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Review Article

CHARACTERISTICS AND ANALYTICAL METHODS OF MANNITOL: AN UPDATE

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ABSTRACT

Mannitol is an organic compound, a widely distributed natural sugar alcohol in nature. It is found in various plant species and produced by many microorganisms. Mannitol is about 50% as sweet as sucrose, has a low glycaemic index and inert nature, making it suitable to be used in many food products. Mannitol is an osmotic diuretic administering through the iv route and having many clinical usages and is one of the well-known excipients in many different types of formulations. This is also used to increase the dissolution of drugs having solubility problems. Mannitol can be used as a drug and excipient. The goal of this work was to summarize the important physicochemical properties, mechanism of action, production, applications, incompatibilities, polymorphism, and particularly the analytical methodologies published in the last five decades for quantification. Relevant articles related to analytical methods were identified through a search of the English-language literature indexed in Medline, PubMed, ScienceDirect and google scholar from 1970 to till date. The search terms were benign estimation of mannitol, determination of mannitol, methods for determination of mannitol, HPLC and Spectrophotometry method for estimation of mannitol. The methods described in USP, IP, and BP are also described. The presented review also outlines the further scope of research in the field of development of analytical methods.

Keywords: Analytical methods, Mechanism of action of mannitol, Mannitol, Biosynthesis, Polymorphism

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INTRODUCTION

One of the naturally occurring alcohols found in vegetables and fruits is Mannitol, and it is widely used as an osmotic diuretic [1]. The Joseph Louis Proust discovered mannitol in the year 1806 [2]. This is sweet and available as a white, odorless crystalline powder or free-flowing granules [3]. The *D*-enantiomer of Mannitol, *D*-Mannitol ((2R, 3R, 4R, 5R)-hexane-1,2,3,4,5,6-hexol) (fig. 1) can be used by IV or oral route [4]. The physical properties of Mannitol are given under table 1.

Table 1: Physical properties of mannitol

Properties	Remark		Reference
CAS No.	69-65-8		[1]
Synonyms	*D*-Mannitol, mannite, manna sugar, cordycepic acid, manicol, mannidex, osmitrol, osmosal, resectisol		
Mol formula	$C_6H_{14}O_6$		
Mol. weight	182.17		
Melting Point	166-168 °C		
Boiling Point	290-295 °C		
pKa at 18 °C	13.50		
Solubility (water)	1 gm in ~5.5 gm water, 83 ml alcohol, more soluble water (hot), Insoluble-ether, Soluble-pyridine, aniline, aqueous solutions of alkalies, 1 gm dissolves in 18 ml glycerol		
Solubility (others)	Media	Solubility	
	Ether	Insoluble	
	Pyridine	Soluble	
	Aniline	Soluble	
	Alkalies (Aq.)	Soluble	
	Glycerol	1 gm in 18 ml	

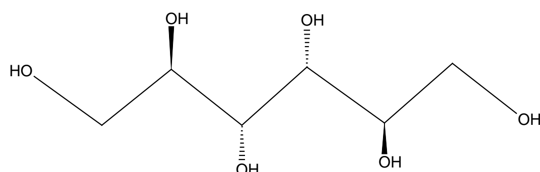


Fig. 1: Structure of mannitol

Some clinical conditions, e. g., acute renal failure and cerebral edema, IV administration of Mannitol induces dieresis [5]. Mannitol is also used in neurology and neurosurgery because of its property of causing dehydration [6]. Mannitol is recommended in increased ocular pressure [7]. This is also used for the assessment of renal function since it is excreted unchanged through the kidneys, thus accumulated in abnormal renal function resulting in cellular dehydration [8]. Mannitol is also known to cause temporary disruption of the blood-brain barrier allowing better penetration of chemotherapeutic drugs [9, 10]. Mannitol is the most used enteric contrast in magnetic resonance enterography due to better depiction, more availability, and lower cost [11]. Mannitol is clinically proved in improving airway function in cystic fibrosis with an acceptable safety profile [12]. The IDPM bronchial provocation test to evaluate bronchial responsiveness in asthma [13].

The market size of mannitol is USD 209.4 million [14] and possibly reaching USD 418.3 million by 2024 [15]. Mannitol is one of the essential medicines in the list of most of countries [16]. Due to its sweet taste (about half than sucrose), low hygroscopicity and cooling sensation (heat of solution is -28.9 cal/g at 25 °C), it is also used in the preparation of chewable tablets [17]. Mannitol is one of the low-digestible sugar with negligible or minimum effect on blood

glucose levels and low calories (1.6 cal/g) is additional advantage, especially for diabetic people [18].

Mannitol is quite common excipient diluent (10–90%, w/w) in tablet formulations [19]. It is soluble in water, non-hygroscopic, non-toxic, and has moderate resistance towards heat [20]. This is generally recognized as safe and frequently used in solid dosage forms [21]. High porous particles increase the surface area, which is an additional advantage due to which, when incorporated with API, water solubility and dissolution rate increases [22]. Other than this, Mannitol is also used for thickening aqueous antacid suspensions of $Al(OH)_2$ (>7%) and as one of the components of SR tablet formulations and plasticizers in soft-gelatin capsules [23]. Mannitol is also a free-radical scavenger, which may be the reason for acting as a neuroprotectant [24]. Mannitol hexanitrate is used in the treatment of hypertension because of its vasodilatory action [25].

Mannitol is slightly acidic (pH 6.3); thus it requires additional alkaline components in proprietary preparations for adjustment of pH and usually, sodium carbonate is used [26]. The solutions of mannitol (>10% w/v), if kept at room temperature, show the appearance of crystals but can be solubilized by increasing the temperature [27]. For example, the solubility of mannitol at 14 and 25 °C is 13% and 18% w/v [28, 29].

