Chapter 23

Preparation of Fast-Dissolving Tablets Based on Mannose

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Recent developments in fast dissolving (or fast disintegrating) tablets have brought convenience in dosing to elderly and children, who have trouble swallowing tablets. Fast-dissolving tablets dissolve or disintegrate in the mouth without any extra fluid, and so they are highly useful for those who need to take medicine in the absence of water. The key properties of fast-dissolving tablets are fast absorption of water into the core of tablets and disintegration of associated particles into individual components for fast dissolution. The strategy of making fast-dissolving tablets presented in this study is based on using carbohydrates that have extremely high water solubility. D-Mannose is a naturally occurring sugar with aqueous solubility of 2.5 mg/ml that can be compressed at a low pressure. Therefore, mannose was chosen as the main excipient. Tablets with high porosity were made in a 3-step process. First, mannose powder was compressed into a tablet with reasonable strength. Second, this compact was exposed to relative humidity higher than the critical relative humidity of mannose to absorb water. Third, tablets were dried to gain mechanical strength. The disintegration mechanism was studied.

Introduction

Oral administration of a tablet is the most popular dosage form; however, parts of the populations such as children and the elderly have difficulties in swallowing tablets and capsules *(1)*. Fast-dissolving tablet technologies, as a new dosage form in pharmaceutical industry, have been gaining attention recently. Fast-dissolving tablets disintegrate or dissolve in the mouth without requiring extra fluid to help swallowing. Moreover, they are very useful for those who need to take medicine without immediate access to water. The name "fast-dissolving" indicates that these tablets dissolve quickly, and it implies that the tablets disintegrate into smaller particles. Fast-dissolving tablets combine the advantages of liquid dosage form, i.e., convenient drug administration, and solid dosage form, i.e., easy handling and accurate dosing. When a fast-dissolving tablet is administered, it disintegrates or dissolves in the saliva and is swallowed into the stomach. The time to reach from the mouth to the stomach is estimated to be between 5 and 10 minutes *(2-4)*. This fast passage to the stomach provides a better opportunity for the medication to be absorbed through the membrane of the buccal cavity, pharynx, and esophagus for improved bioavailability *(5,6)* and quick onset of drug action.

Currently, fast-dissolving tablets are prepared by several methods, such as freeze-drying, molding, sublimation, and direct compression. Each method has its own advantages and limitations. Common approaches to making fast-dissolving tablets are maintaining high porosity of the tablet matrix, incorporation of highly water-soluble excipients in the formulation, and addition of quick disintegrating agents *(7-10)*. Superporous hydrogel particles have been shown to be suitable disintegrating agents for fast-dissolving tablets *(11)*. Regardless of the preparation methods, the key properties for fast-dissolving tablets are fast absorption or wetting of water into the tablets, followed by disintegration of associated particles into individual components. These properties require excipients with high wettability, and a tablet structure consisting of a highly porous network. Since the strength of a tablet is directly related to the compression pressure, while porosity is inversely related to the compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength.

The strategy of making fast-dissolving tablets presented in this study involves using a highly water-soluble carbohydrate as the main excipient. After the initial screening of a large number of candidate materials, D-mannose was chosen as the main excipient. D-Mannose is a naturally occurring carbohydrate with an aqueous solubility of about 2.5 g/ml. The compressibility of mannose at low pressure was observed to be very reasonable. For these properties, mannose was investigated as the main excipient for making fast-dissolving tablets.

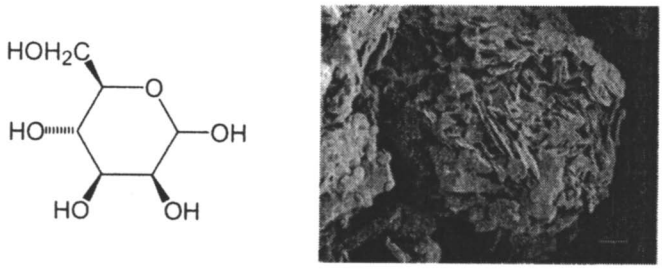

Figure 1. Chemical structure of D-mannose and an SEM picture of D-mannose particles.

