Biological and Pharmaceutical Bulletin Advance Publication by J-STAGE
DOI:10.1248/bpb.b23-00625

Advance Publication
December 16, 2023

Biological and Pharmaceutical Bulletin
Regular Article

Development of a New Jelly Coating Technology (Oral Jelly Coating) to Improve Prescribed Medication Adherence

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Summary

Tablets are the most commonly prescribed dosage form for oral drug administration. Historically, improvement of medication adherence of tablets has been facilitated through, for example, the use of smaller tablets, distinctive shaped tablets and sugar-coated tablets. In addition, new formulation technologies such as orally disintegrating tablets (OD tablets), micro tablet-type granules, jellies, and film formulations are making it possible to create more easily ingested dosage forms. We have developed a new oral jelly coating formulation that can be applied to any sized tablet without reducing the size of the formulation. It was found that this new jelly layer formed on the tablet surface improved the tablet's slipperiness with an appropriate amount of water, while ensuring no change in the dissolution profile. In addition, the jelly layer was ensured storage stability over time without affecting the dissolution profile. Although further studies are needed, this coating technology can quickly change the tablet surface to a jelly-like state after the tablet is taken, giving the tablet the same slipperiness as if it were taken in jelly, making it easier to pass through the pharynx, and thus improving medication adherence.

Keywords

film coating, oral jelly coating, slipperiness, medication adherence

1. Introduction

Oral drug delivery is currently the gold standard in the pharmaceutical industry, regarded as the safest, most convenient and most economical method of drug delivery with the highest patient compliance [1, 2]. Among oral formulations, tablets and capsules are the most preferred dosage forms, but there are several limitations with these, including choking and swelling discomfort in geriatric and pediatric patients [3, 4].

From a pharmaceutical aspect, tablets are the most commonly prescribed dosage form as they offer a convenient form of drug administration based on the following: tablet uniformity, stability throughout extended and diverse storage conditions, and the ability to be easily produced using high-speed compression, labelling, and packaging technology. In reality, tablet production technology is constantly undergoing improvements to enhance the ability to deliver with precision, a desired drug in a dosage form intended for immediate or extended therapeutic effects [5, 6].

However, some groups of patients may find it difficult to swallow tablets or capsules. These groups include the elderly, children, and patients with neurodevelopmental disorders, as well as patients with nausea or who are on reduced liquid- or food-intake diets [7, 8].

Over the last several decades, from the perspective of formulation design, changes in tablet shape (downsizing and distinctive shaped tablets) and coatings (sugar coating) have been investigated. Recently, new formulation technologies such as orally disintegrating tablets (OD tablets), micro tablet-type granules, jelly dosage forms and film dosage forms have made it possible to create dosage forms that are easier to take [2, 9, 10]. The technological progress of OD tablets has been noteworthy, and many pharmaceutical manufacturers have established their own unique technology ranging from the original mold molding (first generation) to wet pressure molding (second generation) and dry pressure molding technology (third generation) [11, 12, 13].

Although advantages of OD tablets are significant, Abey FB and Urgurlu T have summarized several challenges and limitations of OD tablets, i.e., their relatively weak mechanical strength, difficulty in maintaining palatability by masking bitterness, protection from moisture during manufacturing and storage, and the necessity for measures that take into consideration absorption from the oral mucosa [14]. In fact, there is a clinical report on OD tablets showing that the tablet often disintegrated in the oral cavity and remained in the pharynx, resulting in incomplete absorption of the prescribed dose of the drug [15].

Technology has been developed to reduce the size of the medication into granules to make it easier to take, and to coat the surface with a gelling component to make it slippery in the oral cavity. Gelation-induced mini-tablets; GEMTAB (mini-tablets film-coated with a gelling agent), have been developed and launched in recent years by a Japanese pharmaceutical company. Elsewhere, mini-tablets that swell just after coming into contact with water have been also investigated as another option to improve ingestion [16]. However, at present it is difficult to guarantee the content uniformity of individual mini-tablets because the tableting technology for precisely loading material into small multiple dies has not been well established [17]. Accordingly, mini-tablets are marketed as granular tablets, in which more than 20 tablets are enclosed in a “unit-dose package” [18, 19].

On the other hand, products to assist in swallowing, such as thickening agents or medication-aid jellies, have become frequently used in medical institutions and nursing facilities in recent years. It is reported that such products may contribute to reducing the bitterness of the drug [20] and may promote normal swallowing action [21]. The usefulness of thickening agents as swallowing aids has been studied, and it has been shown that when

people with dysphagia use thickening agents, they may reduce the speed of swallowing in the pharynx and help prevent aspiration [22, 23]. However, it has been noted that thickening agents and medication-aid jellies may change the pharmacokinetics of active agents due to extending tablet disintegration time [24-26].

Considering the above, we set out to develop a new tablet coating technology. We aimed to create a new coating technology that allows the tablet surface to change quickly into a jelly-like state after a patient takes the tablet, giving it the same slipperiness as if it were taken with thickening agents, thus allowing it to easily pass through the pharynx. The basic structure of our new oral jelly coating (hereinafter referred to as "OJ-coated tablet") is three-layered, as shown in Fig. 1. The structure was designed to have a foaming layer containing carbonate as the innermost layer (1st layer) closest to the core tablet containing the drug, and a jelly layer containing the jelly material and acidic substances as the outermost layer (3rd layer). In addition, a separation layer (2nd layer) was set in between both layers to prevent direct contact between the acidic substances and carbonates during manufacturing and storage. With this design, it is expected that problems caused by OD tablets disintegrating in the oral cavity can be solved. As a result, there will be no change in the original disintegration properties of the tablet. It is also expected there will be no changes in pharmacokinetics. Our preliminary results show that the OJ coating technology can be applied to tablets of normal size and acceptable storage stability, being unaffected by humidity.

2. Materials and methods

2.1 Materials

Hypromellose (HPMC, TC-5E 3 mPa/s, TC-5M 4.5 mPa/s, manufactured by Shin-Etsu Chemical Co., Ltd.), sodium bicarbonate (SHC, sodium hydrogen carbonate, manufactured by AGC Inc.), xanthan gum (XG, San Ace S, manufactured by San-Ei Gen F.F.I. Inc.), hydroxypropyl cellulose (HPC-SL, made by Nippon Soda Co., Ltd.), citric acid hydrate (CAH, citric acid hydrate, made by Showa Kako Co., Ltd.) and talc (ML115, made by Fuji Talc Industries, Ltd.) were used as a coating material. In addition, anhydrous ethanol (anhydrous ethanol, Konishi Co., Ltd.) was used as the solvent for the coating preparation.

Acetaminophen (N-acetyl-p-aminophenol: APAP, Tokyo Chemical Industry Co., Ltd.) was used as the test drug in the core tablet. In addition, lactose hydrate (Dilactose R, Freund Corporation), microcrystalline cellulose (Ceolus PH-102, Asahi Kasei Corporation) and magnesium stearate (Plant, Taihei Chemical Industry Co.) were used as a core tablet (Table 1).

2.2 Method

2.2.1 Preparation of the core tablet

APAP, lactose hydrate and microcrystalline cellulose were placed in a polyvinyl bag and mixed well, then magnesium stearate was added and mixed lightly to make a mixed powder. The mixed powder was compressed using a rotary compressor (VIRGO 19, Kikusui Seisakusho., Ltd) into oval tablets of 400 mg tablet weight, 14.0 mm in length, 7.0 mm in width, and approximately 4.7 mm in thickness; these were the core tablets.

2.2.2 Preparation of the HPMC-coated tablet

For the HPMC-coated tablets used for comparison, HPMC (TC5-M) was dissolved in purified water to a concentration of approximately 9.1% w/v, and the solution was coated at 5% of the core tablet weight. The coating process for the HPMC-coated tablet was performed

using a fully automatic film coating machine (HICOATER-LABO, Freund Corporation), as shown in Fig. 2.