Mannitol increases the shelflife of foodstuffs by reducing the tendency of sugars to crystallize [29]. Mannitol and sorbitol are isomers; the only difference is the orientation of the C2 hydroxyl group [30]. The solution form of mannitol is not affected by dilute acids or alkalis, or oxidation by oxygen present in the atmosphere provided catalysts are not present to initiate the reaction [31]. Mannitol does not undergo Maillard browning and caramelization [32] because of not possessing a carbonyl group in its structure [33]. The literature review related to this communication is presented under fig. 2. Relevant articles related to analytical methods were identified through a search of the English-language literature indexed in Medline, PubMed, ScienceDirect and google scholar from 1970 to till date. The search terms were benign estimation of mannitol, determination of mannitol, methods for determination of mannitol, HPLC and Spectrophotometry method for estimation of mannitol.

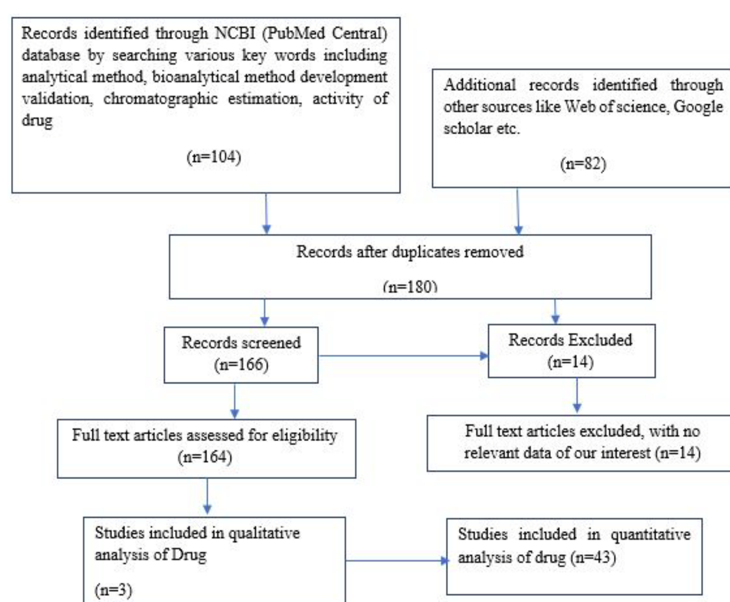


Fig. 2: Data of literature review of mannitol (1970-till date)

Pharmacokinetics and pharmacodynamics

Mannitol, when administered orally, is absorbed poorly by the GI tract and may cause osmotic diarrhea. It should be given parenterally for systemic effect and excreted by kidneys within 30-60 min. Mannitol is not reabsorbed by tubular reabsorption and secretion [34]. About 80% of the given dose is excreted unchanged in the urine in 3 h [34].

After being administered intravenously, it causes a reduction of intracranial pressure by increasing the tonicity of blood plasma. The blood-brain barrier restricts the entry of mannitol, but increased tonicity draws water from the parenchyma of the brain reducing intracranial pressure. This water is then excreted through the kidney in urine and thus mannitol indirectly increases the mild dehydration of brain cells [35]. The tonicity of blood plasma increases by mannitol and draws water into intravascular space from out vitreous humor in the eye causing lowering of intraocular pressure and damage to the retina is prevented [36]. Mannitol along with fluid increased the urine output in fluid overload caused by oliguria. But the usage of mannitol in such cases becomes obsolete since it may precipitate acute tubular necrosis [37]. During excretion it draws water and other toxic materials too, decreasing their concentration in blood [38]. IDH is one of the common symptoms due to a decrease in osmolarity of blood serum. However, the benefit of mannitol in long term for the prevention of IDH is not much clear [39, 40].

Mannitol production methods

There are many methods through which mannitol is either extracted naturally (Plants) or produced via different chemical or microbial and biosynthesis methods. For mannitol extraction from plants sources, supercritical fluid and subcritical fluid technology was extensively employed [41, 42]. In the chemical synthesis method, mannitol production is induced in the presence of catalyst by the hydrogenation of *D*-glucose and *D*-fructose mixtures [43-45]. In the enzymatic method, the conversion of D-fructose directly into D-mannitol allowed in the vicinity of MDH and FDH allowed in presence of cofactors (NADH or NADPH) (fig. 4A, 4B and 4C) [46, 47]. In the fermentation method production of mannitol 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* (fig. 4) [48-53]. Further to increase mannitol production, engineered strain prepared by knocked out technology such as *Lactobacillus lactis, Leuconostoc pseudomesenteroides. S. cerevisiae* etc [54-58]. Currently, recombinant strain of *Escherichia coli* with insertion of other strain genes encoded to increase or facilitate production most commonly employed (fig. 4) [59-61].

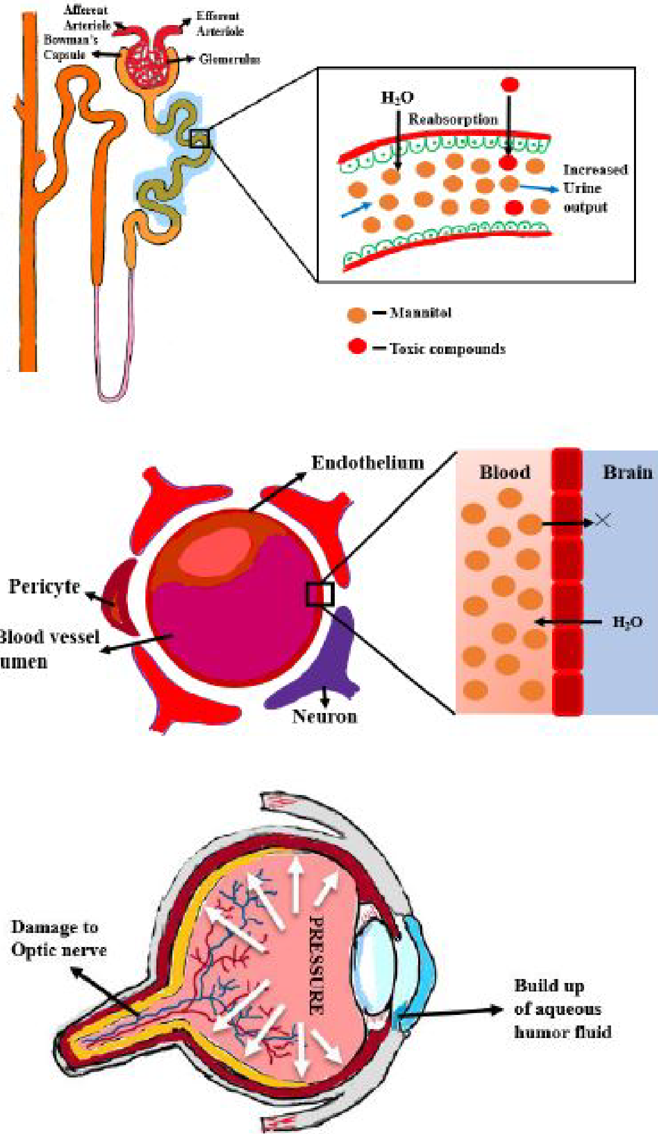


Fig. 3: Mechanism of action of mannitol (a) Proximal convoluted tubules, (b) Blood-brain barrier, and (c) Intraocular pressure (IOP)