Figure 1 shows the molecular structure of D-mannose and a scanning electron microscopy (SEM) image of the raw material. As seen in the SEM image, mannose powder has a highly porous structure, which may help generating large surface areas when the powder is compressed into tablets. The pores between crystals are expected to allow fast absorption of water by capillary force. The particles have spherical shape and possess good flowability. To prepare tablets with high porosity, the following three steps process was applied. First, the mannose powder was compressed into a tablet at relatively low pressure. Second, the compact was placed in a humidity chamber with relative humidity higher than the critical relative humidity of the mannose. Third, the tablets gained significant mechanical strength after they were taken out from the humidity chamber and dried. The disintegration mechanism of the mannose tablet and factors affecting tablet strength were studied.

The effects of moisture on the properties of tablets, including appearance, color, hardness, disintegration, dissolution and bioavailability, were investigated in detail. It was found that the tablet hardness increased when the tablet first gained moisture and subsequently lost it during storage *(12)*. Hardness, disintegration and dissolution of the tablets did not change much on exposure to ambient room conditions. However, after equilibration under high humidity, an initial decrease in tablet hardness occurred. After drying, the moisture-treated tablets increased their hardness again, which exceeded the initial hardness level *(13,14)*. It appears that the partial loss of moisture induced recrystallization of D-mannose, which was dissolved in the absorbed moisture on the surface of the particles *(15)*. The binders used in the tablet preparation are also known to increase the tablet strength after partial loss of moisture during drying *(16)*. The objective of this research was to develop a new fast-dissolving tablet formulation based on mannose as the main ingredient.

Materials and Methods

Materials

Mannose powder was purchased from Hofman International Inc. (Calgary, Canada).

Preparation of Tablets

Tablets were compressed on a single punch Carver Laboratory Press (Carver Inc., Wabash, IN) at different compression pressures, using plane-face punches with diameter of 0.5 inch.

Moisture Treatments

The prepared tablets were placed in a Drykeeper desiccator (Sanplatec Corp., Osaka, Japan) with 75% RH at 25°C, which was created by placing a saturated sodium chloride solution in the Drykeeper desiccator. The tablets were taken out after 4 hours and air dried for 8 hours at 25 °C or at room temperature. The tablet hardness and the disintegration time were measured.

Disintegration Test

Fast-dissolving tablets are supposed to disintegrate in the mouth by saliva. The amount of saliva is limited and no simulated tablet disintegration test in the mouth was found in United States Pharmacopeia. Since it is difficult to apply a general disintegration test to reflect real conditions, a new simple testing device was designed as shown in Figure 2 to evaluate the disintegration times of various formulations.

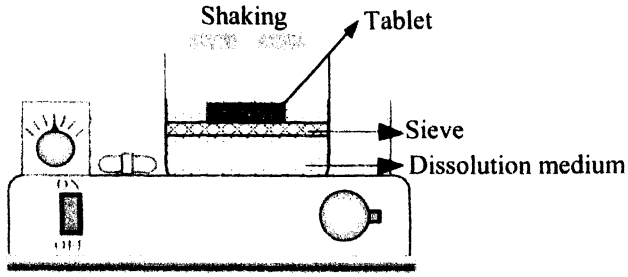

Figure 2. A device for disintegration testing of fast-dissolving tablets.

A 10-mesh sieve was placed inside a glass cylinder in such a way that 2 ml of a dissolution medium could be filled between the bottom of the cylinder and the sieve. 3 ml of water were poured into the device so that there was 2 ml of water below the sieve and 1 ml of water above the sieve. The device was placed on a reciprocal shaking bath (Precision, Winchester, VA), keeping the temperature at 37 °C. When the tablet was immersed into the disintegration medium, the shaker was run in horizontal back and forth motions at 150 rpm. The time until particles of the tablet went through the sieve was recorded as the disintegration time.

Hardness of Tablet

The hardness of the mannose tablets was determined using a VK 200 Tablet Hardness Tester (Vankel, 36 Meridan Road, Edison, NJ 08820).

Moisture Sorption Isotherms

Moisture sorption isotherms of superporous hydrogel (SPH) particles were determined using a Symmetric Gravimetric Analyzer Model 100 (SGA-100, VTI Corporation, Hialeah, FL). Sample particles (5.0 mg, 44-106 μm) were placed in the sample holder and dried at 60 °C for 3 hours. The relative humidity was then set to zero until stable mass was recorded, and the balance was zeroed. The sorption balance was programmed to generate relative humidity steps in an absorption/desorption cycle. The target relative humidity used during the absorption stage under a continuous nitrogen flow of 200 cm^3/min was in the range of 10–90% relative humidity. The relative humidity was held at each 5% relative humidity increments until equilibrium was reached.