2.2.3 Preparation of the OJ-coated tablet

For the 1st layer (Foaming layer) of OJ-coated tablets, hypromellose (TC-5E) and SHC were dissolved in purified water, then the solution was coated to achieve 0-4% of the core tablet weight, with 2% set as the standard amount.

For the 2nd layer (Separation layer), hypromellose (TC-5E) was dissolved in purified water, then the solution was coated to achieve a range of 0-1% of the core tablet weight, with 1% set as the standard amount.

For the 3rd layer (Jelly layer), hydroxypropyl cellulose (HPC-SL) was dissolved in anhydrous ethanol, then xanthan gum and citric acid hydrate were added to the solution with stirring for uniform dispersion. This dispersion was studied in the range of 3-10% of the core tablet weight, with 5% set as the standard amount.

The three-layer coating described above to OJ-coated tablets was set, respectively, within the range where each layer could perform its function as designed, and total coating time was feasible in commercial production.

The coating process for the OJ-coated tablet was performed using the same fully automatic film coating machine as for the HPMC-coated tablet. The coating procedures for the foaming, separation and jelly layers are shown in Fig. 2. The production scale for the various test samples in this study was 700 tablets.

2.2.4 Observation of the cross-sectional shape

Coating of the OJ-coated tablet was performed with the foaming, separation, and jelly layers at 2%, 1% and 5% as standard amount, respectively; these tablets were split in the short-diameter direction with a cutter knife, and the split surface was photographed with a scanning electron microscope (SEM, VHX-D500, Keyence Corporation) to measure the thickness of each layer.

2.2.5 Evaluation of sliding property on acrylic plate

The OJ-coated tablets were coated with the foaming, separation and jelly layers at a ratio of 2%, 1% and 5% as standard amount of the core tablet weight, respectively. Conventional tablets were coated with HPMC-coating at a rate of 5% of the core tablet weight. The sliding property was visually evaluated on an acrylic plate tilted at 30°, as shown in Fig. 3. After slightly wetting the bottom of each tablet with a damp sponge, the tablet was placed on the acrylic plate, and immediately 30 mL of water was poured from a height of 1 cm, approximately 2 cm from the top side of the tablet on the plate, for approximately 3 seconds. Ten tablets each of the OJ-coated tablet and conventional tablet were evaluated.

2.2.6 Dynamic evaluation of slipperiness using agar jelly

Next, dynamic evaluation of the slipperiness was performed using agar jelly. Agar jelly at 1% w/v was prepared using Japanese Pharmacopoeia agar (type: PS-8, Ina Food Industry Co., Ltd.). The agar was heated to dissolve it, and the dissolved agar was poured into a square plastic dish (BIO-BIK BALANCE DISHES AS-DM, length per side: 70 mm, height: 22 mm, Ina-Optika Co., Ltd.) until the dish was full, then allowed to cool and harden. An agar square was removed from the dish, and a boring hole of 4 mm diameter was made vertically from the top surface of the agar jelly using a cork borer; the jelly was then placed back into the plastic dish. After a tablet was placed vertically in the hole, the agar jelly was immediately placed on the sample stand of the texture-analyzer described below, and the sample tablet was pressed in at a constant speed. The stress generated during the pressing was continuously

measured. The tablets were measured three times each, with HPMC-coated tablets, uncoated tablets and two types of OJ-coated tablets with different jelly layer thicknesses.

The texture-analyzer was a small tabletop testing machine (EZ Test EZ-SX, Shimadzu Corporation) with a measuring arm that moves up and down to compress the sample via a probe, continuously measuring the stress. Starting with a distance of 2-3 mm between the tablet and the probe, the probe was moved vertically and downward at a test speed of 5 mm/min. The test was terminated when the tablet was completely buried in the agar jelly after confirming that the tablet gradually passed through the hole in the agar jelly. The above test procedure is shown in Fig. 4.

2.2.7 Evaluation of dissolution

The dissolution properties of OJ-coated tablets were evaluated in terms of (1) jelly layer effect, (2) foaming layer effect, and (3) separation layer effect. The evaluation was conducted using test samples with different amounts of coating, depending on the purpose of the evaluation. Based on the preliminary investigation, the amount of (1) the jelly layer and (2) the foaming layer were set to demonstrate a jelly-like effect, while that of (3) the separation layer was set to test the suppressed reaction of the jelly layer and foaming layer.

The apparatus and procedure of the dissolution test were in accordance with the dissolution test method 2 (paddle method) of the Japanese Pharmacopoeia General Test (JP18), using a dissolution tester (NTR-6100A, Toyama Sangyo Co., Ltd.). The dissolution test solution selected was pH 1.2 medium (JP18 dissolution test medium 1), which is specified as model gastric juice, or purified water with normal acidity for the purpose of determining differences between the formulations. The test was performed at 50 rpm using 900 mL of dissolution medium that was heated to 45°C for degassing, and then equilibrated to 37.0°C ± 0.5°C. Six of each type of tablet were used, and samples were taken at 5, 10, 15, 30, and 45 minutes after the start of the test. The dissolution profile was evaluated by measuring the dissolution of APAP on medium filtered through a GMF membrane filter (Whatman™) with a pore size of 0.45 μm, using high-performance liquid chromatography under the following conditions:

<High-performance liquid chromatography conditions for APAP measurement>
HPLC: Shimadzu LC20A
Column: InertSustain C18 (4.6 mm × 15 cm, 5 μm)
Column temperature: 40°C
Mobile phase: A mixture of diluted acetic acid (1 in 1000) and acetonitrile (17:3)
Flow rate of mobile phase: 1.0 mL per minute
Injection volume: 10 μL
Detector: An ultraviolet spectrophotometer (wavelength: 243 nm)

(1) Effect of the jelly layer

To evaluate the effect of the jelly layer on the dissolution profile, only the jelly layer, excluding both the foaming layer (SHC) and separation layer, was coated at 3%, 5%, and 10% of the core tablet weight to produce OJ-coated tablets as shown in Table 1. The amount of jelly coating per unit surface area of the core tablet was calculated as 4.5 mg/cm^2 for 3% coating, 7.5 mg/cm^2 for 5% coating, and 15.0 mg/cm^2 for 10% coating. Dissolution studies were performed to evaluate the dissolution profile of 2 media as pH 1.2 and purified water.

(2) Effect of the foaming layer (ratios of CAH and SHC)

It was assumed that carbon dioxide gas generated by the reaction between CAH in the jelly layer and SHC in the foaming layer would be needed for the detachment of the jelly layer in the digestive tract. Therefore, as shown in Table 2, the ratio of the foaming layer to the weight of core tablets was varied to 1%, 2%, 3% and 4% (containing 1.44 mg, 2.88 mg, 4.32 mg and 5.76 mg of SHC, respectively), by fixing the separation layer: jelly layer ratio at 1%:5% (containing 2.40 mg of CAH). At this condition, the SHC:CAH ratios were set to 0.6, 1.2, 1.8, and 2.4. When the SHC:CAH ratio is 1.2, SHC and CAH are equimolar with the expectation of a complete reaction. The dissolution studies were performed using the medium of purified water.

(3) Effect of the separation layer

Because the foaming layer containing SHC and the jelly layer containing CAH may come into contact with each other and react during coating or storage, potential changes in dissolution profiles with and without a separation layer were determined. As shown in Table 3, test samples of OJ coating with the jelly and foaming layer were set at a rate of 5% (containing 2.40 mg of CAH) and a rate of 2% (containing 2.88 mg of SHC) of the tablet weight to achieve a SHC:CAH molar ratio of 1.2. The test sample of OJ coating with separation layers were set at a ratio of 1% of core tablet weight. The test sample of OJ coating without a separation layer was prepared as only 2 layers OJ coating. The dissolution profile was investigated using the medium of purified water.