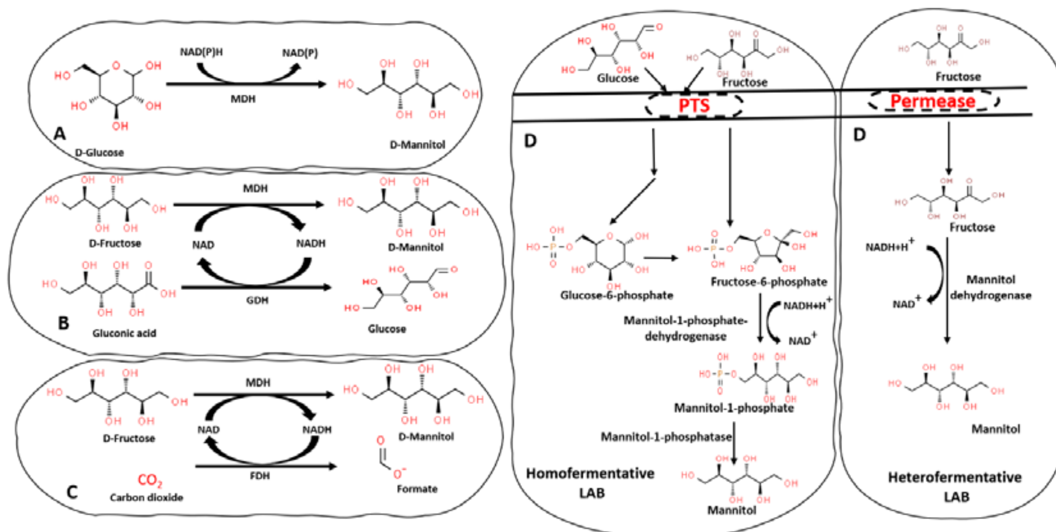


Fig. 4: Production of mannitol

Applications

Mannitol is considered and listed as a GRAS sweetener according to FDA, thus widely used as a food additive in the food industry to mask the bitter taste of ingredients. Its sweetness is about 50-70% that of sucrose with cooling taste due to negative heat of solution. In humans, 75% of the total consumed mannitol's fermentation occurs in the intestinal flora and only 25% is absorbed before urinary excretion. Previous works of literature also suggest that mannitol is prebiotic via altering large intestinal fermentation mechanism and produces more butyrate and propionate amounts [62]. After absorption mannitol, interacts with $NAD^+$and produces fructose and acetyl CoA. In the presence of fructokinase, fructose is converted into the two forms of fructose diphosphates that arrive further at the triose-phosphate cycle for the metabolism of mannitol. So, the overall process is insulin-independent; thus no significant alteration in blood glucose level occurs. In this respect, mannitol can also be used in food products for diabetic people. Mannitol via reducing the crystallization tendency of carbohydrates will also be able to increase the shelf-life of food products [43]. Due to the low hygroscopic nature of crystalline mannitol in the highly humid environment, too, it provides stability to products as additives [49]. However, if daily mannitol intake exceeds above 20 g, it may exert a laxative effect [48].

As already mentioned, that mannitol has low hygroscopic nature, produces negative heat of solution, masks the unpleasant bitter taste of ingredients, and provides sweet, cooling taste, thus most commonly used excipient in granular powders, chewable tablets, and gums [63, 64].

In injectable formulations, mannitol can be employed as a dehydrating agent and as a diuretic in the treatment of glaucoma and hydrocephalic condition. In freeze-dried reconstitution type injection, the addition of mannitol is done as suspending and thickening agent and it also provides antioxidant effects [65]. Hypertonic mannitol solution enhances the permeation of water-soluble drugs and macromolecules in CNS chemotherapy via surging permeability of the blood-brain barrier [66].

Mannitol also works as a strong antioxidant, thus scavenge free hydroxyl radical to reduce the damage against neurological disorders. The free radical activity of particles<10 μm in air pollution, mannitol may reverse the depletion of supercoiled plasmid DNA [67]. In few previous works, Eggleston et al. and Eggleston and Harper (2006) found that mannitol can be used as a sensitive indicator via the enzymatic method (mannitol dehydrogenase catalyst) to determine mannitol deterioration in sugarcane industries [68, 69].

Polymorphism and incompatibility studies

Mannitol shows multiple polymorphic phases, i.e., α, β, δ [70, 71], and all are approved for as carriers of dry powder inhalers [20]. The α form shows the fastest growth rate and its seeds tend to form the same type of polymorph. Whereas, seeds of α or β form appears from β polymorph and α form forms δ polymorph [72-74]. Although the δ form is the least stable, its superior compaction properties increasingly increase its importance as an excipient, particularly for tablet manufacturing. The most thermodynamically stable polymorph is the β-form. The δ form, however, showing the least stability but stable even up to 5 y up to 25 °C under dry conditions [22, 74]. Mannitol shows five different crystal planes; (011), (010), (120), (110) and (210) [75]. The δ form crystals are available commercially and can be used for the preparation of two other polymorphic forms. The α polymorph may be prepared by antisolvent precipitation using acetone and water. The melt crystallization method can be used for the preparation of β form [76].