Scanning Electron Microscope

Powder samples were adhered to the scanning electron microscope (SEM) sample holder by double-faced copper paper. The tablet samples were broken by a shock of a blade so that the exposed surface did not have contact with the blade. The samples were then mounted to a sample holder and sputter-coated for three minutes. Images of the prepared samples were then taken by a SEM.

Results and Discussion

Isothermal Moisture Absorption of Mannose

An isothermal moisture absorption test was conducted to examine moisture absorption into the mannose powders. The moisture absorption property is

important for finding the optimal condition for formation of liquid bridging as well as the drying process. As shown in Figure 3, the moisture absorption into mannose powders was almost negligible up to 70% relative humidity at 25°C, and then the water absorption increased linearly with the relative humidity. Thus, 70% relative humidity is the critical value for mannose.

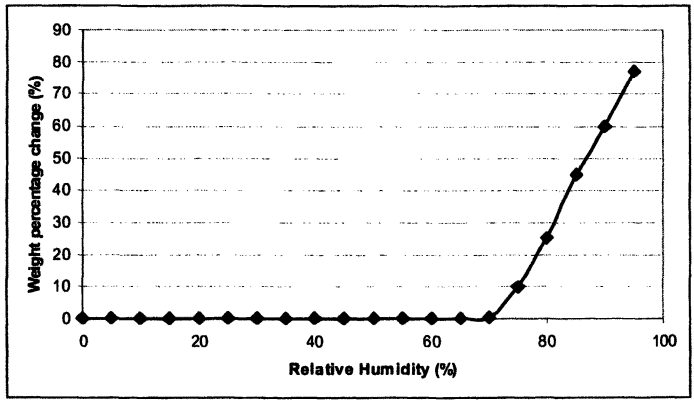

Figure 3. Isothermal moisture absorption of mannose powders.

Mechanisms of Fast Disintegration of Mannose Tablets

It was observed that water penetration into mannose tablets was instantaneous. The void space inside the tablet was quickly filled with water, unless the porosity of the tablet was too low to allow effective water penetration. Water penetration alone, however, cannot explain the fast disintegration property of mannose tablets because some tablets with intermediate pore size did not disintegrate fast. This observation can be explained by fast dissolution of mannose molecules inside the tablet due to their high aqueous solubility, which weakens the whole structure of the tablet. The tablet cannot withstand its structure and collapses, resulting in its disintegration. To test this hypothesis, disintegration tests of mannose tablets in different media were carried out. Mannose tablets compressed at 300 lbs with 0.5 inch punches were used as sample tablets for the test. The experimental conditions were kept the same except for the disintegration media, which consisted of different concentrations of mannose solutions and other solvents.

Results of the disintegration tests are summarized in Table I. It was observed that the time for the media to penetrate into the tablet was negligible compared to the whole disintegration times in all cases. The disintegration time increased as the mannose concentration in the medium increased. Solubilities of mannose in pyridine and ethanol are 0.29 g/ml and 0.004 g/ml, respectively *(17)*.

Both the concentration of the solution and the solubility of the material affect the dissolution process. Therefore, it appears that the dissolution rate of the material determines the disintegration kinetics of the tablets. Since the main mechanism of disintegration is quick dissolution of mannose, it is critical to maximize the inner surface of the tablet to improve the fast disintegration behavior of mannose tablets.

Table I. Disintegration test results of D-mannose tablets in different disintegration media.

Disintegration media	Water	Mannose soln. (0.1 g/ml)	Mannose soln. (0.2 g/ml)	Mannose soln. (0.4 g/ml)
Disintegration time (sec)	7.0 ± 0.3	11.1 ± 2.1	14.0 ± 2.3	18.7 ± 1.6

Disintegration media	Mannose soln. (0.6 g/ml)	Mannose soln. (2.5 g/ml)	Pyridine	Ethanol
Disintegration time (sec)	36.9 ± 16.3	> 7,200	532 ± 50	> 7,200

Effect of Moisture Treatment on the Hardness and Disintegration of Mannose Tablets

To test the effects of porosity and duration of moisture treatment on the properties of the resultant tablets, a series of tablets were prepared. As shown in Table II, the compression force ranged from 100 to 1000 lbs. The tablets were then placed in a 75% relative humidity chamber and sampled at 3, 4, 6 and 8 hours. The tablet strength was tested by a hardness tester. Disintegration tests of these tablets were performed as described above, and the thickness and diameter of the tablets were measured before and after the treatment to calculate the extent of volume reduction.