2.2.8 Evaluation of preliminary stability

To confirm the stability of the OJ-coated tablet over time, we evaluated the stability of OJ-coated tablets made with 2%, 1% and 5% of the foaming, separation and jelly layer, respectively. Thirty tablets were sealed in high-density polyethylene bottles (TIB-35, Taisei Kako Co., Ltd.) with a polyethylene cap, and then stored under accelerated conditions (40±2°C, 75±5% RH) for 3 months. After storage, the dissolution profile was evaluated using the medium of purified water.

3. Results

3.1 Observation of the cross-sectional shape

As shown in Fig. 5, the foaming, separation and jelly layer were formed in this order from the core tablet, and their respective thicknesses were found to be approximately 30-40 μm, 15-20 μm and 90-100 μm for OJ-coated tablets with the foaming, separation and jelly layers coated at 2%, 1% and 5%, respectively, of the core tablet weight.

3.2 Evaluation of sliding property on acrylic plate

As shown in Fig. 6, all 10 OJ-coated tablets began to come off the acrylic plate immediately after the water flowed from the top side and were observed to slide down quickly without sticking to the acrylic plate. On the other hand, all units of the HPMC- coated tablets remained adhered to the acrylic plate even after the specified amount of running water was completed, and it was observed that the materials of HPMC coating adhered to the acrylic plate when checked after the test.

3.3 Dynamic evaluation of slipperiness using agar jelly

Fig. 7 shows the results of the texture-analyzer study of tablet passage through the agar jelly. The test samples of OJ coating manufactured with 2%, 1% and 5% of the foaming, separation, and jelly layer, respectively, were used. As indicated by the texture-analyzer stress curves, the tablets with the greatest stress on the agar jelly at the time of probe contact were the uncoated tablets, and the stress tended to increase as the probe was lowered. The stress curve of the uncoated tablets always showed higher stress than those of either the

HPMC-coated tablets or OJ-coated tablets at all time points.

The stress curves of the HPMC-coated tablets and OJ-coated tablets showed a similar curve transition from the point of contact between the probe and the tablet to around halfway to the end of the contact point (about 6 mm after the tablet was pushed in). However, the stress of OJ-coated tablets didn't noticeably increase thereafter, while the stress of HPMC-coated tablets tended to increase gradually.

3.4 Evaluation of dissolution

(1) Effect of the jelly layer

The results of the dissolution test using a medium of pH 1.2 as the model gastric juice are shown in Table 4 and Fig. 8. The test sample of OJ coating with only the jelly layer, without a foaming or separation layer, showed delayed dissolution of APAP at 5 and 10 minutes after the start of the test, compared to uncoated tablets. In particular, the test sample of OJ coating with a jelly layer at a rate of 10% (15 mg/cm^2) showed an apparent delay in dissolution at 5 minutes after the start of the test. However, for all test samples, the dissolution rate of APAP at 30 minutes after the start of the test was more than 85% in the medium of pH 1.2.

The results of dissolution tests examining the differences between formulations using purified water as the dissolution medium are shown in Table 5 and Fig. 9. In the test samples of only the jelly layer, obvious delayed dissolution of APAP was observed immediately after the start of the test in all proportions of the test samples of OJ coating compared to the uncoated tablets. The dissolution rate of APAP in the test samples with the lowest coverage, 3% jelly layer (4.5 mg/cm^2), was 82.3% at 30 minutes after the start of the test. The decrease in dissolution rate with 5% and 10% coated (7.5 and 15.0 mg/cm^2, respectively) was even more pronounced, with an APAP dissolution rate of approximately 50% at 30 minutes after the start of the test.

(2) Effect of the foaming function (CAH and SHC)

Next, to study the dissolution profile of the foaming layer, the separation and jelly layers were coated at fixed ratios of 1% and 5%, respectively, and the foaming layer was coated at varying ratios of 1%, 2%, 3% and 4% (SHC:CAH ratio of 0.6, 1.2, 1.8 and 2.4, respectively). The dissolution profiles of the OJ-coated tablet were evaluated using the medium of purified water. The test jelly-layer-only (SHC:CAH ratio 0) was used as a control. The results are shown in Table 6 and Fig. 10.

The test samples of OJ coating with only a jelly layer reproduced the results of "(1) Effect of the jelly layer", showing obviously lower dissolution rate of 5.6% at 5 minutes, 18.5% at 10 minutes, 51.8% at 45 minutes after the start of the test. In contrast, the test samples of OJ coating with a 1% foaming layer (equivalent to an SHC:CAH ratio of 0.6) had an APAP dissolution rate of 22.3% at 5 minutes after the start of the test, and an 87.4% dissolution rate at 30 minutes. In the test sample of OJ coating with a 2% foaming layer (equivalent to an SHC:CAH ratio of 1.2, theoretically equivalent to an acid and base), the APAP dissolution rate was 16.0% after 5 minutes of testing and was still above 90% after 15 minutes. On the other hand, the test samples of OJ coating with 3% and 4% foaming layers (equivalent to SHC:CAH ratios of 1.8 and 2.4) tended to have lower APAP dissolution rates at 5 and 10 minutes after the start of the test, compared to the test coating tablet with 2% foaming layer (equivalent to an SHC:CAH ratio of 1.2).

(3) Effect of the separation layer

The effect of the separation layer on the dissolution profile was also examined. Using the test sample of OJ coating with 5% of jelly layer and 2% of foaming layer (equivalent to

an SHC:CAH ratio of 1.2), the dissolution profiles of each test formulation with and without a separation layer were evaluated. The results are shown in Table 7 and Fig. 11. The test samples of OJ coating without the separation layer had APAP dissolution rates of 63.5% and 78.0% after 15 and 30 minutes of testing, respectively, whereas the test samples with the separation layer had clearly improved APAP dissolution rates of 92.3% and 96.6% after 15 and 30 minutes of testing, respectively.

3.5 Evaluation of preliminary stability

For OJ-coated tablets, Table 8 and Fig. 12 show the results of evaluation of temperature and humidity stability over time for test samples of OJ coating with 2%, 1% and 5% of the foaming, separation and jelly layers, respectively, evaluated under accelerated conditions. There was no change in appearance after 3 months. Although a slight increase in dissolution rate at 5 minutes was found in OJ-coated tablets after 3 months, no difference in dissolution profile was observed after 10 minutes to 45 minutes. These results indicate that acceptable stability can be expected with appropriate packaging.

4. Discussion

We investigated the development of a new coating technology that could overcome some of the challenges of OD tablets: mechanical strength, bitter taste masking, moisture resistance and absorption from the oral mucosa [14], and one that would not require miniaturization, such as gelation-induced mini-tablets: film coating with a gelling agent [16].

We aimed to develop a new coating technology that would improve drug adherence by quickly transforming the tablet surface into a jelly-like state after the tablet is taken, imparting a slipperiness similar to that of a tablet taken with a jelly, thereby facilitating passage through the pharynx. This study examined the tablet slipperiness and tablet dissolution properties of the new OJ coating technology.

