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Effect of powder characteristics on oral tablet disintegration

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ABSTRACT

This report describes an investigation of the factors affecting disintegration time in the mouth (DTM) of rapidly disintegrating tablets. The relation between DTM and stationary time of upper punch displacement (STP) was examined using a tableting process analyzer (TabAll). Results indicated that the bulk density of mixed excipient powder used for tablet preparation affects both DTM and STP. As the value of bulk density increased, STP became longer and DTM shorter. The results of a combination of granules and powder with or without a drug showed liner relation between apparent volume (reciprocal of bulk density) and DTM ($r^2 = 0.7332$). For a DTM less than 60 s, a formulation with a bulk density greater 0.5 g/mL should be chosen with a compression force of 5 kN. The hardness of tablets could be greater than 3 kg if at least one high-compressibility excipient was used in the formulation.

1. Introduction

In a society in which people are living longer, drug dosage forms that can improve elderly patient compliance are needed. Many elderly patients find it difficult to swallow tablets or capsules (Hanawa, 1997). For this reason, rapidly disintegrating tablets (RDT) have been developed. RDT are a convenient oral dosage form for patients who have difficulty swallowing conventional tablets or capsules, because the tablet rapidly disintegrates with a small amount of water or saliva in the oral cavity. Recently, companies have developed various types of RDTs by freeze-drying (Seager, 1998), a molding tableting system (Kato et al., 2001), and using saccharides (Mizumoto et al., 2005). However, these methods require specific apparatus or techniques for the manufacturing of RDTs. Therefore, the development of a method that does not require any special apparatus is needed.

Previous studies reported that RDT can be prepared by direct compression using microcrystalline cellulose in combination with low-substituted hydroxypropylcellulose or spherical sugar granules (Watanabe et al., 1995; Ishikawa et al., 2001). In addition, a novel method for predicting disintegration time in the mouth (DTM) of RDT by compaction analysis using a tableting process analyzer (TabAll) has been reported (Shibata et al., 2004). Stationary time of upper punch displacement (STP) can be used to predict disintegration time. The change in upper punch displacement during compaction is shown in Fig. 1. Time stopping displacement on upper punch displacement profiles during compaction of tablet was defined as STP, which correlated with DTM. This result suggested that some common factor influences STP and DTM.

The aim of this study was to find a method for screening new RDT formulations and determining the factors affecting tablet disintegration in the mouth. First the factors affecting STP was investigated using a variety of powders. Then, the relation between factors affecting STP and DTM of RDT was evaluated to find a useful screening method.

2. Experimental

2.1. Materials

Low-substituted hydroxypropylcellulose (L-HPC, LH-11; Shin-Etsu Chemical, Tokyo), microcrystalline cellulose (MCC; PH-102, PH-M25; CEOLUS®-PH102, Avicel®-PH-M25, respectively, Asahi Kasei Chemicals Tokyo), lactose for direct compression (DR; Dilactose®R, Freund Industry, Tokyo), crospovidone (NF grade, Polyplasdone XL®, ISP Japan, Tokyo) and D-mannitol powders (Towa Chemical Industry, Tokyo) were used as powder excipients. Purified D-mannitol spheres (NP108; Nonpareil-108®, Freund Industry, Tokyo), MCC spheres (SCP100, SCP203; CELPHERE®SCP100, CELPHERE®SCP203, Asahi Kasei Chemicals) and aluminum hydroxide gel granules (Cyugai Pharmaceutical, Tokyo) were used as granulated excipients. Magnesium stearate (MS; Wako Pure Chemical Industries, Osaka) was used as a lubricant. Ascorbic acid and acetaminophen were JPXIV grade obtained

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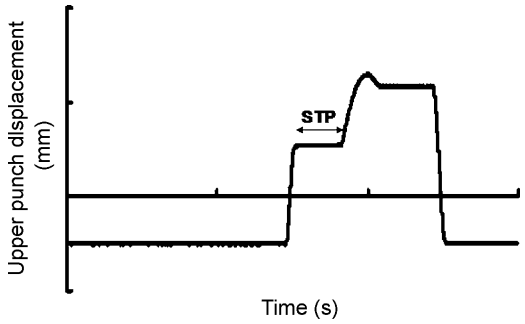

Fig. 1. Change in upper punch displacement during compaction (STP is stationary time of upper punch displacement).

