A novel method to quantitatively evaluate slipperiness and frictional forces of solid oral dosage forms and to correlate these parameters with ease of swallowing

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Abstract

Patient adherence to oral solid dosage forms depends majorly on the ease of swallowing of these formulations. Conventional methods of evaluating this property is not reflective of the actual scenario as endogenous factors, such as adhesion to the mucus membranes from the oral cavity to the stomach, are not considered. Therefore, we developed a novel method based on the use of a creep meter to measure frictional resistance between various dosage forms and artificial skin as physical properties related to the ease of swallowing formulations. First, the sample was subjected to load (0.5 N for 5 s) from the top, corresponding to tongue press. Next, the sample was moved in the horizontal direction at a speed of 1 mm/s while keeping the vertical load, and the frictional force generated between the artificial skin of the plunger and the sample surface was measured for 15 s. The frictional force was measured under dry conditions and after the sample was immersed in water. According to the novel in vitro evaluation method of slipperiness developed in this study, it is possible to design a slippery and easy-to-swallow formulation that could contribute to improved patient adherence.

Keywords: Slipperiness, Frictional force, Static friction coefficient, Kinetic friction coefficient, Film coating formulation

1. Introduction

Oral intake of a drug requires the act of swallowing. The ease or difficulty in swallowing is one of the important quality characteristics of formulations that is directly linked to medication adherence. Swallowing is a reflex exercise that transports solids and liquids from the mouth into the stomach, through the pharynx and esophagus [1].

The special purpose food system in Japan has specified the hardness, cohesion, and adhesion values for food for individuals with dysphagia [2]. On the other hand, the physical properties of solid drugs, regarding ease of swallowing, is not specified. A questionnaire-based survey in adults and elderly persons revealed that a 7.0–8.0 mm tablet and a rounded tablet with a 6.0 mm radius were easy to swallow [3-6]. A questionnaire survey in pediatric patients revealed that the bitterness of medicines such as prednisolone powder drastically affected the palatability of drug products [7]. Quantitative evaluation of bitterness using a taste sensor is possible and, therefore, some medications can be objectively evaluated [8-10].

In the elderly, the tongue becomes weak, which makes swallowing difficult. Brain diseases may also affect swallowing ability. In addition, patients who develop cerebral infarction need to orally take antiplatelet drugs and anticoagulants for treatment and relapse prevention [11]. In patients with poor swallowing function, the drug may remain in the region between the oral cavity and the pharynx. For example, bisphosphonate preparations have been reported to cause severe esophagitis and ulceration following adhesion to the oral cavity, esophagus, and other parts of the alimentary canal. Therefore, patients are usually instructed not to lie down for 30 min after taking such preparations, which is extremely inconvenient for the patient [12]. The slippage of drug is thought to be related to this problem. Previous studies have reported the estimation of adhesion and slipperiness of pharmaceutical products by determining the distance for which the moistened products slipped on an acetate plate [13-14]. However, this method does not accurately and quantitatively measure the slipperiness of pharmaceutical products, because the acetate plate differs significantly from the human mucosa, and a certain load is not applied to the pharmaceutical products. An analytical method using a tensile tester to measure the coefficient of friction of the material has been standardized by the Japanese Industrial Standard Committee (JISC) [15]. However, the JISC method of measuring friction coefficient cannot be used to measure spherical formulations or those with a rolling form, as it only measures flat samples. In addition, it is difficult to reflect conditions in the oral cavity where the sample is immersed in water, which is how medicines are usually administered orally. Therefore, no studies have quantitatively evaluated the slipperiness of solid oral dosage forms.

In this study, we developed a new test method using a creep meter as a method to evaluate the slipperiness of a formulation. The sample was moved in the horizontal direction under a constant load in the vertical direction, with a plunger, to which an artificial skin film was attached, and the frictional resistance of the sample surface was measured to evaluate the slipperiness. The creep meter is

commonly used to measure the friction of industrial products, and to measure the cohesion and adhesion of food [16-17]. Although there are reports of use of the tribological characteristics analyzer [18], there is no report on the measurement of the frictional force of oral solid formulations for internal use. Therefore, we measured the frictional force as an index of the slipperiness of oral solid formulations for internal use, such as tablets and capsules. Furthermore, as a secondary evaluation, the ease of picking of the formulation and handling was also measured.

