Granulation of Core Particles Suitable for Film Coating by Agitation Fluidized Bed II. A Proposal of a Rapid Dissolution Test for Evaluation of Bitter Taste of Ibuprofen

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To prepare powdered drugs that do not have a bitter taste, a film coating covering the surfaces of the core particles is required. The dissolution rate of ibuprofen from the coated particles changes according to the physical properties of the core particles. In this study, the effects of the physical properties of granules prepared by using several scales of agitation fluidized beds on the drug dissolution rate were investigated. The dissolution rate of ibuprofen decreased when the apparent density and shape factor of the granules increased. In contrast, the dissolution rate of the drug increased with the friablility of the granules increased. Thus, the structures of the granules appear to affect the dissolution rate of the drug to a large degree. A rapid dissolution test that can be used to investigate the early dissolution rate of ibuprofen *in vitro* was proposed to evaluate the taste-masking level of the coated particles. The bitter taste-masking level of the coated particles was successfully confirmed by using this novel test method.

Key words masking bitter taste; core particle; agitation fluidized bed granulation; dissolution rate; rapid dissolution test

Creating drugs that are easy to ingest is an important element in promoting adequate patient compliance, thereby enabling successful medical treatment.[1)] The development of medicines that are easier to ingest has thus attracted special interest from the viewpoints of treatment compliance and marketability.[2,3)] Powdered drugs are a useful dosing form for patients who can't swallow tablets.[4)] Ibuprofen [(*RS*)-2-(4-isobutylphenyl)propanoic acid] is a widely used over-the-counter nonsteroidal anti-inflammatory drug that is highly effective and safe for the treatment of moderate pain and fever. However, powdered ibuprofen has a strong, astringent and bitter taste that must be masked to make it easier to ingest. Powdered drugs are often coated with a film to mask their bitter taste of drugs[1—7)]; such films can control the dissolution rate of the drug in the mouth, and are considered suitable for masking bitter tastes. A spouted bed with draft tube[8—11)] is an efficient means of coating powdered drugs with a film. First, however, core particles of the powdered drugs with properties suitable for film coating must be prepared; to accomplish this, the drugs are often manufactured using agitation fluidized beds granulation.[12—14)]

In our previous paper,[1)] the formulation of core particles was optimized. Core particles were granulated using differently sized granulators and were then coated using a coater. The dissolution pattern of the coated ibuprofen particles differed when granulators of different sizes were used to prepare the granulated core particles. Therefore, the effect of the granule properties on the dissolution rate of the drug should be investigated because the dissolution rate may affect the efficacy of the drug. Although several studies have reported, the effects of particle's diameter,[15)] fillers and excipients[16)] on the dissolution rate of drugs. However in previous study, particle size was so large over 500 μm; not enough for good ingest ability.[1)] In addition, drug content ratio was not so high because of with starting large excipients seeds. Few studies have examined the detailed effects of the small core particle's structure and physical properties on the dissolution rate with high content ratio of drug. Here, we report the relationships between the major physical properties of the core particles, such as the mass median diameter, apparent density, friability and shape factor, and the dissolution rate of ibuprofen.

As mentioned above, masking the taste level of the coated particles is the most important subject when producing powdered drugs. To evaluate taste-masking level, a sensory test using volunteers is usually conducted. However, a sensory test using volunteers is not the optimal method of evaluating the taste-masking level because such evaluations might differ according to the masking method, the evaluations are based on the subjective judgements and the test might be tasked volunteer's body. Therefore, several methods have been used to evaluate the taste-masking level of coated particles *in vitro*, including the dissolution test,[17)] the simple dissolution test,[18)] and the taste sensor test[19,20)]; however, evaluations performed according to these methods also differ according to the coating method that was used to coat the particles. Thus, few simple-and-easy-to-use test methods are available for evaluating and predicting the taste masking level of coated particles. To predict the taste masking level of coated particles, the early dissolution rate of drug, which reflects the dissolution rate of the drug in the mouth, must be determined.

In this study, to accomplish this, a rapid dissolution test that can be used to investigate the early dissolution rate of a drug was established.

Experimental

Samples The formulation of the core particles and coating film listed in the previous paper.[1)] Core particle formulation No. 1 listed in the previous paper[1)] was adopted in this study.