Cares-Pacheco *et al.*, [77] described α polymorph was found to be the most energetically active form supporting the usage of this form in a dry powder inhaler (DPI), due to its needle-shaped crystalline structure. The Raman spectra of α and β forms are quite similar; only the δ polymorph shows unique peaks helpful in distinguishing from other polymorphic forms. Some of the differences are described in table 2 and structural differences are shown in fig. 5.

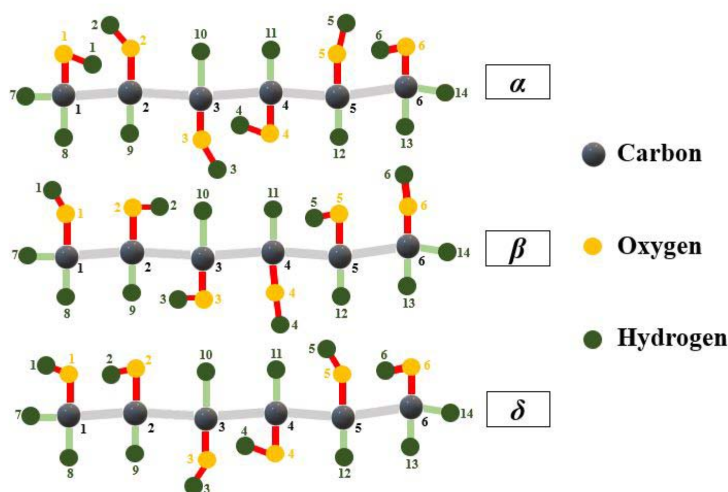


Fig. 5: The structures of polymorphs of mannitol (α, β, and δ)

Table 2: Some differences of properties of polymorphs of mannitol [78, 79]

Properties	α	β	δ
Stability	Intermediate stability	Most stable	Least stable
Types	orthorhombic	orthorhombic	monoclinic
Enthalpy of fusion (kJ mol^{-1})	52.1±0.9	53.5±0.4	52.1±0.9
Raman spectra (single peak)	1030, 1130, 1355 cm^{-1}	876, 1037 and 1136 cm^{-1}	1054 and 1250 cm^{-1}
Shape	Needle fragment, colorless	Lath, colorless	Lath, colorless
Melting point	166 °C	166.5 °C	165.8 °C

Mannitol is neutral towards atmospheric oxygen in catalysts' absence and stable in the dry state [80]. Maillard reaction is a coloring reaction between reducing sugars and amino groups [81] to form Schiff bases, but in the absence of any carbonyl group, mannitol is stable even at the high

temperature and does not generate different flavor and brown color [82]. As a rule, drug excipients are a significant part of a medication item, with the dynamic compound present in generally modest quantities [83]. The incompatibilities are given in table 3.

Table 3: Mannitol incompatibilities with drugs

Drug	Remark/Possible mechanism	References
Atenolol	Hydrogen-bond between the-NH_2 of atenolol and mannitol's–OH/C–H/CH_2 groups	[84, 85]
Acetaminophen	DSC peaks shows interaction with mannitol	[86]
Cimetidine	Transit time in small intestine shortened after administering mannitol tablet and solution	[87]
Granisetron	FTIR and DSC studies shows interaction	[88]
Carbamazepine	DSC studies shows incompatibility with mannitol	[89]
Omeprazole	Variations in ratios of *S*-and *R*-omeprazole sodium	[90]
Sildelafil	API curve changes in DSC possibly due to degradation	[91]
Primaquine	FTIR indicates intermolecular links and possible chemical incompatibility	[92]

Analytical methods

The analytical method should be acceptable for its intended purpose [93]. The scientific basis for the development of formulation is done through information gained during pharmaceutical development. Diluents or excipients are added to form appropriately sized solid dosage forms (e. g., tablets) and constitute a major proportion. They may also be used as a coating material for the protection of undesirable organoleptic properties of drug substances [94]. To obtain data related to quantitation, analytical methods are required. For this purpose, various types of instrumental methods are used for the determination of analytes, e. g., chromatography methods, spectrophotometry methods, electroanalytical methods, and hyphenated techniques are widely used. The available literature also indicates that Mannitol can be determined by using a few of these versatile methods.

The UV spectrophotometry, IR, and H^1 NMR graphs of mannitol are shown under fig. 6, 7, and 8, respectively.

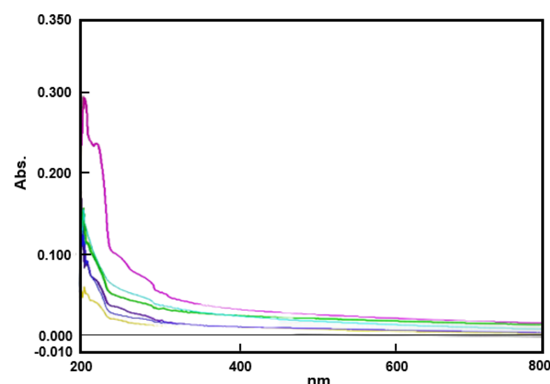
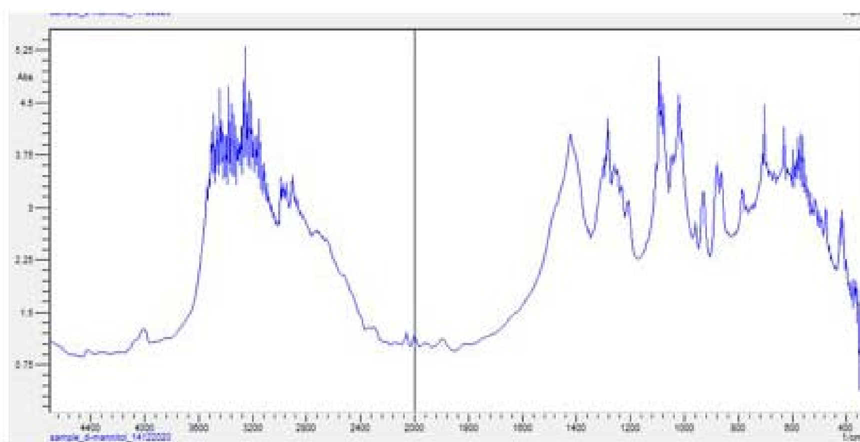


