Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

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Mannitol

1. Nonproprietary Names

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

2. Synonyms

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

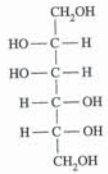
3. Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

4. Empirical Formula and Molecular Weight

$C_6H_{14}O_6$ 182.17

5. Structural Formula



6. Functional Category

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

7. Applications in Pharmaceutical Formulation or Technology

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

Mannitol may be used in direct-compression tablet applications,[1-5] for which the granular and spray-dried forms are available, or in wet granulations.[6] Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.[7,8]

In lyophilized preparations, mannitol (20-90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.[9-12] A pyrogen-free form is available specifically for this use.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (< 7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,[13] and 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 GI tract, but in large doses it can cause osmotic diarrhea, *see* Section 14.

8. Description

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

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

9. Pharmacopeial Specifications

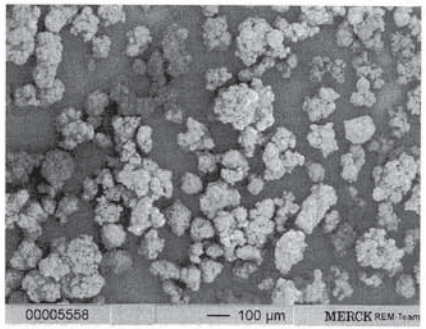
Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
Solution appearance	+	+	—
Melting range	166-169°C	165-170°C	164-169°C
Specific rotation	+137° to +145°	+23° to +25°	+137° to +145°
Acidity	+	+	+
Loss on drying	≤ 0.30%	≤ 0.5%	≤ 0.3%
Chloride	≤ 0.007%	≤ 50 ppm	≤ 0.007%
Sulfate	≤ 0.01%	≤ 100 ppm	≤ 0.01%
Arsenic	≤ 1.3 ppm	–	≤ 1 ppm
Lead	–	≤ 0.5 ppm	—
Nickel	+	≤ 1 ppm	—
Heavy metals	≤ 5 ppm	–	—
Reducing sugars	+	+	+
Sulfated ash	≤ 0.10%	≤ 0.1%	—
Sorbitol	–	≤ 2.0%	—
Bacterial endotoxins	–	+[a]	—
Assay	≤ 98.0%	98-101.5%	96-101.5%

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

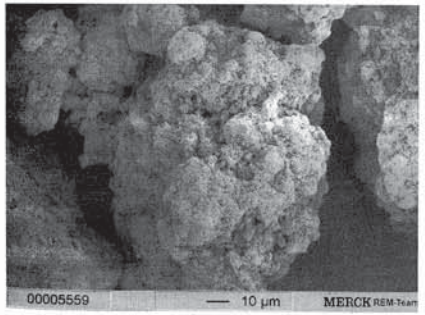
10. Typical Properties

Compressibility: *see* Figs. 1 and 2.[a]
Density (*bulk*): 0.430 g/cm^{3}[b] for powder; 0.7 g/cm^{3}[b] for granules.
Density (*tapped*): 0.734 g/cm^{3}[b] for powder; 0.8 g/cm^{3}[b] for granules
Density (*true*): 1.514 g/cm^{3}[b]
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 (3960 cal/g)
Heat of solution: -120.9 J/g (-28.9 cal/g) at 25°C
Melting point: 166-168°C
Moisture content: *see* Fig. 3.[b]

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



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

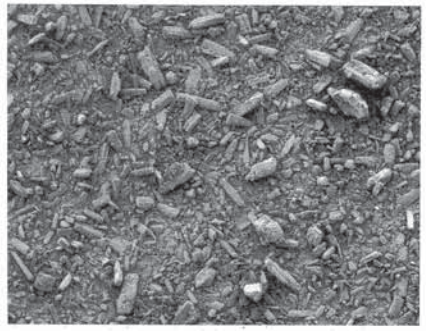


Osmolarity: a 5.07% w/v aqueous solution is iso-osmotic with serum.

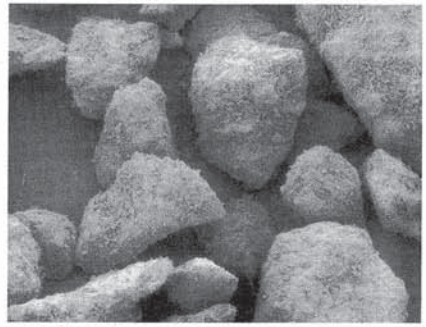
Particle size distribution: maximum of 0.1% greater than 500 µm and minimum of 90% greater than 200 µm in size for *Pearlitol 300 DC*; maximum of 20% greater than 500 µm and minimum of 85% greater than 100 µm in size for *Pearlitol 400 DC*; maximum of 0.5% greater than 841 µm and minimum of 90% greater than 150 µm in size for *Pearlitol 500 DC*. Average particle diameter is 250 µm for *Pearlitol 300 DC*, 360 µm for *Pearlitol 400 DC* and 520 µm for *Pearlitol 500 DC*.[14] *See* Fig. 4.[a]

Refractive index: n_D^{20} = 1.333

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



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



Solubility: *see* table below.

