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Unlocking the Potential of Pearlitol: A Novel Excipient for Optimized Drug Delivery

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ABSTRACT :

Pearlitol is known for its high compressability in tablet formulation. Mannitol, a naturally occurring sugar alcohol utilized in a variety of industries, including food, cosmetics, and medicines, is marketed under the Pearlitol brand. Pearlitol, a sugar alcohol with several uses, is the component of Pearlitol, a high-performance excipient. Because of its exceptional compressibility, stability, and non-hygroscopic nature, it finds extensive usage in the food, cosmetic, and pharmaceutical industries. Pearlitol is frequently used in pharmaceuticals as a diluent or filler in oral dispersible dose forms, tablet formulations, and capsule formulations. It functions as a cooling, low-calorie sweetener in the food sector, which makes it perfect for diabetic and sugar-free products. Pearlitol is a popular constituent in a variety of formulations due to its wide range of applications, pleasant flavour, and chemical inertness.

INTRODUCTION

Pearlitol is a common osmotic diuretic and one of the naturally occurring alcohols present in fruits and vegetables. This is pleasant and comes in the form of free-flowing granules or a white, odorless crystalline powder [1]. D- Mannitol ((2R, 3R, 4R, 5R)-hexane-1,2,3,4,5,6-hexol), the D-enantiomer of pearlitol can be administered orally or intravenously [2]. It is also used to make chewable tablets because of its low hygroscopicity, sweet flavour (approximately half that of sucrose), and cooling sensation (the solution's heat is -28.9 cal/g at 25 °C) [3]. In tablet formulations, pearlitol is a fairly common excipient diluent (10–90%, w/w) [4]. It has a moderate resistance to heat, is non-toxic, soluble in water, and is not hygroscopic [5]. This is generally recognized as safe and frequently used in solid dosage forms [6]. An additional benefit of using high porosity particles with active pharmaceutical ingredient is that they improve the surface area [7]. In addition, pearlitol is employed as a plasticizer in soft- gelatin capsules, as well as a component of sustained release tablet formulations and for thickening aqueous antacid suspensions of aluminium hydroxide (>7%) [8]. By decreasing the propensity of carbohydrates to crystallize, pearlitol prolongs the shelf life of foods [9]. The direction of the C2 hydroxyl group is the only distinction between sorbitol and pearlitol, which are isomers [10]. As long as catalysts are not available to start the reaction, diluted acids, alkalis, or atmospheric oxygen cannot oxidize pearlitol in its solution form [11].

HISTORY Early Development (1980s)

1. Research beginnings: In the 1980s, Roquette, a French-based company, began researching new excipients for the pharmaceutical industry.
2. Mannitol focus: Roquette focused on Mannitol, a sugar alcohol with known benefits in pharmaceutical applications.
3. Spherical particle development: Researchers developed a process to create spherical Mannitol particles, which would later become Pearlitol.

Launch and Expansion (1990s-2000s)

1. Launch of Pearlitol: In the early 1990s, Roquette launched Pearlitol, a range of spherical mannitol excipients.
2. Initial applications: Pearlitol was initially used in tablet and capsule formulations, providing improved flowability and compressibility.
3. Expansion into new markets: As Pearlitol's popularity grew, Roquette expanded its reach into new markets, including dry powder inhalers and other respiratory applications.

Continued Innovation (2010s-present)

1. New grades and applications: Roquette continued to innovate, introducing new grades of Pearlitol and exploring new applications, such as 3D printing and hot melt extrusion.
2. Regulatory approvals: Pearlitol received regulatory approvals from various agencies, including the Food and Drug Administration and European Medicines Agency
3. Global availability: Today, Pearlitol is available globally, with Roquette's worldwide distribution network ensuring reliable supply and support.