Fig. 6: Overlay UV spectra of mannitol (1,5,10,20,50,100 µg/ml



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	729.12	0.5199	0.0452	738.77	724.30	7.0976	0.3229
2	814.00	1.0543	0.1566	829.43	811.10	15.3676	0.5384
3	863.18	0.7586	0.0599	869.93	861.25	5.7817	0.1597
4	1026.17	1.3963	0.6989	1046.43	997.24	45.5220	11.5213
5	1160.23	2.1193	0.0625	1173.73	1158.30	29.3558	0.2105
6	1279.82	2.3812	0.0208	1280.79	1276.93	9.1095	0.0331
7	1366.62	1.0011	0.0122	1367.59	1328.05	34.0475	-0.5609
8	1507.43	2.6086	0.7792	1529.62	1478.50	113.4755	19.8940
9	1601.95	2.1741	0.5821	1613.52	1592.31	38.8954	5.6685
10	2471.88	0.6828	0.0015	2473.81	2197.02	162.9167	-1.5407
11	2971.47	1.0175	0.0395	2990.76	2956.04	34.5986	0.6601
12	3507.70	1.4769	0.3241	3555.92	3479.73	93.7151	9.2944

Fig. 7: IR spectra of mannitol

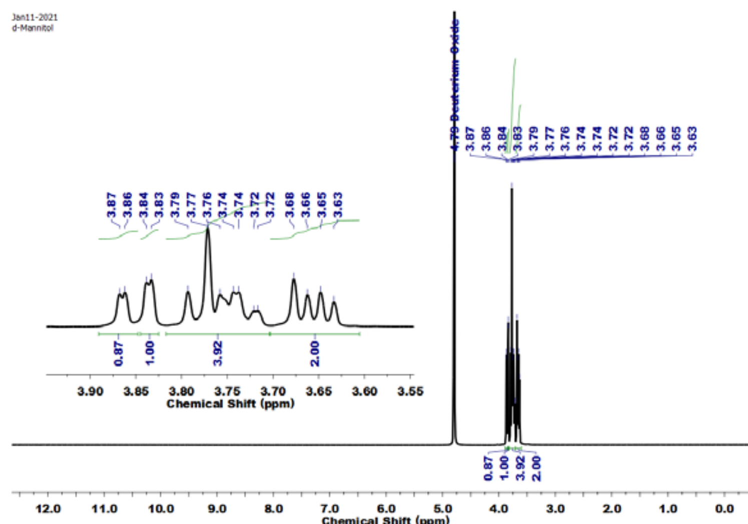


Fig. 8: H-NMR of mannitol

Spectrophotometry methods

Spectrophotometry is a widely accepted analytical technique in the pharmaceutical industry for different analytical processes. The applications of spectrophotometry are expanding all the time [95].

Mannitol was also determined by using an enzyme for successful estimation by UV spectrophotometry. For this, mannitol dehydrogenase was used by many researchers. A few microorganisms like *Pseudomonas fluorescense* and *Rhodobacter sphaeroides*, *Thermotoga maritima,* and *Thermotoga neapolitana* are known to produce mannitol dehydrogenase. These enzymes convert mannitol into fructose in the presence of Nicotinamide adenine dinucleotide (NAD+), an essential cofactor that participates in fundamental biological processes. The reduced form of NAD+absorbs light in the UV region and can be measured at 340 nm [96]. The absence of chromophore in the chemical structure is a possible reason for the absence of direct spectrophotometry analysis. This is also evident by scanning dilutions in the UV visible range (fig. 6).

The spectrophotometry methods published in various sources are presented in table 4.

Chromatography methods

The complex samples require separation of analyte first before final analysis and this is well evident that chromatography methods are the most suitable methods for the same. Currently, many different chromatography methods are available, classified mainly based on the mobile phase [105].

The published chromatography methods are given in table 5.

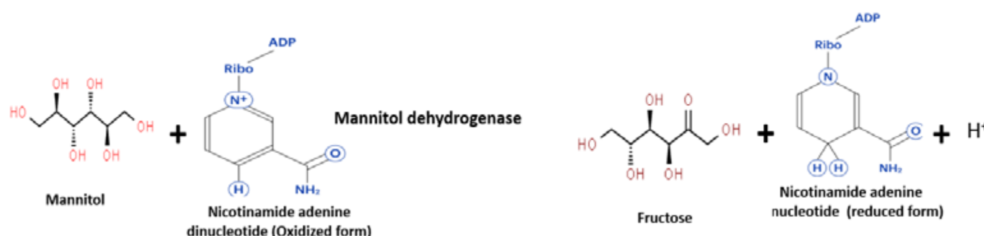


Fig. 9: Reaction of mannitol with NAD+in the presence of mannitol dehydrogenase

Table 4: Summary of spectrophotometry methods of mannitol

Method	Source of enzyme	wavelength	Application	Reference
UV	*Lactobacillus brevis*	340 nm	Serum samples (dogs)	[97]
UV	*Lactobacillus brevis* or *Leuconostoc mesentroids*	340 nm	Determination in urine	[98]
UV	*Agaricus bisporus*	340 nm	Determination of mannitol in polysaccharides and glycoproteins	[99]
Fluorometric assay	-	λex = 350 nm and λem = 460 nm	Fungal and mycorrhizal extracts	[100]
UV	-	λ_{ex} = 340 nm and λ_{em} = 455 nm		
UV	*Leuconostoc mesenteroides*	340 nm	human blood or serum	[101]
UV	*Leuconostoc mesenteroides*	340 nm	Determination in juice of sugarcane	[69]
UV	*Mannitol dehydrogenase.*	340 nm	lactulose–mannitol ratio in urine	[102]
UV	*Mannitol dehydrogenase*	340 nm	Urine	[103]
UV	*Mannitol dehydrogenase*	340 nm	Urine	[104]