The US FDA recommends coating of tablets to improve the slipperiness of tablets [19-20]. However, to further enhance the slipperiness, optimization of the coating formulation is required. Therefore, using the method of measuring slipperiness developed in this study, we evaluated various coating formulations and examined whether they could be used for the development of slippery formulations.

2. Methods

2.1. Materials

2.1.1 Measurement of friction resistance of solid oral dosage forms

The six types of solid oral dosage forms, often used to treat patients with conditions that typically affect swallowing ability, evaluated in this study and a list of additives used in these formulations are shown in Table 1. The manufacturing sources were: aspirin, dihydroxyaluminum aminoacetate and magnesium carbonate tablet (Uncoated tablet; Bufferin combination tablets A81, Eisai Co., Ltd.), enteric coated aspirin tablet (Acrylic coated tablet; Bayaspirin®100 mg, Bayer Pharmaceutical Co., Ltd.), ticlopidine hydrochloride tablet (Hypromellose coated tablet; Panaldine® 100 mg tablets, Sanofi Co., Ltd.), dabigatran etexilate methanesulfonate capsule (Hydroxypropylmethyl cellulose capsule; Prazaxa® capsules 75 mg, Nippon Boehringer Ingelheim Co., Ltd.), diltiazem hydrochloride sustained release capsule (Hard gelatin capsule; Herbesser® R capsules 100 mg, Mitsubishi Tanabe Pharma Co., Ltd.), and nifedipine capsule (Soft gelatin capsule; Adalat® capsule 5 mg, Bayer Pharmaceutical Co., Ltd.).

Table 1 Additives of solid oral dosage forms

Sample Name	Components
Uncoated tablet	Aspirin, dihydroxyaluminum aminoacetate, magnesium carbonate, corn starch, saccharin, saccharin sodium hydrate, talc, D-mannitol
Acrylic coated tablet	Aspirin, powdered cellulose, corn starch, methacrylic acid copolymers, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate

Hypromellose coated tablet	Ticlopidine hydrochloride, lactose hydrate, corn starch, carmellose, polyvinyl alcohol, sucrose fatty acid ester, hypromellose, titanium oxide, macrogol 6000, talc, silicon dioxide dimethylpolysiloxane
Hydroxypropylmethyl cellulose capsule	Dabigatran etexilate methanesulfonate, tartaric acid, powdered acacia, hypromellose, dimethylpolysiloxane, talc, hydroxypropylcellulose, carrageenan, potassium chloride, titanium oxide, hypromellose
Hard gelatin capsule	Diltiazem hydrochloride, ammonio methacrylate copolymer, talc, corn starch, white soft sugar, fumaric acid, povidone, gelatin, sodium lauryl sulfate
Soft gelatin capsule	Nifedipine, concentrated glycerin, saccharin sodium hydrate, mentha oil, macrogol 400, gelatin, glycerin, titanium oxide

To investigate the magnitude of the frictional resistance sensorially, we included konjac jelly (Konnyakubatake, Mannanlife Co., Ltd.) and soft chewy candy (HI-CHEW™, Morinaga Co., Ltd.) as generally well eaten foods to image eating experience. These results were compared with measured values of solid oral dosage forms.

2.1.2 Measurement of frictional resistance of tablet coating formulations

The US Food and Drug Administration (FDA) reported the effect of film coating on the "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules" guide, which enhance the ease of swallowing tablets. In section *2.1.1* we compared the differences in slipperiness of formulations with completely different dosage forms and shapes, while in this section, we measured the slippage of tablets of the same formulation and different coating agents. The coating agents are shown in Table 2. Opadry® (Colorcon™) is a widely used general premix coating agent based on standard hypromellose. Opadry® EZ White is a prescription agent supplemented with polysaccharide guar gum used to facilitate slippage during swallowing. Opadry® and Opadry® EZ White contain titanium oxide to ensure light stability. Opadry® EZ Clear formulation is a modified form of Opadry® EZ White, from which titanium oxide is eliminated to enhance the slippery nature. The frictional force of the uncoated tablet (19 mm, major axis; 9.3 mm, minor diameter; and 7.55 mm, thick) formulated with lactose and crystalline cellulose and after coating with these three coating agents was determined.

