



Fast-melting tablets based on highly plastic granules

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Abstract

Highly plastic granules that can be compressed into tablets at low pressure were developed to make fast-melting tablets (FMTs) by compression method. The highly plastic granules are composed of three components: a plastic material, a material enhancing water penetration, and a wet binder. One of the unique properties of the highly plastic granules is that they maintain a porous structure even after compression into tablets. The porous and plastic nature of the granules allows fast absorption of water into the compressed tablet for fast melting/dissolution of the tablet. The prepared tablets possess tablet strength and friability that are suitable for multi-tablet packages. The three-component highly plastic granules provide an effective way of making FMTs by compression.

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1. Introduction

Recent developments in fast-melting tablets (FMTs) (also called fast-dissolving tablets or fast disintegration tablets, or FDTs) provide a convenient solution for patients who have difficulties in swallowing tablets and other solid dosage forms. The solid FMT dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of suffocation risk [1,2]. The primary beneficiaries for FMTs are pediatric and geriatric patients, bedridden or developmentally disabled patients, patients with per-

sistent nausea, and patients who have little or no access to water. The benefits of FMTs can be extended to more general patients of daily medication regimens, if the FMT dosage form has improved mechanical properties, fast disintegration time, and pleasant taste. The key properties of FMTs are fast absorption of water into the core of the tablets and disintegration of associated particles into individual components for fast dissolution [3,4].

There are several technologies that produce commercially available FMTs. Although these technologies meet the special requirements for FMTs to some extent, none of them has all the desired properties. The currently available technologies have been reviewed in the literature [1,2,4–6]. The technologies are usually grouped according to the method used in

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making FMTs: freeze drying method, molding method, and compression method. The compression method is the most widely used method for making FMTs. Some are focused on unique granulation methods, such as the spray-drying method [7] and flash-heat processing to create shear form [8]; some are focused on selecting specific excipients such as water-insoluble calcium salts [9], specific disintegrant combination [10], and specific sugar combination [11]; and some are focused on special treatment after compression, such as sublimation [12], sintering [13], and humidity treatment [14].

Recently, we have developed a FMT formulation based on highly plastic granules which can be compressed at low pressure to form fast-melting pharmaceutical tablets. The highly plastic granules were produced by wet granulation of a plastic material and a water penetration enhancer. This paper presents the rationale and example tablet formulations of the highly plastic granule technology.

2. Materials and methods

2.1. Materials

Maltrin® QD 580 is maltodextrins in quick-dispersing porous powder forms sold by Grain Processing Corp. (Muscatine, IA). Maltrin® 180 is the nonporous powder form of Maltrin® QD 580. Mannogem™ EZ Spray is spray-dried mannitol from SPI Pharma. Inc. (New Castle, DE). StarLac™ (spray-dried solid containing 15% maize starch and 85% alpha-lactose monohydrate) was purchased from Roquette American, Inc.

Claritin® RediTabs® was from Cardinal Health Inc./Schering-Plough; Alavert™ Loratadine ODT (orally disintegrating tablets) was from CIMA Inc./Wyeth Consumer Healthcare; Excedrin® QuickTabs™ was from Ethypharm/Bristol-Myers Squibb; and Benadryl® Fastmelt™ was from Yamanouchi Pharma/Pfizer Inc.

2.2. Granulation method 1

Maltrin® QD 580 of size between #20 and #60 sieves was used. Maltrin® QD 580 and Mannogem™ EZ Spray were mixed together, and sucrose solution

(70% w/w) was added to the mixture while granulation. The mixture went through a #18 sieve and air dried at room temperature. The dried mixture went through a #30 sieve.

2.3. Granulation method 2

Maltrin® QD 580 of size between #20 and #60 sieves was used. Mannogem™ EZ spray particles were passed through a #50 sieve. Maltrin® QD580 and Mannogem™ EZ Spray were mixed. The mixture was put into a Kitchen-Aid mixer (St. Joseph, MI), and the speed of the mixer was kept at 1 during dry mixing. The dry mixing took place for 5 min. Sucrose solution was pumped into the mixer by a peristaltic pump (Minipuls 2, Gilson, France) at a rate of 40 ml/min. After all of the binder solution was introduced, the mixer continued to run for 2 more min. The wet mass was passed through a #8 sieve.

