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Optimization of Highly Porous Mannitol Preparation using Ammonium Bicarbonate and Citric Acid as Templating Agents with Spray Drying Technique

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Abstract: This study investigates the effect of ammonium bicarbonate and citric acid as templating agents using spray drying techniques to improve the porosity of D-mannitol powder. It has been shown that textural properties, such as surface area and pore volume produced, are affected by the type and concentration of templating agents, inlet temperature, and outlet temperature of spray drying. The structure of mannitol powder produced changes considerably due to the change in its textural properties to particle powder with high porosity, surface area, and pore volume. The results show that the ratio of D-mannitol to ammonium bicarbonate 10:5 w/w% with water solvent temperature of 30°C, spray drying inlet temperature of 120°C, and spray drying outlet temperature of 70°C, resulting in the highest porosity, surface area, and pore volume. The surface area of mannitol increased by 3 fold, followed by an increase in pore volume by 5.45 fold and pore diameter by 1.52 fold. The results of the scanning electron microscope (SEM) are consistent with the results of the surface area measurement using the Surface Area Analyzer (SAA). The resulting spray-dried mannitol powder with a high specific surface area allows it to be used as an excipient in solid formulations of oral preparations.

Keywords: D-mannitol, porous mannitol, templating agent, ammonium bicarbonate, citric acid

1. INTRODUCTION

Mannitol is a versatile excipient that can be engineered to meet the diverse formulation development needs of pharmaceutical dosage forms [1]. In the last decade, the use of mannitol as an alternative to fillers/binders in solid formulations of oral preparations has increased significantly. Its non-hygroscopic nature with low moisture content and high solubility in water (216 g/L) makes mannitol a desirable excipient, especially for moisture-sensitive active substances [2], [3]. Mannitol has also been used as a diluent in the tableting process in direct compression and wet granulation [4].

Although mannitol is water soluble, it has a small specific surface area and pore volume that allow drug loading into mannitol to be low [5]. Therefore, it is necessary to engineer mannitol powder by changing particle morphology and increasing surface area and pore volume to increase the capacity of active drug substances. Engineering mannitol into highly porous particles can provide advantages, including increasing the amount of drug confined to the internal cavity of porous excipients, increasing the rate of drug release into the dissolution medium, increasing the

rate of drug adsorption, and producing uniformity of levels and doses given by controlling the particle size of drugs and excipients in dosage forms [5]. In addition, increasing the porosity and surface roughness of particles can increase tablet crushability by promoting the bonding mechanism between solid surfaces in compact agglomerates [6], [7].

The templating agent is a material added in the process of making porous particles to maximize the formation of pore structures. The use of templating agents promotes some advantages, including producing uniform pore size and structure, good pattern repeatability, easy organization, having many template variations, and easily removing templates by solvent or calcination [8]. Many materials can be used as templating agents, including surfactants, sucrose, lactose, citric acid, and ammonium bicarbonate. Pang et al. [9] examined the effect of citric acid, malic acid, tartaric acid, and lactic acid as templating agents in the preparation of mesoporous silica and found that the higher the concentration of templating agents increased the diameter and volume of pores. Then, the templating agent needs to be removed by washing the spray-dried powder with ethanol to produce porous powder [10].

Previous studies by Ebrahimi et al. and Saffari et al. [11]–[13] successfully developed highly porous organic powders using the spray drying technique based on a templating concept. The preparation of highly porous particles using the spray drying technique is ideal for preparing particle carriers since it allows the formation of spherical particles and has the advantages of being able to produce products with high quality, easy to control, and fast drying process [14], [15]. Therefore, we developed particle engineering through the spray drying technique to increase the internal porosity and surface area of D-mannitol using ammonium bicarbonate and citric acid as the templating agents. Previous studies have shown that ammonium bicarbonate as a templating agent can form pores and does not leave residue on the spray-dried powder [16], [17], while templating agent with citric acid requires washing using ethanol can remove citric acid residue and produce porous powder particles [5].

