AMERICAN JOURNAL OF PHARMTECH RESEARCH

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Phase Transition Method Use for Preparation of Mouth Dissolving Tablet

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ABSTRACT

Mouth dissolving tablets (MDTs) prepared by the crystalline / phase transition method has focused on decreasing the dissolution (or disintegration) time of the tablets in the mouth, while maintaining sufficiently high mechanical strength to withstand handling during manufacturing, packaging, and transportation. The key to developing a successful MDTs formulation by the phase transition method is to select the right excipients. In general, MDTs are made of highly hydrophilic materials and possess highly porous structures for fast water absorption into the tablet. After heating MDTs, the median pore size of the tablets was increased and tablet hardness was also increased due to phase conversion into the tablets. It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making MDTs without any special apparatus.

Keywords: Mouth dissolving tablets; Phase transition; crystalline transition; Sugar alcohol.

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Received 06 May 2014, Accepted 28 May 2014

Please cite this article in press as: Suryawanshi ND *et* Phase Transition Method Use for Preparation of Mouth Dissolving Tablet. American Journal of PharmTech Research 2014.

INTRODUCTION

In recent years, in accordance with changes in lifestyle, a demand has arisen for the development of dosage forms that can be readily handled and taken by many patients. In particular, the development of solid dosage forms that can rapidly disintegrate or dissolve even when taken orally without water is necessary to assist in the treatment of elderly people. With respect to various compositions and manufacturing methods of orally disintegrating or mouth dissolving tablets, numerous studies have therefore been reported.[1-3] For example, a solution or suspension of a drug and excipients was poured into the pockets of a blister pack sheet formed beforehand, and then freeze-dried or vacuum-dried to make an mouth dissolving (MD) product.[4-5] The oral disintegration time of the product produced by these methods was very short because of its highly porous structure and the high solubility of sugar alcohol (SA) or saccharide used as the diluent in the product. However, the disadvantage of this product was its lack of mechanical strength. In another preparation method, Mouth dissolving tablets (MDTs) have been produced by using wet powder containing a drug and subsequent drying in an oven.[6] Such processes could provide tablets with excellent inter oral disintegrating properties and a rather high degree of hardness. However, they require special apparatuses, since it is impossible to compress the wet powder with conventional tabletting machines.

On the other hand, a new method of preparing MDTs without any special apparatus has been reported. Mizumoto et al. reported that MDTs can be manufactured using a combination of saccharides with low and high moldability.[7] We focused on the melting points of SA, and proposed a novel method to prepare MDTs with sufficient hardness by involving the phase transition of SA.[8] In our preparation method, MDTs were produced by compressing and subsequently heating tablets that contained two SAs, one with a high and one with a low melting point. Before the heating process, the tablets did not have sufficient hardness because of low compactibility. The tablet hardness was increased after the heating process. A combination of two SAs and the heating process was needed to prepare MDTs with sufficient hardness. It was concluded that tablet hardness was related to the increase in inter-particle bonds or the bonding surface area in tablets induced by the phase transition of the low melting point SA.

Saccharides with different compression characteristics

There are a lot of pharmaceutical excipients that have been used in the development of MDTs that are currently on the market. Few pharmaceutical excipients, however, achieve both fast disintegration and high mechanical strength, and pharmaceutical scientists have struggled to

balance the two opposing properties. Pharmaceutical excipients can be categorized so as to facilitate formulation design. For example, pharmaceutical saccharides (sugars) have been divided into two groups based on their physicochemical properties.[7-9] One group consists of low compressibility saccharides that exhibit rapid disintegration in th mouth when made into tablets. These saccharides include mannitol, lactose, glucose, sucrose, xylitol, and erythritol. The other group consists of highly compressible saccharides that yield high mechanical strength. The sugars in this category are maltose, sorbitol, maltitol, and trehalose (Table 1). Combinations of sugars from each group can be optimized to develop successful MDTs.

When coating and granulating a mixture containing a low compressibility saccharide and a high compressibility saccharide, compressibility of the former can be improved so that adequate mechanical strength is obtained while maintaining rapid disintegration.