Table 1
Basic formulation of tablets used in this study

Materials	PH102:NP108			PH-M25:NP108			DR:NP108		
	5:5	7:3	9:1	5:5	7:3	9:1	5:5	7:3	9:1
NP108	100	60	20	100	60	20	90	54	18
PH102	100	140	180	–	–	–	–	–	–
PH-M25	–	–	–	100	140	180	–	–	–
DR	–	–	–	–	–	–	90	126	162
CrosPVP	–	–	–	–	–	–	20	20	20
MS	2	2	2	2	2	2	2	2	2
Total (mg)	202	202	202	202	202	202	202	202	202

from Maruishi Pharmaceutical (Osaka); ethenzamide also was JPXIV grade obtained from Yoshida Pharmaceutical (Tokyo).

2.2. Preparation of tablets

Tablet formulations are shown in Tables 1 and 2. The NP108 and MCC or DR were mixed in various weight ratios (5:5, 7:3, 1:9) and drug was added in some formulations. When the mixture of NP108 and DR was used, 10% crospovidone was added to the mixture. Then MS (1%) was added to all formulations. The mixture was directly compressed to tablets using a tableting process analyzer (Model N-30EX, TabAll, Okada Seiko, Tokyo) equipped with flat-faced punches 8 mm in diameter, using a compression force of 5 kN and press speed of 10 tablets/min. Compressibility of the materials was evaluated by comparing punch displacement profiles during the compaction process, which could be measured by TabAll. Data were recorded using Daatsu II software (Okada Seiko, Tokyo).

2.3. Measurement of powder and tablet characteristics

Using a tapping density analyzer (Tapdenser KYT-1000, Seishin Enterprise, Tokyo), with a 20-cm^3-volume cylinder, bulk density was calculated from the powder weight in the cylinder.

Table 2
Formulation of tablets containing a model drug

	PH102:NP108 (5:5)		PH-M25:NP108 (7:3)		DR:NP108 (7:3)	
	5%	25%	5%	25%	5%	25%
Drug	10	50	10	50	10	50
NP108	95	75	57	45	51	39
PH102	95	75	–	–	–	–
PH-M25	–	–	133	105	–	–
DR	–	–	–	–	119	91
CrosPVP	–	–	–	–	20	20
MS	2	2	2	2	2	2
Total	202	202	202	202	202	202

The crushing tolerance of the tablets (hardness) was measured with a digital crushing tolerance machine (TS-50N, Okada Seiko, Tokyo). An average of 10 tablets was used for the hardness value. Porosity was calculated from the results of the absolute density measured with a multivolume pycnometer (Accupyc 1330, Shimadzu, Kyoto) and apparent density calculated using the weight, diameter, and thickness of tablets.

2.4. Measurement of DTM

Three healthy volunteers, who supplied informed consent, washed out their mouths with water. After 30 s, they were randomly assigned a prepared tablet and the time required for disintegration of the tablet in the mouth. The time at which each volunteer put the tablet on his/her tongue was recorded. The volunteers were instructed not to chew or drink water while the tablet disintegrated. Immediately after disintegration, the volunteers rinsed their mouths with water to avoid ingesting the materials. If the tablet did not disintegrate within 120 s, disintegration time was defined as greater than 120 s. Three measurements were averaged to obtain an individual oral disintegration time. In this method, the DTM of commercial RDTs, Takepron OD and Gaster® D, were 63 ± 13 s and 57 ± 19 s, respectively.

3. Results and discussion

3.1. Effect of powder characteristics on stationary time

In previous studies, DTM of tablets with formulations shown in Table 1 decreased with an increase in STP, relaxation time of upper punch displacement (RTP), and relaxation time of die wall force (RTD) (Shibata et al., 2004). The negative correlation between DTM and these parameters suggests that a common factor influences STP, RTP, RTD, and DTM. Therefore, the factors affecting these parameters were investigated. STP was chosen for this study because three parameters were correlated with each other (data not shown), and STP had a stronger correlation to DTM compared to the other parameters. To simplify the study, single materials were used instead of formulations.