2.4. Tablet preparation and its strength

The granules were compressed into tablets at 300 lbs in a 1/2 in. die by a Carver press (Carver Inc., Wabash, IN). The weight of each tablet was 500 mg. Tablet strength was measured by a texture analyzer (TA XT2®, Texture Technologies Corp., Scarsdale, NY). The force that caused a diametrical failure (i.e., clear breaking) of a tablet was taken as the indicator for the tablet strength.

2.5. Disintegration test

This method is a modified version of the method developed by Dor et al. [15]. The method utilized the texture analyzer. A tablet was adhered to the bottom of a probe, which was attached to the load cell, with a very thin layer of glue or a double-sided copper tape. With constant force, the tablet was introduced to a filter paper soaked with water, which was connected to a water reservoir. When the tablet started to disintegrate, the rate of movement that the probe traveled showed a sudden increase. This increased rate continued until the tablet disintegrated. The point where the increased rate of movement was stopped was taken as the disintegration time.

2.6. Scanning electron microscope

The powder samples were adhered to the scanning electron microscope (SEM) sample holder by a double-sided copper tape. The tablet samples were broken by a shock of a blade so that the exposed surface did not contact with blade. The samples were mounted to a sample holder and then sputter coated with gold-palladium in the presence of argon gas using a Hummer I sputter coater (Anatech Ltd., Denver, NC). Pictures of the prepared samples were taken by a JEOL JSM-840 SEM (JEOL USA, Inc., Peabody, MA) using a 5 kV accelerating voltage, a 28 mm working distance, and a probe current of 3×10^{-11} A.

3. Results and discussion

To understand important parameters necessary for fast melting of tablets, several commercially available

FMTs were examined by SEM. Fig. 1 shows the pictures of horizontal cross-sections of commercially available FMTs including Claritin® RediTabs® (A), Alavert™ Loratadine ODT (B), Excedrin® QuickTabs™ (C), and Benadryl® Fastmelt™ (D). The Claritin® RediTabs® is made by freeze drying, which is also known as the Zydis® technology. As shown in Fig. 1(A), the tablet structure shows a lot of pores large than 10 μm. Saliva can easily penetrate into the tablet to disintegrate it almost instantaneously. However, the tablet strength is very limited, and thus special packaging is necessary to prevent breakage of the tablets during shipping or handling. The other three tablets in Fig. 1(B), (C), and (D) were prepared by compression method, and the cross-sections show lack of pores with a size larger than 10 μm. This explains significantly longer disintegration time of the compressed tablets than that of the freeze dried one. The mechanical strength of the compressed tablets, however, is much higher than that of the freeze dried formulations. To combine the fast melting and the