Key Milestones

1. 1985: Roquette begins researching new excipients, including mannitol.
2. 1992: Pearlitol is launched, initially for tablet and capsule applications.
3. 2001: Roquette expands Pearlitol's reach into dry powder inhaler applications.
4. 2015: Roquette introduces new grades of Pearlitol, including Pearlitol SD and Pearlitol 50C.
5. 2020: Pearlitol receives regulatory approvals for use in 3D printing and hot melt extrusion applications[12-13].

METHODOLOGY :

Excipient name : Pearlitol

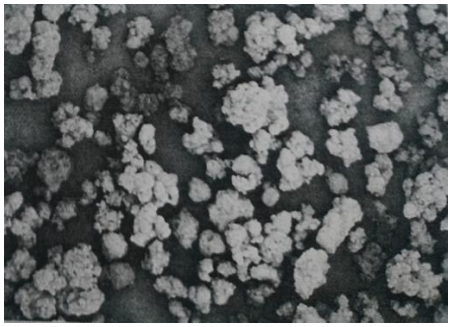
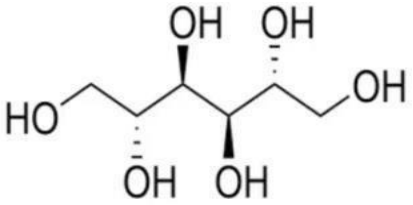


Fig 1 : Pearlitol

Synonyms : Cordycepic acid , Mannogem , manna sugar ,D-mannite ,mannitol

Chemical Properties :

1. **Chemical structure:**



2. **IUPAC name :** (2R,3R,4R,5R)-hexane -1,2,3,4,5,6-hexol
3. **Molecular formula :** C6H14O6
4. **Molecular Weight :** 182.17 gm / mol
5. **pH:** Neutral to slightly acidic in aqueous solutions (5–7)
6. **Stability:** Stable under normal conditions; does not readily oxidize or degrade.
7. **Non-Reducing Sugar:** Does not react with amino groups (useful for Maillard-reaction-free formulations).
8. **CAS registry no. :** 69-65-8 (D-Mannitol) [14-15].

TYPES OF PEARLITOL WITH IT'S GENERAL INFORMATION

Table 1.1 : Types Of Pearlitol With Its General Information[15].

Product name	Main characteristics	specificity	Particle size distribution Dv10µm	Particle size distribution Dv50µm	Particle size distribution Dv90µm
PEARLITOL® 100 SD	Direct compression grades-instant release form	Low reducing sugar content	20	100	185
PEARLITOL® 150 SD	Direct compression grades-instant release form	Low reducing sugar content	60	115	185
PEARLITOL® 200 SD	Direct compression grades-instant release form	Low reducing sugar content	65	150	240

PEARLITOL® 200 GT	Direct compression grades-instant release form	Low capping, higher drug load and improved flowability and tabletability	90	150	260
PEARLITOL SW-F 200	Direct compression grades-instant release form	Wheat free	100	160	260
PEARLITOL® 300 DC	Direct compression grades-instant release form	Wheat free	215	350	500
PEARLITOL® 400 DC	Direct compression grades-instant release form	Wheat free	205	400	615
PEARLITOL® 25 C	Crystaline grades	Wheat free	3.5	24	55
PEARLITOL® 50 C	Crystaline grades	Wheat free	6	55	130
PEARLITOL® 160 C	Crystaline grades	Wheat free	32	160	315
PEARLITOL® ProTec	Direct compression grades-moistur sensitive active ingrediant	Co-processed mannitol dehydrated starch	50	120	200
PEARLITOL® Flash	Direct compression grades- disintrigant for orally disintegrating tablets	Co-processed mannitol starch	80	200	300
PEARLITOL® CR-H	Direct compression grades- controlled release form	Co-processed hydroxypropyl Methylcellulose mannitol	60	140	290