Fig. 2 shows the STP of four materials, which are often used as tablet excipients, divided by three particle sizes, except L-HPC, which was smaller than 150 μm. STP increased in the order of CrosPVP < PH102 < DR, independent of particle size. For L-HPC, the value of STP varied by particle size. In addition, the appearance of the powders varied with particle size. Powder of particle size 75–150 μm was more bulky than powder with a particle size less than 75 μm, which suggests that the bulk density of the powder influences STP.

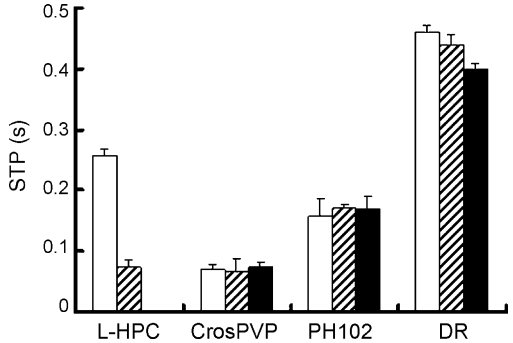

Fig. 2. Effect of particle size of powder on stationary time. Particle size: (■) >150 μm; (▨) 75–150 μm; (□) <75 μm. Each column represents the mean ± S.D. of three experiments.

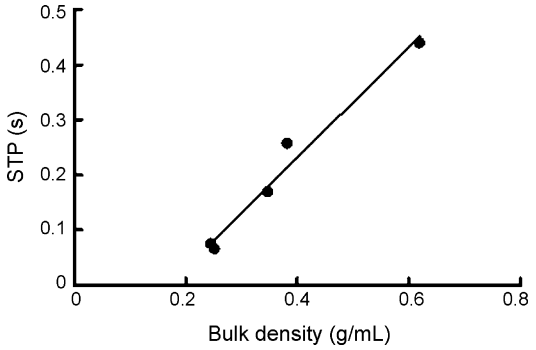

Fig. 3. Relation between bulk density and STP. Particle size of 75–150 μm was used for CrosPVP, PH-102, and DR.

The effects of particle size of L-HPC and PH102 on bulk density were compared. For L-HPC, the bulk density of particle size 75–150 μm was 0.25 g/mL but was 0.38 g/mL for particles less than 75 μm. In contrast, the bulk densities of PH102 powders with particle size of 75–150 μm and less than 75 μm were 0.35 g/mL and 0.31 g/mL, respectively. Bulk density of L-HPC, but not PH102, depends on particle size.

The relation of bulk density of various powders and STP is shown in Fig. 3. A linear correlation exists between bulk density and STP (r^2 = 0.974). Therefore, bulk density of the powder influences STP in these materials.

The relation between STP and bulk density depends on the mechanical structure of the TabAll machine. When bulk density is low, the lower punch was adjusted to a lower position to allow fill of 200 mg of powder. In this case, the lowest position of the upper punch must be set during a series of tableting procedures to obtain the same compression force. This shortens the distance between two position adjustment nuts. When the lever of the upper punch moves between these two nuts without touching, the upper lever stands still. The duration that the lever stands still was detected as STP. Thus, STP depended on bulk density, but not on compression of the powder.

3.2. Relation between bulk density of powder and DTM of tablets containing model drugs

Previous results indicated that powder bulk density correlates with STP. Therefore, a relation between bulk density of powder and DTM was investigated using the formulations shown in Table 1. For all formulations, DTM decreased with an increase in powder bulk density with a good correlation (Fig. 4). Thus, bulk density appears to affect DTM.