Table 2 Additives of coating agents

Sample Name	Components

Opadry®	Hypromellose, titanium dioxide, macrogol, others
Opadry® EZ White	Hypromellose, guar gum, titanium dioxide, talc, others
Opadry® EZ Clear	Hypromellose, guar gum, talc, others

(Uncoated tablet: Lactose monohydrate, cellulose powder, partially pregelatinized maize starch, colloidal anhydrous silica, magnesium stearate).

2.2 Frictional resistance measuring instrument

The measurements were conducted using the tribological characteristics analyzer RE 2-33005 (Creep Meter, Yamaden Co., Ltd.). The system can move the sample stage horizontally while applying a constant load vertically to the sample. The purpose was to measure, *in vitro*, the frictional resistance generated between the formulation and the oral cavity or gastrointestinal mucosa. A collagen sheet, a semipermeable membrane for dialysis, or an artificial skin (Sapplare®; Idemitsu Technofine Co., Ltd.) was examined as an artificial mucous membrane, and we adopted the Sapplare®, which has the most stable measurement value. Sapplare® is an industrial product, which is considered to closely mimic the skin. Its surface physical properties are more consistent than collagen sheets derived from natural products; therefore, it is possible to compare and evaluate the frictional resistance of various samples.

2.3 Measurement

The sample was fixed to a plastic plate (50 mm × 20 mm × 2 mm) with ethylene vinyl acetate coating to avoid rolling displacement when the load was applied to the sample during frictional force measurement. In addition, to avoid changes in the surface properties of the sample due to moisture in the air, it was stored in a desiccator containing silica gel for approximately 1 day after fixation to ensure it was dry and then it was measured.

The flow chart of the measurement procedure of maximum static frictional force and kinetic frictional force is shown in Fig. 1. The sample fixed to the plastic plate was set on the sample stand of the tribological characteristics analyzer. First, the sample was subjected to a load (0.5 N for 5 s) applied from the top corresponding to tongue press. Next, the sample stand was moved in the horizontal direction at a speed of 1 mm/s while keeping the vertical load, and the frictional force generated between the artificial skin of the plunger and the sample surface was measured for 15 s. The load of 0.5 N was set based on a previous research report [21]. Slipperiness was inferred from the frictional resistance produced when moving in the horizontal direction at a speed of 1 mm/s. Six samples were measured at room temperature. The frictional force was measured under dry and water immersion conditions. Under immersion conditions, the sample was placed at the bottom of a plastic container and water was added to completely cover the sample before it was used for measurement of frictional force. For studying the effects of food, konjac jelly and soft chewy candy were also used along with

the pharmaceutical formulations, and the frictional force was measured under dry conditions.

2.4 Data analysis

The maximum static frictional force corresponding to the force applied to the sample from the tongue to the pharynx until it starts to move was the maximum value of the frictional resistance force after the load was applied. The kinetic frictional force corresponding to the frictional force when moving the sample from the tongue or pharynx toward the esophagus was the average value of the force for 1 second after the sample started to move for 2 s. From the measured maximum static frictional force and kinetic frictional force, the static and kinetic friction coefficients were calculated according to the following formula:

$\mu = F/N$

where, μ is the friction coefficient, F is the frictional force, and N is normal force.

Six samples were measured for each dosage form, and the values are expressed as mean ± standard deviation. For comparison between multiple groups, the Dunnett test was conducted for data showing homoscedasticity, and the Games-Howell test was used for data showing heteroscedasticity. A $p < 0.05$ was considered to indicate significant difference.

3. Results

3.1 Comparison between frictional force of various dosage forms

3.1.1 Frictional force curve

Frictional force of various dosage forms was measured, and Fig. 2 shows representative measurements of each sample. A large difference was observed in the time course of the frictional forces of the G and H food samples. The soft chewy candy in H showed a typical frictional force curve in the measurement method and the pattern showed a maximum point of frictional force as soon as the sample started to move, which then reduced and vibrated finely. The large peak observed immediately after the start of the measurement was defined as the maximum static frictional force, and the average value measured for 1 s of the 2 s after the start of the measurement was taken as the kinetic frictional force.