Physical Properties

1. **Appearance :** White, crystalline powder or granules
2. **Taste:** Sweet
3. **Odor:** Odorless
4. **Melting Point:** Approximately 165–169°C (sublimes under vacuum)
5. **Boiling Point:** Decomposes before boiling
6. **Solubility in Water:** Freely soluble (216 g/L at 25°C)
7. **Hygroscopicity**: Non-hygroscopic
8. **Density (Bulk) :** 0.430 g/cm³ for powder
   0.7 g/cm³ for granules
9. **Density (Tap) :** 0.734 g/cm³ for powder
   0.8 g/cm³ for granules
10. **Density (True):** 1.514 g/cm³
11. **Dissociation Constant :** pKa = 13.5 at 18°C
12. **Flash point :** < 150 °C.
13. **Flowability :** Powder is cohesive and granules are free flowing

14. Heat of combustion: 16.57 kJ/g (3.96 kcal/g)

15. Heat of solution: -120.9 J/g (-28.9 cal/g) at 25°C

16. Compressebility:

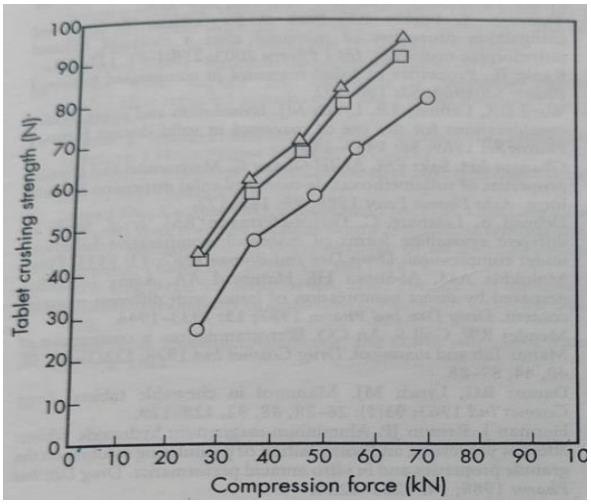


Fig 2: Compression characteristics of granular Pearlitol,

O : Pearlitol 300DC

□:Pearlitol 400DC

▲: Pearlitol 500DC

17. Tablet diameter: 20 mm

18. Lubricant: magnesium stearate 0.7% w/w for Pearlitol 400DC and Pearlitol 500DC; magnesium stearate 1% w/w for Pearlitol 300DC.

19. Osmolarity: a 5.07% w/s aqueous solution is isoosmotic with serum [14-15].

20. Particle size distribution :

Pearlitol 300 DC maximum of 0.1% greater than 500 µm and minimum of 90% greater than 200 µm in size;

Pearlitol 400 DC: maximum of 20% greater than 500 µm and minimum of 85% greater than 100 um in size; Pearlitol 500 DC: maxumum of 0.5% greater than 841 µm and minimum of 90% greater than 150 um in size.Average particle diameter is 250 µm for Pearlitol 300 DC, 360 µm for Pearlitol 400 DC and $20 µm for Pearlitol 500 DC [16]

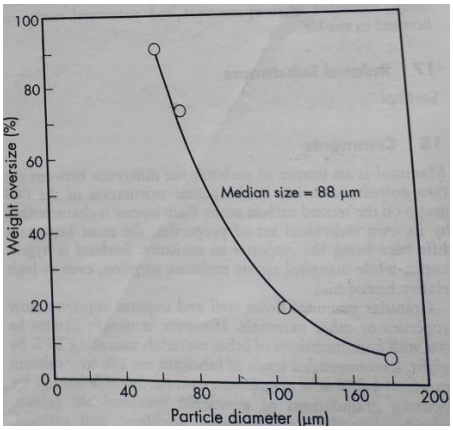


Fig 3: Particle size distribution of pearlitol powder

21. Moisture content:

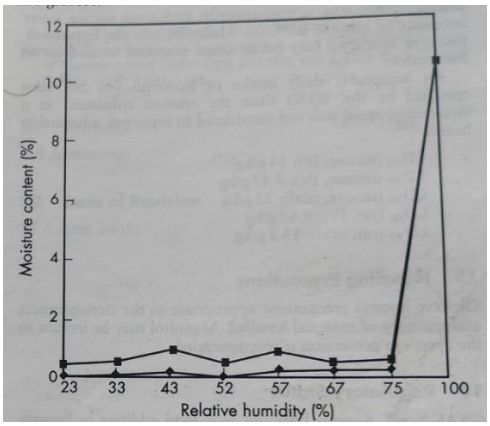


Fig 4 : Sorption-desorption isotherm for mannitol.

