



Human sensory testing of loperamide hydrochloride preparations for children to improve their palatability

Yutaka Inoue*, Shunichi Funato, Rina Suzuki, Yuki Morita, Isamu Murata and Ikuo Kanamoto

Faculty of Pharmaceutical Sciences, Josai University, Japan

Received: 25-01-2015 / Revised: 24-02-2015 / Accepted: 27-02-2015

ABSTRACT

The purpose of the present study was to evaluate taste by a human sensory test and the physicochemical properties of loperamide hydrochloride preparations for children (Preparations A, B, and C). Evaluation of bitterness revealed significant differences between preparation C and preparation A or B. In contrast, the results of solubility and palatability with a human sensory test revealed differences between preparation A and preparation C. Measurement of sugar content revealed that the preparations all had equivalent sugar content. Measurement of particle size distribution and scanning electron microscopy revealed differences in the particle size and particle surface morphology for each preparation. A dissolution test revealed that Preparation C had a briefer period prior to dissolution than the other preparations. The taste and palatability of a preparation were presumably the result of differences in the rate of dissolution of the principal agent, types of additives, and the process by which a preparation is manufactured. In other words, the characteristics of each preparation were revealed by evaluation of their physical properties and human sensory test

Keywords: human sensory test, palatability, physicochemical property, loperamide hydrochloride

INTRODUCTION

When patients take a pharmaceutical, they tend to dislike taking it if the pharmaceutical is bitter or unpalatable^{1, 2}. Difficulty taking a pharmaceutical leads to less compliance, which can in turn reduce its efficacy and result in a worse quality of life. The dissolution of preparations such as fine granules, dry syrups, and orally disintegrating tablets in the mouth can be anticipated based on the preparation's properties, and patients are acutely aware of a preparation's taste and palatability. Most pharmaceuticals are taken orally, and the good taste and easy palatability or bad taste and poor palatability of oral preparations greatly affect patient compliance. Aspects of the taste and palatability of a preparation, such as its bitterness, can be improved by masking bitterness through techniques such as coatings and inclusion of certain additives in the preparation³⁻⁴.

As one of its efforts to reduce medical expenses, the Japanese Government recommends that medical facilities use generic pharmaceuticals

(generics). An important task for medical personnel is to select generics that are safe for patients, efficacious, and highly palatable. Generics contain the same ingredients as brand-name pharmaceuticals (brand-name drugs) but they contain different preservatives, coloring agents, and excipients, so physicians and pharmacists often question their quality⁵. Generics are cheaper than brand-name drugs and have the same quality. However, many medical experts feel that there is a lack of clinical information on the clinical efficacy and safety of these drugs and inadequate information on the properties of preparations⁶. Thus, this clinical information and information on the properties of preparations are crucial to determining whether to dispense a brand-name drug or a generic. However, assessment of the taste and palatability of a preparation is difficult, and a comprehensive evaluation of a preparation, i.e. whether it tastes good or bad and whether it is palatable or not, often depends on human sensory perceptions as gauged by a human sensory test. A human sensory test directly gauges human sensory perceptions, so it offers the

*Corresponding Author Address: Yutaka Inoue, Laboratory of Drug Safety Management, Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado-shi, Saitama, 3500295, Japan; E-mail: yinoue@josai.ac.jp

advantage of providing direct information on a preparation, such as its taste and palatability⁷⁻⁹. Thus, information on a preparation, such as its taste and palatability, can presumably be gauged via a human sensory test in most instances. However, assessments of taste and palatability in a human sensory test are affected by participants' sex, age, and differences in taste due to diet, so uniform, objective assessment is difficult. An extremely interesting proposition would be to perform a human sensory test as well as to objectively assess the taste and palatability of preparations.

Given a child's limited ability to swallow, children are often prescribed medication in forms that other patients with limited ability to swallow can take, such as powders, fine granules, granules, and dry syrups. The taste and palatability of preparations for children may affect patient compliance. However, preparation information such as the taste and palatability of fine granules for children is seldom provided in clinical practice. Previous studies of tulobuterol and teprenone by the current authors assessed and compared the taste of pharmaceutical preparations using a human sensory test and taste sensors. Results of those studies revealed a correlation between results of a human sensory test and readings from taste sensors, indicating the usefulness of human sensory testing and taste sensors. A correlation between results of human sensory testing and evaluation of the physicochemical properties of preparations might be identified in terms of the taste and palatability of preparations. Identification of this correlation would allow objective assessment in place of a human sensory test and provide a valuable source of information for clinical practice and development of preparations.

