate, such as WFI, can be obtained if the water is first deionized. The best stills are constructed from types 304 or 316 stainless steel and coated with pure tin, or are made from chemical-resistant glass.

**12 Incompatibilities**

In pharmaceutical formulations, water can react with drugs and other excipients that are susceptible to hydrolysis (decomposition in the presence of water or moisture) at ambient and elevated temperatures. Water can react violently with alkali metals and rapidly with alkaline metals and their oxides, such as calcium oxide and magnesium oxide. Water also reacts with anhydrous salts to form hydrates of various compositions, and with certain organic materials and calcium carbonate.

**13 Method of Manufacture**

Unlike other excipients, water is not purchased from outside suppliers but is manufactured in-house by pharmaceutical companies. As naturally occurring water has a variety of contaminants, many treatment processes have been developed to remove these. A typical pharmaceutical water purification system contains several unit operations designed to remove various components. The selection of the most appropriate system and its overall design are crucial factors in ensuring that water of the correct quality is produced.

To produce potable or drinking water, insoluble matter is first removed from a water supply by coagulation, settling (clarification), and filtering processes. Pathogenic microorganisms present are then destroyed by aeration, chlorination, or some other means. Water may also be rendered free of viable pathogenic microorganisms by active boiling for 15–20 minutes. Activated carbon filters are employed to remove chlorine and many dissolved organic materials found in water, although they may become a breeding ground for microorganisms. The palatability of the water is improved by aeration and charcoal filtration.

Purified water suitable for use in pharmaceutical formulations is usually prepared by purifying potable water by one of several processes, such as distillation, deionization, or RO.\(^1\,^2\)

The quality attributes of WFI are stricter than those for purified water. Consequently, the preparation methods typically vary in the last stage to ensure good control of WFI quality. Methods for the production of WFI are the subject of current debate. The Ph Eur 6.3 indicates that only distillation would give assurance of consistent supply of the appropriate quality, but permits distillation, ion exchange, RO or any other suitable method that complies with regulations on water intended for human consumption laid down by the competent authority. The USP 32 and the JP XV permit the use of RO in addition to distillation and ultrafiltration. In the past 10–15 years, RO has become the most common way to produce pharmaceutical purified water, either as a final treatment step or as a pretreatment step for the distillation stills.

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**Deionization** An ionic exchange process is based on the ability of certain synthetic resins to selectively adsorb either cations or anions, and to release (exchange) other ions based on their relative activity. Cationic and anionic ion exchange resins are used to purify potable water by removing any dissolved ions. Dissolved gases are also removed, while chlorine, in the concentrations generally found in potable water, is destroyed by the resin itself. Some organics and colloidal particles are removed by adsorption and filtration. Resin beds may, however, foster microbial life and produce pyrogenic effluent unless adequate precautions are taken to prevent contamination. Another disadvantage is the type of chemicals required for resin regeneration. A continuous deionization system, which represents a combination of ion exchange and membrane separation technologies, uses an electrical current to continuously regenerate the ion exchange resin simultaneously with the water treatment process, eliminating the need to handle powerful chemicals. Ion exchange units are normally used today to treat raw feed water prior to distillation or RO processing.

**Reverse osmosis** Water is forced through a semipermeable membrane in the opposite direction to normal osmotic diffusion. Typically, membranes range between 1–10 Å and reject not only organic compounds, bacteria and viruses, but also 90–99% of all ions. It is common to use double-pass RO systems with two filtration stages connected in series. Such systems meet requirements for USP purified water and WFI. However, EU regulations do not allow RO to be used as a final treatment step for the production of WFI.