▲: Sorption equilibrium moisture

□: Desorption equilibrium moisture

22. Refractive index: n = 1.333

23. Specific surface area: 0.37-0.39 m²/g

24. Solubility:

Table no 1.2: Solubility of pearlitol [14-15]

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

Method of Manufacture

Using hot alcohol solvents, pearlitol can be extracted from the dried sap of manna and/or other specific natural sources. Pearlitol can be made via a variety of chemical, microbiological, and biosynthetic processes, or it can be derived organically from plants. Supercritical and subcritical fluid technologies were widely used to extract mannitol from plant sources [17-18]. In the chemical synthesis approach, D-glucose and D-fructose mixes are hydrogenated to produce pearlitol in the presence of a catalyst [19-20]. D-fructose can be converted directly into D mannitol via the enzymatic approach when malate dehydrogenase is nearby, and formate dehydrogenase can be converted when cofactors such nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate are present [21-22]. In the fermentation method production of pearlitol is done via reduction of different substrates such as fructose, glucose, glycerol, and sucrose via different microorganism strains such as Aspergillus candidus, Lactobacillus intermedius, Candida Parapsilosis, Penicillium [23-24]. Further to increase pearlitol production, engineered strain prepared by knocked out technology such as Lactobacillus lactis, Leuconostoc pseudomesenteroides. S. cerevisiae etc [25-26]. Currently, recombinant strain of Escherichia coli with insertion of other strain genes encoded to increase or facilitate production most commonly employed [27-28].

Functional Category

Diluent; diluent for lyphilized preparations; tablet and capsule diluent, tonicity agent .

Applications in Pharmaceutical Formulation or Technology

Pearlitol is commonly utilized in pharmaceutical formulations and food goods. It is largely employed in pharmaceutical preparations as a diluent (10-90% w/w) in tablet formulations, where it is especially useful because it is non-hygroscopic and so can be used with moisture-sensitive active components [29-30]. Pearlitol can be utilized in direct compression tablet applications [31-32], where granular and spray-dried forms are available, or in wet

granulations [33]. Granulations with pearlitol have the benefit of being quickly dried. Tablet applications include antacids, glyceryl trinitrate pills, and vitamin preparations. Pearlitol is often utilized as an excipient in the creation of chewable tablet formulations because of its negative heat of solution, sweetness, and "mouth feel" [34- 35].

Pearlitol has been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7%),

as a plasticizer in soft-gelatin capsules as a compound of sustained release tablet formulation [36], and as a carrier in dry powder inhalers [37-38]. It is also used as a diluent in rapidly dispersing oral dosage forms [39-40]. It is used in food as a bulking agent. Pearlitol is used therapeutically as an osmotic diuretic, a diagnostic agent for kidney function, an adjuvant in the treatment of acute renal failure, and an agent to reduce intracranial pressure, cerebral edema, and intraocular pressure. Given orally, pearlitol is not absorbed significantly from the gastrointestinal tract, but in doses it can cause osmotic diarrhea.

Handling Precautions

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

Stability and Storage Conditions:

Pearlitol is stable in both dry and aqueous solutions. Filtration or autoclaving can be used to sterilize solutions, and they can be autoclaved multiple times without causing any physical or chemical problems (41). Pearlitol is slightly acidic (pH 6.3), hence it requires additional alkaline components in patented preparations to balance the pH, typically sodium carbonate [42]. Pearlitol solutions (>10% w/v) appear as crystals at ambient temperature, but can be dissolved by increasing the temperature [43]. Pearlitol, for example, has 13% and 18% w/v solubility at 14 and 25 °C, respectively [44-45]. The bulk material should be stored in a well sealed container in a cool, dry location. Pearlitol in solution is unaffected by dilute acids or alkalis, or by oxygen in the atmosphere, as long as no catalysts are present to activate the reaction [46]. Pearlitol in solution is not affected by cold, dilute acids or alkalis, nor by ambient oxygen in the absence of catalysts. Pearlitol does not undergo Maillard browning or caramelization [47] because it lacks a carbonyl group in its structure [48].