Loperamide hydrochloride is widely used in clinical practice. Loperamide hydrochloride is an antidiarrheal that stimulates the μ -opioid receptors and inhibits gastrointestinal motility. Loperamide hydrochloride for use by children is sold in the form of fine granules and dry syrups. However, loperamide hydrochloride is a bitter drug. When given to children, children may refuse to take the drug because of the taste or palatability, i.e. bitterness, of a preparation. Thus, children have less compliance with taking their medication, reducing its efficacy.

The current study used loperamide hydrochloride granules and dry syrup for children to examine the correlation between a human sensory test and the physicochemical properties of those preparations. The purpose of the present study was to evaluate taste by a human sensory test and the physicochemical properties of loperamide

hydrochloride granules and dry syrup for children (Preparations A (brand medicine), B and C (generic medicines)). Accordingly, between a human sensory test and the physicochemical properties of those preparations examine the correlation via measurement of particle size distribution, observation of particle morphology using scanning electron microscopy (SEM), measurement of sugar content analysis, and a dissolution test.

MATERIALS AND METHODS

Materials: Three different loperamide hydrochloride preparations for children were used in the present study: loperamide hydrochloride in its original form, Lopemin[®] Fine Granules for Children 0.05% (Lot NO. 026AAG, 032BBJ, Janssen Pharmaceutical K.K., Preparation A), and in two generic forms, Taiyo[®] 0.05% Loperamide HCL (Lot NO. AX1423, BH1193, Teva Pharma Japan Inc., Preparation B) and Lopeald[®] Dry Syrup 0.05% (Lot NO. AS01, Shiono Chemical Co., Ltd., Preparation C) (Table 1). Loperamide hydrochloride powder (Lot no. 23922603) from Wako Pure Chemical Industries, Ltd. was used. All other reagents were of special reagent grade.

Human gustatory sensation tests: Human gustatory sensation tests were performed with 41 healthy human volunteers (18 males, 23 females, mean age: 22.7±3.5 years). This study was fully explained to potential volunteers and then their consent was obtained. Volunteers were given 0.2 g of each preparation in random order and asked to place it in their mouths. Volunteers then evaluated the preparation after it remained in their mouths for 15 s. After each evaluation, volunteers immediately spit out the preparation and gargled with 25 mL of water. Each subject then evaluated the next preparation 15 min later to keep their evaluation from being influenced by the previous preparation. Evaluation was performed using a structured rating scale. Volunteers evaluated gustatory sensation using 6 items: "bitterness," "sweetness," "solubility," "roughness," "palatability," and "overall impression" (Scheme 1). This experimental protocol was approved by the Ethics Committee of Josai University.

Measurement of the intensity of bitterness: The intensity of bitterness was measured in accordance with Katsuragi's method¹⁰⁻¹¹. The standard for bitterness was quinine hydrochloride at concentrations of 0.01, 0.3, 0.10, 0.30, and 1.0 mM according to 46 healthy human volunteers (21 males, 25 females, mean age: 22.6±1.2 years). Two mL of a solution with a varying concentration of quinine hydrochloride was kept in the mouth for 5 s. After tasting, volunteers scored increasing

concentrations of the standard solution with scores of 0,1, 2, 3, and 4. Volunteers evaluated the bitterness of each preparation after it remained in their mouths for 15 s. After each evaluation, volunteers immediately spit out the preparation and gargled with 25 mL of water. Each subject then evaluated the next preparation 15 min later to keep their evaluation from being influenced by the previous preparation. This experimental protocol was approved by the Ethics Committee of Josai University.

Sugar content according to a refractometer:

The sugar content of each preparation was determined with an Atago Master-N1 sugar refractometer (Atago Co., Ltd., Japan) using concentrations of 2, 10, and 20 $\mu\text{g/mL}$.

Measurement of particle size distribution: The particle size distribution in each preparation was measured using a dynamic light-scattering instrument (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd., Worcs, U.K.). The particle size distribution was characterized using the mass median diameter $d(0.5)$.