**Membrane filtration** Membrane filters are surface-type filters, which stop particles larger than the pore size at the upstream surface of the polymeric membrane. Microfiltration uses membranes with pores in the 0.1–1.0 µm range, which can filter out particles of dust, activated carbon, ion exchange resin fines, and most microorganisms. Ultrafiltration uses membranes that reject not only solid particles but also dissolved matter with a high molecular weight. The 'molecular weight cut-off' point of such membranes varies in the range 10 000–100 000 Da, and bacteria, endotoxins, colloidal contaminants, and large organic molecules can be removed.
14 Safety

Water is the base for many biological life forms, and its safety in pharmaceutical formulations is unquestioned provided it meets standards of quality for potability and microbial content; see Sections 9 and 18. Plain water is considered slightly more toxic upon injection into laboratory animals than physiological salt solutions such as normal saline or Ringer's solution.

Ingestion of excessive quantities of water can lead to water intoxication, with disturbances of the electrolyte balance.

Sterile water for injection (WFI) should be free from pyrogens.

LD50 (mouse, IP): 25 g/kg

15 Handling Precautions

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

16 Regulatory Status

Included in nonparenteral and parenteral medicines licensed in the UK and USA.

17 Related Substances

Bacteriostatic water for injection; carbon dioxide-free water; de-aerated water; hard water; soft water; sterile water for inhalation; sterile water for injection; sterile water for irrigation; water for injection (WFI).

Bacteriostatic water for injection

Comments: The USP 32 describes bacteriostatic water for injection as sterile water for injection that contains one or more suitable antimicrobial agents.

Carbon dioxide-free water

Comments: Purified water that has been boiled vigorously for 5 minutes and allowed to cool while protecting it from absorption of atmospheric carbon dioxide.

De-aerated water

Comments: Purified water that has been boiled vigorously for 5 minutes and cooled to reduce the air (oxygen) content.

Hard water

Comments: Water containing the equivalent of not less than 120 mg/L and not more than 180 mg/L of calcium carbonate.

Soft water

Comments: Water containing the equivalent of not more than 60 mg/L of calcium carbonate.

Sterile water for inhalation

Comments: The USP 32 describes sterile water for inhalation as WFI sterilized and suitably packaged. It contains no antimicrobial agents or other added substances, except where used in humidifiers or other similar devices, and where liable to contamination over a period of time.

Sterile water for injection

Comments: The USP 32 describes sterile water for injection as WFI sterilized and suitably packaged. It contains no antimicrobial agents or other substances.

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

18 Comments

In most pharmacopeias, the term ‘water’ now refers to purified or distilled water.

Without further purification, ‘water’ may be unsuitable for certain pharmaceutical applications; for example, the presence of calcium in water affects the viscosity and gel strength of algin and pectin dispersions, while the use of potable water affects the clarity and quality of cough mixtures, and the stability of antibiotic liquid preparations.

Water commonly contains salts of aluminum, calcium, iron, magnesium, potassium, sodium, and zinc. Toxic substances such as arsenic, barium, cadmium, chromium, cyanide, lead, mercury, and selenium may constitute a danger to health if present in excessive amounts. Ingestion of water containing high amounts of calcium and nitrate is also contraindicated. National standards generally specify the maximum limits for these inorganic substances in potable water. Limits have also been placed on microorganisms, detergents, phenolics, chlorinated phenolics, and other organic substances. The WHO and national bodies have issued guidelines for water quality, although many countries have their own standards for water quality embodied in specific legislation.

See Table IV.

Table IV: Limits for inorganic substances in potable water (mg/L).

