

# Mannitol

## 1 Nonproprietary Names

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitol

USP–NF: Mannitol

## 2 Synonyms

*Compressol*; Cordycepic acid; *C\*PharmMannidex*; E421; *Emprove*; *Ludiflash*; manita; manitol; manna sugar; mannit; D-mannite; mannite; mannitolium; *Mannogem*; *Pearlitol*.

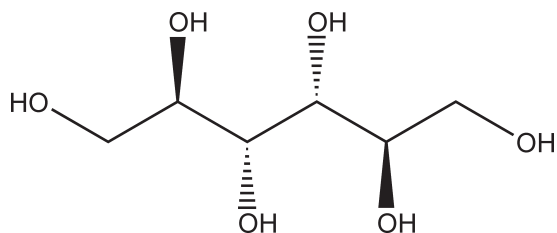
## 3 Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

## 4 Empirical Formula and Molecular Weight

$C_6H_{14}O_6$  182.17

## 5 Structural Formula



## 6 Functional Category

Lyophilization aid/plasticizing agent; sweetening agent; tablet and capsule diluent; tonic agent.

## 7 Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.<sup>(1,2)</sup>

Mannitol may be used in direct-compression tablet applications,<sup>(3,4)</sup> for which the granular and spray-dried forms are available,<sup>(5)</sup> or in wet granulations.<sup>(6,7)</sup> Granulations containing mannitol have the advantage of being easily dried. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and ‘mouth feel’.<sup>(7,8)</sup> It is also used as a diluent in rapidly dispersing oral dosage forms.<sup>(9,10)</sup>

Mannitol has been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has also been used as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,<sup>(11)</sup> as a carrier in dry powder inhalers,<sup>(12,13)</sup> and as a diluent in rapidly dispersing oral dosage forms.<sup>(14,15)</sup>

In lyophilized preparations, mannitol (20–90% w/w) has been used as a carrier to produce a stiff, homogeneous cake that improves

the appearance of the lyophilized plug in a vial.<sup>(16–18)</sup> A pyrogen-free form is available specifically for this use.

Mannitol is used in food applications as a bulking agent.

## 8 Description

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

Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.<sup>(19)</sup>

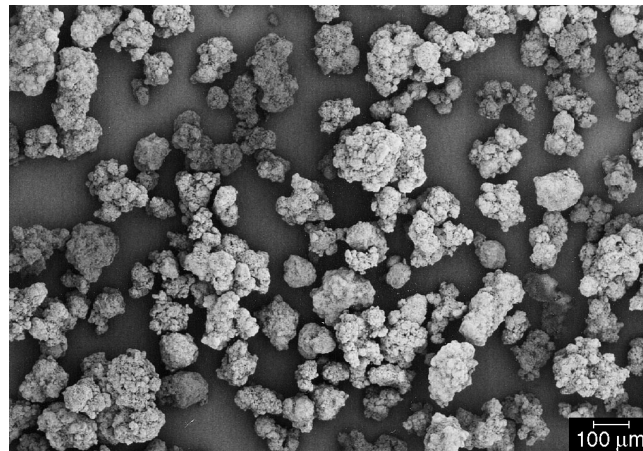
## 9 Pharmacopeial Specifications

See Table I. See also Section 18.

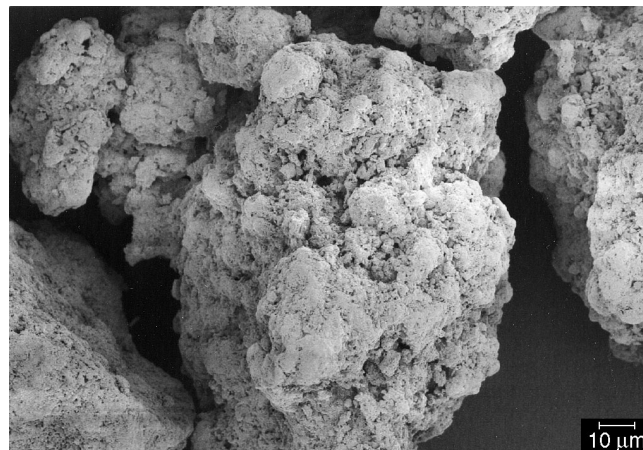
## 10 Typical Properties

*Compressibility* see Figure 1.