With respect to the slipperiness, the OJ-coated tablets showed good sliding property without adhesion of the coating components, which was observed with the HPMC-coated tablets during the first evaluation using an acrylic plate (Fig. 6). Furthermore, in the study of slipperiness using agar jelly, the stress curves of HPMC-coated and uncoated tablets when passing through the agar jelly were linear, whereas the stress of OJ-coated tablets similarly increased in the initial stage of passage, but the stress at the end point was about half of that of HPMC-coated tablets (Fig. 7). This result indicates that the OJ-coated tablets showed a clear improvement in slipperiness. It is considered that the difference in stress between the OJ-coated and HPMC-coated tablets may be induced by the moisture in the agar jelly. In other words, the slipperiness of the surface of the OJ-coated tablets changed to a jelly-like state due to the moisture of agar jelly, whereas adhesion of the HPMC coating was increased by the moisture of agar jelly, which was similar to the phenomenon shown using the acrylic plate.

Recently, it was reported that a clinical study of gel-coated tablets by adding jelly-like slipperiness to the tablet surface, in a study group of 100 healthy volunteers, showed improved medication adherence by making it easier for the drug to pass through the throat in comparison with non-gel-coated tablets [27]. According to the report, it is expected that the OJ-coated tablets, which clearly showed improved slipperiness in our experiments, could reduce adhesion to the throat in actual drug administration situations. Further evaluation will be conducted, including clinical sensory testing of slipperiness and analysis of the formed jelly surface.

As for the sequential investigation on the effects of the three layers of the OJ-coated

tablet on the dissolution profile, it was observed in the first investigation into the effect of jelly layer that the dissolution of APAP from the OJ-coated tablets was decreased compared to the uncoated tablets immediately after the start of the test, but more than 85% of APAP was released from the OJ-coated tablets 30 minutes after the dissolution test began, in a medium of pH 1.2 (Table 4, Fig. 8). On the other hand, when purified water was used as the dissolution medium, a marked dissolution delay was observed that correlated with the amount of OJ coating (Table 5, Fig. 9). This may be caused by the fact that xanthan gum as a jelly base material has been shown to have decreasing gel strength under acidic conditions [28], whereas it forms a strong gel in purified water, which is assumed to have caused the remarkable dissolution retardation under nonionic conditions. Since it has also been reported that the extent of prolongation of the disintegration times differed according to the disintegrants contained in the tablet [29], the dissolution profile was evaluated only at the media of pH 1.2 and purified water in this study, but additional investigation of dissolution profile in other test media reflecting gastrointestinal conditions and comparative studies using different compositions of core tablets would be required.

Regarding the second investigation on the effect of the foaming layer on the dissolution profile: In dissolution profiles of the fixed amount of jelly layer with various amounts of separation layer and foaming layer (SHC:CAH ratio) in purified water, it was shown that the addition of a coating of the foaming layer containing SHC accelerated the dissolution of APAP by removal of the jelly layer; when the SHC:CAH ratio was 1.2, rapid dissolution was observed from the start of the test, and almost 100% dissolution of APAP was observed after 30 minutes. On the other hand, the delayed dissolution profiles at 1.8 and higher of SHC:CAH ratios were speculated to be caused by the delayed entry of purified water into the core tablet (Table 6, Fig. 10). This might be caused by an increased foaming layer coating per unit area as the SHC content increased. It was thus considered that an appropriate SHC:CAH ratio at the setting of coating amount is important in order to obtain appropriate dissolution behavior.

As to the third investigation on the effect of the presence of the separation layer, the dissolution rate after 15 minutes was more than 90% for the test sample with the separation layer, while an obvious dissolution delay was observed for the test sample without the separation layer (Table 7, Fig. 11). This clearly showed that the separation layer is needed to suppress the contact between SHC and CAH during the coating process for proper dissolution of the active ingredient from the OJ-coated tablets.

With respect to the stability of OJ-coated tablets under accelerated test conditions after 3 months of storage, a slight change in tablet release rate was observed at the 5-minute time point. However, no clear difference was observed after 10 minutes (Table 8, Fig. 12). We think that further investigation would be needed in the future, although the slight change at 5 minutes has less impact on quality of tablet. In this study, we investigated the development of a new coating technology using conventional manufacturing processes, with the aim of overcoming some of the challenges of OD tablets and gelation-induced mini-tablets (film coating with a gelling agent) [14, 16].

The manufacturing process used for the OJ-coated tablets in this study did not require any special equipment such as that used in the above gelation-induced mini-tablets. This means that the manufacturing equipment for conventional film coating tablets could be used, without requiring a lengthy manufacturing process. This coating machine is already owned by many pharmaceutical manufacturing establishments. From a manufacturing perspective, we believe that the commercial production of OJ-coated tablets can be performed using

existing manufacturing facilities at many manufacturing sites.

5. Conclusions

The new oral jelly coating formulation we developed demonstrated an effective slipping property, quickly transforming the tablet surface into a jelly-like state without affecting the dissolution profile, as we expected. Furthermore, the OJ-coated tablets showed acceptable storage stability in accelerated test conditions.

It is considered that this coating technology can be adapted to normal-sized tablets without reducing the size of the tablet formulation.

Although further studies are needed, it is expected that the OJ-coated tablets will allow for easier passage through the pharynx, and thus improve adherence of drug administration, thanks to this formulation's unique properties.

Acknowledgments

We are grateful to Professor Shoji Fukushima, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, for providing advice about evaluation methods, etc., at the planning stage of this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflict of interest.

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Table 1. Formulation of the core tablet and the jelly coating tablet for evaluating dissolution profile

	Raw Material	Quantity (mg)
Core tablet	Acetaminophen	40.0
	Lactose hydrate	276.0
	Microcrystalline cellulose	80.0
	Magnesium stearate	4.0
	Total	400.0

	Raw Material	Quantity (mg)/Core tablet 400 mg			
		0%	3%	5%	10%
Jelly Layer	Xanthan gum	0.00	4.20	7.00	14.00
	Talc	0.00	1.32	2.20	4.40
	Hydroxypropyl cellulose	0.00	5.04	8.40	16.80
	Citric acid hydrate	0.00	1.44	2.40	4.80
	Anhydrous ethanol	0.00	48.00	80.00	160.00
	Total of jelly layer	0.00	12.00	20.00	40.00
	Layer per unit surface area (mg/cm^2)	0.00	4.51	7.52	15.04

Table 2. Formulation of OJ coating with several SHC:CAH ratios for evaluating dissolution profile

Layer	Raw Material	Quantity (mg)/Core tablet 400 mg			
		SHC:CAH			
		0.6	1.2	1.8	2.4
Foaming	Hypromellose	2.56	5.12	7.68	10.24
	Sodium hydrogen carbonate	1.44	2.88	4.32	5.76
	Purified water	21.60	43.20	64.80	86.40
	Subtotal of foaming layer	4.00	8.00	12.00	16.00
	Amount of film to tablet weight (%)	1	2	3	4
	Layer per unit surface area (mg/cm^2)	1.50	3.01	4.51	6.02
Separation	Hypromellose	4.00	4.00	4.00	4.00
	Purified water	36.00	36.00	36.00	36.00
	Subtotal of separation layer	4.00	4.00	4.00	4.00
	Amount of film to tablet weight (%)	1	1	1	1
	Layer per unit surface area (mg/cm^2)	1.50	1.50	1.50	1.50
Jelly	Xanthan gum	7.00	7.00	7.00	7.00
	Talc	2.20	2.20	2.20	2.20
	Hydroxypropyl cellulose	8.40	8.40	8.40	8.40
	Citric acid hydrate	2.40	2.40	2.40	2.40
	Anhydrous ethanol	80.00	80.00	80.00	80.00
	Subtotal of jelly layer	20.00	20.00	20.00	20.00
	Amount of film to tablet weight (%)	5	5	5	5
	Layer per unit surface area (mg/cm^2)	7.52	7.52	7.52	7.52

The SHC contents were varied from 1%, 2%, 3% and 4% relative to the core tablet weight, and the ratio of the separation layer: jelly layer was fixed to 1%:5% in test samples of the OJ-coated tablets to assess dissolution.