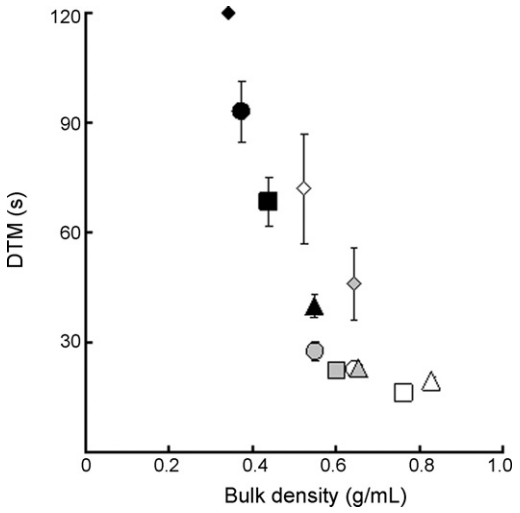

Fig. 4. Relation between disintegration time in the mouth and bulk density: (♦) PH102; (●) PH102:NP108 = 9:1; (■) PH102:NP108 = 7:3; (▲) PH102:NP108 = 5:5; (◊) PH-M25; (○) PH-M25:NP108 = 9:1; (□) PH-M25:NP108 = 7:3; (△) PH-M25:NP108 = 5:5; (⧫) DR (with CrosPVP); ( ) DR:NP108 = 9:1; (◯) DR:NP108 = 7:3; (△) DR:NP108 = 5:5 (■). Each point represents the mean ± S.D. of three experiments.

Drugs with different physicochemical properties (ascorbic acid as a water-soluble drug, acetaminophen and ethenzamide as low-solubility drug) were added to the formulations as model drugs. Formulations of tablets containing model drugs are shown in Table 2. The ratio of NP108 was fit to the ratio that produced the shortest DTM (from earlier studies), and drug was added at 5% or 25%. The relation between DTM of tablets containing model drugs and the bulk density of powders containing model drugs is shown in Fig. 5. Addition of ascorbic acid had little effect on the bulk density of the formulation, and short DTM values were maintained for all formulations. For acetaminophen and ethenzamide, as the content of drug increased, bulk density of the powder tended to decrease and DTM tended to increase. These results indicate that powder bulk density influences the DTM of tablets, and the same relation was observed for all cases examined. This suggests that rapidly disintegrating tablets can be obtained using powder with high bulk density.

3.3. Effect of other powder characteristics on DTM

A relation exists between powder bulk density and DTM. The DTM values of tablets containing NP108 and tablets without NP108 (PH102, PH-M25, and DR + CrosPVP) but containing 1% MS were compared. The DTM of tablets containing NP108 was faster than

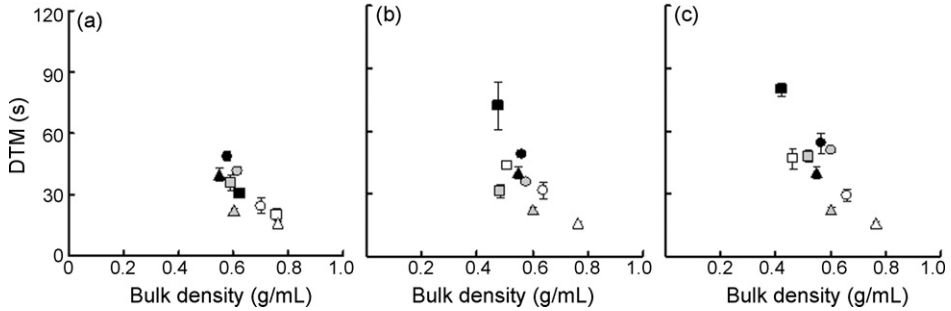

Fig. 5. Relation between disintegration time in the mouth of tablets containing (a) ascorbic acid, (b) acetaminophen, and (c) ethenzamideand bulk density. Content of drugs: (▲) 0% PH102:NP108; (●) 5% PH102:NP108; (■) 25% PH102:NP108; (△) 0% PH-M25:NP108; (○) 5% PH-M25:NP108; (□) 25% PH-M25:NP108; (△) 0% DR:NP108; (◯) 5% DR:NP108; (■) 25% DR:NP108. Each point represents the mean ± S.D. of three experiments.

