Note

Potential Use of Magnesium Oxide as an Excipient to Maintain the Hardness of Orally Disintegrating Tablets during Unpackaged Storage

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This study aimed to clarify the effects of magnesium oxide (MgO) on the hardness of orally disintegrating tablets (ODTs) during storage. ODTs containing a range of MgO concentrations were prepared by direct powder compression and stored for up to 4 weeks in an unpackaged condition at 40°C, with 75% relative humidity. Tablets that did not contain MgO showed a significant decrease in hardness after one week in storage, while those containing MgO at a mass fraction of ≥4% maintained their hardness for up to 4 weeks. The tablet disintegration times after storage were equivalent to those observed before storage (approximately 30 s), regardless of the MgO level. Furthermore, the dissolution behavior of a model drug (acetaminophen) from the ODTs was not affected by the level of MgO. These findings revealed that the addition of MgO suppressed the reduction in ODT hardness during storage in the unpackaged state, without delaying tablet disintegration or inhibiting drug release.

Key words orally disintegrating tablet; relative humidity; unpackaged state; dissolution test

Introduction

Orally disintegrating tablets (ODTs) are solid oral preparations that disintegrate in mouth saliva or a small amount of water promptly, defined as within 30 s by the U.S. Food and Drug Administration (FDA).[1)] This dosage form is very useful for infants, elderly people or patients with difficulty swallowing, and in patients with limited water intake.

Initial ODT formulations were relatively soft, and care was required during handling.[2)] However, recently developed ODTs have good disintegration properties and a higher level of hardness.[3,4)] However, ODTs contain strongly hydrophilic materials that absorb water and swell; therefore, exposure to moisture decreases tablet hardness, increasing the risk of cracking or chipping during handling.[5)] Therefore, it is important to ensure the quality of the preparation to minimize any reduction in tablet hardness due to moisture absorption. Several solutions to this problem using additives have been reported to date, but elaborate processing of the additives is required before tablet preparation.[6,7)] Further research is required to develop a convenient method of preparing an ODT that exhibits rapid disintegration while maintaining its hardness during storage under high humidity.

Magnesium oxide (MgO) is widely used as an effective and safe laxative and antacid. Previous studies have shown that the hardness of tableted MgO increases during storage under high humidity in the unpackaged state.[8,9)] We have previously investigated the inhibitory effect of MgO on the decrease in hardness during storage of tablets, and the mechanism underlying this effect.[10,11)]

The present study investigated the inhibitory effect of MgO on the decrease in ODT hardness due to moisture absorption. At the same time, we investigated the disintegration of ODTs and drug dissolution from these tablets and evaluated the usefulness of MgO as an additive for maintaining the hardness of ODTs.

Experimental

Test Materials In the present study, Japanese Pharmacopoeia acetaminophen (APAP; Iwaki Seiyaku Co., Ltd., Tokyo, Japan) was used as a model drug, after grinding using a jet mill (NC-400; Nano-Engineering, Co., Ltd., Yamaguchi, Japan) to an average diameter of 31.2 μm. Anhydrous dibasic calcium phosphate (GS grade; Kyowa Chemical Industry Co., Ltd., Kagawa, Japan) and lactose monohydrate granules (Dilactose® S; Freund Corporation, Tokyo) were used as fillers. Carmellose (NS-300®; NICHIRIN CHEMICAL INDUSTRIES, Ltd., Hyogo, Japan) and vegetable-derived magnesium stearate (TAIHEI CHEMICAL INDUSTRIAL Co., Ltd., Osaka, Japan) were used as the disintegrant and lubricant, respectively. We used MgO (Kyowa Chemical Industry Co., Ltd.) that had been passed through a 150-μm sieve and had an average diameter of 13.3 μm. Other reagents complied with the Japanese Pharmacopoeia, seventeenth edition (JP17), or were of analytical grade.

Preparation of Powder Formulations According to the constituent ratio shown in Table 1, the powders without magnesium stearate (total amount, 990 g) were mixed for 5 min at rotation speed and revolution of 28 and 30 rpm, respectively (PowMixer, Cross Rotary Model-Laboratory Type [CM-3]; Tsukasa Industry Co., Ltd., Aichi, Japan). Magnesium stearate (10 g) was then added to the mixed powders to achieve a final concentration of 1%, followed by 2 min of mixing under the same conditions to obtain the formulation powders.