Observation of particle morphology using SEM:

A scanning electron microscope (Hitachi, model S3000N, Japan) was used to observe the surface and shape of the particles in each preparation. SEM was performed with a metal coating and a voltage of 15 kV.

Evaluation using a dissolution test: The content of loperamide hydrochloride in each preparation was weighed to the mg. A dissolution test was performed using the paddle method of dissolution behavior as specified in the 16th edition of the Japanese Pharmacopoeia. The dissolution medium was distilled water and a phosphate buffer, pH 6.8 (900 mL, $37\pm 0.5^\circ\text{C}$). The rate of agitation of the paddle was 50 rpm. Standard dissolution was performed more than 85% in 15 minutes of loperamide hydrochloride granules in accordance with guidelines on generic. A phosphate buffer, pH 6.8, was used to simulate dissolution of loperamide chloride from the preparation in the mouth. Samples (10 mL) were withdrawn at various time intervals using a syringe and filtered through a $0.45\mu\text{m}$ membrane filter. The filtered loperamide solutions were used as the mobile-phase solution in HPLC. The drug concentrations in the solution were determined using HPLC (e2695, Waters Co., Japan), and an Inertsil[®] ODS-3 column ($4.6\text{ mm}\times 150\text{ mm}$, $\phi 5\mu\text{m}$; GL Science, Inc. Japan) was used. The flow rate was adjusted to about 6 minutes to serve as the retention time for loperamide hydrochloride. The column temperature was set at 40°C , and the injection volume was 100

μL . Loperamide hydrochloride dissolution was determined using a mobile phase of phosphate/triethylamine hydrochloride/acetonitrile (1/45/54, v/v/v). The measurement wavelength for loperamide hydrochloride dissolution was 214 nm.

Statistical Analysis: Results are presented as mean \pm standard deviation, and statistical significance was evaluated using the Tukey Kramer Test.

RESULTS

Human gustatory sensation tests: Human sensory test results for Preparations A, B, and C are shown in Fig. 1. In the human sensory test, significant differences in the attributes “bitterness,” “roughness,” “palatability” and “overall impression” were noted. Significant differences in the attribute “sweetness” were not noted. Preparation C scored highest for the attribute “bitterness” (bitterness score: 6.7), and significant differences between that score and scores for Preparations A and B were noted ($p<0.001$). Preparation B scored highest for the attribute “roughness” (roughness score: 5.8), and significant differences between that score and scores for Preparations B and A were noted ($p<0.05$). Significant differences between the scores for Preparations B and C were not noted. Preparation A scored highest for the attribute “solubility” (solubility score: 7.1), and significant differences between that score and scores for Preparations A and C were noted ($p<0.05$). Significant differences between the scores for Preparations A and B were not noted. Preparation A scored the highest for the attribute “palatability” (palatability score: 3.3), and significant differences between that score and scores for Preparations A and C were noted ($p<0.001$). Preparation A scored highest for the attribute “overall impression” (overall impression score: 4.8), followed by Preparation B (overall impression score: 3.9) and then Preparation C (overall impression score: 2.1). Preparation Chad the lowest overall impression score. Significant differences between that score and scores for Preparation A ($p<0.001$) and Preparation B ($p<0.01$) were noted.

Measurements of the intensity of the bitterness of Preparations A, B, and C are indicated. Preparation Chad the most intense bitterness (bitterness score: 3.20) while Preparations A and B had equivalent bitterness scores (about 1.6). Significant differences in the score for Preparation C and scores for Preparations A and B were noted ($p<0.001$). Significant differences in the scores for Preparations A and B were not noted.

The sugar content in each preparation was determined using concentrations of 2, 10, and 20 $\mu\text{g/mL}$. The sugar content in each preparation at a concentration of 2 $\mu\text{g/mL}$ was about 0.1% for Preparation A and about 0.3% for Preparations B and C. The sugar content in each preparation at a concentration of 10 $\mu\text{g/mL}$ was about 1.7% for Preparations A, B, and C. The sugar content in each preparation at a concentration of 20 $\mu\text{g/mL}$ was about 3.6% for Preparations A, B, and C. The sugar content in the preparations at all three concentrations (2, 10 and 20 $\mu\text{g/mL}$) was equivalent.