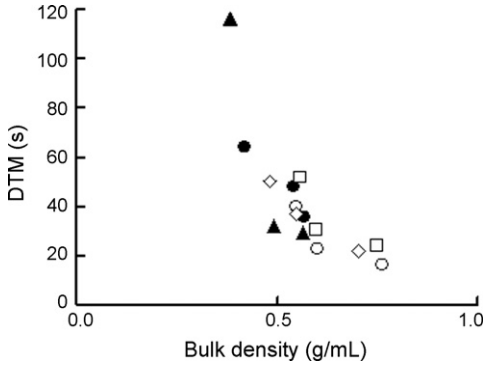

Fig. 6. Relation between DTM and bulk density when (○) NP108 was replaced with (●) Mannit; (◊) SCP100; (□) CP203; or (▲) aluminum hydroxide.

those of tablets without NP108. For all cases, tablets without NP108 possessed longer DTM values of about 30 s. The relation between DTM and bulk density without NP108 was the same as that with NP108 as shown in Fig. 4. Bulk density increased with an increase in the mixing ratio of NP108, because the bulk density of NP108 is large (0.78 g/cm^3). It is possible that the relation between DTM and bulk density is dependent on the amount of NP108 in the tablet.

Possible explanations for shorter DTM values with increasing NP108 amounts include the following: the bulk density alone; the presence of granules that provide high bulk density; and the water-soluble characteristic of NP108. Thus, NP108 was replaced with D-mannitol powder, MCC spheres (SCP100 or CP203), or aluminum hydroxide gel granules. The formulation was prepared with the following weight ratios: PH102:additive = 5:5, PH-M25:additive = 7:3, and DR:additive = 7:3. The relation between bulk density and DTM of tablets containing NP108 or other additives is shown in Fig. 6.

D-mannitol powder, although chemically the same as NP108, can have greater water-solubility because of its smaller particle size. For tablets containing D-mannitol powder, the DTM was 20–30 s longer and bulk density was smaller than that of tablets containing NP108.

SCP100 and CP203 are water-insoluble granules that have a bulk density similar to NP108, 0.71 and 0.95 g/mL, respectively. They had nearly the same powder bulk density and DTM as NP108, which suggests that water solubility does not affect DTM, but powder bulk density and granule content may have some effect.

Aluminum hydroxide gel granules, which have low density (0.36 g/mL), were used. Although in granule form, the DTM values were longer and had a linear relation with bulk density, which suggests that bulk density of the powder, not granule form, was the important influence on DTM.

The relations between DTM and tablet characteristics of hardness and porosity have been reported (Kitazawa et al., 1975; Bi et al., 1999; Sugimoto et al., 2001). Thus, the effect of these factors on DTM was compared. Fig. 7 shows the relation between DTM and powder bulk density, hardness of tablets, and porosity of tablets. Bulk density and DTM showed significant correlation ($r = 0.798$). Tablet hardness and DTM also showed a significant relation ($r = 0.619$), but it was lower than that between powder bulk density and DTM. No significant correlation ($r = 0.268$) was found between tablet porosity and DTM (Fig. 7c).

The thickness of the tablets was similar, 3.0 mm for all formulations except that involving DR, which had 3.2 mm thickness. Thus, the compression ratio correlated with powder bulk density, which is the reason why bulk density correlated with DTM.

Table 3
Bulk density of powder and hardness of tablets using various powders and granules

Formulation	Bulk density (g/mL)	Hardness (kg)
PH102	0.34	20<
PH-M25	0.64	8.0
DR (CrosPVP10%)	0.52	2.4
NP108	0.78	1.3
SCP100	0.71	–
CP203	0.95	–
Aluminum hydroxy gel	0.36	9.8

(–) Tablet was not obtained with compression force of 5 kN.

3.4. Hardness of tablets

Results suggested that the bulk density of a formulation before compression could predict DTM. For RDT, tablet hardness is as important as DTM, but it is hard to fulfill both requirements (Oshima et al., 2003). As mentioned earlier, a weak correlation exists between tablet hardness and DTM. Therefore, it is possible to obtain tablets with suitable hardness and DTM. In practical use, RDTs generally have a DTM value less than 60 s and a hardness value of least 3 kg. Therefore, the formulation with a powder bulk density of 0.5 g/mL (Fig. 7) was chosen to investigate factors that influence tablet hardness.

