Evaluation of Disappearance Time and Palatability of Foams in the Oral Cavities of Healthy Volunteers, and Preparation of Drug-Containing Foam Formulations for Use in the Treatment of Oral Mucositis

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Oral mucositis is one of the most common adverse effects of radiation and chemotherapy in treatments of cancers. Some clinical guidelines have focused on the prevention and treatment of oral mucositis, and thus, a mouthwash containing drugs is often recommended. In this study, we aimed to evaluate the disappearance time and palatability in the oral cavities of healthy volunteers in foams prepared from different concentrations of the three viscosity grades of methylcellulose (SM-4, -100, -400). In addition, we prepared foam formulations of drugs (benzydamine, dexamethasone, allopurinol and rebamipide) for use as a prevention and treatment of oral mucositis. There was a significant relationship between the foam drainage ratios at 5–15 min and the disappearance time in the oral cavities. The significant relationship of foam densities to the foam disappearance time and overall palatability in a clinical study was observed. Thus, the foam density is considered an important parameter and reflects these clinically important properties. The foam from SM-4 has the longest disappearance time and the best palatability followed by foams from the 4 and 1% SM-4. Drug contents in drug-containing foam formulations which were prepared with 1–4% SM-4 represented 101–112% of the loaded drug contents, and the relative standard deviations of drug contents were <2.2%, which suggests that these formulations had pharmaceutically acceptable properties. This is the first report in regard to foam formulations containing drugs for the prevention and treatment of oral mucositis, and these formulations could be potentially useful for the prevention and treatment of oral mucositis.

Key words oral mucositis; foam formulation; drainage ratio; disappearance time; palatability

Introduction

Oral mucositis is one of the most common adverse effects of radiation and chemotherapy in the treatment of cancers. It has been reported that oral mucositis occurs in 20 to 40% of patients receiving standard cancer chemotherapy and 80% of patients receiving high-dose chemotherapy. Oral mucositis is often very painful, interferes with oral intake, and worsens QOL. Oral mucositis is an important problem in clinical settings, and is sometimes the dose-limiting toxicity of cancer therapy. In addition, severe oral mucositis could be associated with severe weight-loss, receiving nutrition through a gastrostomy tube or intravenous line resulting in discontinuation of eating by mouth, and life-threatening systemic sepsis from severe infections in patients treated with cancer therapy. Therefore, prevention and treatment for oral mucositis are clinically important.

Some guidelines have been focused on prevention and treatment of oral mucositis. The guidelines from the Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO) recommended the usefulness of basic oral care, cryotherapy, photobiomodulation (laser and other light therapy), and intravenous keratinocyte growth factor (KGF)-1, and parenteral and oral glutamine for prevention of oral mucositis. Morphine and a benzodamime mouthwash were also recommended for prevention and treatment of oral mucositis by the guidelines. In addition to these drugs, the mouthwash with anti-inflammatory drugs and anti-oxidants, such as dexamethasone, polaprezinc, rebamipide and allopurinol were reported to be effective, although the guidelines mention that the evidence for each of these agents was insufficient. Thus, the mouthwash, or gargling of drugs could be beneficial for prevention and treatment of oral mucositis. However, mouthwash of gargling can cause the pain or the risks of choking and aspiration, which may lead to reduced adherence to its use.

Foam is defined as a thermodynamically unstable system that involves a dispersion of gas in a liquid or a solid. Most commonly, foam has a volume fraction of 0.5–0.9, and the size of bubbles in foam is between 0.1–3 mm. Foam is characterized as light-weight compared with liquid and is easily spread. Pharmaceutical applications of foam formulations have been reported for some treatments. Pharmaceutical products as foams were mostly formulations applied to the skin. Rectal foam formulations of 5-aminosalicylate and budesonide have been introduced as pharmacotherapy for ulcerative colitis. For rectal treatments, foam distributes more uniformly and seems to persist longer in the colon compared with a liquid enema. The properties of foam make foam formulations containing drugs beneficial for application in the oral cavity for the treatment of oral mucositis because they can reduce...
pain and the risks of choking and aspiration. Furthermore, it is expected that the duration of foam in the mouth could be longer than that of mouthwash; therefore, the drug delivered as a foam is likely to retain in the oral cavity. However, to our knowledge, there are currently no reports about the preparation and the use of foam formulations for the application of drugs to prevent and treat oral mucositis. Additionally, there are no studies that show the relationship between the physical properties of foam formulations and their palatability, which has affected acceptance of and adherence to the use of foam formulations.