**SEM 1:** Excipient: mannitol; manufacturer: Merck; magnification: 50×; voltage: 3.5 kV.



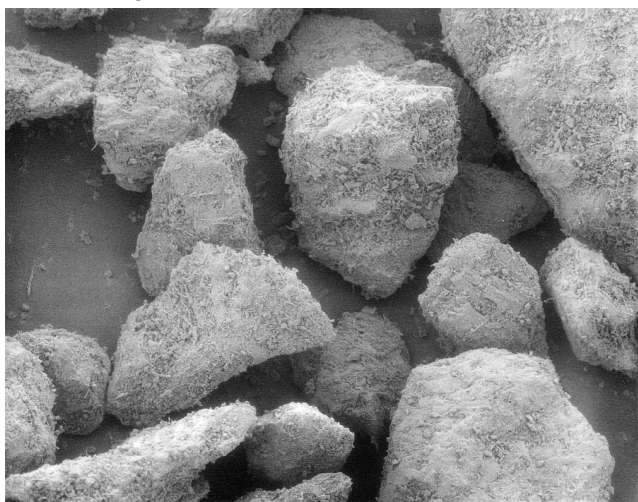
**SEM 2:** Excipient: mannitol; manufacturer: Merck; magnification: 500×; voltage: 3.5 kV.



**SEM 3:** Excipient: mannitol powder; manufacturer: SPI Polyols Inc.; lot no: 3140G8; magnification: 100 $\times$ .



**SEM 4:** Excipient: mannitol granular; manufacturer: SPI Polyols Inc.; lot no: 2034F8; magnification: 100 $\times$ .



#### Density (bulk)

0.430 g/cm<sup>3</sup> for powder;  
0.7 g/cm<sup>3</sup> for granules.

#### Density (tapped)

0.734 g/cm<sup>3</sup> for powder;  
0.8 g/cm<sup>3</sup> for granules.

**Density (true)** 1.514 g/cm<sup>3</sup>

**Dissociation constant** pK<sub>a</sub> = 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.

**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  $\mu$ m and minimum of 90% greater than 200  $\mu$ m in size;

**Pearlitol 400 DC:** maximum of 20% greater than 500  $\mu$ m and minimum of 85% greater than 100  $\mu$ m in size;

**Pearlitol 500 DC:** maximum of 0.5% greater than 841  $\mu$ m and minimum of 90% greater than 150  $\mu$ m in size.

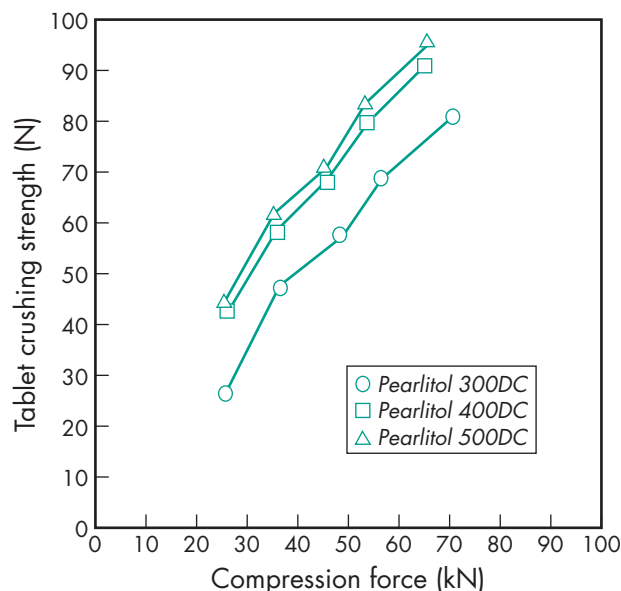
**Table I:** Pharmacopeial specifications for mannitol.