Table 3. Formulation of OJ coating with and without the separation layer for dissolution evaluation

Layer	Raw Material	Quantity (mg)/Core tablet 400 mg	
		SHC:CAH ratio: 1.2	
		With Separation Layer	Without Separation Layer
Foaming	Hypromellose	5.12	5.12
	Sodium hydrogen carbonate	2.88	2.88
	Purified water	43.20	43.20
	Subtotal of foaming layer	8.00	8.00
	Amount of film to tablet weight (%)	2	2
	Layer per unit surface area (mg/cm^2)	3.01	3.01
Separation	Hypromellose	4.00	-
	Purified water	36.00	-
	Subtotal of separation layer	4.00	-
	Amount of film to tablet weight (%)	1	-
	Layer per unit surface area (mg/cm^2)	1.50	-
Jelly	Xanthan gum	7.00	7.00
	Talc	2.20	2.20
	Hydroxypropyl cellulose	8.40	8.40
	Citric acid hydrate	2.40	2.40
	Anhydrous ethanol	80.00	80.00
	Subtotal of jelly layer	20.00	20.00
	Amount of film to tablet weight (%)	5	5
	Layer per unit surface area (mg/cm^2)	7.52	7.52

A jelly layer containing 2.40 mg of the CAH and a foaming layer containing 2.88 mg of the SHC; SHC:CAH ratio of 1.2 was fixed to assess the dissolution profile of the OJ-coated tablets with/without the separation layer.

Table 4. Dissolution rate of the OJ-coated tablets with only jelly layer in pH 1.2 medium

Content of Jelly layer (%)	Layer per unit surface area (mg/cm^2)	Rate of dissolution (%)				
		5	10	15	30	45
0	-	90.7 ± 5.0	90.7 ± 2.0	100.5 ± 1.0	101.3 ± 1.0	101.6 ± 1.0
3	4.5	57.9 ± 8.4	81.9 ± 2.4	89.6 ± 3.2	96.5 ± 2.9	98.9 ± 2.1
5	7.5	49.5 ± 8.1	78.4 ± 4.3	87.2 ± 4.4	94.0 ± 3.7	96.8 ± 2.6
10	15	10.9 ± 14.6	57.9 ± 13.4	75.3 ± 11.0	92.9 ± 6.5	97.5 ± 3.2

Core tablets were coated with the jelly layer only at ratios of 0%, 3%, 5% and 10% relative to the core tablet weight (jelly coating quantity per unit surface area was calculated as 4.5 mg/cm^2, 7.5 mg/cm^2 and 15.0 mg/cm^2, respectively) to assess the dissolution profile in pH 1.2 medium.

Table 5. Dissolution rate of the OJ-coated tablets with only jelly layer in purified water

Content of Jelly layer (%)	Layer per unit surface area (mg/cm^2)	Rate of dissolution (%)				
		5	10	15	30	45
0	-	81.6 ± 3.0	92.6 ± 4.3	95.5 ± 3.4	99.0± 1.5	100.1 ±1.2
3	4.5	30.3 ±10.4	51.3 ± 8.8	66.4 ± 7.1	82.3 ± 3.8	89.5 ± 2.3
5	7.5	5.6 ± 10.1	18.5 ±19.0	30.4 ±29.4	43.5 ±37.8	51.8 ±40.2
10	15	0.0 ± 0.0	17.3 ±11.0	27.6 ±15.7	53.7 ±26.0	66.0 ±22.7

Core tablets were coated with only the jelly layer at ratios of 0%, 3%, 5%, and 10% relative to the core tablet weight (jelly coating quantity per unit surface area was calculated as 4.5 mg/cm^2, 7.5 mg/cm^2 and 15.0 mg/cm^2, respectively) to assess the dissolution profile in purified water.

Table 6. Dissolution rate of the OJ-coated tablets with several SHC:CAH ratios in purified water

Content of Foaming layer (%)	SHC:CAH ratios	Rate of dissolution (%)				
		5	10	15	30	45
0	0	5.6 ± 10.1	18.5 ± 19.0	30.4 ± 29.4	43.5 ± 37.8	51.8 ± 40.2
1	0.6	22.3 ± 28.4	65.2 ± 24.1	76.5 ± 18.6	87.4 ± 12.9	92.9 ± 9.2
2	1.2	16.0 ± 13.2	78.1 ± 16.6	92.3 ± 12.3	96.6 ± 4.8	98.4 ± 2.9
3	1.8	1.7 ± 4.1	50.2 ± 17.7	68.7 ± 15.1	85.0 ± 10.3	90.8 ± 7.9
4	2.4	7.5 ± 14.8	48.4 ± 27.5	69.3 ± 18.1	89.0 ± 6.5	92.5 ± 4.4

Core tablets were coated with the jelly and foaming layer containing SHC at ratios of 0%, 1%, 2%, 3% and 4% relative to the core tablet weight (at the ratio of SHC:CAH; 0, 0.6, 1.2, 1.8 and 2.4, respectively) to assess the dissolution profile in purified water.

Table 7. Dissolution rate of the OJ-coated tablets with/without separation layer in purified water

	Rate of dissolution (%)				
	5	10	15	30	45
Uncoated tablets	81.6 ± 3.0	92.6 ± 4.3	95.5 ± 3.4	99.0 ± 1.5	100.1 ± 1.2
with separation layer	16.0 ± 13.2	78.1 ± 16.6	92.3 ± 12.3	96.6 ± 4.8	98.4 ± 2.9
without separation layer	22.7 ± 22.8	50.9 ± 40.0	63.5 ± 30.0	78.0 ± 19.9	87.4 ± 10.9

The OJ-coated tablets coated with 5% jelly layer and 2% foaming layer (equivalent to an SHC:CAH ratio of 1.2) against plan tablets (Uncoated tablets), to assess dissolution profiles by additional coating with or without the separation layer in purified water.

Table 8. Dissolution profile of the OJ-coated tablets after 3 months storage in accelerated conditions

	Rate of dissolution (%)				
	5	10	15	30	45
Initial	16.0 ± 13.2	78.1 ± 16.6	92.3 ± 12.3	96.6 ± 4.8	98.4 ± 2.9
After stability test (Accelerated for 3 months)	47.7 ± 8.9	81.5 ± 7.7	89.4 ± 6.3	96.4 ± 3.3	98.4 ± 1.6

Preliminary stability of the OJ-coated tablets was assessed after 3 months storage under accelerated conditions (40 ± 2℃, 75 ± 5% RH).

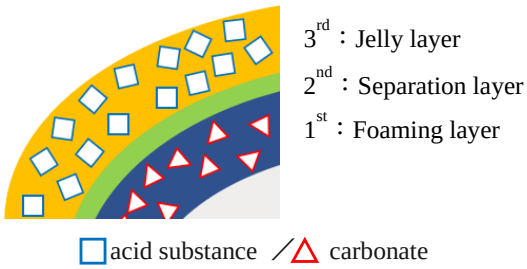

Fig. 1. Basic structure of Oral Jelly coating

1st layer : Foaming layer including carbonates as the main excipient – To react with the acidic substance in the 3rd layer after dosing, and to promote the detachment of the 3rd layer and elution of the active ingredient(s); 2nd layer : Separation layer – To prevent direct contact between carbonates in the 1st layer and acidic substances in the 3rd layer during manufacturing and storage; 3rd layer : Jelly layer includes jelly material and acidic substances as main excipients – To change the tablet surface to a jelly-like state after dosing with a small amount of water.