In this study, we aimed to evaluate the disappearance time and palatability in the oral cavities of healthy volunteers in foams prepared from different concentrations of various types of methylcellulose. In addition, we prepared foam formulations containing benzydamine, dexamethasone, allopurinol and rebamipide, which are used for the treatment of oral mucositis, and evaluated their pharmaceutical characteristics.

**Experimental**

**Materials** Three viscosity grades of methylcellulose (SM-4, -100, and -400, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) and a foam pump (Pump Foamer, F7, estimate discharge volume, 0.8 g; Daiwa Can Company, Tokyo, Japan) were kindly provided for use in this study. Benzydamine (Comb-Blocks, Inc., San Diego, CA, U.S.A.), dexamethasone (Comb-Blocks, Inc.), allopurinol and rebamipide (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) were purchased. All reagents used for the study were reagent-grade products.

**Preparation of Foam** We prepared 12 different foams from 3 to 5 different concentrations of the three types (viscosity grades) of methylcellulose. Methylcellulose (SM-4, -100, and -400) were added in purified water with stirring, and prepared to 1, 2, 4, 6 and 8% for SM-4, 0.2, 0.6 and 1% for SM-100, and 0.1, 0.4, 0.6 and 0.8% for SM-400. Each methylcellulose solution was added to a foam pump, and each foam was generated by discharging from the pump. The foams were used for all tests after the priming of pumping (discharging the foam for 6 times).

**Measurement of Viscosity of the Methylcellulose Solutions** The viscosity of the methylcellulose solutions at 4 and 23°C were measured by a L/A rotor Viscometer type-B (TVB-10, Toki industrial Co., Ltd., Tokyo, Japan).

**Measurement of Foam Density** To measure the foam density, the vessel (72.14 mL) was filled with the foam discharged from a foam pump, and the weight of foam was immediately measured at 23°C. The foam density was calculated by the weight of foam divided by the volume of vessel.

**Measurement of Foam Drainage Ratio** To evaluate the free drainage of foam, the foam drainage ratio was measured according to the method reported previously with modifications.

Briefly, each foam (5.0 g) was put in a funnel, and the drained foam solutions were collected for 60 min at room temperature (25 ± 1°C). The foam drainage ratio (%) was estimated using the weight of the collected solutions divided by the initial weight.

**Evaluation of the Disappearance Time and Palatability of Placebo Foams in Healthy Volunteers** To measure the disappearance time and overall palatability of the placebo foams, the clinical trial enrolled 15 healthy volunteers (7 men and 8 women; age, 23.1 ± 0.9 years). We performed a randomized crossover trial, which comprised 12 placebo forms (Table 1). The study protocol was approved by the Ethics Committee of the University of Shizuoka (approved number, 1–7) and the subjects participated in the trial after providing written informed consent. The foam was discharged from the foam pump with one push, and the subjects were asked to put the foam into their oral cavity and hold the foam until they felt it had disappeared. They evaluated the overall palatability of each foam using a visual analogue scale (VAS) in which a score of 100 indicated “good palatability.” Simultaneously, the subjects scored the VAS of hardness, smoothness, and adhesion, in which a score of 100 indicated the strongest sensation (very hard, very smooth and very adherent, respectively). The disappearance time of the foam in the oral cavity was defined based on the declaration of the subjects and measured by an investigator with a stopwatch. At the end of the time, all subjects spat out the residual material in the oral cavity and immediately rinsed their mouths out with water. Then, they evaluated the preferability of the foams using a 5-point verbal rating scale (VRS) as follows: 1, extremely unfavorable; 2, unfavorable; 3, neither; 4, preferable; 5, extremely preferable. The preferability of the foams was defined as the total number of answers of 4 (preferable) and 5 (extremely preferable) by the subjects. Subjects were given a 15-min interval before testing the next foam.