The particle size distribution for Preparations A, B, and C is indicated. The median diameter of particles in each preparation of loperamide hydrochloride was 165.6 μm for Preparation A, 188.7 μm for Preparation B, and 53.0 μm for Preparation C. Preparation A had particles that were mostly 200 μm in size, Preparation B had particles that were mostly 224 μm in size, and Preparation C had particles that were mostly 56 μm in size. In addition, Preparation C was found to have a wide range of particle sizes ranging from small to large.

The particle morphology in each sample was observed using SEM. The particle morphology in each preparation was found to differ. Preparations A and B mostly had particles of about 200 μm while Preparation C mostly had particles of about 50 μm . In addition, particles in Preparations A and C were found to have a smooth surface. Particles in Preparation B were found to have a rough surface. A dissolution test of each preparation was performed in distilled water and in a phosphate buffer, pH 6.8. The test indicated that the dissolution behavior of the 3 preparations differed. In the dissolution test with distilled water, Preparation C had the briefest period prior to dissolution, followed by Preparation A and then Preparation B. In the dissolution test with a phosphate buffer, pH 6.8, to simulate conditions inside the mouth, results mirrored the test with distilled water. In other words, Preparation C had the briefest period prior to dissolution, followed by Preparation A and then Preparation B. Preparation C had similar dissolution behavior in both test solutions, and Preparation C had a briefer period prior to dissolution than the other preparations.

DISCUSSION

This study compared the taste and palatability of brand-name drugs and generics by performing a human sensory test and evaluating the physicochemical properties of loperamide

hydrochloride preparations for children. Observations of particle morphology using SEM and measurements of particle size distribution (Figs. 3 and 4) indicated that Preparation B had a larger particle size and rougher particle surface. Thus, these properties may have led to its increased score for the attribute "roughness" in the human sensory test (Fig. 1). Particles in Preparations A and C had a smooth surface, which is presumably why they had lower scores for roughness than Preparation B. The roughness of a preparation in the mouth results in poor palatability and is reported to be a factor for noncompliance¹². Preparation B had a significantly higher score for roughness than the other preparations, which is presumably the reason for its poor palatability and low overall impression. A dissolution test was performed in distilled water and in a solvent (phosphate buffer, pH 6.8) simulating the inside of the mouth (Figs. 5 and 6). Results of that test indicated that Preparation A had a slower period prior to dissolution in the phosphate buffer, pH 6.8, in comparison to its dissolution behavior in distilled water. However, differences in the dissolution behavior of the other 2 preparations in distilled water and in the phosphate buffer, pH 6.8, were not noted. In comparison to the other 2 preparations, Preparation C had the briefest period prior to dissolution of the principal agent. A preparation's dissolution rate is an important aspect to consider in clinical practice. Several brand-name and generic preparations are reported to have different dissolution rates^{13, 14}. A large contact surface area between a sample and a solvent typically results in a better dissolution rate^{15, 16}. Observations of particle morphology using SEM and measurements of particle size distribution (Figs. 3, 4) revealed that Preparation C had a D50 of 53 μm , which means it had a smaller particle size than the other 2 preparations. The larger specific surface area and larger contact surface between the solvent and preparation particles may have led to the brief period prior to dissolution. Preparations A and B had a large D50, and this may be why they had a longer period prior to dissolution. Preparation C had the lowest score for the attribute "solubility" (Fig. 1) in the human sensory test. Preparation C is a dry syrup containing particles with a wide range of sizes, so large particles only begin to dissolve in the mouth. This may be why the preparation had a low score for solubility in the human sensory test. The only additives that Preparation C contained were sucrose and aromatic agents, which contrasted with Preparations A and B. Preparation C lacks a binder like that found in Preparations A and B (hydroxypropyl cellulose), so fine particles are not formed. Thus, Preparation C dissolved faster after a briefer period than the other preparations when