On the other hand, the frictional force of the highly slippery sample like konjac jelly was smooth without having a peak, indicating the maximum static frictional force, and only the kinetic frictional force could be measured. Characteristic patterns were observed in each dosage form. Frictional forces measured under dry and immersion conditions are called dry and lubricated frictional force, respectively, and a large difference was observed between them in all curves of A to F. In the solid oral dosage forms except for hard gelatin capsule, the lubricated frictional force was smaller than the dry frictional force and the shape of the curves were smooth. Only the hard gelatin capsule showed different curve shapes, and a clear peak was observed in the frictional force curve of the lubricant.

206 Figs. 3 and 4 show mean ± standard deviation of the static friction coefficient and kinetic
207 frictional force, respectively obtained from six measurements.
208
209 *3.1.2 Static friction coefficient*
210 Under dry conditions, the static friction coefficients of the acrylic coated tablet, hypromellose
211 coated tablet, and hypromellose capsule were larger than those of the uncoated tablet. The static
212 friction coefficient of the acrylic coated tablet was the largest, and the value was similar to that of the
213 soft chewy candy. The static friction coefficient of the hard gelatin capsule was similar to that of the
214 uncoated tablet. Moreover, the soft gelatin capsule had smaller values than the uncoated tablet, and
215 the soft gelatin capsule formulation had the most ease beginning to move of all the experimental
216 samples. Since the uncoated tablet had a trace amount of powder particles peeled off from the surface,
217 we thought that this acted as a roller and reduced the frictional force. It is surmised that the coefficient
218 of static friction is reduced because medium chain fatty acid triglyceride is generally applied as a
219 release agent to the surface of the soft gelatin capsule. The coefficient of static friction of the konjac
220 jelly could not be calculated because the maximum static frictional force could not be detected.
221 The static friction coefficients under immersion conditions were smaller than those under dry
222 conditions except for that of the hard gelatin capsule, which indicated that the presence of water made
223 it easier to slide.
224
225 *3.1.3 Kinetic friction coefficient*
226 Fig. 4 shows the kinetic friction coefficients of solid oral dosage forms, konjac jelly, and soft
227 chewy candy. The coefficient of kinetic friction of konjac jelly, which is generally considered to be a
228 slippery food, is very small (about 0.1), and that of soft chewy candy, which is considered relatively
229 non-slip is about 0.3.
230 Under dry conditions, the kinetic friction coefficients of the acrylic and hypromellose coated
231 tablets were larger than that of the uncoated tablet. The kinetic friction coefficient of the hard gelatin
232 capsules was approximately the same as that of the uncoated tablet, but that of the soft gelatin capsule
233 was approximately half of that of the uncoated tablets and they were adequately slippery.
234 The kinetic friction coefficient in water immersion conditions is less for all formulations than dry
235 condition indicating that it is slippery in water. When the uncoated tablet and each formulation were
236 compared, only the acrylic coated tablet showed a higher tendency, which was about 1.8 times the
237 kinetic friction coefficient of the uncoated tablet. On the other hand, the kinetic friction coefficient of
238 the hypromellose coated tablet and the hypromellose capsule was about 1/2 that of the uncoated tablet
239 and showed a tendency to slip.
240
241 **3.2 Comparison between coating *agents***

3.2.1 Frictional force curve

An example of the frictional force curve of each sample coated with three different coating film formulations on uncoated tablets of the same size and shape is shown in Fig. 5. In all the tablets, the frictional force decreased in water than in the dry condition, and the shape of the graph also changed markedly. Under dry conditions, the frictional resistance oscillated, but the value was small and showed a smooth curve under immersion conditions.

3.2.2 Comparison of static friction coefficient

The static friction coefficients of the uncoated tablet and the three coating agents are shown in Fig. 6. Opadry® showed the largest static friction coefficient under dry conditions, and its value was comparable to that of the soft chewy candy in Fig. 3. There was no difference in the static friction coefficients of Opadry® EZ White and Opadry® EZ Clear, which were both smaller than that of Opadry®, but larger than that of the uncoated tablet. Under dry conditions, the results suggested that the coated tablet was harder to slide out than the uncoated tablet.

Under immersion condition, the static friction coefficients of Opadry® EZ White and Opadry® EZ Clear were smaller than those of the uncoated tablet and Opadry®. These results indicate that under dry conditions, the coated tablets were less slippery than the uncoated tablets were. On the other hand, Opadry® EZ White and Opadry® EZ Clear made their respective tablets easier to move out than the uncoated tablet in water, but there was no notable difference.