Table 1: Compression characteristics of various saccharides with their hardness, disintegration time and melting points. (modified from Mizumoto et al.)[7]

	Saccharides	Hardness (kp)	Disintegration time (sec)	Melting point (°C)
Low compressibility	Mannitol	0	<10	166
	Lactose	0	<10	202 (anhydrous) 214 (monohydrate)
	Erythritol	0	<10	122
	Xylitol	0	<10	93–95
	Glucose	0.2	<10	146 (a-D-) 150 (b-D-)
High compressibility	Sucrose	0.5	<10	186
	Sorbitol	2.2	>30	95
	Maltitol	2.5	>30	150
	Trehalose	3.4	>30	97
	Maltose	6.8	>30	102 (monohydrate)

For example, when mannitol was granulated with maltose solution as a binder in a fluidized-bed, mannitol's low compressibility was improved. After compression, an adequate hardness of 5.9 kp, and a low friability of 0.65 % were observed while maintaining a fast disintegration time of 20 sec.[7] This formulation approach produced a viable MDT with adequate mechanical strength and quick disintegration in the mouth. One suggested factor affecting a saccharide's compressibility was related to surface free energy as measured by the Owens–wendt plot.[7] The high compressibility saccharides had the surface free energy of a very high-polar component relative to the low compressibility sugars. Moreover, IR measurements showed many hydroxyl groups on the surface of the high compressibility particles. It is assumed that the surface free energy of the highly polar components is due to the hydroxyl groups on the particle surface and that this hydrophilic

substituent affects the cohesive properties of each particle to improve compressibility. The surface free energy of the polar components of the saccharides affects their compressibility.[7] Another mechanism for increasing hardness is suggested to be a crystalline transition, which will be discussed more in the following section. After granulation, amorphous maltose exists on the surface of the mannitol particles.

During the conditioning process, the amorphous maltose adsorbs moisture resulting in crystallization of the maltose. The resulting particles stick to each other more strongly, which results in increased tablet mechanical strength.[7]

Pharmaceutical sugars are widely used in making tablets. They are safe, easy to handle, and have a sweet taste. However, their compressibility or dissolution properties are not generally sufficient to make MDTs and the development of novel sugars (i.e., sugar derivatives), which have both high compressibility and dissolution, is desired.

Crystalline transition method

The crystalline transition method (CTM) makes use of the phase transition of pharmaceutical excipients, especially sugars, from the amorphous to crystalline [10] state to improve tablet mechanical strength while maintaining porosity. Amorphous forms of sugars have higher compressibility than crystalline forms,[11-12] so they can contribute to high tablet porosity. However, amorphous sugars have a tendency to absorb more moisture than crystalline ones, which means that the tablets containing amorphous sugars are more sensitive to moisture. An amorphous state is metastable and will tend to convert to a thermodynamically stable crystalline state over time. The amorphous state can be easily prepared by freeze-drying or spray drying. For example, a MDT was prepared by compressing a mixture of mannitol and amorphous sucrose.[13] Mannitol and sucrose were used as a diluent and a binder, respectively. A blend of the two was compressed at varying compaction pressure and exposed to various conditions of temperature and humidity to induce phase transition. [13] The storage temperature and humidity affected the rate of crystalline transition and it was shown that the faster the crystalline transition, the faster the rate of increase in tablet tensile strength. [13- 15] Higher storage temperatures or higher relative humidity led to a faster moisture uptake and also crystallization of the amorphous material resulting in a faster increase in the tablet mechanical strength. [13- 15]

The mechanism of the CTM can be understood by using the moisture sorption model of amorphous sucrose. [16] Amorphous sucrose is hygroscopic and can absorb ambient moisture, leading to the formation of hydrated amorphous material. The absorbed water can act as a plasticizer and also influence free volume due to breakage of hydrogen bonds between the

molecules in the solid. This can lower the glass transition temperature (Tg) to, or below, the operation temperature changing it from a glassy to a rubbery state.[17] The hydrated amorphous material with increased physical reactivity may not hold a relatively large amount of moisture. Therefore, the loss of moisture might induce crystallization of the amorphous sucrose with the release of the absorbed water. The hydrated amorphous sucrose in an MDT can be converted into the crystalline form and the crystalline sucrose forms new internal contact points in the tablet (Figure. 1).[13-14] When MDTs are prepared by CTM, a level of 10–20 % amorphous sucrose in the tablet is suggested.[13-15] The tensile strength increases with an increasing percentage of amorphous sucrose due to its good compactability. However, the higher amorphous content causes a longer disintegration time in the mouth. Furthermore, it affected the structure of the tablets: the tablets with higher initial porosity shrank, whereas the tablets with lower porosity expanded due to the recrystallization of the sucrose.[15] The tensile strength of the tablet remarkably increased during storage, although the porosity of the tablet seemed hardly changed.