**Preparation of Foam Formulations Containing Drugs for the Treatment of Oral Mucositis** Foam formulations containing drugs for the treatment of oral mucositis were prepared. We added benzydamine to a 2% methylcellulose solution, dexamethasone to 1, 2 and 4% methylcellulose solutions, allopurinol to 2 and 4% methylcellulose solutions and rebamipide to a 2% methylcellulose solution. The contents of benzydamine, dexamethasone, allopurinol and rebamipide were 2.81, 1.25, 12.5 and 31.25 mg/mL, respectively, in the solutions. Each drug foaming mixture was put into a foam pump, and each foam formulation was produced by discharging from the pump. The loaded contents in one push of foam
formulation (0.8 g of foam) discharged from the pump were 2.3, 1.0, 10 and 25 mg for the formulations of benzydamine, dexamethasone, allopurinol and rebamipide, respectively.  

Measurement of Drug Content of the Foam To determine the drug contents in the foam formulations, the foam discharged from the foam pump by one push was weighed. The foam was disappeared by adding 1% ethanol and was diluted to the appropriate concentrations in water (benzydamine), 3.3% methanol (dexamethasone), 0.1 M hydrochloric acid (allopurinol), or 0.05 M sodium hydroxide (rebamipide) for analysis. The concentrations of benzydamine, dexamethasone, allopurinol, and rebamipide in the diluted solutions were determined by the UV absorbance at 306, 254, 250, and 230 nm, respectively, and the drug contents in each form formulation were calculated.

Statistical Analysis The data are presented as the mean and standard deviation (S.D.) or relative standard deviation (R.S.D.). The statistical analysis was performed using GraphPad Prism v.5.02 software (GraphPad Software, San Diego, CA, U.S.A.). The correlations were evaluated by unweighted linear regression, and the p value was calculated using Pearson correlation coefficients. A statistically significant difference was noted at p < 0.05.

Results and Discussion
Physical Properties of Placebo Foams Table 1 shows the values of viscosity of the 12 solutions. The values of viscosity increased as the concentration of each grade of methylcellulose increased, and the viscosity at similar concentrations of the grades increased as the numerical value of the viscosity grade in the methylcellulose increased. The values of viscosity at 4 °C were higher than those at 23 °C, except for the 8% SM-4 solution.

We produced the foams by discharging them from a foam pump. For the pump used in this study, the mechanism that produces the foams is the mixing of the solution with surfactant and air without using high pressure gas. Constant volume produces the foams is the mixing of the solution with surfactant and air without using high pressure gas. Constant volume

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the oral cavity and influence the efficacy of drugs in foam formulations. In this regard, foam stability in the oral cavity could be the primary property of foam formulations for the treatment of oral mucositis, although it is necessary to clarify the release behavior of drugs from the foam. Furthermore, the foam drainage ratio could reflect the foam disappearance time used in this clinical study.

The palatability of oral dosage is one of the important fac-

**Fig. 2.** Foam Disappearance Time in the Oral Cavity (A) and Visual Analogue Scale (VAS) of Overall Palatability (B) for 12 Foams in Healthy Volunteers

Each column represents the mean and standard deviation of 15 volunteers.

**Fig. 3.** Relationship between the Foam Drainage Ratio of 12 Foams at 5 (A), 10 (B), 15 (C) and 20 min (D) and the Disappearance Time in Oral Cavity in Healthy Volunteers

Each point represents the mean.
tors that influences their medication adherence.\textsuperscript{27–29} VAS is widely used for evaluating the levels of pain or palatability in human subjects\textsuperscript{30,31} and we have previously reported that we could quantitative assessed the palatability and ease of taking for some formulations.\textsuperscript{29,32} As shown in Fig. 2B, the VAS score of overall palatability was the highest (79.0) in foam from the 2\% SM-4 followed by foams from the 4 and 1\% SM-4 (68.0 and 67.8, respectively). The VAS scores of hardness, smoothness and adhesion in the foams ranged from 6.7–41.7, 62.1–82.5 and 13.3–80.1, respectively (Table 2). The VAS scores of hardness, smoothness and adhesion in the foams ranged from 6.7–41.7, 62.1–82.5 and 13.3–80.1, respectively (Table 2). The 5-point rating scale for preferability was the highest for the foam from 2\% SM-4; 73\% of subjects answered that they preferred it (Table 3). The foam from 2\% SM-4 was suggested to have the best palatability and preferability of all the foams tested in this clinical study.

