Effect of Food Thickener on Dissolution and Laxative Activity of Magnesium Oxide Tablets in Mice

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The present study examined the dissolution of magnesium oxide (MgO) from MgO tablets placed in a food thickening agent (food thickener) and its effects on laxative activity. We prepared mixtures of MgO tablets suspended in an aqueous suspension and food thickeners in order to evaluate the dissolution of MgO. The results of the dissolution tests revealed that agar-based food thickeners did not affect the MgO dissolution. In contrast, some xanthan gum-based food-thickener products show dissolution rates with certain mixtures containing disintegrated MgO tablets suspended in a food thickener that decrease over time. However, other xanthan gum-based food-thickener products show dissolution rates that decrease immediately after mixing, regardless of the time they were allowed to stand. In order to investigate the laxative activity of MgO, we orally administered a mixture of MgO suspension and food thickener to mice and observed their bowel movements. The animal experiments showed that when agar-based food thickeners were used, the laxative activity of MgO was not affected, but it decreased when xanthan gum-based food thickeners were used.

Key words  food thickener; magnesium oxide; laxative activity; dissolution rate; agarose gel; xanthan gum

Materials and Methods

Dissolution Test

Samples

We used Magmitt® 500mg Tablets (M Tablets) made by Kyowa Chemical Industry Co., Ltd. (Japan). A deglutition aid jelly for oral administration (jelly-wafer) developed by Ryuukakusan Co., Ltd. (Japan) was used. As food thickeners, we used the xanthan gum-based thickeners, Tsururinko Quickly (Tsuru-Q; Clinico Co., Ltd., Japan) and Neo-highitoromeal III (Neo Hi-toro III; Food-Care Inc., Japan), and an agar-based thickener, Ultra-agar (Ina Food Industry Co., Ltd., Japan), which has the same constituents as jelly-wafers.

Food Thickeners and Line Spread Test (LST)

In accordance with the Classification of Modified Diet for Dysphagic Persons in 2013 of the Japanese Society of Dysphagia Rehabilitation (JSDR), we measured food thickeners...
prepared at various concentrations by using plastic measuring plates in a LST. That is, we injected a food thickener (20 mL) into a metal ring (30 mm in diameter), lifted the ring after 30s, and measured the distance (mm) that the samples travelled after 60s, a mean (n=3) in six directions were defined as the LST value.

Preparation of Food Thickener

The food thickeners were each prepared in accordance with their respective indications in order to produce moderately thick concentrations (equivalent to an LST score of 32 to 36 mm). Moreover, moderate thickness refers to the amount of thickness that is first tried by patients with dysphagia. We prepared Tsuru-Q at 3.5% (w/v), Neo Hi-toroIII at 2.3% (w/v), Ultra-agar at 0.9% (w/v). Because the jelly-wafers were already in a jellied state, we used the products as they were. Then, 3 mL of food thickener that was prepared at various concentrations or 3 mL of jelly-wafer was mixed with suspending and disintegrating the MgO tablets in 2 mL of water.

Dissolution of Mixture Consisting of M Tablet Suspension and Food Thickener

After one M tablet was suspended and disintegrated in 2 mL of water at room temperature, 3 mL of a food thickener that was prepared at various concentrations or 3 mL of a jelly-wafer was mixed and allowed to stand for 30 min at room temperature. The entire mixtures were subsequently placed in dissolution vessels and dissolution testing was performed on the samples. The dissolution test solution was collected and measured using a micropipette. Moreover, untreated M tablets were used as a control. The dissolution tests were conducted in accordance with the dissolution testing procedures of the Japanese Pharmacopoeia; we performed dissolution using an 8-shaft dissolution tester (NTR-8000AC; Toyama Sangyo Co., Ltd., Japan) and performed dissolution using a first fluid (pH 1.2) as the dissolution test solution by paddle method at 50 rpm with 6 vessels. Sampling times were 30, 60, and 120 min.

The dissolution rate of MgO was calculated by quantifying and calculating the eluted magnesium using atomic absorption spectrophotometry (atomic absorption spectrophotometer AA-6500; Shimadzu Corporation, Japan).

Animal Experiments

Animals Used in the Present Study

We bought 6-week-old male Crl:CD1(ICR) mice from Charles River Laboratories Japan Inc. and performed the experiments after a 1-week preliminary breeding period. One group comprised five mice, which were independently bred under the following conditions: room temperature of 22 ± 3°C, humidity level of 50 ± 20%, and light period from 7:00 a.m. to 7:00 p.m. In addition, during breeding, the mice had free access to food and water.