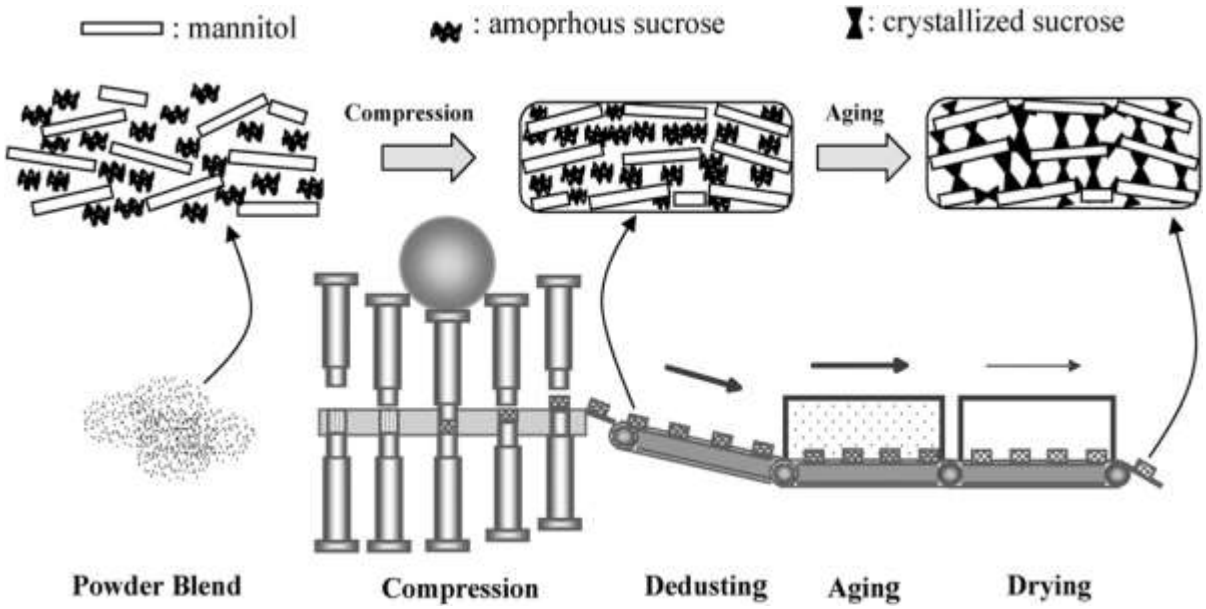

Figure 1: Schematic illustration of the manufacturing process of MDTs prepared by the crystalline transition method using mannitol and amorphous sucrose (modified from ref. 13 and 26).

Conditioning of tablets at a certain temperature and humidity was also investigated, and involved different kinds of pharmaceutical polymers, such as polyvinylpyrrolidone (PVP), or other excipients.[18-21] For example, highly water-soluble polymers absorb moisture and form new contact points as the amorphous sugars described above do, although crystal transition seems a rare occurrence in the case of polymers.[18] Similar to the CTM, the mechanical strength of the tablets

can be increased significantly with humidity conditioning. This increase might be due to the formation of liquid bridges in the presence of moisture, and then formation of solid bridges after drying.[21-22] As shown in Figure. 2, as water molecules from the atmosphere are adsorbed onto the surface of the particles (A), the water molecules form a liquid film with the vapor pressure over the adsorbed moisture layer equal to P2 (B). The adsorbed moisture layer will dissolve the particles and the dissolution in the adsorbed moisture will lead to a decrease in the vapor pressure P2 (C). The decrease in P2 is effectively offset by the increase in the temperature of the film and the particles caused by the heat released on condensation of the water vapor. The moisture sorption happens spontaneously and the thickness of the condensate film grows as long as P1>P2. The solid continues to dissolve until saturating the film, maintaining the vapor pressure over the adsorbed moisture layer (P2). After drying, a solid bridge occurs and increases the bonding between the particles (D).[22]