As summarized in Table II, the tablet strength improved after the treatment. The strength gained by tablets compressed at 100 lbs was not significant in all cases. On the other hand, the tablets compressed at 1,000 lbs gained some strength, but their disintegration times were significantly increased. Tablets compressed at 300 lbs gained strength gradually with moisture treatment time, but the disintegration times remained essentially the same. These different responses to moisture treatment may indicate differences in the pore size distribution inside the tablet, especially the lower portion of the size distribution. Tablets compressed at 100 lbs do not contain enough small pores for the moisture layers to merge together to make liquid bridges. On the other hand, tablets compressed by 1,000 lbs have many small pores. With excess amount of small pores and lack of large pores, the tablet porosity and surface area inside the tablet significantly decreased leading to the observed slow disintegration.

This point is also supported by the volume reduction data. With about the same amount of water absorbed, the volume reductions tend to increase with increase in compression. Therefore, it is very important to find the optimal pore distribution, with enough small pores to merge and gain strength and at the same time sufficient large pores necessary for disintegration.

Table II. Effects of moisture treatment on the properties of tablets made at different compression pressures.

Moisture treatment (hours)	Compression force (lb)	Hardness (KP)	Disintegration time (sec)	Volume reduction (%)
0	100	1.5 ± 0.2	5.1 ± 1.4	
	300	2.5 ± 0.3	7.7 ± 1.5	
	600	4.2 ± 0.1	10.4 ± 0.2	
	1,000	4.6 ± 0.6	15.2 ± 3.2	
3	100	2.1 ± 0.3	5.6 ± 0.7	4.1 ± 2.2
	300	4.7 ± 0.6	13.0 ± 0.2	5.7 ± 1.1
	600	5.7 ± 1.7	22.7 ± 1.4	6.1 ± 1.0
	1,000	6.1 ± 0.6	35.1 ± 1.1	5.2 ± 0.7
4	100	2.3 ± 0.6	5.4 ± 0.8	4.5 ± 0.8
	300	4.9 ± 0.8	11.4 ± 0.9	5.9 ± 1.3
	600	5.1 ± 0.7	23.5 ± 2.5	6.9 ± 1.3
	1,000	6.7 ± 0.6	47.1 ± 5.5	6.2 ± 1.3
6	100	2.8 ± 0.8	5.5 ± 0.9	5.6 ± 3.8
	300	4.1 ± 0.3	13.0 ± 0.4	5.7 ± 0.8
	600	5.1 ± 0.9	32.0 ± 6.0	7.3 ± 0.9
	1,000	6.5 ± 1.0	38.0 ± 1.6	7.4 ± 1.3
8	300	5.6 ± 0.1	15.6 ± 0.3	7.1 ± 1.5
	600	5.4 ± 0.5	35.5 ± 4.7	8.7 ± 1.7
	1,000	6.1 ± 0.6	42.8 ± 2.4	8.4 ± 1.1

Additional visual confirmation of the tablet structural changes was gained from SEM images (Figure 4). The image of a tablet compressed at 300 lbs without humidity treatment shows some individual particles that are still not merged together. However, after humidity treatment small pores were significantly decreased or had merged but larger pores were still intact, allowing fast absorption of water into the tablet core. The tablet compressed at 1000 lbs after humidity treatment, however, revealed many merged pores and few large pores, blocking the absorption of water into the tablet core. Although the images were taken at different magnifications, a comparison of the amount of pores

larger than 10 μm revealed that the tablet compressed at 300 lbs after humidity treatment had many more pores than the tablet compressed at 1000 lbs after humidity treatment. This visual examination supports the results from the hardness and disintegration tests.