3.2.3 Comparison of kinetic friction coefficient

Fig. 7 shows the kinetic friction coefficients of the uncoated tablet and three coating agents. Opadry® showed the largest kinetic friction coefficient, which was approximately three times that of the uncoated tablets under dry conditions. Opadry® EZ White and Opadry® EZ Clear were also approximately twice as much as that of the uncoated tablet.

Under immersion conditions, Opadry® EZ Clear, Opadry® EZ White, and Opadry® showed smaller kinetic friction coefficients than the uncoated tablet. Opadry® EZ White and Opadry® EZ Clear had kinetic friction coefficients that were approximately two-thirds and one-third that of Opadry®. The kinetic friction coefficient of Opadry® EZ Clear was approximately the same as that of konjac jelly.

4. Discussion

Patient adherence to oral solid dosage forms depends majorly on the ease of swallowing of these formulations. Conventional methods of evaluating this property is not reflective of the actual scenario as endogenous factors, such as adherence to the mucus membranes from the oral cavity to the stomach, are not considered. Therefore, we developed a novel method based on the use of a creep meter to

measure frictional resistance between various dosage forms and artificial skin as physical properties related to the ease of swallowing formulations.

The static friction coefficient is a physical property value indicating the ease of movement of the formulation. The static friction coefficient under dry conditions is considered to be the physical property of the individual formulation related to the frictional resistance generated when moving the drug from the state where the drug adheres to the dry oral mucosal surface of Sjögren's syndrome or dry mouth patients. On the other hand, the static friction coefficient under water-immersion conditions can be considered to be the physical property of the formulation related to the frictional resistance produced when the formulation on the surface of the oral cavity or esophagus wet with saliva or water is applied. The kinetic friction coefficient under dry conditions is a physical property value of slipperiness of the formulation. Since it is rarely taken without water or saliva, it is not a physical property value related to ease of swallowing, but it is one of the characteristics of the formulation. On the other hand, the kinetic friction coefficient under water immersion conditions is a physical property value related to how slippery the formulation is on the gastrointestinal tract surface when it is taken with water.

The static friction coefficient of the solid oral dosage forms, konjac jelly and soft chewy candy is plotted on the horizontal axis, and the kinetic friction coefficient is plotted on the vertical axis, and scatter plots are shown in Fig. 8. Focusing on food samples under dry conditions, konjac jelly has an easy-to-slip physical property with small static friction and kinetic friction coefficient, but soft chewy candy is difficult to move because it has a large static friction coefficient but is slippery due to its small kinetic friction coefficient. The fact that the coefficient of friction is 1 or more means that the frictional force is generated more than the normal force, and it is considered that strong adhesion is caused between the formulation and the artificial skin.

Film coating agents are used to mask the unpleasant taste and odor of the drug, improve light stability, and enhance the visibility of the printing on the formulation to improve identification. In addition to these important functions, the coating agent is also considered to contribute to making tablets easier for patients to swallow. In the dry condition, the formulations having static and kinetic friction coefficients exceeding 1 were the acrylic coated tablet and the hypromellose coated tablet. In coated tablets and capsules whose main surface composition is hypromellose, both static and kinetic friction coefficient in water immersion conditions were greatly reduced to about 0.2. It is considered that this caused part of hypromellose to be instantaneously dissolved in water and act as a lubricant between the formulation and the artificial skin. On the other hand, the acrylic coated tablet exhibited a static kinetic friction coefficient of about 0.8, even under water immersion conditions, it did not decrease as much as it did with hypromellose. Since this acrylic coating tablet is an enteric coating, which dissolves only at neutral pH or higher and does not dissolve in water, it can be said that it did not act as a lubricant similar to hypromellose. An enteric coated tablet tends to adhere more easily to

the oral cavity than hypromellose and be less slippery when taken with water. Next, frictional forces of the main components of the hard-capsule shell were compared with those of hypromellose and gelatin. Gelatin tended to move more easily in dry condition, and hypromellose more easily moved in water condition. This is thought to be because hypromellose dissolves more rapidly in water than gelatin and plays the role of a lubricant. That is, when taking a capsule with water, it can be said that the hypromellose capsule has a smaller adhesion and is movable. On the other hand, hard and soft capsules of gelatin had static and kinetic friction coefficients of about 0.4 to 0.7 for both formulations under dry conditions, but the static friction coefficient for hard capsules alone increased under water immersion conditions, exceeding 1. Therefore, hard capsules showed adherence to the mucosal membranes. While soft capsules, especially of large diameters, may be difficult to swallow, their shell is more slippery than that of hard capsules.