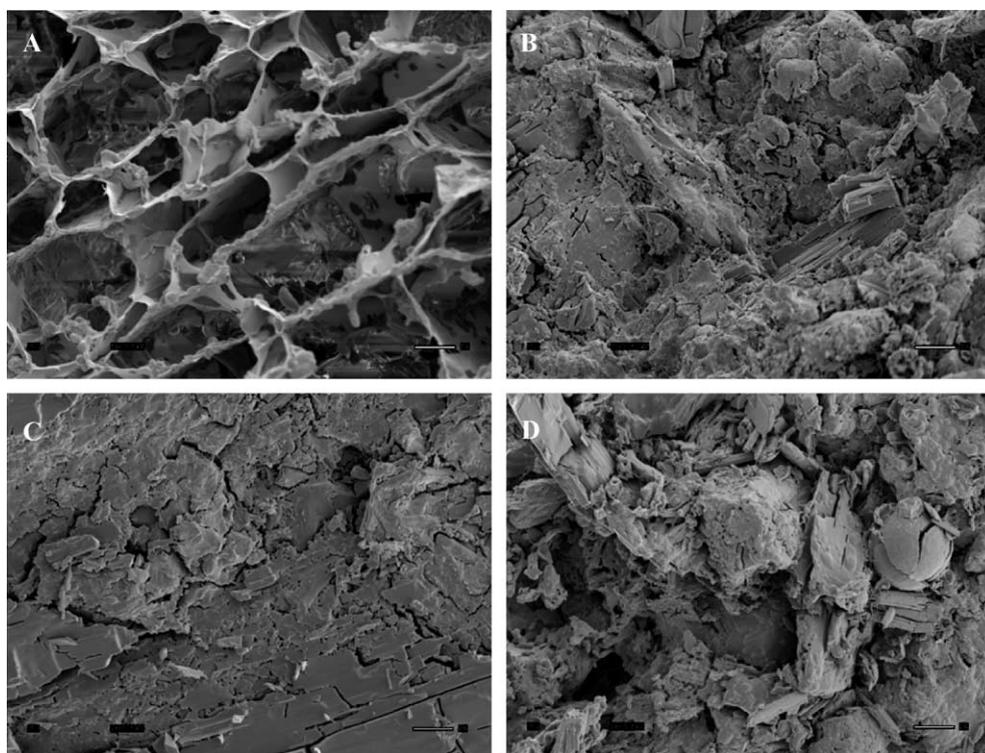


Fig. 1. SEM pictures of horizontal cross-sections of tablets from (A) Claritin® RediTabs®, (B) Alavert™ Loratadine ODT Cima Labs, (C) Excedrin® QuickTabs™, and (D) Benadryl® Fastmelt™ (Magnification: 1000×).

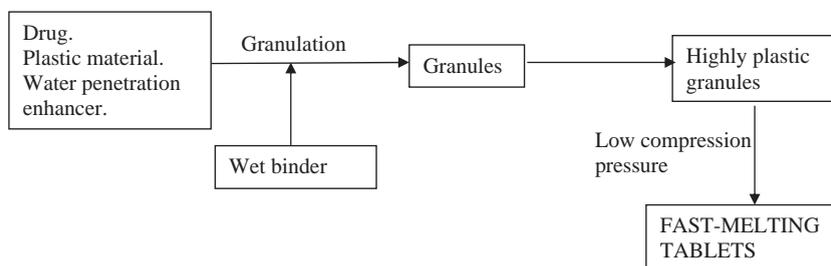


Fig. 2. A general processing step for making highly plastic granules and fast-melting tablets.

high mechanical strength properties, compressed tablets with inner porous structure were designed.

In our approach, three components were combined to prepare highly plastic granules that can be compressed and yet maintain porous structure between granules for quick absorption of water into the tablet. The three components used were a plastic material, a water penetration enhancer, and a binder. The general processing step for mixing the three components by wet granulation to obtain highly plastic granules is shown in Fig. 2.

3.1. Importance of a plastic material

Granules were prepared by the Granulation method 1 with 20% and 80% by weight of Maltrin[®] QD 580 and Mannogem[™] EZ Spray, respectively. Another type of granules composed of 20% and 80% by weight of Maltrin[®] 180 and Mannogem[™] EZ Spray were made by the same procedure. The same weight of the two granules was compressed as described in the method section. The hardness of the tablets with Maltrin[®] QD 580 and Maltrin[®] 180 was 65.2 N and 7.3 N, respectively. Maltrin[®] 180 has exactly the

same molecular structure as Maltrin[®] QD 580, and the only difference is the bulk density. Maltrin[®] 180 is a nonporous version with the packed bulk density of 0.61 g/cc while Maltrin[®] QD 580 is a porous version with the packed bulk density of 0.40 g/cc. Maltrin[®] 180 is specially treated so that the Maltrin[®] 180 particles are connected and create Maltrin[®] QD 580 with large porous morphology, as shown in Fig. 3. Because of its porous structure, Maltrin[®] QD 580 creates more plastic deformation than Maltrin[®] 180 when compressed under the same condition. The major difference between the two granules is the use of the different types of maltodextrin. The tablet strength is significantly increased when Maltrin[®] QD 580 was used. The mixture of microsponges, porous polymeric microspheres and drug was shown to have high compressibility due to the plastic deformation of the sponge-like structure of microsponges [16]. Evaluation of the mechanical properties of low crystalline powder celluloses showed that they started plastic deformation at relatively lower compression pressures while the total volume reduction was comparable to microcrystalline celluloses and powder celluloses [17]. The granules with large pores