Equipment and Conditions For the wet granulation of the core particles, agitation fluidized beds (MP-10, 25, 100, 400; Powrex Co., Ltd.) were used. The binder solution was sprayed through a binary nozzle located at the

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Table 1. Operating Conditions of Agitation Fluidized Bed

	MP-10	MP-25	MP-100	MP-400
Vessel diameter [m]	0.25	0.40	0.70	1.00
Powder feed weight [kg]	1.6	6.0	35	63
Agitator rotational speed [s^{-1}]	4.2—6.7	3.2	2.0—2.7	1.3
Air flow velocity [m^3/min]	1.3	2.5	9.0	21.8
Air temperature [°C]	60	60	60	60
Binder solution feed rate [g/min]	15—40	50—100	150—300	350
Spray nozzle insert [i.d., mm]	1.0	2.2	2.2	2.2
Spray air flow quantity [Nl/min]	50	200	750	600

Table 2. Core Particle's Physical Properties for Investigation Their Structure

	MP-10	MP-25	MP-100	MP-400
Mass median diameter of granules [μm]	283	293	280	255
Apparent density of granules [kg/m^3]	351	504	453	418
Friability of granules [—]	8.38	3.57	3.41	3.40
Shape factor of granules [—]	0.7278	0.8040	0.7441	0.7675

top of the vessel. The powder samples mentioned above were granulated and dried under the conditions listed in Table 1. The resulting granules were passed through a sieve and particles under 850 μm in size were retained. For the film coating, a spouted bed with draft tube (GPCG-1; Powrex Co., Ltd.) was used. The large size particles over 500 μm in diameter had coated thickly because of small surface areas. Therefore for the detail investigation of the influences of granule's physical properties, granules had been sieved to have the size range under 500 μm were fed into the coater. The coating liquid listed in the previous paper[1] were used to coat the surface of core particles, followed by the drying under the conditions listed in the previous paper.[1] After drying, the coated particles were again passed through a sieve and particles sieved to have the size range under 500 μm in size were retained.

Size Distribution, Apparent Density, Shape Factor, Surface Observation, Friability and Dissolution Test The granule physical properties and drug dissolution rate were investigated by method listed in the previous paper.[1]

Rapid Dissolution Test The initial dissolution rate of ibuprofen from the particles was investigated using a Touch Mixer, MT-51 (Yamato Scientific Co., Ltd.). A total of 20 ml of JPXV[21] dissolution medium No. 2 (pH 6.8) was pored into a 50 ml volume glass beaker and particles including 0.15 g of ibuprofen were added to the beaker; the dissolution medium and the particles were then mixed in the beaker at an operating speed set at 7 for 10 s. After mixing, 7 ml of the test medium was aspirated using a 10 ml syringe. The test medium was then filtered through a membrane filter (pore size of 0.45 μm). Three volunteers evaluated this solution. The concentration of ibuprofen in the filtrate was determined using a spectrophotometer at 225 nm and HPLC (Separation Module: 2695, Dual Absorbance Detector: 2487, and a personal computer, Waters Corporation). A TSK-GEL ODS-80Ts column (4.6 mm×150 mm; TOSOH CORPORATION) was used. The mobile phase consisted of acetonitrile (0.629), water (0.32), methanol (0.05) and phosphoric acid (0.001). The speed of the moving fluid was about 1.0 ml/min.

Sensory Evaluation of Ibuprofen's Bitter Taste Sensory tests of the threshold value for ibuprofen's bitter taste were conducted using three volunteers. They were well trained and could distinguish the differences of the ibuprofen solution's concentration. To investigate volunteer's mouth inside pH, pH tester (pH-Fix 2.0—9.0; MACHEREY-NAGEL) was used. The volunteer's mouth inside pH was about 6—7. Therefore we adopt JPXV dissolution medium No. 2 (pH 6.8) in this test. They held 20 ml of solution of ibuprofen 125, 250, 500, 780, 870, 1000, 1300 μg/ml of JPXV dissolution medium No. 2 (pH 6.8), respectively, in the mouth for 10 s and then washed their mouth with 20 ml JPXV dissolution medium No. 2 (pH 6.8) following each test. This result implies that the bitterness threshold concentration of ibuprofen was 1000 μg/ml in this test medium. They also evaluated test medium obtained by rapid dissolution test above mentioned. After the mouth was thoroughly rinsed with JPXV dissolution medium No. 2 (pH 6.8), 2 ml of the test medium was evaluated for 10 s in the mouth. And then the sample particles, containing 0.15 g of ibuprofen, were prepared using agitation fluidized bed granulation and coated using a spouted bed with draft tube. After the mouth was thoroughly rinsed with JPXV dissolution medium No. 2 (pH 6.8), the subjects then evaluated the taste of the drug by placing the powder in their mouths along with water.