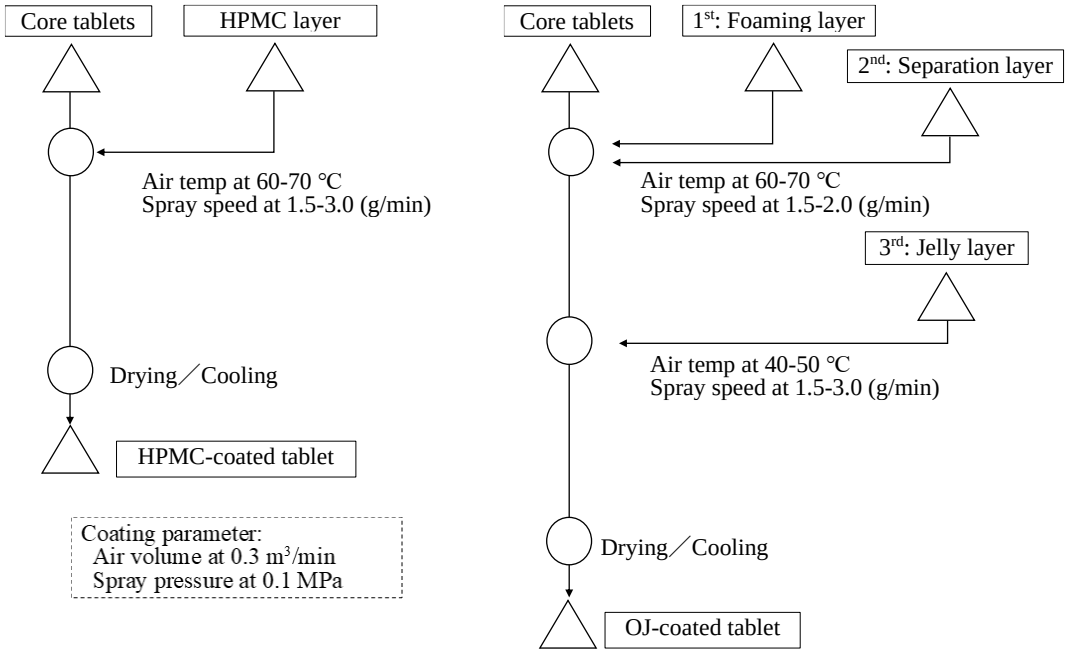

Fig. 2. Fundamental manufacturing process for HPMC or OJ coating

For the OJ-coated tablets, continuous film coating of 1st Foaming layer, 2nd Separation layer and 3rd Jelly layer to core tablets in a sequential order was performed by each coating parameters.

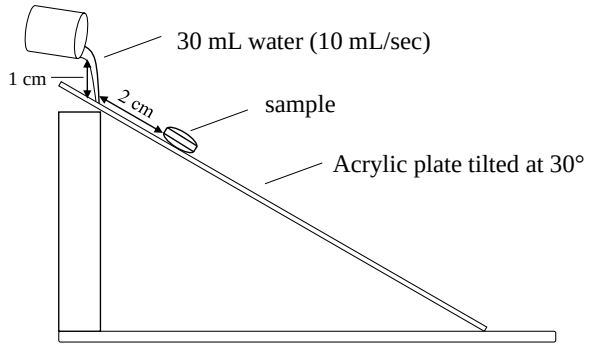

Fig. 3. Evaluation model for sliding property using an acrylic plate

An OJ-coated tablet and HPMC-coated tablet, respectively, were put on an acrylic board tilted at 30° after slightly wetting the bottom aspect of each tablet with a moist sponge. The sliding property of each tablet was assessed as a qualitative method.

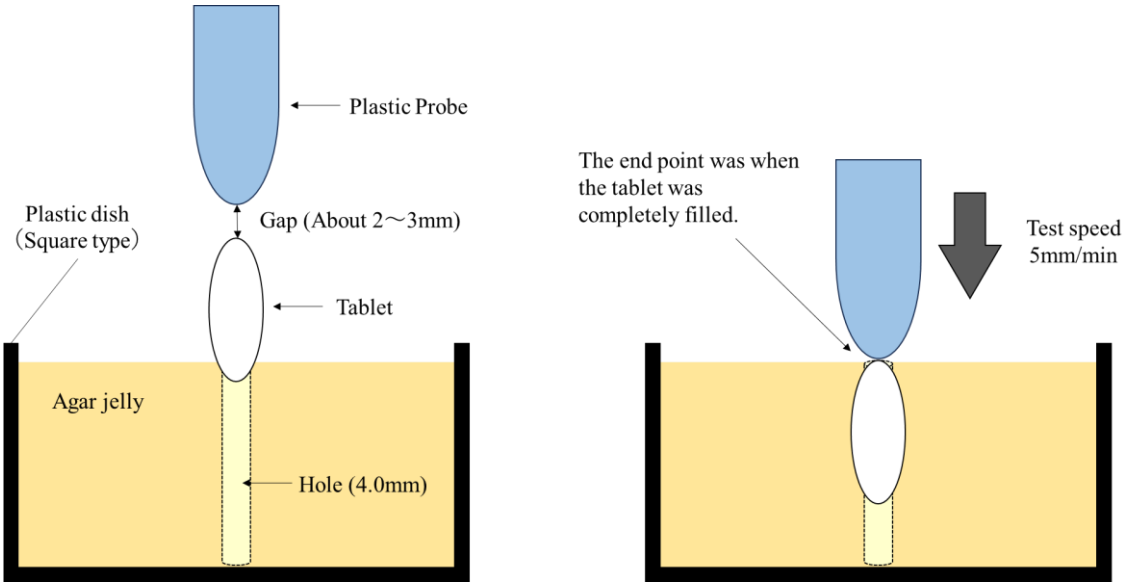

Fig. 4. Method for measuring stress generated when a tablet passes through agar jelly

After making a hole in the agar jelly and placing the tablet vertically in the hole, the sample tablet was pressed in at a constant speed using a small tabletop testing machine (EZ Test EZ-SX, Shimadzu Corporation). The probe was moved vertically downward at a testing speed of 5 mm/min, and the test was terminated when the tablet was completely buried in the agar jelly.

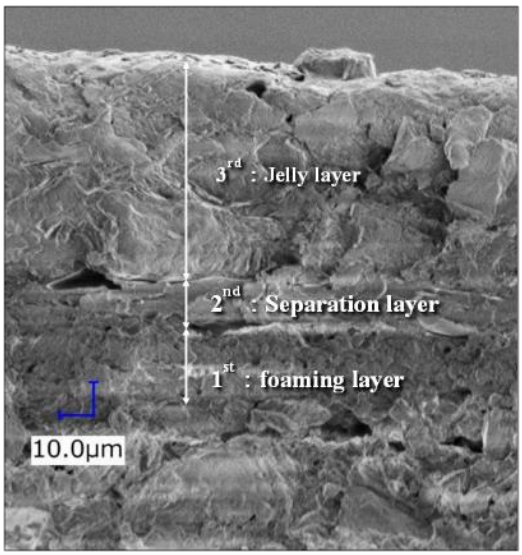

Fig. 5. Scanning electron micrographs of the cross-sectional shape of the OJ coating (1000x)

The thickness of foaming, separation and jelly layer were approximately 30 to 40 μm, 15 to 20 μm and 90 to 100 μm, respectively.