The selection of templating agent optimization using citric acid and ammonium bicarbonate is based on previous research, indicating that citric acid and ammonium bicarbonate templating agents have succeeded in producing high pore volume and leaving no residue in the final mannitol mesopore [14], [17]–[21]. This study aims to optimize the effect of inlet temperature and outlet temperature on the results of D-mannitol porosity. The selection of inlet temperature and outlet temperature is based on the theory presented by Peng et al. [17].

2. MATERIALS AND METHODS

2.1. Materials and Instruments

D-mannitol, Ammonium Bicarbonate, and citric acid were obtained from Merck, Germany. Meanwhile, solvent ethanol pro analysis was obtained from E. Merck. The instruments used in this research include a stirrer (Stuart Hotplate Stirrer CB162), analytical balance (Ohauss PA 214), Spray Dryer (Buchi Mini Spray Dryer B-290), SEM (JSM-6510LA), and Quadrasorb Evo surface area analyzer (Boynton Beach FL).

2.2. Preparation of Mannitol Mesopore

Mannitol mesopore was prepared by dissolving D-mannitol with citric acid or ammonium bicarbonate and 100 mL of deionized water using a stirrer for 20 minutes (Table I). The solution was then dried using a Buchi B-290 spray dryer, 100% aspirator, 8 mL/min pump rate (25% of the maximum rate), 50 mBar pressure, and 12 L/min dispersion air flow rate. The spraydried powder

was collected and stored in a desiccator. The water content of the spray-dried powder was calculated by weighing the spray-dried powder before and after the drying process in an oven at 105°C for 4 hours [23].

Table 1. Design of mesoporous mannitol using literature approach [15], [16]

No.	Amount of D-mannitol (g)	Amount of citric acid (g)	Amount ammonium bicarbonat (g)	Spray dryer inlet temperature (°C)	Spray dryer outlet temperature (°C)
1.	15	2	-	170	100
2.	15	2	-	150	80
3.	10	1	-	150	80
4.	10	1	-	170	100
5.	10	-	5	120	70
6.	10	-	5	150	80

2.3. Removal of Citric Acid Templating Agent

To produce porous mannitol, the citric acid templating agent in the spray-dried powder was removed using a previously reported method [10], [23]. The removal method of the citric acid templating agent was carried out by mixing 1 g of dry powder from the spray dryer with 40 mL of ethanol using a stirrer at 600 rpm for 24 hours at room temperature of 25°C until the citric acid was completely dissolved into ethanol. Furthermore, the filtrate was filtered using a vacuum filter. Finally, the filtrate was oven-dried at 40°C [23]. The research conducted by Pang et al. and Saffari et al. [9], [11], [13] show that washing citric acid using ethanol at a ratio of 1 g:40 mL has produced mesoporous mannitol without ethanol residue in the final powder.

2.4. Characterization of Porous Mannitol

2.4.1. Scanning Electron Microscopy (SEM)

Morphological shape testing was carried out on D-mannitol and optimum mesoporous mannitol. The samples were prepared by platinum plating for 130 seconds and were observed using SEM at an accelerating voltage of 5 kV with several magnifications until appropriate morphological images were obtained.

2.4.2. Surface Area Analyzer (SAA)

The spray-dried mannitol powder was tested for surface area, pore volume, and pore diameter using a Quadrasorb evo surface area analyzer (Boynton Beach, FL). The samples were vacuumed for 16 hours before the measurement using nitrogen gas sorption and desorption techniques. Specific area, pore size, and pore volume were calculated based on Brunauer-Emmet-Teller (BET) analysis.

2.5 Statistical analysis

All data were expressed as mean ± standard deviation (SD). Computerized data were statistically described using Microsoft Excel v.10.0 (Microsoft, USA).

3. RESULTS AND DISCUSSION

3.1. Yield from Spray Drying

The spray-drying mannitol using ammonium bicarbonate as a templating agent yielded a greater yield than citric acid as a templating agent (Table II). Furthermore, the highest yield was obtained in the mixture of 5% ammonium bicarbonate and 10% D-mannitol dried at an inlet temperature of 120°C and an outlet temperature of 70°C. The spray-dried mannitol with citric acid

as a templating agent experienced stickiness during the spray-drying process. This study found that very wet particles stuck to the walls of the dryer. This is in line with [24], explaining that the particle attachment to the dryer wall is a phenomenon in small-scale spray drying. Direct deposition of wet or semi-dry particles on the drying chamber walls is the main reason for low spray drying yields on a small scale, where the chamber walls are usually very close to the atomizer [13], [24]. Under these conditions, the droplets tend to hit the wall directly, causing the wet particles not to have enough time to dry completely. Another reason may be lowering the glass transition temperature, which can lead to sticky particles. The decreased wall deposition can explain the higher yield of the spray drying process during spray drying due to the effective encapsulation properties, which remain non-sticky due to the higher glass transition temperature [25], [26].