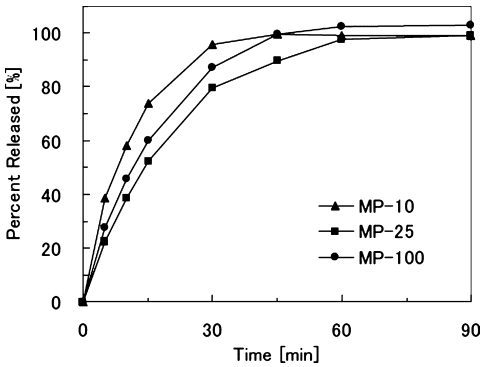

Fig. 1. Dissolution Rate of Ibuprofen
Core particles were prepared using three different scale granulator.

Results and Discussion

Effects of Core Particle's Properties on Drug Dissolution Rate from Coated Particles Figure 1 shows the dissolution rate of ibuprofen from the coated particles. Three different sizes of granulators were used to prepare the core particles. Table 2 lists the granule properties. A spouted bed with draft tube was used to coat the core particles prepared using MP-10, MP-25 and MP-100, as listed in this table. After the core particles were manufactured, they were coated using the spouted bed with draft tube. The amounts of film were core particle's 10%. As shown in Fig. 1, the ibuprofen dissolution rate from the coated particles differed according to the different sizes of the granulators that were used to granulate the core particles. In spite of the core particle's mass median diameter were almost the same, and the amount of coating film were same, the dissolution rate of ibuprofen were unequal. Drug dissolution rate from granules prepared by a large-scale granulator often decreased because of scale effect. Granules prepared by a large-scale granulator were affected strong energy during the granulation because powder

weight was increased in a large-scale granulator and then their structure became thick. However, in this figure, the dissolution rate of ibuprofen prepared by middle-scale granulator was the slowest among three size of granulator. As shown in Table 2, granule's physical properties were different. It seemed that granule's structure became different. It was thus considered that core particle's structure affect on the dissolution rate of drug considerably. To investigate the differences in the particle structures, the surfaces of the particles were examined using SEM (Fig. 2). In these figures, a) and b) show coated particles and core particles, respectively. As shown in MP-10 a), MP-25 a) and MP-100 a) of Fig. 2, the surfaces of the coated particles were uniform and appeared about the same for all three particles. In contrast, the structures of the core particles illustrated in MP-10 b) and MP-25 b) of Fig. 2 differed. The MP-25 b) particle's structure was thick, and the dissolution rate of ibuprofen from such coated particles was relatively slow. On the other hand, the MP-10 b) particle's structure seemed porous, and the dissolution rate of ibuprofen from such coated particles was relatively fast. To investigate the effect of the granule's structure on the dissolution rate of ibuprofen from coated particles in detail, core particles with various different physical properties were prepared by using three vessel sizes of agitation fluidized beds and coated by using a spouted bed with draft tube.