Texture could influence the palatability of both food and pharmaceutical dosage form. In our clinical study, no apparent relationship between overall palatability and parameters of texture including hardness, smoothness and adhesion, were observed. Further investigation for relationship between the

Table 2. Visual Analog Scale (VAS) Score of Hardness, Smoothness and Adhesion of the Foams in the Clinical Study

| Methylcellulose and concentration | VAS score |
|-----------------------------------|-----------|
|                                   | Hardness  | Smoothness | Adhesion  |
| SM-4                              |           |            |           |
| 1\%                               | 20.9 ± 21.9 | 76.8 ± 18.6 | 53.7 ± 28.7 |
| 2\%                               | 27.1 ± 18.9 | 77.1 ± 16.5 | 66.6 ± 21.3 |
| 4\%                               | 38.5 ± 22.1 | 74.0 ± 15.3 | 70.9 ± 13.1 |
| 6\%                               | 41.7 ± 29.8 | 62.1 ± 27.7 | 80.1 ± 12.8 |
| 8\%                               | 37.7 ± 27.4 | 67.1 ± 27.5 | 75.5 ± 22.7 |
| SM-100                            |           |            |           |
| 0.2\%                             | 7.7 ± 6.1  | 79.2 ± 18.7 | 26.6 ± 23.6 |
| 0.6\%                             | 22.9 ± 16.5 | 73.5 ± 25.5 | 51.2 ± 25.4 |
| 1\%                               | 17.3 ± 12.4 | 82.5 ± 16.4 | 40.5 ± 26.5 |
| SM-400                            |           |            |           |
| 0.1\%                             | 6.7 ± 14.4  | 67.2 ± 32.3 | 13.3 ± 22.8 |
| 0.4\%                             | 25.4 ± 18.6 | 71.6 ± 23.4 | 50.9 ± 23.0 |
| 0.6\%                             | 24.6 ± 16.5 | 73.1 ± 15.4 | 47.9 ± 28.0 |
| 0.8\%                             | 19.3 ± 19.0 | 70.4 ± 23.2 | 41.1 ± 26.8 |

Data represent the mean and standard deviation from 15 volunteers.

Table 3. Five-point Verbal Rating Scale (VRS) for Preferability of Placebo Foams in the Clinical Study

| Methylcellulose and concentration | 5-point verbal rating scale | Preferable (4 and 5) |
|-----------------------------------|-----------------------------|---------------------|
|                                  | 1   | 2   | 3   | 4   | 5   |                     |
| SM-4 1\%            | 0 (0) | 2 (13) | 5 (33) | 3 (20) | 5 (33) | 8 (53) |
| 2\%                  | 1 (7) | 0 (0) | 3 (20) | 7 (47) | 4 (27) | 11 (73) |
| 4\%                  | 0 (0) | 4 (27) | 4 (27) | 3 (20) | 4 (27) | 7 (47) |
| 6\%                  | 2 (13) | 3 (20) | 4 (27) | 3 (20) | 3 (20) | 6 (40) |
| 8\%                  | 7 (47) | 3 (20) | 3 (20) | 2 (13) | 0 (0) | 2 (13) |
| SM-100 0.2\%       | 3 (20) | 4 (27) | 7 (47) | 0 (0) | 1 (7) | 1 (7) |
| 0.6\%                | 1 (7) | 3 (20) | 4 (27) | 4 (27) | 3 (20) | 7 (47) |
| 1\%                  | 3 (20) | 3 (20) | 2 (13) | 7 (47) | 0 (0) | 7 (47) |
| SM-400 0.1\%       | 9 (60) | 1 (7) | 4 (27) | 1 (7) | 0 (0) | 1 (7) |
| 0.4\%                | 1 (7) | 1 (7) | 5 (33) | 6 (40) | 2 (13) | 8 (53) |
| 0.6\%                | 0 (0) | 4 (27) | 4 (27) | 7 (47) | 0 (0) | 7 (47) |
| 0.8\%                | 2 (13) | 7 (47) | 2 (13) | 3 (20) | 1 (7) | 4 (27) |

The data outside the brackets represent the number and the data inside the brackets represent the percentages of subjects. The fifteen volunteers evaluated the acceptability of the foams using a 5-point verbal rating scale as follows: 1, extremely unpreferable; 2, unpreferable; 3, neither; 4, preferable; 5, extremely preferable. The acceptability of foams was indicated based on the number of volunteers who answered 4 (preferable) and 5 (extremely preferable).