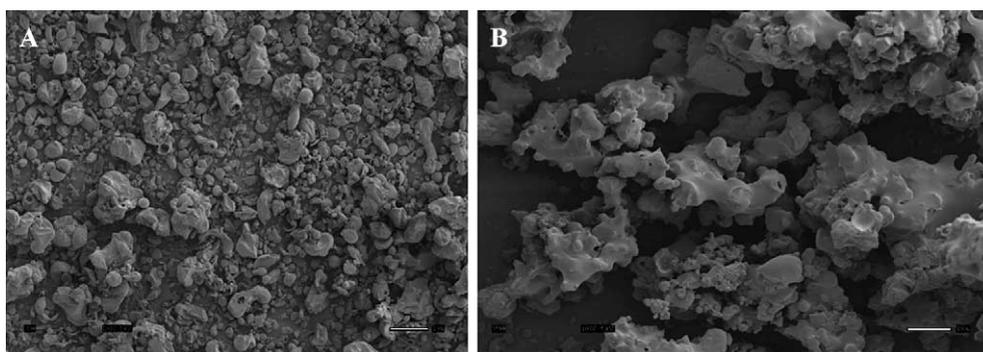


Fig. 3. SEM pictures of (A) Maltrin[®] 180 and (B) Maltrin[®] QD 580.

Table 1
Effect of the different proportions of a plastic material (Mannogem) and a water penetration enhancer (Maltrin) on tablet hardness

Percentage of material in the mixture		Hardness (N)
Mannogem™ EZ spray (%)	Maltrin® QD 580 (%)	
100	0	5.2 ± 0.8
90	10	5.4 ± 1.0
80	20	4.2 ± 0.7
70	30	4.0 ± 1.0
50	50	6.1 ± 0.6
20	80	8.4 ± 0.2
0	100	9.1 ± 0.3

experience low compression energy loss. In addition, the large pores in granules create more chance for particle rearrangement, plastic deformation and brittle fracture upon compression and hence the tablet hardness is high [18].

3.2. Importance of a wet binder

Maltrin® QD 580 and Mannogem EZ™ Spray were mixed without wet granulation in different proportions as listed in Table 1. The mixture was then compressed as described above. As shown in the table, there was no significant increase in the tablet hardness at any mixing proportions of the two components. Without the wet granulation step and the binder, the direct compression of these two materials did not yield tablets with desirable strength. It was assumed that adding a binder to the plastic materials might lead to a good bonding among particles for making tablets with high mechanical strength.

A mixture of Maltrin® QD 580 (20%) and Mannogem™ EZ Spray (80%) was granulated using different concentrations of sucrose solution according to the Granulation method 2. While the volume of the sucrose solution was the same, the sucrose concentration ranged from 10% to 70%. The results, as shown in Table 2, indicate that as the concentration of the sucrose solution increases, the hardness increases substantially due to more plastic deformation, inducing better bonding. The fast disintegration time is most likely due to the preservation of porous structures by using binder solutions with high sucrose concentrations.

Effectiveness of the binder solutions of polyvinylpyrrolidone (PVP) and hydroxypropyl methylcel-

lulose (HPMC) was evaluated [19]. It was observed that as the concentration and viscosity of the binder solution increased, the radial tensile strength of the tablet increased [19]. However, the high viscosity of these polymers after dissolution makes them less attractive to use as a binder solution in this application.

It was found that the compressibility of the granules was decreased when granulating a drug with high solubility, e.g., ascorbic acid. The high compressibility was obtained when the minimum amount of water was used [20]. This indicates that when highly soluble materials are granulated, the amount of water added should be controlled. After the wet granules are dried, the solidified binder dissolves quickly upon contact with water. The type and quantity of a binder in solutions for wet granulation can be adjusted to make the granules with desirable physical properties, such as high plasticity and good binding property.

3.3. Importance of a water-penetrating enhancer

The proportion of a plastic material (e.g., Mannogem™ EZ Spray) and a water penetration enhancer (e.g., Maltrin® QD 580) in the highly plastic granules was varied as shown in Table 3, while the mixture was granulated using the same amount of sucrose solution according to the Granulation method 2. As the proportion of Mannogem™ EZ Spray increased, the tablet hardness increased as well as the tablet disintegration time. The optimal proportion of the two components should be based on the balance between high strength and fast disintegration time. The low hardness of tablets made of 60:40 (Mannogem: Maltrin) granules may be due to the loss of the granule plasticity resulting from dissolution of a large portion of Maltrin® QD 580 during granulation.