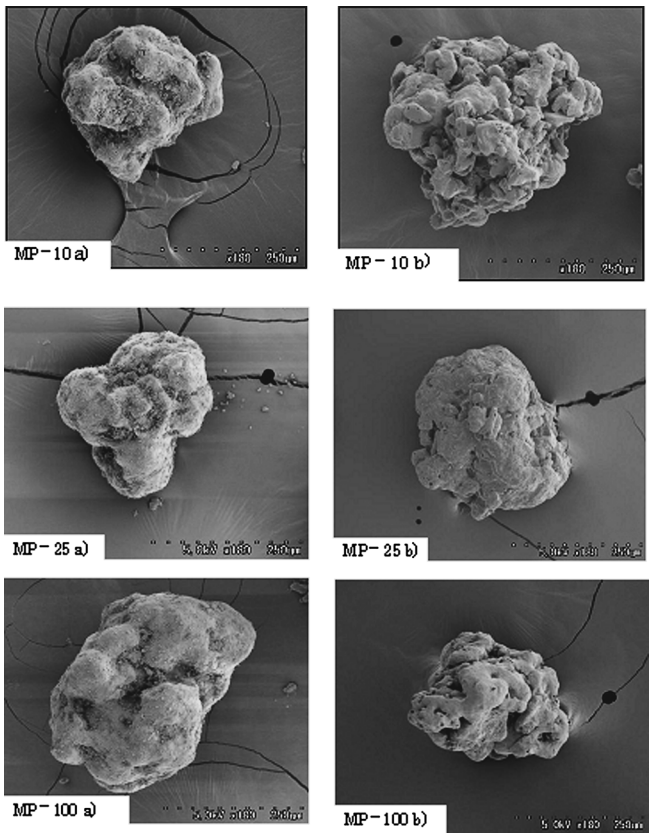

Fig. 2. Photographs of Core Particles and Coated Particles Prepared Different Scale of Granulator

MP-10 a) prepared using MP-10, coated; MP-10 b) prepared by MP-10, uncoated; MP-25 a) prepared by MP-25, coated; MP-25 b) prepared by MP-25, uncoated; MP-100 a) prepared by MP-100, coated; MP-100 b) prepared by MP-100, uncoated.

Figure 3 illustrates the effect of the various core particle's physical properties on dissolution rate of ibuprofen from 10% coated particles by comparing 70% dissolution time. Ibuprofen dissolution standard is settled over 70% in Japan.[22] In addition, near 70% percent release, dissolution rate of drug changes dramatically. To investigate the effect of core particles physical properties on drug dissolution rate with high accuracy, we should pay attention ibuprofen 70% dissolution time. As shown in these figures, the dissolution rate of ibuprofen decreased when the apparent density and shape factor of the particles increased. A large apparent density of the core particles was considered to indicate a thicker particle structure. Water was unable to penetrate such particles with thick structures rapidly. Therefore, the dissolution rate of ibuprofen from thick core particles decreased. In this study, we manufactured small size particles, the core particles surface area was very important because the surface area of small particles became larger than the surface area of large size particles. The surface area of spherical core particles was also smaller than the surface area of roughly shaped core particles. Therefore the necessary amount of coating film enough for covering the surface of core particles for good masking depends on the surface area of core particles. We adopted particles shape factor as an indicator of particle's surface area for simple, rapid method to grasp particle's physical property. Few studies have investigated the detailed effects of the small size core particle's shape factor as an indicator of surface area of particles on the dissolution rate of drug from coated particles. As a result, the dissolution rate of ibuprofen decreased when shape factor was increased. It was considered that the surface area of core particles decreased and core particles became spherical shape when shape factor was increased. Therefore coating film thickness became more uniformly and dissolution rate was controlled.

By contrast, the dissolution rate of ibuprofen increased when the friability of the particles increased, even though they were coated with the same film material. Few studies have reported the detailed effects of the small size core particle's friability on the dissolution rate of drug from coated particles. The attrition of the core particles was thought to

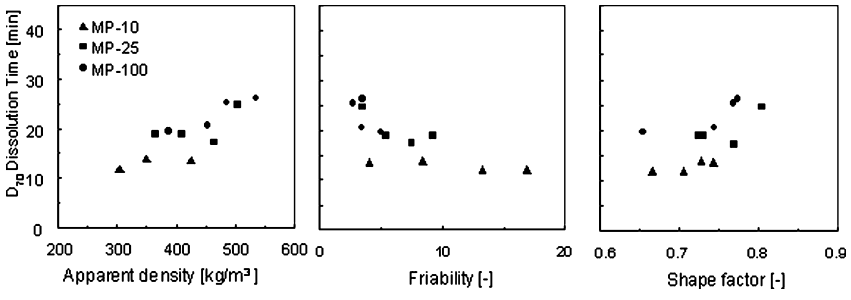

Fig. 3. Effects of Apparent Density, Friability, Shape Factor on Drug Dissolution Time, D_{70}

occur during the coating process if core particles didn't have enough strength to stand vigorous jet of air during coating process. If the attrition was occurred during the coating process, a lot of fine particles were generated. It was very difficult to coat fine particles surface completely because fine particles had large surface area. The amount of coating film should be settled minimum for enough masking of bitter taste of drug. Ideally core particles surface area shouldn't be changed during coating process. Therefore the friability of core particles should be observed when core particles were prepared.