Table 5: Summary of chromatography methods for mannitol

Method	Detector	Column	Conditions	Application	Reference
GLC	FID	0.61 m × 0.32 cm. (2 ft. × 0.125 in.) OD, stainless steel column	Column (isothermal), injector and detector temperature 175, 175, and 260 °C	Sorbitol and mannitol in aqueous solutions	[106]
GC	FID	Glass columns (Borosil), 1.22 m × 0.64 cm OD	Isothermal, Temperature: detector, 220°, injection port, 240°. His flow rate 55 ml/min, inlet pressure 40 psi.	Sorbitol and Mannitol in Pharmaceuticals	[107]
GC	MS	Glass columns (6", 1/3'), packed with 3% OV-255	Temperature: Injection port, 250 ° C and column, 212 ° C.	Quantification in CSF with six other sugars	[108]
GC	FID	9 ft × 2 mm, packed with Silar 10C, Chromosorb W/AW (10%)	Temperature: Column, 200 °C; injector, 250 °C; detector, 330 °C; N_2 flow 20 ml/min	with two other sugars in chewing gum and sorbitol in mints	[109]
HPLC	RI	Sugar Pak I (30 cm × 6.5 mm) i.d., 85 °C, pre-column filter	Mobile phase: H_2O, Flow: 0.4 ml/min	Analysis with four other sugars	[110]
HPLC	RI	3/8 in. × 2 ft and 10 µm (end fittings)	Mobile phase: Water-methanol (65+35), flow rate, 2.0 ml/min (800 psig); 55 °C	In chewing gums and confections with two other sugars	[111]
GLC	MS	Glass column (1 m × 2-mm i.d.) packing, OV-17 (3%)	Ionization curr, 300 µA; Ionization nrg, 70 eV; accelerating volt, 3.0 kV; Temperatures: injector, 280 °C, column, 270 °C, ion source 250 °C. Ion multiplier voltage: 1.2-1.4 kV.	With sorbitol (in plasma)	[112]
GC	MS	Glass column, 1.5 m × 2.0 mm (i.d.), packing 3% SP-2340 (75:25, cyanopropyl: methyl silicone gum, 100/120 mesh).	Isothermal; 70 °C/1 min, then 270 °C, 12 °C/min	With 7 other carbohydrates in serum	[113]
HPLC	Differenti al RI	Column.-300 mm × 7.8 mm, 8% crosslinked cation exchange	Mobile phase: H_2O, flow: 1.0 ml/min	With 2 other carbohydrates in meat products	[114]
GC	MS	Glass columns (1 m × 4 mm I.D.) packing, 3% Dexsil-400 or with 1: 1, 3% OV-l/OV-17. temperature, 210 °C	Injection port 20 kPa (Pressure), flow 1.1 ml/min. Split ratio 10:l. EI 70 eV	With 2 other carbohydrates in small tissue samples	[115]
GC	FID	DB-5 capillary, 15 m × 0.53 mm (i.d.)	Temp: Injection 220 °C, detection 300 °C, flow 9.7-9.9 ml/min	Ratios of lactulose/mannitol excretion in urine	[116]
HPLC	RI	300 × 6.5 mm, Sugar Pak I	Mobile phase: water, with calcium (1 ml/l, 50 g/l Ca-EDTA), flow 0.5 ml/min, 85 °C	Lactulose/mannitol ratio	[117]
GC	FID	Capillary, 17 m × 0.25 mm i.d., coating, 0.25 µm OV-17, fused silica	Detector and injector at 300 ℃. The oven temperature programmed 120 to 140 °C.	Lactulose-mannitol pair in urine	[118]
GC	MS	Capillary, 30 m × 0.25 mm fused silica–50% phenyl, 50% methyl polysiloxane, 0.25 µm film thickness	Injector temp 250 °C, oven 150 °C	In CSF and plasma with 7 other moieties; 1,5-anhydrosorbitol, ribitol, arabitol, myo-inositol, xylitol, galactitol and. sorbitol	[119]
GLC	FID	Capillary, 60 m × 0.32 mm ID. fused silica	Detector temperature, 350 °C; injector temperature, 250 °C; Min flow-rate was 75 ml/min	Urinary lactulose and mannitol	[120]
HPLC	Ampero metry	4 mm ID×50 mm, Dionex	Mobile phase: 500 mmol, 0.4 ml/min	Xylitol, sorbitol and D-Mannitol in foods	[121]
HPLC	Ampero metry	250×4.0 mm I.D., 8.5 µm particle size, anion exchange	480 mmol NaOH, flow-rate: 0.4 ml/min.	Lactulose/mannitol ratio in urine	[122]
HPLC	Ampero metry	Carbopac, 4×250 mm, Anion-exchange	Mobile Phase: NaOH 160 and $Zn(CH_3CO_2)_2$ 0.196 mmol/1, flow 1.0 ml/min	Mannitol and disaccharides in serum	[123]
HPLC	Ampero metry	Anion exchange-Dionex PA-10 and PA-100	Mobile phase: NaOH (0.1 M); flow, 1.0 ml min^{-1}	Mannitol and lactulose-human urine	[124]
HPLC	Photomet ry	Supelco TPR-100, 15 cm×4.6 mm I. D	Mobile phase: 2 mmol Na molybdate and 50 mmol HNO_3 (pH 1.4) flow 0.8 ml/min, 600 nm.	D-mannitol and D-sorbitol in foodstuffs	[125]
GC	MS	30m×30.25 mm I. D, HP-5 fused-silica capillary, coating-0.25 µm 5% phenyl methyl silicone	Both injection port and transfer line 280 °C, column head pressure 50 kPa. Ionization nrg 70 eV.	In human brain tissues	[126]
HPLC	UV	C_{18} (250 mm × 3:0 mm i.d., 5 µm	75% ACN-water (0.05% TFA, 0.05% heptafluoro-n-butyric acid and 0.1% triethylamine), 0.5 ml/min; λ = 260 nm	With glycerol in human tissues	[127]
HPLC	RI	Amino column Nucleosil 250 × 4.6 mm id	Mobile Phase: ACN: H_2O (7:3, v/v), 1 ml/min	With lactulose in urine	[128]
HILIC	ELSD	250 mm×4.6 mm ID, 5 µm, Gel Amide 80	Mobile Phase: 75:25 (ACN: 0.1% TFA in H_2O), flow 1.0 ml/min	In pharmaceutical formulations	[129]
HPLC	MS/MS	250 mm × 2.1 mm, 5 µm	Mobile Phase: 75% ACN/25% 5 mmol of ammonium acetate in H_2O to 40% ACN/60% 5 mmol of ammonium acetate in H_2O (pH = 6.84) 10 min	With lactulose and sucrose in human urine	[130]