Incompatibilities

Potassium chloride or sodium chloride can be used to salinate pearlitol itol solutions that are 20% w/v or more. [49]. There have been reports of precipitation when plastic is exposed to a 25% w/v pearlitol solution [50], as well as sodium cephapirin at 2 and 30 mg/ml. 20% w/v aqueous pearlitol solution cannot be used with this concentration. Pearlitol may form compounds with some metals, such as iron, copper, and aluminum, and is incompatible with xylitol infusion. Pearlitol, which reduces sugar impurities, has been linked to a peptide's oxidative breakdown in a lyophilized form [51]. Cimetidine was discovered to be reduced by pearlitol as opposed to sucrose [52].

Safety

Animals and plants naturally contain pearlitol, a sugar alcohol that is also found in trace amounts in practically all vegetables. If pearlitol is taken orally in large amounts, it may have laxative effects [53]. "Excessive consumption may have a laxative effect" should be written on the product label if it is employed as an agent and daily ingestion of more than 20g foods as a bodying is predictable. Pearlitol is not significantly metabolized after intravenous injection and is only slightly reabsorbed by the renal tubule; approximately 80% of a dose is eliminated in the urine in 3 hours [54]. A number of negative reactions to pearlitol have been documented, mostly after the therapeutic use of 20% w/v aqueous intravenous infusions [55]. Because a far smaller amount of pearlitol is used as an excipient than is used therapeutically, there is a lower likelihood of adverse reactions. However, using pearlitol as an excipient may result in allergic or hypersensitivity reactions. Since the amount of pearlitol used as a sweetener was not thought to pose a health risk, the World Health Organization has not established an appropriate daily dose [56].

Pharmacopeial specifications for pearlitol

Table 1.3 : Pharmacopeial specifications for pearlitol[14].

Test	JP2001	PhEur 2005	USP 28+
Identification	+	+	+
Character	_	+	_
Solution appearance	+	+	_
Melting range	166-169°C	165-170°C	164-169°C
Specific rotation	+137° to +145°	+23° to +25°	+137° to + 145°e
Conductivity	_	≤20 µs.1/cm	_
Acidity	+	_	+

Loss on drying	≤ 0.3%	≤ 0.5%	≤ 0.3%
Chloride	≤ 0.007%	_	≤ 0.007%
Sulfate	≤ 0.01%	_	≤ 0.01%
Arsenic	≤ 1.3ppm	_	≤ 1ppm
Lead	_	≤ 0.5ppm	_
Nickel	+	≤ 1 ppm	_
Heavy metals	≤ 5ppm	_	_
Reducing sugar	+	≤ 0.2%	+
Residue on ignition	≤ 0.10%	_	_
Related substances	_	≤ 0.1%	_
Bacterial endotoxins	_	≤ 4 IU/g	_
Microbial contamination	_	≤ 100/g	_
Assay (dried basis)	≥ 98.0%	98.0-102.0%	96.0-101.5%

CONCLUSION

Roquette created pearlitol, which is a mannitol-based excipient that is well known for its adaptability in industrial, food, and pharmaceutical applications. Because of its superior compressibility, chemical stability, and low hygroscopicity, it is perfect for tablets, capsules, and cutting-edge technologies like hot melt extrusion and 3D printing. Pearlitol's global availability and regulatory approvals have cemented its reputation as a dependable constituent across industries, enabling breakthroughs in formulation design and manufacturing efficiency. Its value in satisfying changing market demands is demonstrated by its ongoing innovation.

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