Test	JP XV	PhEur 7.4	USP35-NF30
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
Melting range	166–169°C	165–170°C	164–169°C
Specific rotation	+137° to +145°	+23° to +25°	+137° to +145°
Conductivity	—	≤20 $\mu$ S·cm <sup>-1</sup>	—
Acidity	+	—	+
Loss on drying	≤0.3%	≤0.5%	≤0.3%
Chloride	≤0.007%	—	≤0.007%
Sulfate	≤0.01%	—	≤0.01%
Arsenic	≤1.3 ppm	—	≤1 ppm
Lead	—	≤0.5 ppm	—
Nickel	+	≤1 ppm	—
Heavy metals	≤5 ppm	—	—
Reducing sugars	+	≤0.2%	+
Residue on ignition	≤0.10%	—	—
Related substances	—	+	—
Bacterial endotoxins <sup>(a)</sup>	—	≤4 IU/g <sup>(b)</sup>	—
Microbial contamination	—	≤2.5 IU/g <sup>(c)</sup> ≤100 cfu/g	—
Assay (dried basis)	≥ 98.0%	98.0–102.0%	96.0–101.5%

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

(b) For parenteral preparations having a concentration of 100 g/L or less of mannitol.

(c) For parental preparations having a concentration of more than 100 g/L of mannitol.



**Figure 1:** Compression characteristics of granular mannitol (Pearlitol, Roquette Frères).

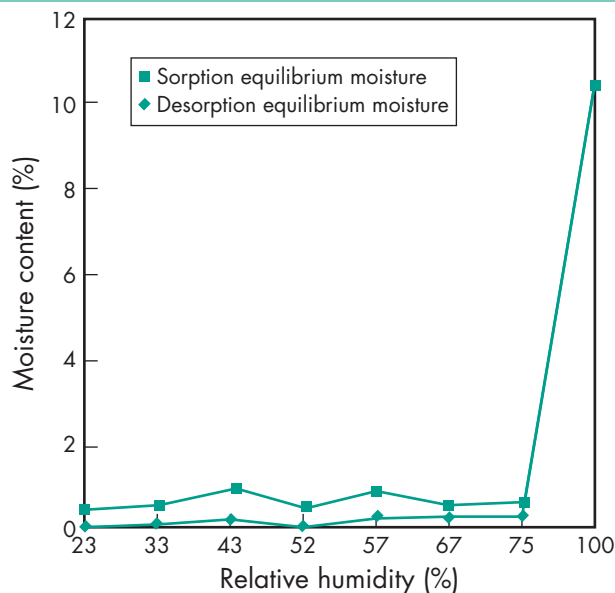
Tablet diameter: 20 mm. Lubricant: magnesium stearate 0.7% w/w for Pearlitol 400 DC and Pearlitol 500 DC; magnesium stearate 1% w/w for Pearlitol 300 DC.

Average particle diameter is 250  $\mu$ m for Pearlitol 300 DC, 360  $\mu$ m for Pearlitol 400 DC and 520  $\mu$ m for Pearlitol 500 DC.<sup>(20)</sup> See also Figure 3.

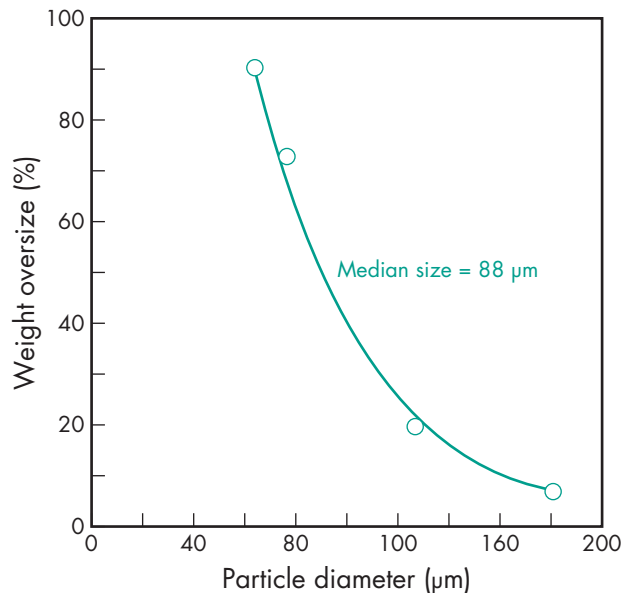
**Refractive index**  $n_D^{20}$  = 1.333