Table 2
Effect of the sucrose concentration in the wet binder on the tablet hardness and disintegration time

Sucrose concentration (%)	Hardness (N)	Disintegration (s)
10	3.6 ± 0.8	14.2 ± 2.5
30	10.8 ± 0.9	15.9 ± 1.0
50	20.1 ± 2.4	14.3 ± 0.7
70	36.5 ± 2.0	14.2 ± 1.2

Table 3
Effect of the different proportions of a plastic material (Mannogem) and a water penetration enhancer (Maltrin) on the tablet properties

Mixture		Hardness (N)	Disintegration (s)
Mannogem™ EZ spray (%)	Maltrin® QD 580 (%)		
95	5	62.4 ± 2.0	22.0 ± 4.7
90	10	43.3 ± 15.9	15.8 ± 0.6
80	20	36.5 ± 2.0	14.2 ± 1.2
60	40	16.0 ± 3.8	22.3 ± 1.0

3.4. Rationale for the three-component system

A plastic material was chosen from plastic excipients which were pharmaceutically known as generally regarded as safe. The plastic material can be porous. The plastic material is water soluble or water dispersible, sometimes almost instantaneously upon contact with water. Plastic deformation of the powders dramatically increases the chance of inter-particle contacts necessary for forming bonds between the particles.

If a plastic material is polymeric, it is essential to prevent formation of a viscous layer of the material at the tablet surface when it dissolves in aqueous medium. One way of making such tablets is to mix the plastic material with a water penetration enhancer at certain ratios and compress them at low pressure resulting in plastic deformation of plastic materials creating intimate contact among the particles. In this process, the plastic particles are separated by water penetration enhancing particles, which prevent formation of a viscous layer on the tablet surface.

Although the plastic materials can make close contacts to increase the chance of bonding by compression, formation of really strong bonding among granules at the pressure mentioned above requires a suitable binder. The binder here can also secure the porous material and water penetration enhancer during granulation. Without the binder these two components can easily be segregated during mixing. If the binder is in the liquid or semi-solid state, it should not significantly destroy the porous structure of the porous materials. One way of

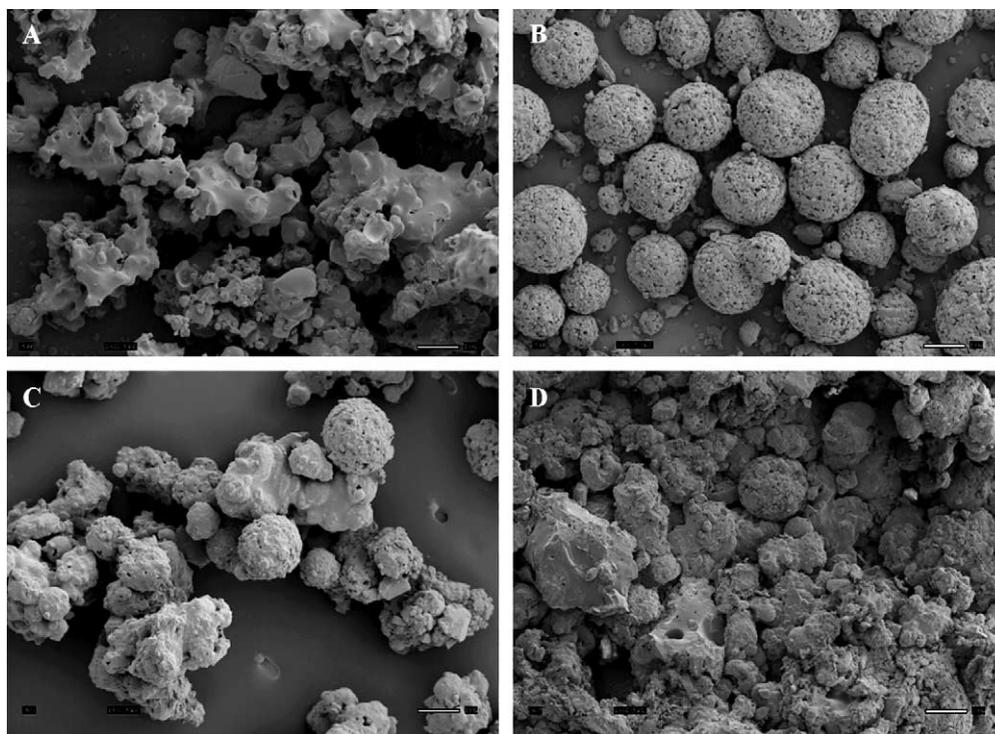


Fig. 4. SEM pictures of (A) Maltrin® QD 580, (B) StarLac™, (C) granules of the both, and (D) resulting tablet with horizontal cross-section.