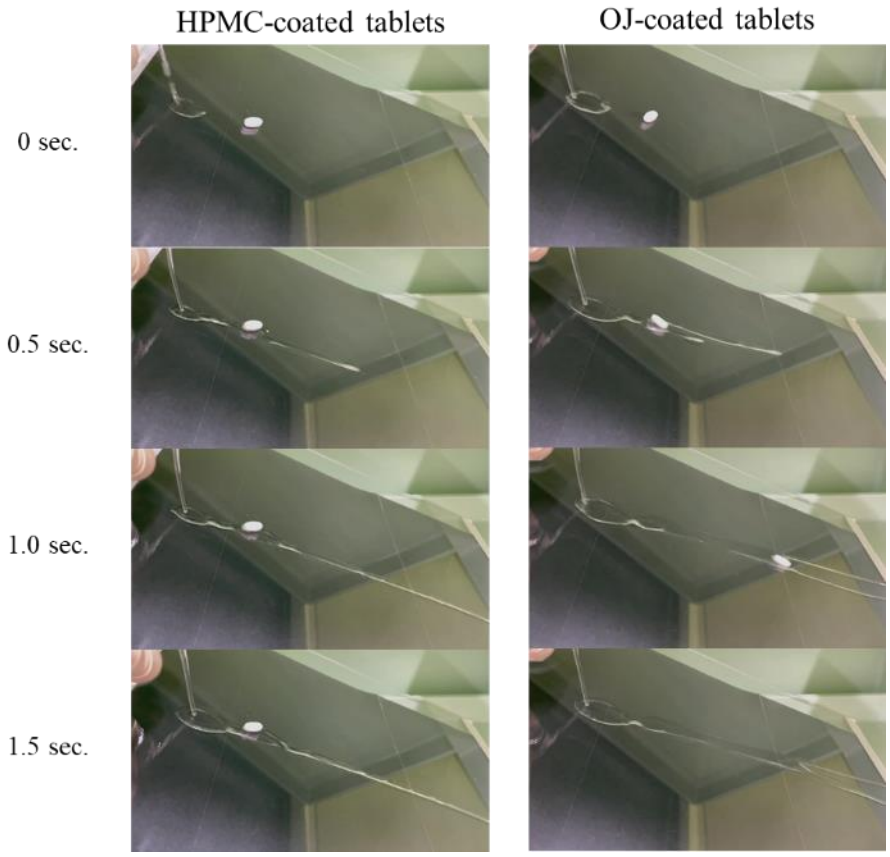

Fig. 6. Observation of the sliding property test

All 10 units of the OJ-coated tablet were found to start sliding down the acrylic plate immediately after pouring water from the upstream side, and quickly slipped off. In contrast, all units of the HPMC-coated tablet were seen to adhere to the acrylic plate, even after completion of the running of the prespecified amount of water. It was observed that the coating base material adhered to the acrylic plate in the HPMC-coated tablets.

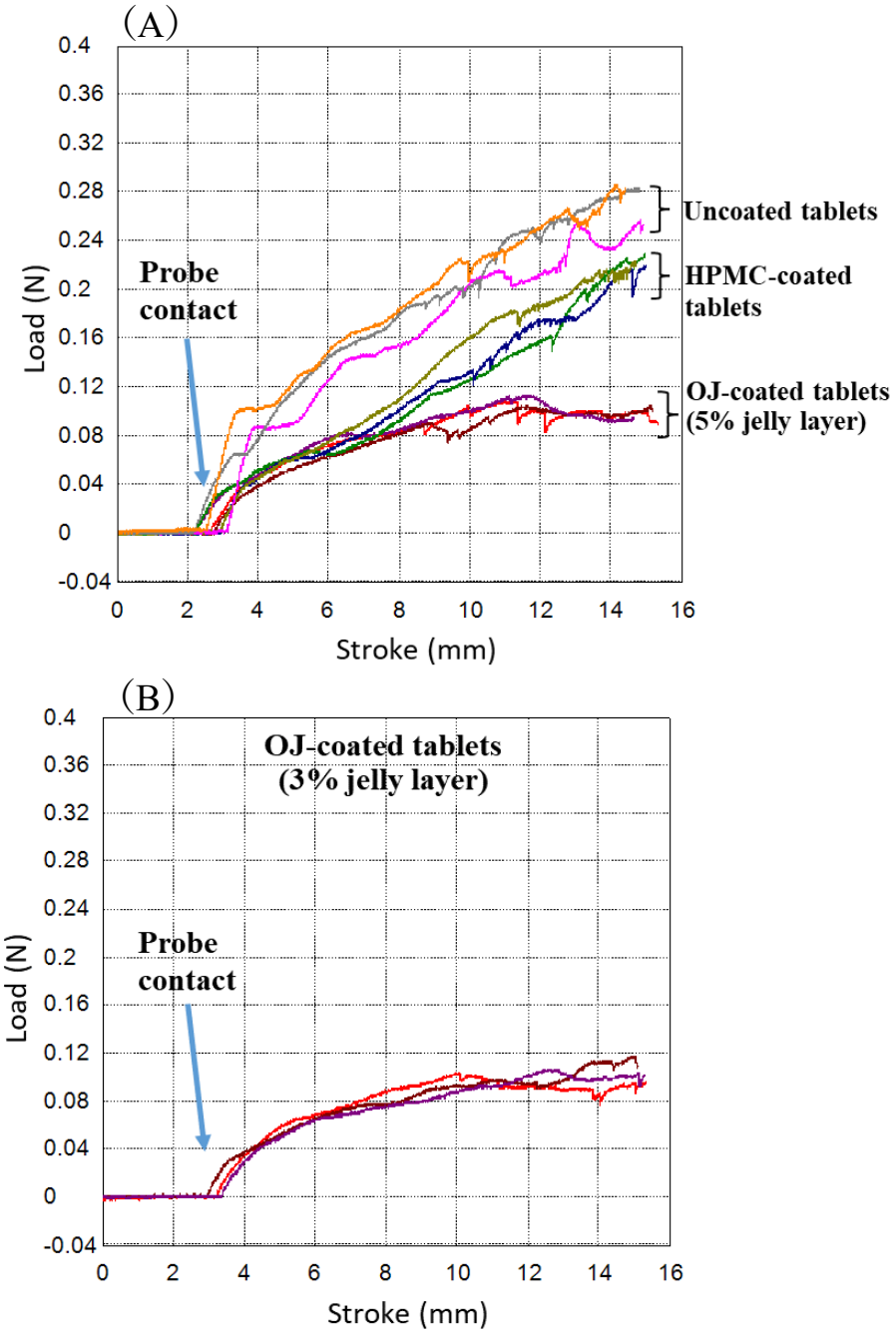

Fig. 7. Stress curve when a tablet passes through agar jelly using a texture-analyzer

Fig. 7A shows the results for uncoated tablets, HPMC-coated tablets and OJ-coated tablets (5% jelly layer). Fig. 7B shows the results of OJ-coated tablets (3% jelly layer). The test was conducted with n=3 for each tablet. Probe contact refers to the point at which the probe was moved at a test speed of 5 mm/min and made contact with the tablet. The test was terminated when the tablet was completely buried in the agar jelly.