subjected to the paddle. Thus, the principal agent in Preparation C dissolves quickly under conditions like those inside the mouth. Faster dissolution of loperamide may account for the bitterness of that preparation. This is presumably why Preparation C had the highest score for the attribute “bitterness” in the human sensory test. Significant differences in the attribute “sweetness” (Fig. 1) of the 3 preparations in the human sensory test were not noted. Measurements of sugar content (Table 2) also indicated that the preparations had almost the same sugar content. The sweetening agent contained in a preparation is reported to help mask bitterness. How effectively bitterness is masked may differ depending on the type of sweetening agent added^{17, 18}. Preparations A, B, and C all had sucrose as a sweetening agent (an excipient). Addition of sucrose as a sweetening agent presumably led to the lack of difference in how effectively bitterness was inhibited. However, Preparation C had a significantly higher score for the attribute “bitterness” (Fig. 1) in the human sensory test and more intense bitterness (Fig. 2) than the other preparations. The taste of a preparation is reported to change as a result of dissolution of bitter ingredients in the preparation and the sweetness, flavor, and aroma of additives¹⁷⁻²⁰. Adding a sour aromatic agent and sourness to a bitter preparation is reported to reduce the preparation’s bitterness and increase its palatability²¹. Thus, a citrus aroma had been added to Preparation A, adding sourness to the principal agent and lessening bitterness. Preparation B included sodium citrate, which may have directly led to the sourness of the preparation and its reduced bitterness. In contrast, Preparation C had only sucrose and aromatic agents to mask bitterness, making it much less effective at masking bitterness than the other preparations. This may be which its bitterness was most apparent. Thus, Preparation C had significantly more intense bitterness than the other 2 preparations, resulting in its poor palatability and low overall impression score in the human sensory test. Of the

preparations, Preparation C had the poorest palatability and lowest overall impression score.

CONCLUSION

A human sensory test was performed and the physicochemical properties of loperamide hydrochloride preparations for children were evaluated. Among the attributes assessed in the human sensory test, “sweetness,” “roughness,” and “solubility” were found to be correlated with assessed physicochemical properties. In addition, the attribute “bitterness” in the human sensory test was found to be correlated with measurement of the intensity of bitterness using quinine hydrochloride. Masked bitterness and improved palatability are major factors that affect the treatment of children and patient compliance. Ascertaining information on a preparation’s properties can provide valuable information to improve patient compliance with medication, assist medical personnel, and help with development of preparations. This information can help with a wide range of treatments tailored to those requirements in clinical settings. In order to give pharmaceuticals appropriately, pharmacists must pay close attention to principal agents and additives as well as the characteristics of preparations and dispense those preparations accordingly.

ACKNOWLEDGEMENT

The authors wish to express sincere thanks to students at Josai University who cooperated in human sensory testing as part of this study.

CONFLICTS OF INTEREST

This study was conducted fairly and impartially and ethical considerations were taken into account. The authors have no relationships with any companies or other commercial entities mentioned in this paper.

Table 1: Additives of each formulation

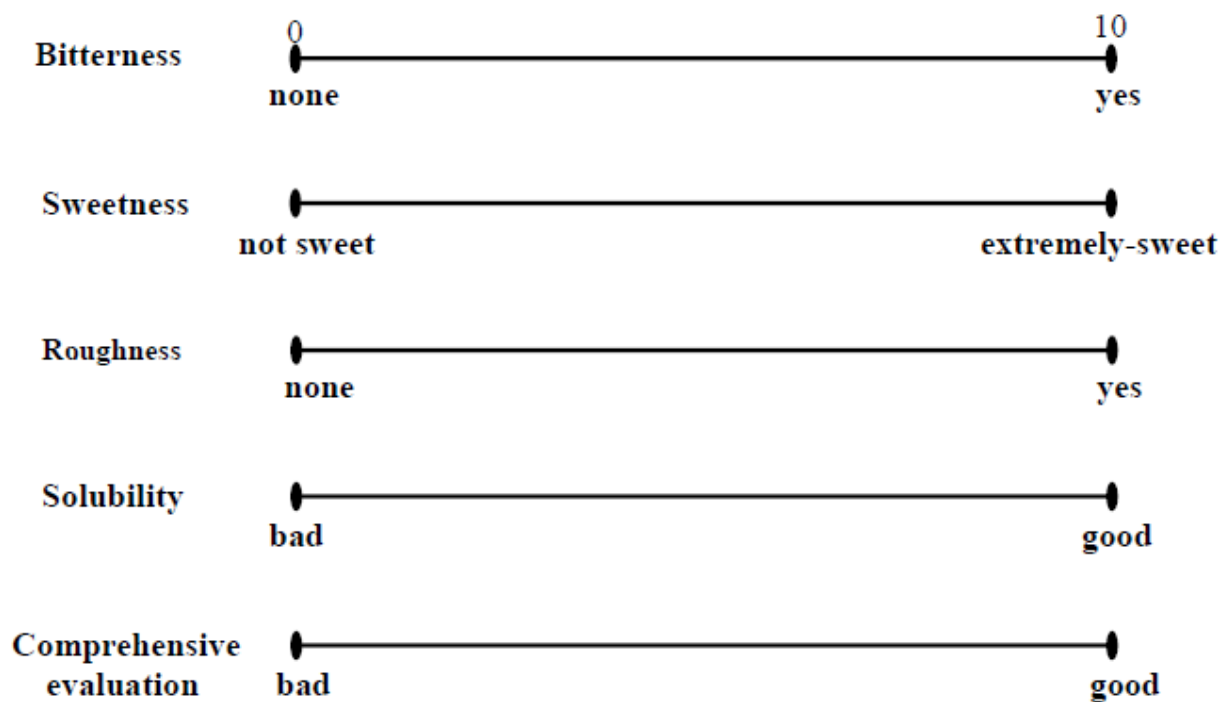
Formulation	Product name	Additives
A	LOPEMIN [®] Fine Granules for Children 0.05%	Sucrose, Magnesium aluminometasilicate, Light anhydrous silicic acid, Magnesium stearate, Hydroxypropyl cellulose (HPC), Carmellose calcium, Sunset yellow FCF, Flavour
B	LOPERAMIDE HCL [®] 0.05% 「TAIYO」	Sucrose, Corn starch, Hydrated silicon dioxide, HPC, Carmellose calcium, Sodium citrate hydrate, Propylene glycol, sunset yellow FCF, Flavour
C	LOPECALD [®] DS 0.05%	White soft sugar, Flavour