HPLC	RI	Amino column (250×4.6 mm,5 µm)	Mobile Phase: ACN: H_2O (86: 14) 1.0 ml/min	Mannitol in Bailing capsules	[131]
HPLC	CAD	Amino, packing, 5 µm shell particles (4.6×250 mm)	Mobile Phase: (Gradient) ACN and H_2O	With 7 other carbohydrates	[132]
HPLC	PAD	Anion exchange column (Pellicular resin), 250×4.0 mm i.d. Temperature 30 °C	Mobile Phase: 480 mmol/l NaOH, flow 0.4 ml/min	Lactulose: mannitol ratio	[133]
LC	MS-MS	150×2.1 mm 100 A aminopropylsilane Restek column, 3 µm, temperature 40 °C	Mobile Phase: (Gradient) 0.1% HCOOH: ACN, flow 0.30 ml/min		
GC	FID	Capillary, 30 m × 0.25 mm (HP-5MS)	Mobile Phase: EtOH: H_2O (80:20), Injector 280 °C, detector 300 °C	With *myo*-inositol and sorbitol in roots of olive tree	[134]
IC	PAD	Column: 4 mm × 250 mm	Mobile Phase: 480 mmol NaOH eluent	Mannitol, sorbitol and glucose-containing powders	[135]
LC	MS/MS	C_{18} column (2.1 mm × 100 mm, 3.5 µm)	Mobile Phase: (Gradient) 10 mmol aq. NH_4HCO_2 buffer (pH 3.5): ACN. Flow: 0.4 ml/min	In human urine with glycerol	[136]
LC	MS/MS	Amino column, 150 × 2 mm, 5 μm 100 A	Mobile Phase: ACN: H_2O, flow 300 μl/min	Urinary lactulose and mannitol	[137]
HPLC	RI	Sugar SP0810 (300 mm × 8.0 mm i.d.) column	Mobile Phase: H_2O, flow 0.5 ml/min	In dessert foods with erythritol, sorbitol, isomalt and xylitol	[138]
UPLC	MS/MS	Amide 1.7 µm, 2.1× 50 mm	Mobile Phase: (Gradient) ACN and H_2O, flow 200 µl/min	Urinary lactulose/mannitol ratio	[139]
HPAE	PAD	Anion-exchange column (4×250 mm)	Mobile Phase: 450 mmol NaOH, flow 0.4 ml/min	Urinary lactulose/mannitol ratio	[140]
LC	MS/MS	Restek Ultramino 150 ×2.1 mm (100A aminopropylsilane), 3 µm	Mobile Phase: (Gradient) 0.1% HCOOH and ACN (+0.1% HCOOH), flow 0.30 ml/min		
LC	MS/MS	Amide (2.1 mm × 50 mm, particle size 1.7 µm)	Mobile Phase: ACN: H_2O: NH_4OH (73:27:0.1, v/v), 0.2 ml/min.	Nonradiolabeled [$^{13}C_6$]mannitol	[141]
HPLC	MS/MS	Amino, 4.6 × 250 mm, 5 µm,	Mobile Phase: 70:30 ACN/10 mmol NH_4. Ac	In Chinese medicine with sorbitol and galactilol	[142]
HPLC	RI	Cation exchange resin (Ca form) (0.3 m long, 7.8 mm ID) [85 °C±1 °C]	Mobile Phase: H_2O, 0.5 ml/min	Bulk	[143]
HPLC	RI	(4 × 25) mm, L19 packing, 9 µm, between 30-85 °C±2 °C	Mobile Phase: H_2O, 0.5 ml/min	Bulk	[144]
HPLC	RI	30 cm ×7.8 mm, mm packed with strong cation exchange resin (Ca form) 9 µm	Mobile phase: H_2O, 0.5 ml/min	Bulk	[145]
GC	FID	6 ft × 32 mm I.D. 1/4 in, Glass packed column	Temperature: Detector, 280 °C, injector 250 °C, initial column temp 220 °C. N_2 (carrier gas) flow rate 30 ml/min	Lactose Mannitol ratio in urine	[146]
GC	FID	Fused 15 m×530 mm, I.D. silica capillary column	220 °C detector and injector temperatures. He (carrier gas) 10 ml/min		
HPLC	ELSD	C_{18}, 300 mm × 6.5 mm i.d.) 10 µm	Mobile Phase: water, 0.5 ml/min	Lactulose and mannitol in urine	[147]
HPLC	RI	CHO-620 cation-exchange column, Temp 85 °C	Mobile Phase: water, 0.4 ml/min	With 5 other sugars in human urine	[148]

Other methods

The alpha and delta polymorphs of mannitol are common contaminants and the beta form is usually used in pharmaceutical preparations. FT-Raman spectroscopy was utilized for quantifying beta form in the presence of a mixture of beta and delta mannitol [149].

A method based on CE equipped with electrochemical detection without derivatization has been developed for sucrose, glucose, mannitol, and fructose estimation in Ligustrum lucidum [150].

Another CE method was developed to detect lactulose and mannitol in urine after oral administration to estimate the intestinal permeability in type I diabetes patients [151].

The CE method for the determination of xylitol, sorbitol, and mannitol as anionic borate–polyol complexes is also performed. The selected wavelength was 215 nm [152].

Quantitative estimation of polymorphs of mannitol by FT-Raman spectroscopic data using both partial least-squares (PLS) regression as well as artificial neural networks (ANNs) performed by Braun et al. [153]

Since mannitol is excreted unchanged through urine in normal pathological conditions, thus for sugar intake can be used as a reference compound. One of the recent research is the determination of sucrose, lactulose, and mannitol in urine by using NMR spectroscopy [154].

DISCUSSION

The history of analysis of Mannitol from 1970 onwards started with Gas-liquid chromatography methods. Gas Chromatography (GC) has incontestable to be a flexible and sensitive analytical technique for comprehensive chemical characterization of food samples [155]. The analytical methods discussed here are also presented in fig. 10.