As mentioned above, core particle's structure was reflected in their physical properties such as apparent density, shape factor and friability. In addition, core particle's structure affected drug dissolution rate from coated particles. Therefore it was important to investigate core particle's physical properties before coating process to predict drug dissolution rate from coated particles.

Investigation of Drug Dissolution Rate from Particles by Two Test Methods Figure 4 illustrates the dissolution rate of ibuprofen from particles with various levels of film coating. A spouted bed with draft tube was used to coat core particles prepared using the MP-400, as shown in Table 2. As shown in Fig. 4, the dissolution rate of ibuprofen from the particles decreased as the ratio of the amounts of the film increased. It was considered that the thickness of the film covering the surface of core particles was increased and then the film tightly controlled drug release. To investigate differences of the structure of the film, the surfaces of the coated particles were examined using SEM (Fig. 5). As shown in Fig. 5, several pores on the surfaces of coated particles were visible when the ratio of the amounts of the film was only a 5%. However, the surfaces of the coated particles smoothened and fewer pores were visible on the surfaces of the coated particles as the ratio of the amounts of the film increased. When the amount of film coating increased, the thickness of the film coating on the coated particles also increased. In addition, the ruggedness of the particles disappeared and particles became spherical shape. It was considered that coating film solution covered pores and hollows of the particles. As a result, the surface area of coated particles decreased. The dissolution rate of ibuprofen decreased because the thicker and more uniform film prevented water from penetrating into the particles. When the coating film was too thick, it hindered the dissolution of ibuprofen from the coated particles. Thus, this medicine might not be very fast acting because of the slow drug dissolution rate. Therefore, determining the minimal amount of film coating required to mask the bitter taste of ibuprofen is important.

The early dissolution rate of ibuprofen from the coated particles in the dissolution test might be helpful for predicting the masking level of the coated particles. However, as shown in Fig. 4, early dissolution rate of ibuprofen was difficult to distinguish among experiments using different amounts of film coating. In a previous study,[18] method of evaluation of bitterness of Clarithromycin (CAM) had been proposed. However that study's method was suitable for specific dosage form; dry syrup. In this dosage form, particles were dispersed with liquid. That study's mini-column method was conducted 60—300 s to evaluate bitterness of CAM. On the other hand, patients ingest powder-form drug during only several seconds with water. Therefore it was difficult to adopt that mini-column method to evaluate bitter taste of ibuprofen powder-form drug because contact time of coated particles and water was different for different dosage form. Taste sensor test[19,20] was also conducted for the evaluation of bitterness of several materials including bitter taste drug. However several materials such as basic drug, antibiotic, amino acid had evaluated using this method and confirmed good correlation with sensory test, all kinds of drug had not evaluated yet. Ibuprofen is acid drug and has bitter, astringent taste. It was considered that it was difficult to evaluate ibuprofens astringently using a taste sensor. To evaluate that short time drug dissolution and bitterness of ibuprofen including astringent taste with high accuracy, a novel dissolution test was needed. A rapid dissolution test that could be used to investigate the early dissolution rate of ibuprofen *in vitro* was proposed. Such examinations may be useful for evaluating the taste-masking level of the coated particles because the early dissolution rate might reflect the dissolution rate of ibuprofen from coated particles while particles are still in the mouth. Figure 6 shows the relationship between the amount of film coating and the concentration of ibuprofen in the rapid dissolution test media. As shown in Fig. 6, concentration of ibuprofen in the test medium was decreased as the amount of coating film was increased. These results indicated that early

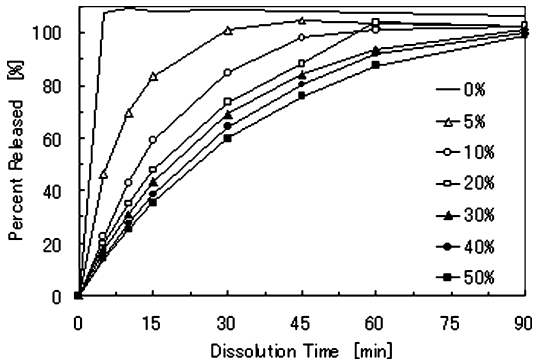

Fig. 4. Dissolution Rate of Ibuprofen from Core Particles with Different Amounts of Film Coatings