Preparation of Model ODTs The formulation powders (250 mg) shown in Table 1 were tableted at a compression pressure of 10 kN using a rotary tableting machine (VIRGO; Kikusui Seisakusho Ltd., Kyoto, Japan); a punch with an

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Table 1. Tablet Formulations

Constituent amounts; mg (w/w %)					
MgO	Acetaminophen	Lactose monohydrate	Anhydrous dibasic calcium phosphate	Carmellose	Magnesium stearate
0 (0%)	12.5 (5%)	147.5 (59%)	75.0 (30%)	12.5 (5%)	2.5 (1%)
2.5 (1%)	12.5 (5%)	145.0 (58%)	75.0 (30%)	12.5 (5%)	2.5 (1%)
5.0 (2%)	12.5 (5%)	142.5 (57%)	75.0 (30%)	12.5 (5%)	2.5 (1%)
7.5 (3%)	12.5 (5%)	140.0 (56%)	75.0 (30%)	12.5 (5%)	2.5 (1%)
10.0 (4%)	12.5 (5%)	137.5 (55%)	75.0 (30%)	12.5 (5%)	2.5 (1%)
12.5 (5%)	12.5 (5%)	135.0 (54%)	75.0 (30%)	12.5 (5%)	2.5 (1%)
250.0 (100%)					

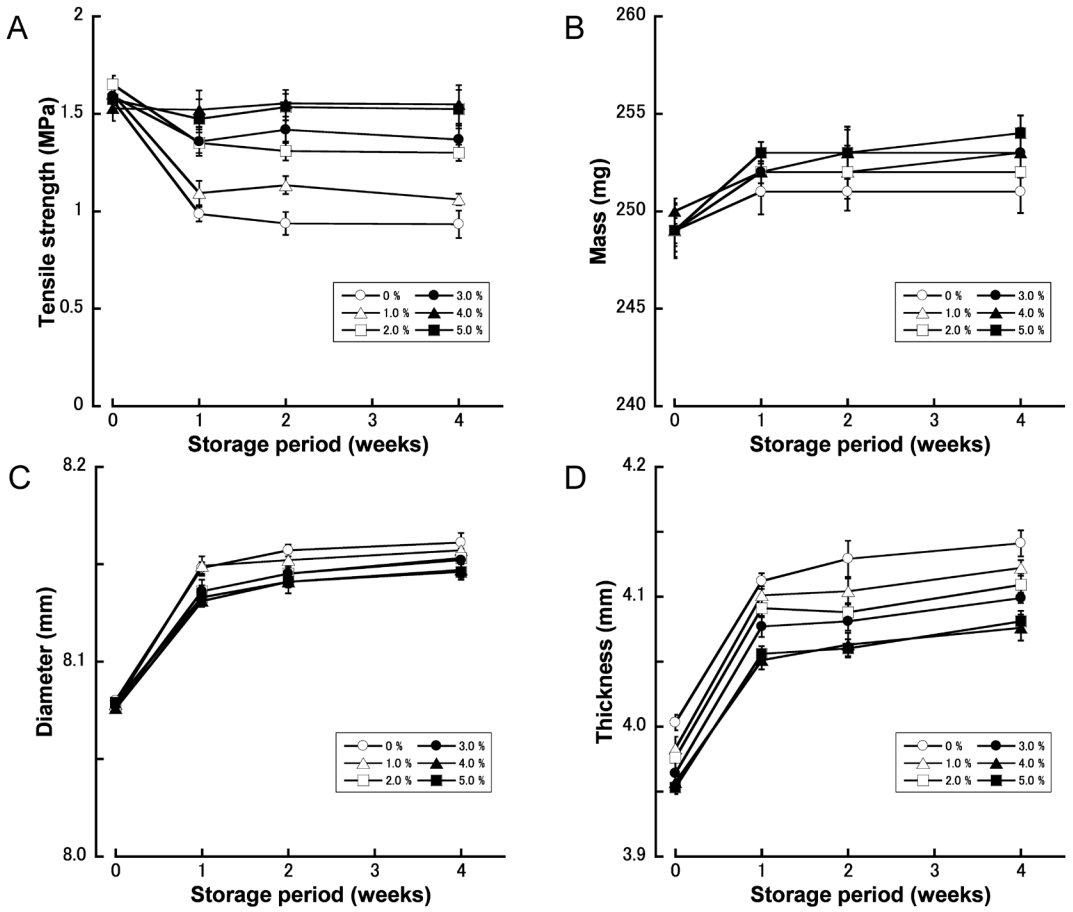

Fig. 1. Effects of Tablet MgO Concentration on (A) Tensile Strength (TS), (B) Mass, (C) Diameter, and (D) Thickness at the Indicated Time Points

The key indicates the concentration of MgO employed. Data represent the means ± standard deviation ($n = 10$).