The animal experiments in the present study were conducted in accordance with the Guidelines for Proper Conduct of Animal Experiments of the Science Council of Japan and were approved by the animal experiment committee of Drug Safety Research Laboratories, Shin Nippon Biomedical Laboratories, Ltd. (approval No. IACUC335-009), where these experiments were conducted. This test facility is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

Drugs Used in the Present Study

The M tablets were suspended and disintegrated in water for injection heated to 80°C or higher (150 mg/mL) and mixed in a ratio of 2:3 with food thickeners prepared at various thicknesses or a jelly-wafer, and after being allowed to stand for 30 min at room temperature, were orally administered to mice.

The dose of MgO used was 600 mg/kg. Laxative activity was confirmed in 90% of mice that received a single oral dose of MgO at 600 mg/kg; therefore, we selected this dose for use in the present study. Moreover, in a previous study, we disintegrated M tablets in a 0.5% carboxymethylcellulose sodium solution and administered this formulation (10 mL/kg) to mice. When MgO (0, 300, 400, 500, 600, 800, 1000 mg/kg, n=10) was orally administered to mice, the laxative activity was increased from 0 to 90% after 8 h of administration. Dose-dependent increases were seen (0, 0, 20, 70, 90, 80, 90% at 0, 300, 400, 500, 600, 800, 1000 mg/kg, respectively).

We performed hourly observations of the conditions of the stools specimens and noted the time when soft stools or diarrhea were observed following administration. We then calculated the number of mice that presented with soft stools or diarrhea.

RESULTS

Dissolution of MgO from the Mixture of M Tablet Suspension and Food Thickener

The dissolution rates of MgO...
120 min after the start of the dissolution test were as follows: jelly-wafer, 100.0%; ultra-agar, 85.9%; Tsuru-Q, 48.0%, and Neo Hi-toro III, 48.3% (Fig. 1).

**Laxative Activity** In the group that received oral administration of samples containing Tsuru-Q as a food thickener, 2 out of 5 mice (40%) presented with soft stools or diarrhea, with peak expression occurring 4 h after administration. In contrast, in the group that received oral administration of samples containing Neo Hi-toro III, Ultra-agar, or jelly-wafer as food thickeners, 5 out of 5 mice (100%) presented with soft stools or diarrhea, with peak expression occurring 6 h after administration (Fig. 2).

**DISCUSSION**

In the present study, we prepared the food thickeners to have LST values of 36 mm, which represents the amount of thickness that is first tried by patients with dysphagia. Because even if food thickeners with different principal constituents are used, if the LST values are the same, it can be assumed that the viscosity values are approximately the same; therefore we attempted a relative evaluation of the food thickeners by using the thickeners having the same LST values. The results of the dissolution test of samples revealed that the dissolution of MgO was low (approximately 48%) 120 min after the start of the test when xanthan gum-based food thickeners (Tsuru-Q and Neo Hi-toro III) were mixed into the M tablet suspension (Fig. 1). In light of the current findings, although xanthan and Neo Hi-toro III were mixed into the M tablet suspension, the dissolution rate of samples revealed that the dissolution of MgO was greater than 80% 120 min after the start of the test. The difference with the present study was the length of time that the samples were allowed to stand for. In the present study, we allowed all samples to stand for 30 min, whereas previous studies did not specifically set a standing time. Moreover, because interviews conducted with those working in clinical practice revealed that up to 30 min is needed to mix food thickeners in an M tablet suspension before administration to patients, we let the solutions used in the present study stand for 30 min. The results of the two studies, which had differing mixture standing times show that when Tsuru-Q was mixed in an M tablet suspension, the dissolution rate of MgO was greater than 80% 120 min after the start of the test. Moreover, the producing companies of these thickeners disclose the amount of xanthan gum in two thickeners. Treatment with carboxymethylcellulose and thickening agents, but not Tsuru-Q, increased the laxative activity at the same level. Laxative activity was lowered when treatment with Tsuru-Q. Because the effect of additive is unknown, these results suggest that effects of additives must be considered when selecting a food thickener.

In conclusion, the agar-based food thickeners did not affect the dissolution of MgO. The animal experiments showed that when agar-based food thickeners were used, the laxative activity of MgO was not affected, but it decreased when xanthan gum-based food thickeners were used. The results of dissolution testing showed that the dissolution rate of MgO and the individual expression of laxative activity are not always consistent. These results suggested that commercially most available food thickeners are associated with changes in pharmacodynamics profiles of clinically useful drug. Food thickeners need to be carefully used in clinical situations.

**Conflict of Interest** The present study was planned by health care practitioners, and was not contracted by Kyowa Chemical Industry Co., Ltd. Yuya Yoshimura and Kazushige Kato are employees of Kyowa Chemical Industry Co., Ltd. There are no other potential conflict of interest to be disclosed.

**REFERENCES**

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