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

Specific surface area: 0.37-0.39 m^2/g[b]

[a] *Handbook of Pharmaceutical Excipients*, First Edition.

[b] Results of laboratory project for third edition.

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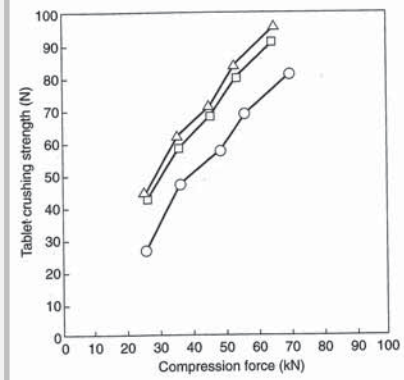

Fig. 1: Compression characteristics of granular mannitol (*Pearlitol*, Roquette Freres).
○ : *Pearlitol FG*
□ : *Pearlitol MG*
△ : *Pearlitol GG2*
Tablet diameter: 20 mm
Lubricant: magnesium stearate 0.7% w/w for *Pearlitol MG* and *Pearlitol GG2*, magnesium stearate 1% w/w for *Pearlitol FG*

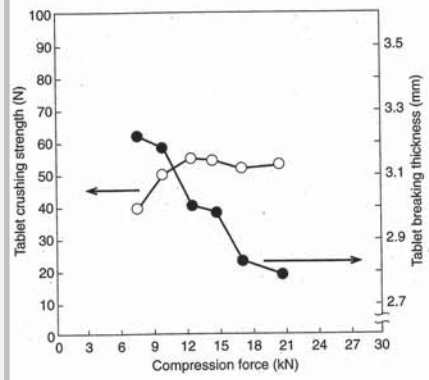

Fig. 2: Compression characteristics of granular mannitol.
Mean tablet weight: 500 mg
Minimum compressional force for compaction: 7.35 kN
Compressional force resulting in capping: 24.5 kN

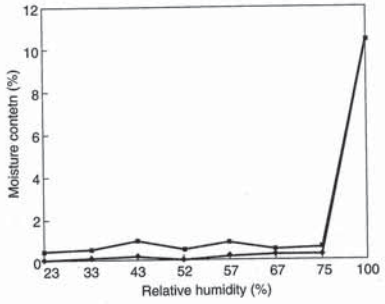

Fig. 3: Sorption-desorption isotherm for mannitol.
◆ : sorption equilibrium moisture
■ : desorption equilibrium moisture

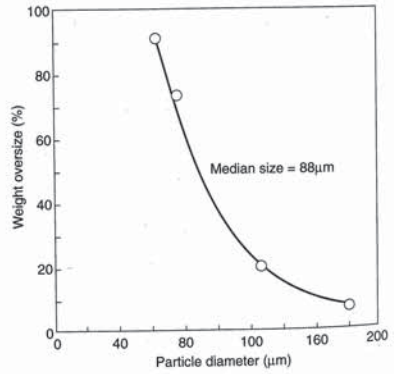

Fig. 4: Particle size distribution of mannitol powder.

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.[15] 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

None reported in the dry state. Mannitol solutions, 20% w/v or stronger, may be salted out by potassium or sodium chloride.[16] Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.[17] Sodium cephapirin at 2 mg/mL and 30 mg/mL is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals (Fe, Al, Cu). Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.[18] Mannitol was found to reduce the oral biovailability of cimetidine compared to sucrose.[19]

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. When consumed orally in large quantities, laxative effects may occur.[20] If 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.[21]

A number of adverse reactions to mannitol have been reported primarily following the therapeutic use of 20% w/v aqueous intravenous infusions.[22] 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.[23]

LD_{50} (mouse, IP): 14 g/kg[24]
LD_{50} (mouse, IV): 7.47 g/kg
LD_{50} (mouse, oral): 22 g/kg
LD_{50} (rat, IV): 9.69 g/kg
LD_{50} (rat, oral): 13.5 g/kg

15. Handling Precautions

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

16. Regulatory Status

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

17. Pharmacopeias

China, Eur, Int, Jpn, Pol, and US.

18. Related Substances

Sorbitol.

19. Comments

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

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

Mannitol has been reported to sublime at 130°C.[25]

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