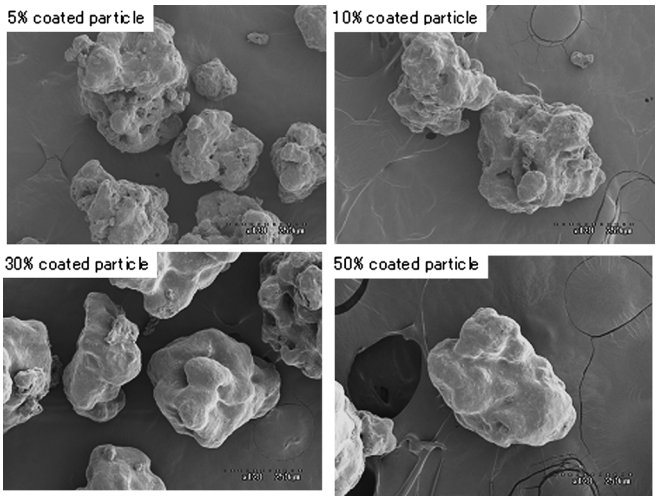

Fig. 5. Photographs of Coated Particles with Different Amount of Film Coatings

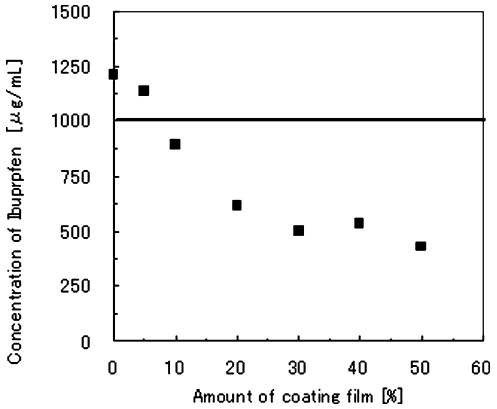

Fig. 6. Relationship between Amount of Film Coatings and Concentration of Ibuprofen Obtained Rapid Dissolution Test

dissolution rate of ibuprofen from the particles decreased as the amount of film coating increased. As mentioned above, the coating film controlled the drug dissolution rate. It was confirmed that the amount of film was also controlled early dissolution rate of ibuprofen. Compare Fig. 4 with Fig. 6, early dissolution rate of ibuprofen from coated particles could be investigated more in detail by using this novel method than conventional one. From the viewpoint of detail investigation of early dissolution rate of drug to predict taste-masking level, a rapid dissolution test is better than conventional dissolution test.

Sensory tests of the threshold value for the bitter taste of ibuprofen were also performed. The dissolution media obtained using the rapid dissolution test were evaluated for several amounts of coated particles. As a result, the volunteers confirmed that the bitter taste of ibuprofen was well masked when a film coating of more than 10% was used. This result implies that the bitterness threshold concentration of ibuprofen was 1000 μg/ml in this test medium. In addition, the volunteers also evaluated several coated particles by placing them in their mouths along with adequate water. As a result, the bitter taste of ibuprofen was well masked in samples containing a film coating of more than 10%. These results imply that the taste-masking level of coated particles can be predicted using the rapid dissolution test to investigate the early dissolution rate of ibuprofen from coated particles. Thus, the taste-masking level can be confirmed using this novel test method.

Conclusions

The physical properties of the core particles affected the dissolution rate of ibuprofen from the coated particles. A detailed investigation of the relationship between the granule's properties and the dissolution rate of ibuprofen showed that the dissolution rate of ibuprofen decreased as the apparent density and shape factor of the core particles increased. In contrast, the dissolution rate of ibuprofen increased when the friability of the particles increased. The structure and surface roughness of the core particles were considered to have strong influences on water penetration into the particles and film thickness. To investigate the early dissolution rate of ibuprofen from coated particles, reflecting the dissolution rate of ibuprofen from the coated particles while the particles are still in the mouth, a rapid dissolution test was established. The taste-masking level was then confirmed by comparing the results of a sensory test and the rapid dissolution test. These results indicate that this novel test can predict the taste-masking level of the coated particles without the need to perform a sensory test.

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