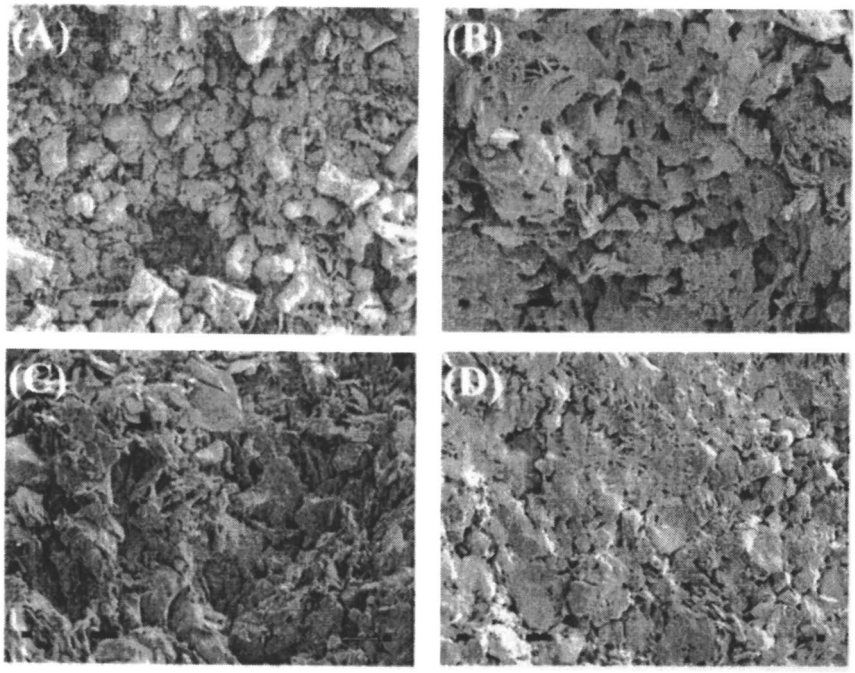

Figure 4. SEM pictures of the cross-sectional (horizontal) views of mannose tablets compressed at different pressures. (A) Tablet compressed at 300 lbs and before humidity treatment (magnification of 500). (B) Tablet compressed at 300 lbs and after humidity treatment at 75% relative humidity for 4 hours (magnification of 700). (C) Tablet compressed at 1000 lbs and before humidity treatment (magnification of 1200). (D) Tablet compressed at 1000 lbs and after humidity treatment at 75% relative humidity for 4 hours (magnification of 500).

The importance of the pore size distribution became evident when tablets made from different particle sizes were compared. Mannose particles of three different particle size ranges, i.e., 75-90 μm, 212-250 μm, and 1000-1400 μm, were collected to make tablets. 300-mg samples of each size range were compressed to make tablets of the same volume, and therefore, the same total pore volumes. The only difference among those three types of tablets was the pore size distribution. Those tablets went through the same moisture treatment,

i.e., 75% relative humidity at 25°C for 4 hours. The results are listed in Table III. Tablet made from the smallest mannose particles showed the highest hardness after vapor sorption. Although there are some fluctuations, the disintegration time of those tablets remained in an acceptable range. The applied compression pressure was such that there was enough total pore volume to ensure fast disintegration. The disintegration time was not very sensitive to the pore distribution as long as the total pore volume was kept constant. However, the tablet strength was dependent on the pore distribution and could be varied by using different initial particle sizes. Smaller particles tend to have more intimate contacts than larger particles, and this may contribute to the observed higher tablet strength. Fracture of the initial particles was limited to the compression stage because of the low compression pressure used in making these mannose tablets.

Table III. Effects of different initial particle size on tablet properties.

		Hardness (KP)		
Particle Size Size (μm)	Initial Volume (mm^3)	Before Vapor Sorption	After Vapor Sorption	Volume Reduction (%)
75-90	345.5 ± 5.3	0.2 ± 0.3	4.3 ± 0.5	8.1±0.3
212-250	347.5 ± 2.4	0.1 ± 0.2	3.7 ± 0.1	7.0±0.7
1000-1400	344.2 ± 3.3	0.3 ± 0.3	3.4 ± 0.4	7.0±0.8

	Disintegration Time (Sec)	
Particle Size Size (μm)	Before Vapor Sorption	After Vapor Sorption
75-90	7.5±0.7	12.1±0.5
212-250	8.4±1.5	10.6±1.2
1000-1400	7.4±1.2	14.9±1.1

Conclusions

The strength of tablets containing mannose was enhanced by the sequential process of moisture absorption and drying. Mannose has a critical relative humidity of 70% at 25 °C. When the relative humidity is kept above this level, mannose particles within the tablet absorb water from the environment, leading to the formation of a liquid layer on the particle surfaces. As the liquid layers on the particles grow, different layers on adjacent particles merge together to form liquid bridges between these particles. Upon drying, these liquid bridges become solid bridges to form stable bonds, which significantly increase the strength of the whole tablet. By optimizing the amount of water absorbed, and therefore, the formation of liquid bridges, the strength of the tablets can be controlled. This method does not significantly reduce the tablet volume, and thus, the pores inside the tablet are maintained for fast disintegration and dissolution.

Acknowledgments

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