8-mm diameter and a curvature of 12R was employed.

Tablet Storage The prepared tablets were kept for 1 d in a desiccator with a bed of silica gel on the base. The tablets were then stored for 1, 2, or 4 weeks in a storage stability testing chamber (LH20-14M; Nagano Science Co., Ltd., Osaka, Japan) at 40°C with 75% relative humidity. The tablets were examined immediately after the end of each storage period.

Measuring Tablet Tensile Strength A Schleuniger tablet hardness tester (8M; Freund Corporation, Tokyo, Japan) was used to measure the load required to break each tablet in the radial direction. This load was then converted to tensile strength (*TS*), a measure of tablet hardness, using formula (1)[12]:

$$TS\ (\mathrm{MPa}) = \frac{10F}{10^6 \pi D^2}\left(2.84\frac{H}{D} - 0.126\frac{H}{H-2Hc} + 3.15\frac{H-2Hc}{D} + 0.01\right)^{-1} \quad (1)$$

Where, F (N) was the load required to break the tablet, D (m) was the tablet diameter, H (m) was the tablet thickness, Hc (m) was the thickness of the convex portion of the tablet, and $H-2Hc$ (m) was, therefore, the thickness of the cylindrical portion. D and H were measured using a digimatic micrometer (Quick Micro MDQ-30M; Mitutoyo Corporation, Kanagawa, Japan). Hc was calculated using the curvature (12R) and the

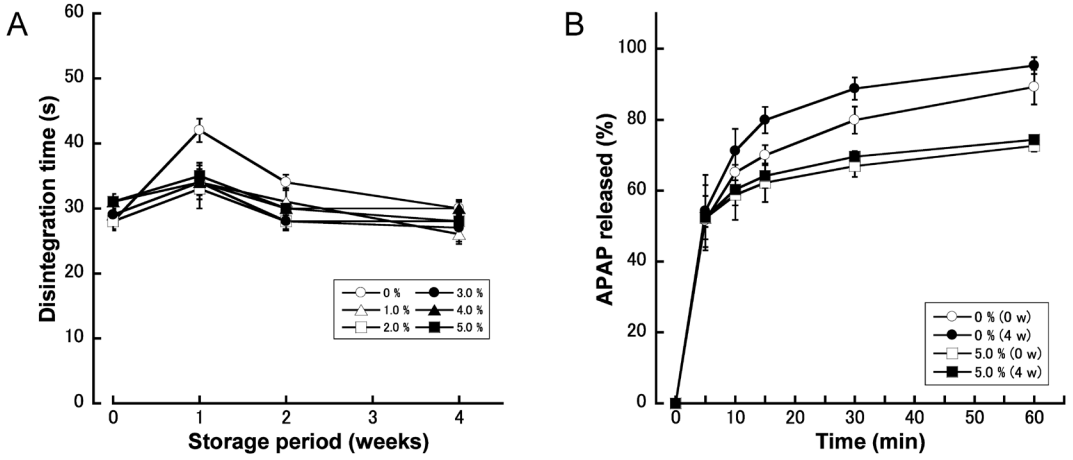

Fig. 2. Effects of Tablet MgO Concentration on (A) Disintegration Time and (B) APAP Release Profiles at the Indicated Time Points

The key indicates the concentration of MgO employed; w, weeks in storage. Data represent the means ± standard deviation (A, $n = 6$; B, $n = 3$).

measured diameter (D).

Measurement of Disintegration Time The time required for tablet disintegration was measured using a disintegration tester (NT-20H; Toyama Sangyo Co., Ltd., Osaka, Japan), in accordance with the JP17 tablet disintegration test. Distilled water at 37 ± 2°C was used as the medium.

It is recommended that the disintegration time (within about 30 s) required by the FDA for ODT be measured in a general disintegration test prescribed in the U.S. Pharmacopoeia.[1] Furthermore, since the apparatus and procedure of the disintegration test of the Japanese Pharmacopoeia are unified with that of the U.S. Pharmacopoeia in terms of international harmonization, the disintegration time was measured by this test.