The static friction coefficient of the uncoated tablet and each coating agent is plotted on the horizontal axis, and the coefficient of dynamic friction is plotted on the vertical axis, and scatter plots are shown in Fig. 9 for the dry and immersion condition. Under dry conditions, Opadry® had both static and kinetic friction coefficients exceeding 1, indicating that it was hard to move and slippery. Although the FDA recommends applying a film coating to make tablets easier to swallow [15, 16], the administration of coated tablets to patients with dry mouth syndrome is not recommended. Uncoated tablets are believed to have good physical properties when considering only their slipperiness under dry condition, but identification codes can be printed on coated tablets, which also has other functions such as masking unpleasant taste and improving stability. Film coatings have recently been shown to have more merits than uncoated tablets and, therefore, tend to be selected. From the viewpoint of material handling suitability, the Opadry® EZ series are better than Opadry®. Although Opadry® EZ White with guar gum added and Opadry® EZ Clear with titanium oxide removed from the coating formulation had smaller frictional resistance, these three coated tablets were found to be less slippery than the uncoated tablet. Since the conditions are dry when a tablet is picked up with the finger, it can be said that it becomes difficult to slip by coating an uncoated tablet, and handling becomes easy. On the other hand, it is preferable that the tablet is easy to slide under the drying condition in the process of manufacturing the tablet at the factory. For example, in the packaging process, ease of sliding of tablets is important for handling tablets to be filled without trouble in the PTP pockets. Opadry® EZ White and Opadry® EZ Clear are preferred for their physical properties over Opadry®, which is a standard film coating formulation, because slippery tablets can be packaged with high speed.

Under immersion conditions, the friction resistance of all three formulations decreased significantly, and the coated tablet became slippery than the uncoated tablet. The kinetic friction coefficient under the condition that water exists between the artificial skin and the tablet surface is considered to be a physical property simulating the resistance when a tablet passes through the pharynx

or esophagus as water is taken along with it. Therefore, we suggest that hypromellose coated tablets are easier to swallow than uncoated tablets when ingested with water. It is also recommended for patients with swallowing difficulty that tablets be placed in the oral cavity only after taking water in the oral cavity so that the tablet does not adhere to mucous membranes. The friction coefficient of Opadry® EZ White, which contains guar gum, was smaller than that of Opadry®. This is thought to have occurred because guar gum, a polysaccharide thickener used as a swallowing aid, acts as a lubricant to reduce frictional resistance. Opadry® EZ Clear is a modification of Opadry® EZ White in which the titanium oxide is removed, and its kinetic friction coefficient was smaller than that of Opadry® EZ White. This is considered to be resistant to slipping because particles of titanium oxide are dispersed in the coating agent and make surface difficult to slip. However, since titanium oxide is an essential additive for imparting light shielding property to a film coating, its removal from the formulation may adversely affect the stability of the active ingredient. Therefore, in this study, we first covered the tablets with Opadry® EZ White and then Opadry® EZ Clear from above, to avoid the non-slippery property of titanium oxide while keeping the light shielding property of the film. The kinetic friction coefficient of Opadry® EZ Clear under immersion conditions was almost equivalent to that of konjac jelly under dry conditions and we confirmed that it was very slippery. In the future, it would be necessary to conduct human sensory test to confirm the findings of this research.

5. Conclusion

Using the novel tribological characteristics analyzer, we were able to evaluate the difference in slipperiness between dosage forms regardless of their shape. In addition, measuring the frictional force between the artificial skin membrane and the formulation under immersion conditions made it possible to conduct evaluations by simulating the conditions of the oral cavity during swallowing of solid drugs with water. Objective and quantitative evaluation of the slipperiness of tablets with various coating formulations was conducted. Therefore, the *in vitro* evaluation method of slipperiness, newly developed in this study, enabled the selection of a formulation that is adequately slippery and easily swallowed, and the design of such a formulation could be expected to contribute to improving patient adherence. In the future, it would be necessary to conduct human sensory tests to confirm the findings of this research.

Conflicts of interest

The authors declare no conflict of interest.

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