3.2. Scanning Electron Microscope (SEM)

SEM is used to study solid powders' morphology and observe the surface and bulk structure. The SEM test results show that the SEM micrograph of D-mannitol underwent morphological changes with ammonium bicarbonate and citric acid as templating agents (see Fig. 1). Furthermore, pure mannitol, which has columnar or prismatic rod-shaped particles, changed its shape to irregular. The most porous mannitol spray-dried powder structure is shown in Figure 1.F, which is the result of mixing 5% w/v ammonium bicarbonate with 10% w/v D-mannitol at a water solvent temperature of 30°C, spray drying inlet temperature of 120°C, and spray drying outlet temperature of 70°C. This figure shows that the processed particles form an interconnected porous network that forms a large amount of porosity. The particle morphology supports the important role of amorphicity in spray-dried powders to achieve good dispersion of mannitol mixture and templating agent to achieve high and uniform porosity of the processed particles [13].

The results of SEM morphology (see Figure 1) generally show the spherical shape of particles for mesoporous mannitol in Figure 1f and 1g and the amorphous shape with a rough and porous outer surface in Figure 1a - 1e, in contrast to pure mannitol which has columnar or prismatic rod-shaped particles. This change in shape and surface on mesoporous mannitol is related to the formation of surface gaps/pores in mesoporous mannitol powder. If connected with the SAA results in Table 2, the more spherical the shape of mesoporous mannitol, the greater the pore volume; this is also supported by research conducted by Zellnitz et. al. [27].

3.3. Surface Area Analyzer (SAA)

The SAA results show that the highest pore surface area was obtained in the mixture of 5% w/v ammonium bicarbonate with 10% w/v D-mannitol at a water solvent temperature of 30°C, spray drying inlet temperature of 120°C and spray drying outlet temperature of 70°C (Table II). Mixing D-mannitol with the templating agent of ammonium bicarbonate successfully increased the surface area of mannitol from 1.167 m^2/g to 3.571 m^2/g, followed by an increase in pore volume from 0.0022 cc/g to 0.012 cc/g and pore diameter from 75.33 Å to 115.2 Å. Furthermore, the use of templating agent type, inlet temperature, and outlet temperature of the drying process greatly affected pore surface area, pore volume, and pore size diameter of mannitol mesopore. This is also supported by the results of scanning electron micrographs of spray-dried mannitol particles. According to [27], SAA indicates particle surface roughness; the greater the SAA, the greater the surface roughness. Increasing particle powders' surface area and pore volume can improve drug loading and enhance the drug carrier release [28].