Evaluation of Model Drug Release The elution characteristics of APAP were evaluated using the JP17 paddle method with an elution tester (NTR-3000; Toyama Sangyo Co., Ltd., Osaka, Japan). Using a dissolution medium of 900 mL distilled water at 37 ± 0.5°C and a paddle rotation rate of 50 rpm, the APAP concentration in the dissolution medium was measured at 5, 10, 15, 30, and 60 min using a spectrophotometer (U-3310; Hitachi High-Technologies Corporation, Tokyo, Japan) at a measurement wavelength of 244 nm.

Evaluation of Tablet Pore Characteristics The tablet pore volume, pore surface area, mean pore diameter, and open pore ratio were measured using an automated mercury porosimeter (AutoPore IV 9500; SHIMADZU CORPORATION, Kyoto, Japan). Five tablets were used for each measurement.

Results and Discussion

In the present study, the hardness of ODTs formulated without MgO had decreased markedly after storage for 1 week. As the concentration of MgO increased in the formulation, the decrease in hardness during storage was attenuated. Furthermore, the addition of ≥4% MgO maintained the initial tablet hardness (observed before storage, Fig. 1A). In addition, the tablet mass during storage tended to increase as the concentration of MgO increased; this effect was observed after storage for 1 week (Fig. 1B). On the other hand, although both tablet diameter (Fig. 1C) and thickness (Fig. 1D) increased during storage, the diameters of the MgO-containing tablets were smaller than that of the MgO-free tablet.

Previous research indicated that hydromagnesite was formed during storage of MgO-containing tablets at 40°C and 75% relative humidity; this resulted from the reaction between MgO and atmospheric moisture and carbon dioxide, forming solid bridges at an early stage (<1 week), which increased tablet hardness.[11] In the present study, tablet mass increased in a MgO concentration-dependent manner within 1 week of storage, indicating that the attenuation of tablet softening involved the same mechanism.

Oka *et al.*[9] also reported that when a commercially available tablet containing MgO as a main ingredient was stored at 40°C and 75% relative humidity, the tablet disintegration was reduced. Disintegration time was slightly prolonged after 1 week of storage, irrespective of the MgO concentration; however, at ≥2 weeks, it was comparable to the time observed before storage (Fig. 2A). This indicated that the inclusion of up to 5% MgO had a negligible effect on the disintegration of ODTs. Furthermore, although less elution of the model drug (APAP) was observed from tablets containing 5% MgO within 10 min after the start of the dissolution test, as compared to the 0% MgO tablets, there was no difference in this elution behavior between the 0- and 4-week storage period (Fig. 2B). This lower elution of APAP was attributed to the inclusion of MgO in the tablet and the hydromagnesite formed during storage. APAP has a phenolic hydroxyl group and a pK_a of 9.5, and dissociation of this functional group under basic conditions shifts the maximum absorption wavelength of APAP to 257 nm.[13] The pH of the test solution after elution testing of the 0% MgO tablets was 5.3 before storage and 4.8 after storage, as compared with 10.1 and 9.7, respectively, for the 5% MgO tablets. This rise in pH due to the dissolution of basic MgO and the generation of hydromagnesite may have reduced the absorbance of APAP at 244 nm during the dissolution test. These results revealed that the presence of 5% MgO in the tablet formulation attenuated the decrease in hardness during storage, without affecting the disintegration time or the elution of a test drug.

The hardness and disintegration of ODTs are considered to be related to the internal structures of the tablets. Therefore, we investigated the effect of MgO on tablet structure during storage (Fig. 3).

In all of the ODTs studied, an increase in the pore volume (Fig. 3A) and open pore ratio (Fig. 3D) was observed after 1