Table 2: Brix measurement of each formulation

Formulation	Concentration of Loperamide ($\mu\text{g/mL}$)					
	2		10		20	
A	0.11	\pm 0.01%	1.69	\pm 0.03%	3.68	\pm 0.03%
B	0.30	\pm 0.04%	1.70	\pm 0.03%	3.61	\pm 0.03%
C	0.37	\pm 0.03%	1.70	\pm 0.03%	3.60	\pm 0.04%

n=4 mean \pm S.D

Scheme 1: List of aspect evaluated by human gustatory sensation test



Palatability

1. Taste problems are difficult to take.
Need to improve the taste.
2. Problems are difficult to take a little taste.
3. The taste can take some issue with no problem.
4. Problems can take.
5. Very easy to take.

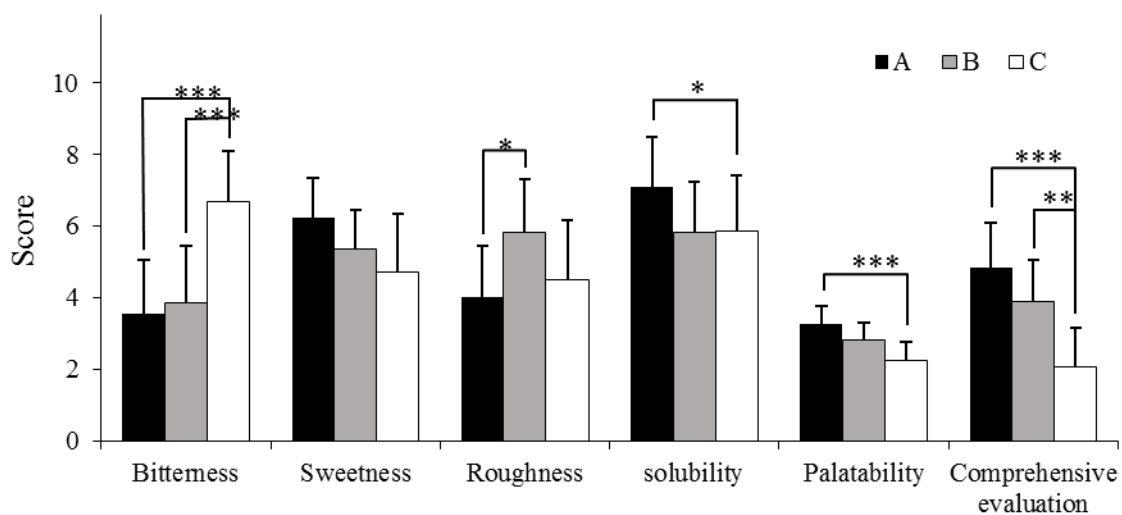


Figure 1: Result of human sensory test * $p < 0.05$, *** $p < 0.001$ (Tukey Kramer Test, $n = 40$, mean \pm S.D.).