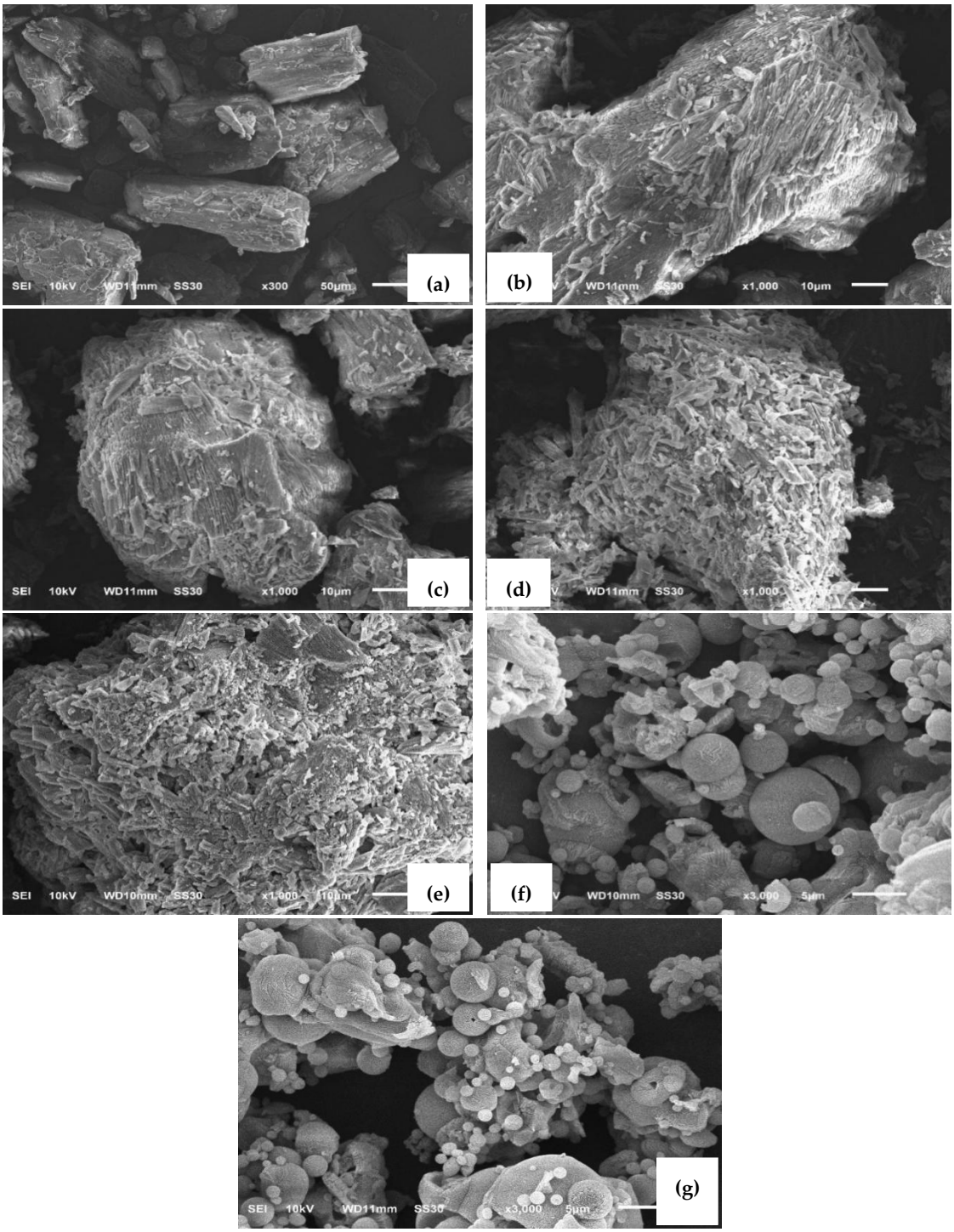

Figure 1. SEM Test Results. (a) D-mannitol; (b) D-mannitol : Citric Acid (15:2), temperature inlet 170 °C, outlet 100°C; (c) D-mannitol : Citric acid (15:2), temperature inlet 150 °C, outlet 80 °C; (d) D-mannitol : Citric acid (10:1), temperature inlet 170 °C, outlet 100 °C; (e) D-mannitol : Citric acid (10:1), temperature inlet 150 °C, outlet 80 °C; (f) D-mannitol : Ammonium bicarbonate (10:5), temperature inlet 120 °C, outlet 70 °C; (g) D-mannitol : Ammonium bicarbonate (10:5), temperature inlet 150 °C, outlet 80 °C