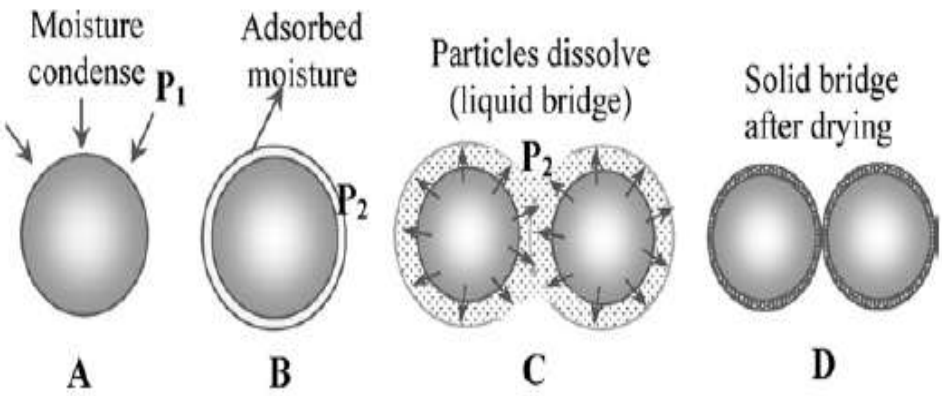

Figure 2: Schematic view of moisture sorption by water-soluble particles explaining the increase in mechanical strength in MDTs before and after moisture conditioning (modified from ref. 22).

Phase transition method (PTM)

Saccharides and sugar alcohols can be categorized not only by compressibility but also by melting point. Based on the melting points (Table 1), they were divided into two groups and investigated using conventional granulation and compression apparatus.[8] Erythritol is the high melting (122°C) and xylitol the low melting (93~95°C) sugar alcohol. Erythritol and xylitol were used as a diluent and a binder, respectively for fluid bed granulation.

After compression, the resulting tablets were placed in a drying oven and heated at a temperature close to the melting point of xylitol (approximately 93°C). Conditions were maintained for a certain period of time and the tablets then allowed cooling to room temperature (Figure. 3). The

hardness of the processed tablets was found to increase with increasing xylitol content.

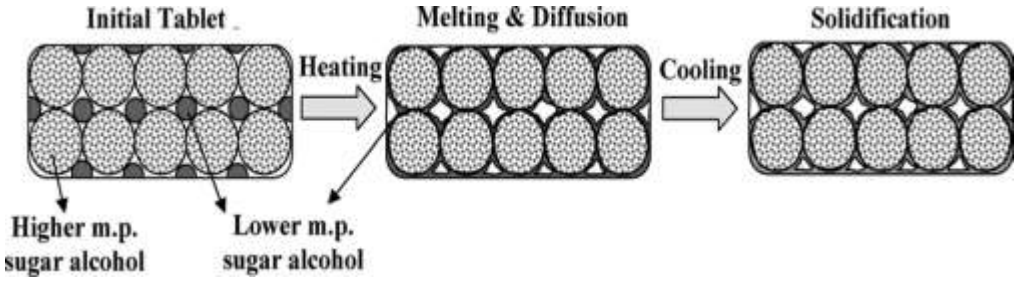

Figure . 3: Schematic illustration of a fast disintegration tablet prepared by the phase transition method using a higher melting (erythritol) and a lower melting (xylitol) sugar alcohol (modified from ref. 8).

Tablet hardness and disintegration time were primarily affected by the heating process, but also by the content of saccharides or sugar alcohols.[8] Heating was found to increase pore size within the tablets. It was suggested that the diffusion of xylitol in the tablets caused increased tablet hardness with increasing pore size. Xylitol melted, diffused, and solidified again in the heated tablets resulting in a greater bonding surface area between the powder particles and increased hardness. Tablets containing about 5% xylitol showed hardness of 4 kp and an oral disintegration time of < 30 sec. [23] It was also suggested that increasing tablet hardness by heating and storage was not dependent on the crystal state of the sugar alcohols, but related to the formation of inter-particle bonds or the increased bonding surface area induced by the melting of xylitol particles and their subsequent solidification upon cooling.[8] Other pharmaceutical materials, such as polyethylene glycol, and wax, have been also applied to the PTM.[24-25]

CONCLUSION

We proposed a new tablet preparation method that employs the phase transition of sugar alcohols. In our method, tablets are produced by compressing a powder containing two sugar alcohols with high and low melting points, and subsequent heating at a temperature between the high and low melting points. Before the heating process, the tablets do not have sufficient hardness because of the low compactibility. The tablet hardness is increased after the heating process. A combination of two sugar alcohols and the heating process is needed to prepare MDTs with sufficient hardness. Tablet hardness is related to the increase of inter-particle bonds or the bonding surface area in tablets induced by the phase transition of the lower melting point sugar alcohol. Manufacturing of MDTs by the present method can be performed without any special apparatus.

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