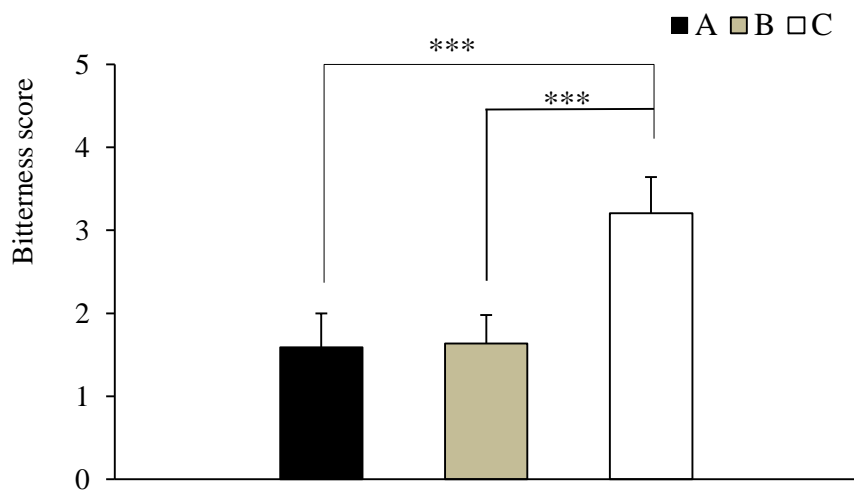


Figure 2: Bitterness intensity measurements for each formulation *** $p < 0.001$ (Tukey Kramer Test, $n = 46$ mean \pm S.D.).

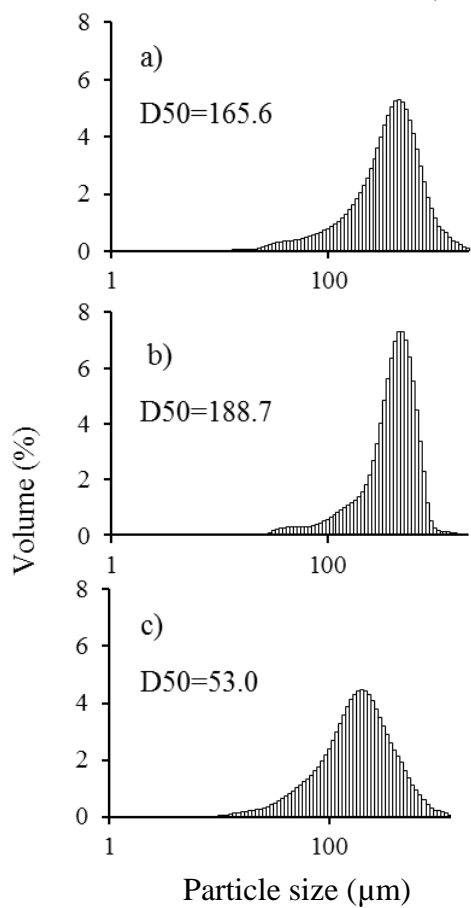


Figure 3: Particle size distribution for each formulation a) Formulation A, b) Formulation B, c) Formulation C