Table 2. Yield and SAA results of mesoporous mannitol powder

Mannitol : templating agent ratio	Temperature Inlet (°C)	Temperature outlet (°C)	Yield (g)	Surface area (m^2/g)	Pore Volume (cc/g)	Pore Size Å
D-mannitol	-	-	-	1.167 ± 0.29	2.197×10^{-3} ± 0.07	75.33 ± 18.13
D-mannitol : Citric Acid (15:2)	170	100	10.364 ± 0.08	1.944 ± 0.43	8.233×10^{-3} ± 0.31	162.9 ± 5.66
D-mannitol : Citric Acid (15:2)	150	80	6.65 ± 0.13	1.688 ± 0.52	3.778×10^{-3} ± 0.27	81.50 ± 5.99
D-mannitol : Citric Acid (10:1)	150	80	4.852 ± 0.18	1.737 ± 0.43	3.272×10^{-3} ± 0.32	72.97 ± 5.95
D-mannitol : Citric Acid (10:1)	170	100	4.063 ± 0.2	1.330 ± 0.29	4.151×10^{-3} ± 0.25	118.7 ± 2.46
D-mannitol : Ammonium bicarbonate (10:5)	120	70	12.405 ± 0.16	3.571 ± 0.86	11.46×10^{-3} ± 0.07	115.2 ± 4.18
D-mannitol : Ammonium bicarbonate (10:5)	150	80	13.764 ± 0.26	2.169 + 0.56	7.864×10^{-3} ± 0.39	133.0 ± 5.64

In this study, using a citric acid templating agent resulted in a much smaller pore surface area and pore volume than an ammonium bicarbonate templating agent. Based on the results, the smaller the concentration ratio of citric acid to D-mannitol, the smaller the pore surface area and pore volume; on the contrary, the higher the inlet temperature and outlet temperature used to dry the mixture of mannitol with citric acid, the larger the pore volume and pore size diameter.

This study used an ammonium bicarbonate templating agent to produce better porous particles than citric acid. This is evidenced by the results of SEM micrographs, where the best porous mannitol particles occur when mixing D-mannitol with ammonium bicarbonate, and proven by measuring the sample's surface area with SAA. The effect of outlet temperature and spray drying inlet temperature in engineering the formation of porous particles greatly influenced the results of pore surface area, pore volume, pore size diameter, and morphological shape of mesoporous particles. In addition, the amount of templating agent affected the formation of particle porosity. This is in line with [17], stating the more ammonium bicarbonate is used, the smaller the pore sizes are produced, and vice versa. Peng et al.'s research shows that porous mannitol can only be obtained when the concentration of ammonium bicarbonate compared to mannitol exceeds 25%. Using an ammonium bicarbonate templating agent in forming porous mannitol is safe since it does not leave residue in the spray-dried powder. This has been proven in [17] that ammonium bicarbonate is completely degraded at 62-70°C.

The formation of porous particles can be explained through the Peclet number (Pe) concept with the formula Pe=k/8D. The coefficient k is the evaporation rate, while the coefficient D is the diffusivity of the solute particles [29]. Based on the Peclet number approach, particle porosity is formed when the evaporation rate of the solvent is higher than the diffusivity of the solute particles. In addition, the spray-drying process affects the formation of hollow particles. Previous research by [30] shows that solvent evaporation is 1000x faster than the diffusivity of mannitol.

Moreover, the formation of porous mannitol is also influenced by the balance of solvent evaporation, which is sufficient to penetrate the shell wall and occurs when the ammonium bicarbonate concentration is increased. However, faster solvent evaporation will accelerate the

particle wall and cause the fusion of the particle pores. Eventually, the fused particles may collapse, and only a few pores result from the spray-dried process [17].

The research results show that high-pore volume mesoporous mannitol has been successfully prepared with templating agent ammonium bicarbonate. The mesoporous mannitol will then increase the solubility and bioavailability of active pharmaceutical ingredients in drug delivery. Kesse et al. and He et al., stated that mesoporous mannitol as drug delivery has several advantages, including increasing drug dissolution and bioavailability, increasing drug stability, controlled and sustained drug release, reducing side effects, and having good biocompatibility [31], [32].

4. CONCLUSION

Highly porous mannitol particles with high surface area and pore volume have been successfully produced through spray drying of mannitol solution containing 5% w/v ammonium bicarbonate and 10% w/v D-mannitol at spray drying inlet temperature of 120°C and spray drying outlet temperature of 70°C. The scanning electron magnetic results correspond to the BET surface area. The study results found that the type and concentration of the templating agent, inlet temperature, and outlet temperature of spray drying affect the formation of porous mannitol. The results of this study enable the engineering production of particles with highly porous structures to improve the dissolution of pharmaceutical preparations. Moreover, the resulting spray-dried porous mannitol with a larger specific surface area can be used as an excipient for solid formulations of oral preparations.

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