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>UK (mg/L)</th>
<th>WHO (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Ammonium</td>
<td>0.5</td>
<td>No limit</td>
</tr>
<tr>
<td>Antimony</td>
<td>0.05</td>
<td>No limit</td>
</tr>
<tr>
<td>Arsenic</td>
<td>0.1</td>
<td>No limit</td>
</tr>
<tr>
<td>Barium</td>
<td>0.1</td>
<td>No limit</td>
</tr>
<tr>
<td>Beryllium</td>
<td>0.05</td>
<td>No limit</td>
</tr>
<tr>
<td>Boron</td>
<td>0.05</td>
<td>No limit</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Calcium</td>
<td>250</td>
<td>No limit</td>
</tr>
<tr>
<td>Chloride</td>
<td>400</td>
<td>250</td>
</tr>
<tr>
<td>Chromium</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Copper</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Cyanide</td>
<td>0.05</td>
<td>0.1</td>
</tr>
<tr>
<td>Fluoride</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Iron</td>
<td>1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Lead</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Magnesium</td>
<td>50</td>
<td>No limit</td>
</tr>
<tr>
<td>Manganese</td>
<td>0.05</td>
<td>0.1</td>
</tr>
<tr>
<td>Mercury</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Nickel</td>
<td>0.05</td>
<td>No limit</td>
</tr>
<tr>
<td>Nitrate (as N)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Nitrate (as NO3)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Nitrite (as NO3)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.2</td>
<td>No limit</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Silver</td>
<td>0.01</td>
<td>No limit</td>
</tr>
<tr>
<td>Sodium</td>
<td>150</td>
<td>200</td>
</tr>
<tr>
<td>Sulfate</td>
<td>250</td>
<td>400</td>
</tr>
<tr>
<td>Zinc</td>
<td>5.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Control of microbiological contamination is critical for waters used in preparation of pharmaceuticals, as proliferation of microorganisms can potentially occur during all stages of manufacture, storage, or distribution. Suitable control is achieved by ensuring that the water system is well designed and well maintained. Purified water that is produced, stored, and circulated at ambient temperatures is susceptible to the establishment of biofilms; therefore, frequent monitoring, high usage, correct flow rate, and appropriate sanitization are all factors that require consideration to ensure that water is satisfactory.\(^{(13)}\)

Monitoring of the whole system is essential in order to demonstrate that correct microbiological quality is achieved. For WFI, the recommended methodology is membrane filtration (0.45 μm) as a large sample size (100–300 mL) is required. For purified water, membrane filtration or plate count methods are typically used depending on the quality requirements of the system. It is important to set appropriate target, alert, and action limits to serve as an indication of action required to bring the quality of water back under control. It is recognized that limits are not intended as pass/fail criteria for water or product batches; however, an investigation regarding the implications should be conducted.\(^{(14)}\)

Validation is conducted to provide a high level of assurance that the water production and distribution system will consistently produce water conforming to a defined quality specification. The validation process serves to qualify the design (DQ), installation (IQ), operation (OQ), and performance (PQ) of the system. The extent of monitoring data required should be defined, with consideration given to whether validation to FDA guidelines is required.\(^{(14)}\) It is also important to have an ongoing control program with respect to maintenance, and periodic reviews of the performance of the water system.

The PubChem Compound ID (CID) for water is 962.

## 19 Specific References


## 20 General References


Rösler R. Water and air, two important media in the manufacture of sterile pharmaceuticals, with regard to the GMP. *Drugs Made Ger* 1976; 19: 130–136.


## 21 Authors

D Dubash, U Shah.

## 22 Date of Revision

27 February 2009.

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## Wax, Anionic Emulsifying

### 1 Nonproprietary Names

BP: Emulsifying Wax  
PhEur: Cetostearyl Alcohol (Type A), Emulsifying  
PhEur: Cetostearyl Alcohol (Type B), Emulsifying

### 2 Synonyms

Collone HV; Crodex A; Cyclonette Wax; Lanette SX; Lanette W.

### 3 Chemical Name and CAS Registry Number

Anionic emulsifying wax [8014-38-8]

### 4 Empirical Formula and Molecular Weight

The PhEur 6.2 specifies that cetostearyl alcohol (type A), emulsifying contains a minimum of 80% cetostearyl alcohol and 7% sodium cetostearyl sulfate. Cetostearyl alcohol (type B), emulsifying contains a minimum of 80% cetostearyl alcohol and 7% sodium lauryl sulfate. A suitable buffer can be added to both.

The BP 2009 describes anionic emulsifying wax as containing cetostearyl alcohol, purified water, and either sodium lauryl sulfate or a sodium salt of a similar sulfated higher primary aliphatic alcohol. See also Section 18.

The BP 2009 specifies that the formula of anionic emulsifying wax is:

- Cetostearyl alcohol 90 g
- Sodium lauryl sulfate 10 g
- Purified water 4 mL