Various available methods are based on this technique based on either MS or FID detector systems. The FID detectors are commonly used for the analysis with the GC system. The utilization of these two detectors may be due to their proven application in food authenticity. Mannitol is a widely distributed sugar alcohol in nature, and FID detectors are sensitive and have a wide linear range making it suitable for determination [156]. Whereas MS detectors overcome the problem related to detection limits because of their high resolution and specificity [157].

The same pattern was observed in the case of mannitol determination based on GC. Methods based on FID were mostly

applied for the determination of other sugars or lactose-mannitol ratio, whereas complex samples, e. g., plasma or serum, GC system based on MS detectors.

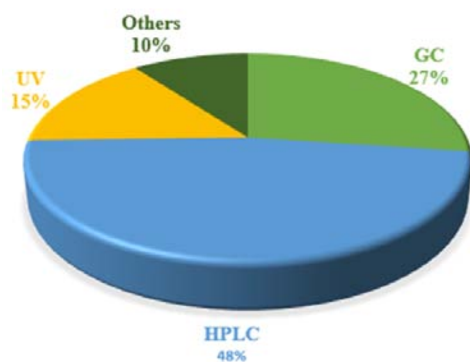


Fig. 10: Available analytical methods for mannitol (1970-till date)

Spectrophotometry is a fundamental technique in many areas of science, with many applications and uses [158]. Various spectrophotometry methods are available for analysis, particularly the lactose-mannitol ratio in urine. However, chromatography methods are also available for the same applications but spectrophotometry is an easy and economical technique. The only factors that limit the usage of the latter are sensitivity and the capability to analyze complex biological samples.

The requirement for better strategies for analysis is normal because of new requests like information and the prerequisites to break down a variety of new types of samples. Many older HPLC techniques can be altered and improved to incorporate new prerequisites and additionally new capacities [159]. Basic measurements for analytical scale columns are in the range of 10–30 cm long and 4–10 mm i. d and smaller dimensions are most efficient and have the advantage of the speed and minimal solvent consumption [160].

The method developed by Yada *et al.* [121] published in the year 1996 also utilizes a short column based on amperometry detection, as claimed by the research group, is about 1000 times more sensitive than all previously HPLC equipped with RI detectors and GC-FID methods. The UPLC method developed by Gervasoni and co-researchers [139] used a column (50 mm length) that separated mannitol and lactulose in just 5 min. Another recent UPLC method for labeled isotopes of mannitol and sucrose simultaneously in brain and plasma with a total run time of 6 min [141].

The intestinal permeability (IP) test is a reasonable, precise strategy for assessing the integrity of the gastrointestinal mucosa without utilizing invasive strategies such as radiology or endoscopy [161]. The utilization of 51Cr EDTA does not generally ensure dependable outcomes since the utilization of a solitary molecule can recognize changes not identified with the penetrability alterations [162].

The assessment of intestinal permeability dependent on the evaluated assimilation of two sugars of various sizes gives more data and higher sensitivity than utilizing solitary sugar. In a physiological condition, the rate of absorption is about 10% for mannitol and under 1% for lactulose. The deficiency of mucosal integrity ought to cause an increment of lactulose retention with a subsequent increment of lactulose-mannitol proportion in the sample of urine [163].

Diverse laboratory methods have been proposed for the measurement of mannitol and lactulose in urine, such as spectrophotometric [102] and enzymatic [69, 97-9, 101-3] methods, gas chromatography [116, 118, 120, 146], and high-performance liquid chromatography [117, 122-23, 128, 133, 137, 139-40, 147].

One of the recent trends in Green Analytical Chemistry is developing straightforward and low-cost ways for the qualitative and/or quantitative determination of various analytes [164]. The aim is to minimize the usage of chemicals and overall energy consumption, analytical waste management, and safety of analysts [165].

In the case of mannitol, various analytical methods reported are presented in the section above. Various spectrophotometry, chromatography, electroanalytical and other methods are available for determination. In most of the analytical methods, water plays an important role as a diluent or mobile phase because of the solubility of mannitol in it. A few chromatography methods are based on non-aqueous phases in some proportion. Proper automation, high pressure, and reducing column sizes and speed maybe some of the approaches for the development of better eco-friendly analytical methods.

CONCLUSION

Mannitol is a drug as well as one of the popular excipients for many formulations. This is poorly absorbed from the intestine and can be used as a sugar substitute for diabetic patients because of its sweet taste. There are many spectrophotometry and chromatographic methods developed and validated for the determination of mannitol in different matrices. The spectrophotometry and chromatography methods are given in Tables 4 and 5 respectively. Mannitol is an aliphatic compound without any aromatic rings which cannot be easily measured under the UV spectrophotometry method. Most of the spectrophotometry methods developed are based on the enzymatic conversion of mannitol into a suitable form for successful determinations. These methods are tedious, requiring additional culture of enzyme, and are time-consuming. Mannitol can be determined by using any other chemical reactions, e. g., coupling with any dye with simple ionic interactions like in acid dye methods or addition of aromatic moiety like benzene in its structure, making it feasible to be identified under UV spectrophotometers. Although some of the chromatographic methods, e. g., HPLC methods, are based on the aqueous mobile phase, these methods are expensive, time-consuming, and require a specific type of columns. In addition, a few reported methods use non-aqueous phases also in mobile phases in some proportion. Researchers should also think about the utilization of green analytical chemistry for mannitol for faster, easy, economical analytical methods safer to analysts as well as to the environment.

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ABBREVIATIONS

United States Pharmacopoeia (USP), Indian Pharmacopoeia (IP) and British Pharmacopoeia (BP), Inhaled dry powder mannitol (IDPM), Intradialytic hypotension (IDH), Mannitol Dehydrogenase (MDH), Formate Dehydrogenase (FDH), Nicotinamide adenine dinucleotide (NAD), Nicotinamide adenine dinucleotide phosphate (NADP), Generally Recognized as Safe (GRAS), Central Nervous System (CNS), Dry powder inhaler (DPI), octadecyl (OD)

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CONFLICT OF INTERESTS

No potential conflict of interest was reported by the authors.

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