achieving this is to use high concentrations of the binder to lower the water activity. Another way of achieving this is to allow only a short contact time for the porous structure not to be destroyed by the binder solution when making granules using relatively low concentrations of the binder. For example, the solvent can be instantly dried after wetting in a fluidized bed granulator, so that the porous structure can be maintained even though a relatively low concentration of the binder is used.

In order to visualize the granulation process, Maltrin[®] QD 580 and StarLac[™] were used. The StarLac[™] particles have distinguished spherical shape and Maltrin[®] QD 580 particles have porous shape. After the binder solution was added, the SEM pictures of the resultant granules were taken. As shown in Fig. 4, the Maltrin[®] QD 580 (A) and StarLac[™] (B) were combined together and most of the porous structure of Maltrin[®] QD 580 maintained (C). As shown in Fig. 4(D), the SEM picture of the horizontal cross-section of the resulting tablet indicated that a lot of pores larger than 10 μm were maintained.

Fig. 5 shows inner structure of the tablet prepared using Granulation method 2. In order to investigate the structure in more detail, pictures of different magnifications were taken and compared. The magnification of Fig. 5(A) and (B) was 40 and 200, respectively. As shown in Fig. 5(A), even though the granules on the tablet surface were more compressed than those of inner part, there are a lot of empty spaces between granules throughout the table where water can be absorbed by capillary force. At higher magnification (B), the detailed distribution

of the pores can be observed. Upon contact with water or saliva, the granules can be easily dissociated and the whole tablet dissolves or melts to form a paste which is easy to swallow. These figures show that FMTs prepared by compression method using the highly plastic granules can have highly porous structures. Moreover, the disintegration time can be very short due to the fast absorption of water by capillary force.

In our formulation processing, an active pharmaceutical or nutritional ingredient can be added at any step during the processing. It can be added to plastic materials before making highly plastic granules, or alternatively, it can be mixed with the highly plastic granules. This simple approach of making FMTs is based on the highly plastic granules that provide desirable properties ideal for making FMTs by direct compression. Because of the simplicity of this formulation processing, other properties, such as taste-masking and/or sustained release properties, can be easily incorporated into FMTs.

4. Conclusion

In this study the three-component system was used for wet granulation to obtain highly plastic granules. These highly plastic granules can be compressed at low pressure to produce fast-melting tablets. The results show that all three components play an essential role in obtaining tablets with more strength and faster disintegration time with low processing cost.

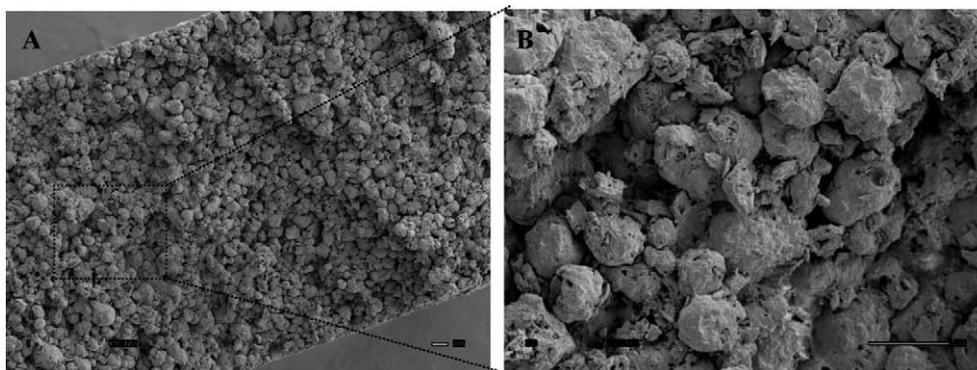


Fig. 5. SEM pictures of horizontal cross-section of a tablet based on the highly plastic granules using Granulation method 2 in (A) low (40 \times) and (B) high magnification (200 \times).

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