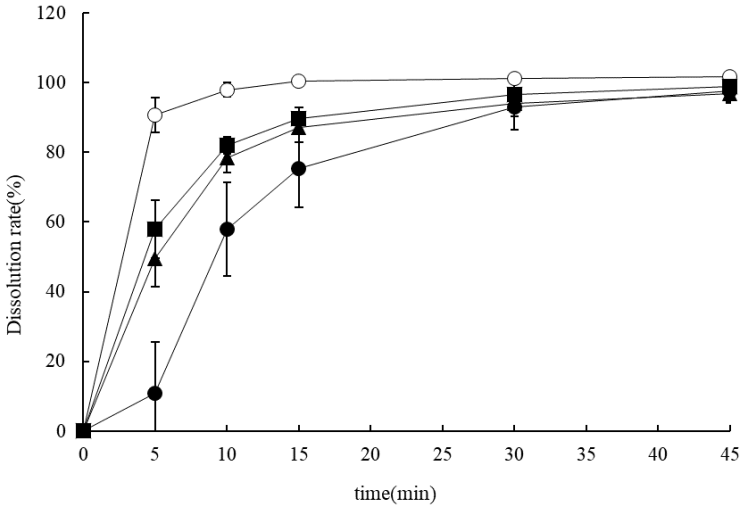

Fig. 8. Dissolution profile of the OJ-coated tablets with only jelly layer in pH 1.2 medium

Core tablets were coated only with the jelly layer at ratios of 0%, 3%, 5%, and 10% relative to the core tablet weight (jelly coating quantity per unit surface area was calculated as 4.5 mg/cm^2, 7.5 mg/cm^2 and 15.0 mg/cm^2, respectively) to assess the dissolution profile in pH 1.2 medium; ○: Uncoated tablets (0%), ■: 4.5 mg/cm^2 (3%), ▲: 7.5 mg/cm^2 (5%), ●: 15.0 mg/cm^2 (10%)

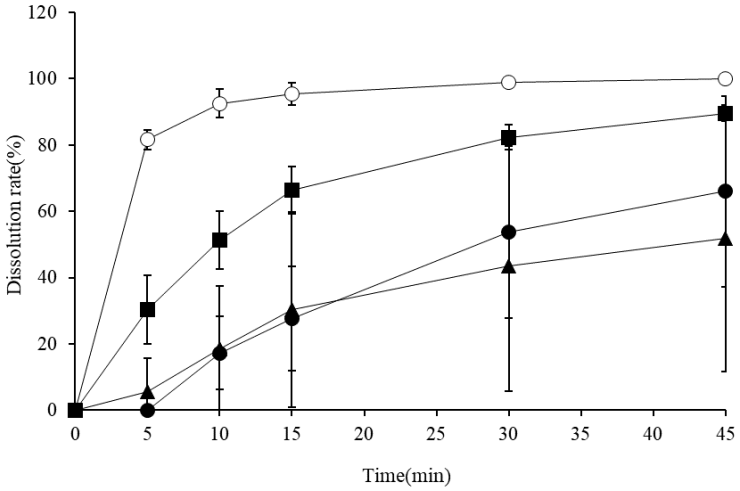

Fig. 9. Dissolution profile of the OJ-coated tablets with only jelly layer in purified water

Core tablets were coated with the jelly layer at ratios of 0%, 3%, 5%, and 10% relative to the core tablet weight (jelly coating quantity per unit surface area was calculated as 4.5 mg/cm^2, 7.5 mg/cm^2 and 15.0 mg/cm^2, respectively) to assess the dissolution profile in purified water; ○: Uncoated tablets (0%), ■: 4.5 mg/cm^2 (3%),▲: 7.5 mg/cm^2 (5%), ●: 15.0 mg/cm^2 (10%)

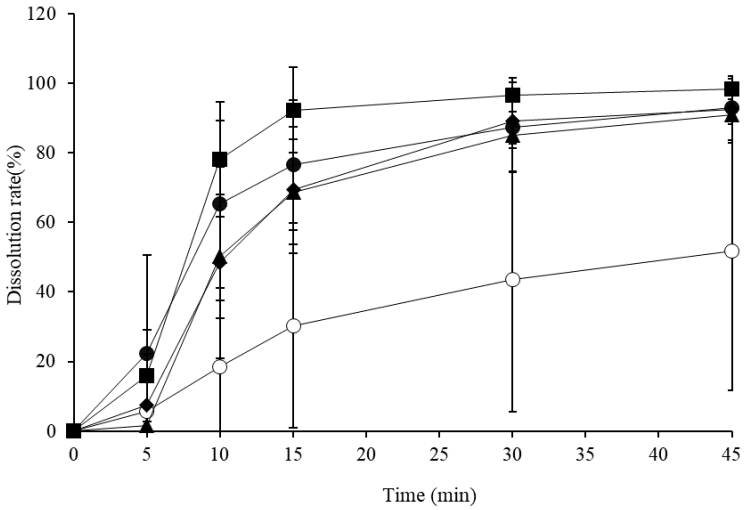

Fig. 10. Dissolution profile of the OJ-coated tablets with several SHC:CAH ratios in purified water

Core tablets were coated with the jelly layer and the foaming layer containing SHC at ratios of 0%, 1%, 2%, 3% and 4% relative to the core tablet weight (at the ratio of SHC:CAH; 0, 0.6, 1.2, 1.8 and 2.4, respectively) to assess the dissolution profile in purified water; ○: SHC:CAH = 0 (0%), ●: SHC:CAH = 0.6 (1%), ■: SHC:CAH = 1.2 (2%), ▲: SHC:CAH = 1.8 (3%), ◆: SHC:CAH = 2.4 (4%)

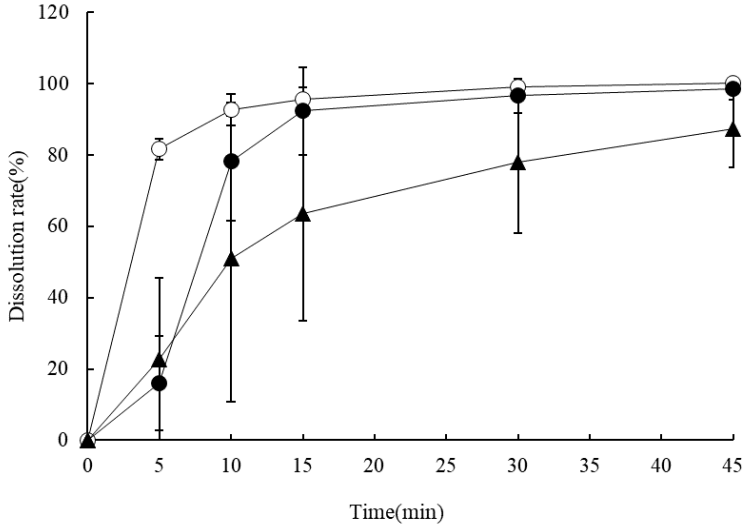

Fig. 11. Dissolution profile of the OJ-coated tablets with or without a separation layer in purified water

Against the OJ-coated tablets coated with 5% jelly layer and 2% foaming layer (equivalent to an SHC:CAH ratio of 1.2), to assess dissolution profiles by additional coating with or without a separation layer in purified water; ○: Uncoated tablets, ●: with separation layer, ▲: without separation layer

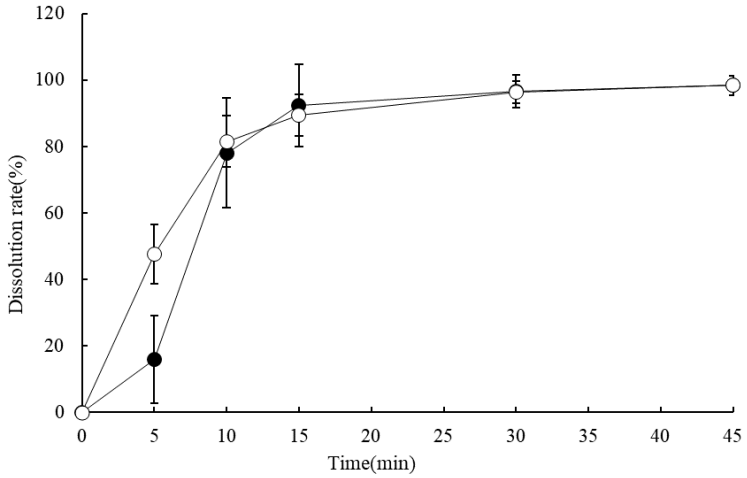

Fig. 12. Dissolution profile of the OJ-coated tablets after 3 months storage in accelerated conditions

Preliminary stability of the OJ-coated tablets was assessed at 3 months storage under accelerated conditions (40 ± 2°C, 75 ± 5% RH). ○: After stability test (accelerated for three months), ●: Initial