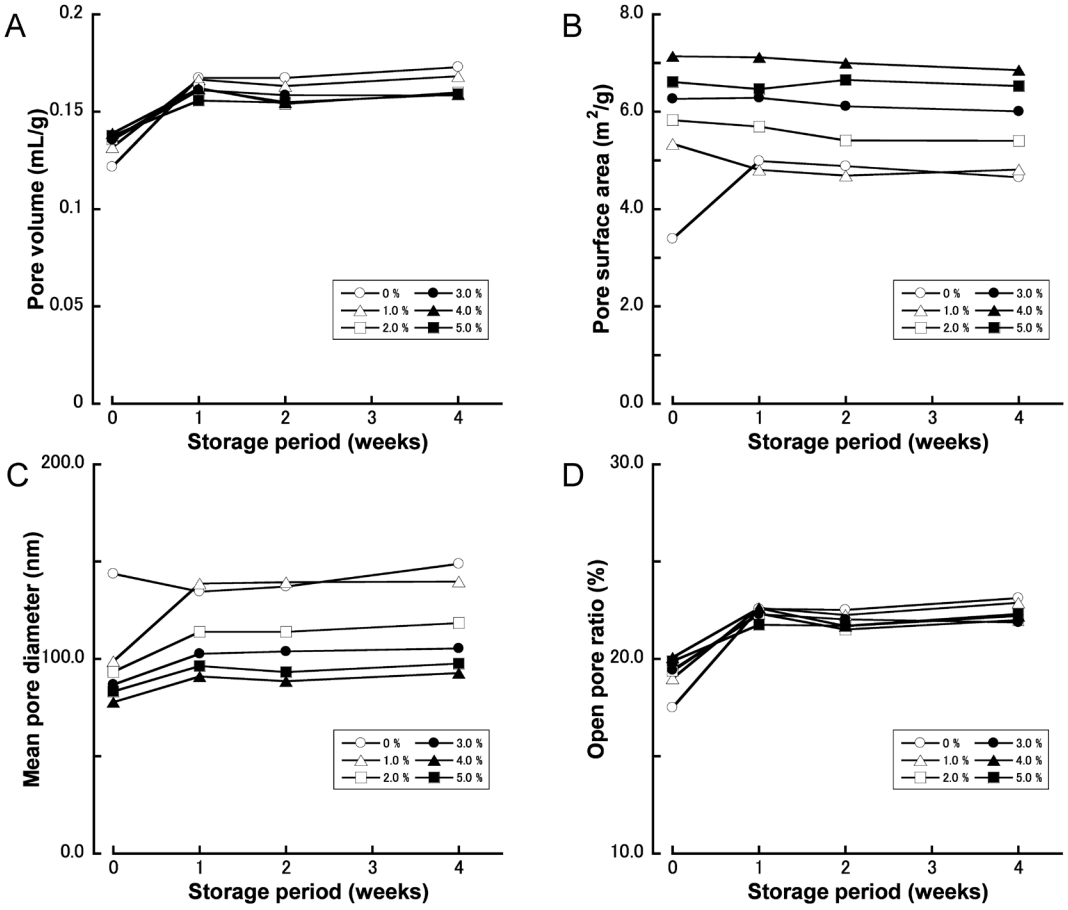

Fig. 3. Effects of Tablet MgO Concentration on (A) Pore Volume, (B) Pore Surface Area, (C) Mean Pore Diameter, and (D) Open Pore Ratio of Tablets at the Indicated Time Points

The key indicates the concentration of MgO employed ($n = 5$).

week of storage. The increases in tablet diameter and thickness (Fig. 1) are due to swelling of the disintegrant, caused by moisture absorption. On the other hand, the pore surface area (Fig. 3B) in the 0% MgO tablet increased after 1 week in storage, while the MgO-containing tablets tended to remain constant or decrease during storage. In contrast, the mean pore diameter (Fig. 3C) tended to increase over time in MgO-containing tablets. This could relate to the MgO-associated interaction with moisture and carbon dioxide to form hydromagnesite, which has a larger specific volume and lower solubility, as reported previously.[11] That is, it was inferred that because MgO disappeared from the tablet pores and hydromagnesite appeared within the gaps and formed solid bridges, the surface area decreased, and the pores expanded.

From these results, it was concluded that the formation of hydromagnesite from MgO maintains tablet hardness by forming solid bridges between particles, while the penetration of liquid into the tablet was maintained because the mean pore diameter became larger over time in storage.

Conclusion

This study indicated that humidity-related reduction in the hardness of ODTs prepared using direct compression could be suppressed by the inclusion of MgO, without affecting tablet disintegration or drug dissolution. We previously reported that MgO suppressed tablet hardness reduction, even when used in combination with a range of fillers and disintegrants.[10] It is expected that MgO could be used as a hardness reduction inhibitor when preparing tablets including ODTs by direct powder compression in the future.

Conflict of Interest The authors declare no conflict of interest.

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