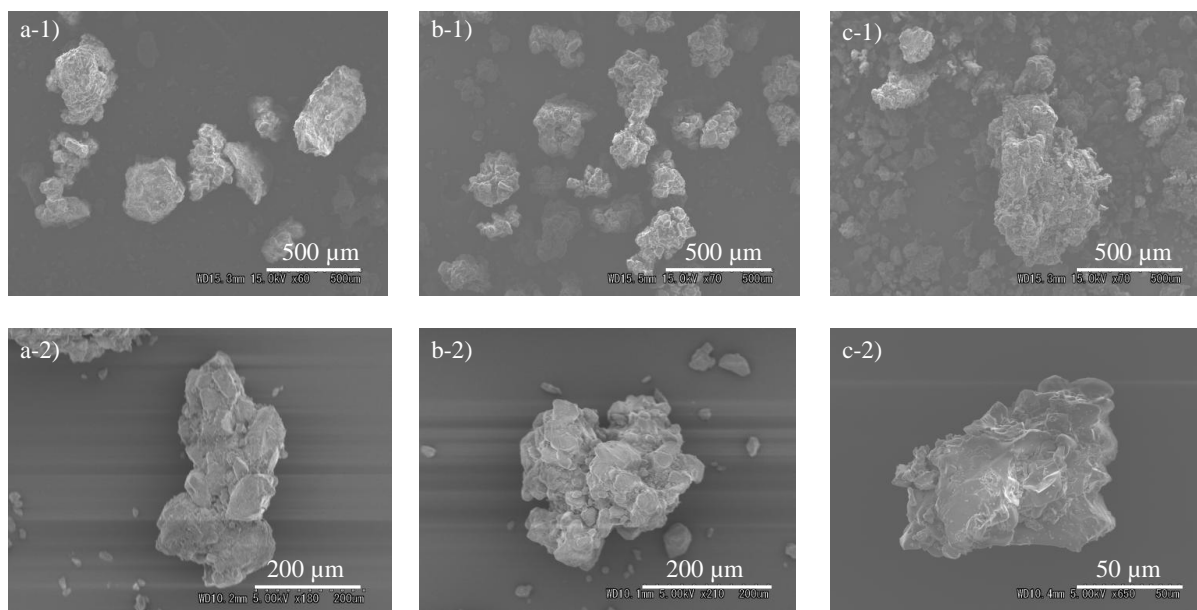


Figure 4: Scanning electron microscopy photograph of each formulation.
 a-1) Formulation A ($\times 60$), b-1) Formulation B ($\times 60$), c-1) Formulation C ($\times 95$),
 a-2) Formulation A ($\times 80$), b-2) Formulation B ($\times 210$), c-2) Formulation C ($\times 650$).

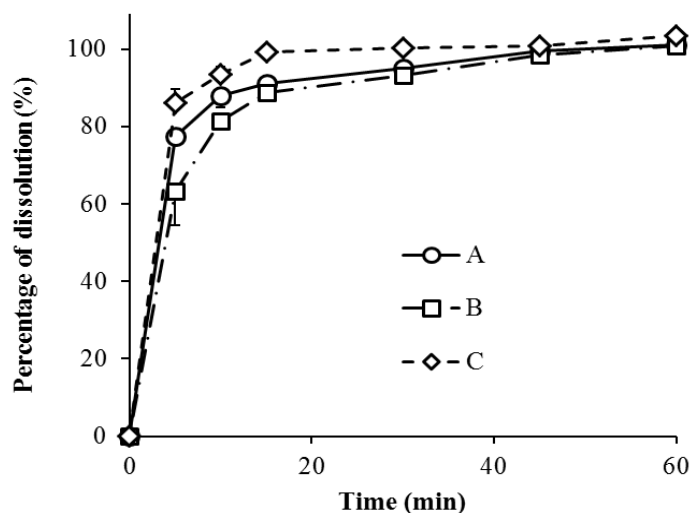


Figure 5: Dissolution test of each formulation using water (n=3).

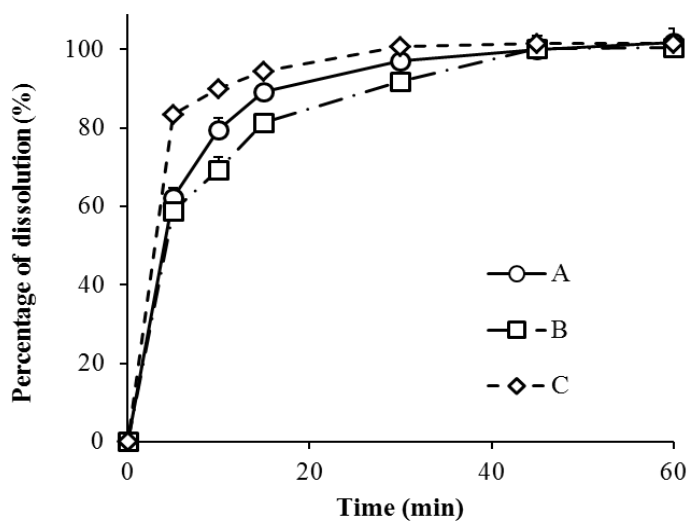


Figure 6: Dissolution test of each formulation using phosphoric buffer pH 6.8 (n=3).

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