**Solubility** see Table II.

**Specific surface area** 0.37–0.39 m<sup>2</sup>/g



**Figure 2:** Sorption-desorption isotherm for mannitol.



**Figure 3:** Particle size distribution of mannitol powder.

**Table II:** Solubility of mannitol.

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

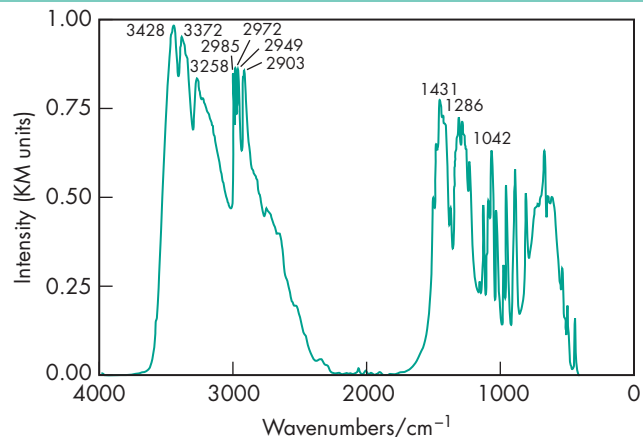
### Spectroscopy

IR spectra *see* Figure 4.

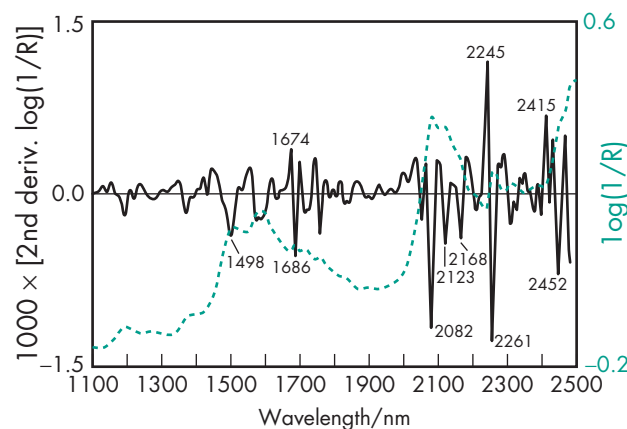
NIR spectra *see* Figure 5.

## 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



**Figure 4:** Infrared spectrum of mannitol measured by diffuse reflectance. Adapted with permission of Informa Healthcare.



**Figure 5:** Near-infrared spectrum of mannitol measured by reflectance.

necessary may be autoclaved repeatedly with no adverse physical or chemical effects.<sup>(22)</sup> In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions.

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

## 12 Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.<sup>(23)</sup> Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.<sup>(24)</sup> Sodium cephalin 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 formation.<sup>(25)</sup> Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.<sup>(26)</sup>

## 13 Method of Manufacture

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



## 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.<sup>(27)</sup> If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement 'excessive consumption may have a laxative effect'. After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.<sup>(28)</sup>

A number of adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions.<sup>(29)</sup> 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.<sup>(30)</sup>

LD<sub>50</sub> (mouse, IP): 14 g/kg<sup>(31)</sup>

LD<sub>50</sub> (mouse, IV): 7.47 g/kg

LD<sub>50</sub> (mouse, oral): 22 g/kg

LD<sub>50</sub> (rat, IV): 9.69 g/kg

LD<sub>50</sub> (rat, oral): 13.5 g/kg

## 15 Handling Precautions

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

## 16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IP, IM, IV, and SC injections; infusions; buccal, oral and sublingual tablets, powders and capsules; ophthalmic preparations; topical solutions). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

## 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 <1196> in the USP35–NF30, the General Chapter 5.8 in PhEur 7.4, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 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.

*Ludiflash* (BASF) is a coprocessed excipient used as a tablet filler, binder, and disintegrant, and contains mainly mannitol with povidone, crospovidone and polyvinyl acetate. It is used for direct compression, and especially for tablets that disintegrate in the mouth.<sup>(32)</sup>

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.

A specification for mannitol is contained in the *Food Chemicals Codex* (FCC).<sup>(33)</sup>

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

## 19 Specific References

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