Hardness of tablets containing various granules and powders are shown in Table 3. Tablets using MCC powder, PH102, or PH-M25, possessed high hardness, while tablets containing DR (+crosPVP) possessed low hardness. Tablets containing aluminum hydroxide gel had a hardness of 9.8 kg. In contrast, tablets could not be prepared using MCC granules, SCP100, or CP203. Therefore, PH102 and PH-M25 were used as models of high-compressibility powder, and aluminum hydroxide gel was used as a model of high-compressibility granules. DR (+crosPVP) was a model of low-compressibility powder, and SCP100 and CP203 were models of low-compressibility granules. Powders and granules were mixed in a ratio of 9:1, 7:3, or 5:5 and compressed at 5 kN.

Fig. 8 shows the hardness and DTM of tablets. One type of tablet containing low-compressibility powder and granules had a hardness of 3.2 kg, however the others had a hardness less than 3 kg. A combination of low- and high-compressibility powder and granule possessed a hardness greater than 3 kg, except for two formulations containing 50% low-compressibility granules. Tablets with a com-

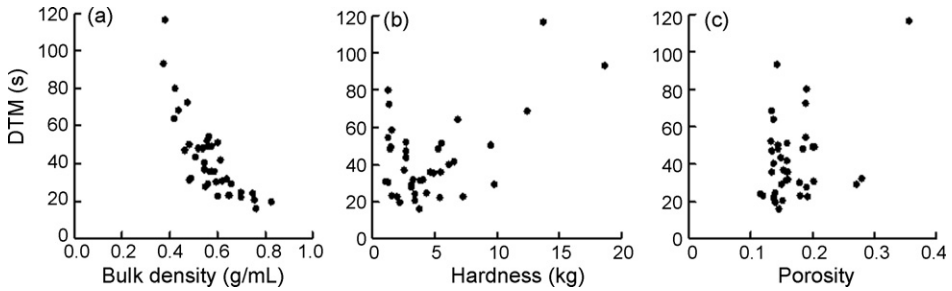

Fig. 7. Relation between DTM and (a) bulk density of powder, (b) tablet hardness, and (c) tablet porosity for all formulations used in the study.

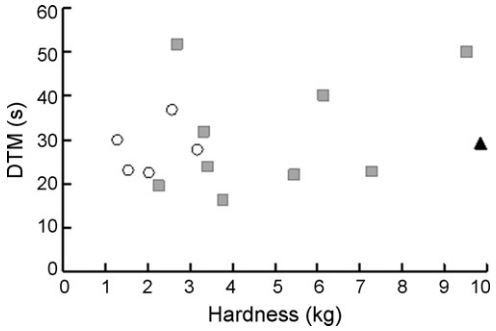

Fig. 8. Combination of excipients on hardness of tablets: (○) low-compressibility granules and low-compressibility powder; (■) high-compressibility granules and low-compressibility powder or low-compressibility granules and high-compressibility powder; (▲) high-compressibility granules and high-compressibility powder.

bination of high-compressibility powder and granules had a low bulk density.

These results suggest that at least one excipient must have high compressibility to achieve sufficient hardness.

4. Conclusions

An investigation of the relation between powder characteristics and disintegration time of tablets in the mouth (DTM) revealed that a high bulk density results in a short DTM. Tablets producing a DTM less than 60 s were obtained when the powder bulk density was greater than 0.5 g/mL. Tablets with a short DTM value tended to possess low hardness; however, the use of high-compressibility excipients in the formulation increased the hardness to values greater than 3 kg. The formulations in this study that contained an ingredient with good disintegration characteristics were MCC and CrosPVP. Formulations without these materials did not disintegrate readily.

A granulation technique often is used for RDT tablets to mask the taste of drugs. Characteristics of the granules, such as bulk density and compressibility, can be measured to aid in the selection of additives to produce rapidly disintegrating tablets.

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