The significant relationships of the foam densities to the foam disappearance time and overall palatability were observed in 12 foam formulations ($r = -0.819, p = 0.001$ and $r = -0.794, p = 0.002$, respectively; Fig. 4). The foam with smaller density showed longer disappearance time and higher palatability. The positive correlation between the foam drainage ratio and foam density suggested that smaller density foam would have higher stability. In addition, in food science, it has been commonly known that foam contained small and uniform babbles provided light and smooth textures in foods and confectionery. Thus, the foam formulation with the

Fig. 4. Relationships between the Foam Densities of 12 Placebo Foams and the Foam Disappearance Time in the Oral Cavity (A) and Visual Analogue Scale (VAS) of Overall Palatability (B)

Each point represents the mean.
Drug content of SM-4  | Foam density (g/cm³) | Foam volume (g) | Drainage ratio (%) | Drug content (mg/g foam) |
|-----------------|------------------|----------------|------------------|--------------------------|
|                 | 5 min            | 10 min         | 15 min           |                          |
| Benzydamine     |                  |                |                  |                          |
| 2%              | 0.078 ± 0.001    | 0.736 ± 0.007  | 24.7 ± 8.3       | 2.95 ± 0.01, 0.32, 104.8 |
|                 |                  |                |                  |                          |
| Dexamethasone   |                  |                |                  |                          |
| 1%              | 0.078 ± 0.001    | 0.738 ± 0.009  | n.d.             | 1.30 ± 0.02, 1.80, 104.1 |
| 2%              | 0.077 ± 0.001    | 0.743 ± 0.015  | 11.5 ± 3.0       | 1.37 ± 0.01, 0.64, 109.2 |
| 4%              | 0.084 ± 0.000    | 0.739 ± 0.004  | n.d.             | 1.36 ± 0.00, 0.33, 108.6 |
| Allopurinol     |                  |                |                  |                          |
| 2%              | 0.078 ± 0.001    | 0.753 ± 0.028  | 29.6 ± 6.7       | 12.6 ± 0.5, 3.86, 100.9  |
| 4%              | 0.091 ± 0.004    | 0.759 ± 0.011  | n.d.             | 12.6 ± 0.3, 2.23, 100.8  |
| Rebamipide      |                  |                |                  |                          |
| 2%              | 0.079 ± 0.000    | 0.772 ± 0.022  | 6.2 ± 2.3        | 35.1 ± 0.6, 1.82, 112.4  |

n.d.: not detected. The foam density and collapse ratio represent the mean and standard deviation (S.D.) of values from foams produced from the three different foam pumps. The drug content in the foam discharged from the formulations represents the mean and S.D., relative standard deviations (R.S.D., %) and % of loaded content of values from foams produced from the three different foam pumps.

smaller density would provide a longer residence time in the mouth and higher palatability in this study. It is likely that these properties would play a crucial role in the efficacy and adherence of foam formulations, and the foam density is considered an important parameter and should be examined when developing a foam formulation.

Pharmaceutical Properties of Drug-Containing Foam Formulations

We prepared foam formulations for use as a prevention and treatment of oral mucositis. Benzydamine, dexamethasone, allopurinol, and rebamipide were selected as therapeutic drugs based on previous reports in which they had been used in mouthwashes. In addition, the content of SM-4 solutions (1–4%) was identified as being the optimal content of SM-4 showed higher viscosity compared to the placebo foam. The drug contents in the foam formulation was likely because of the higher soluble component of the drug and sustained dispersion of the undissolved drugs in the foaming mixture suspensions. Thus, these results suggested that 4% SM-4 in the foaming solution would be more suitable in the case of a suspension, although 2% SM-4 showed the best palatability. The rebamipide foam formulation with 4% SM-4 could not be prepared because the mixture became stuck in the foam pump.

Additional studies for evaluating palatability of the foam formulations and for developing taste-masking methods are necessary. Furthermore, it is likely that there would be large difference of palatability between healthy volunteers and cancer patients suffered from oral mucositis. Further investigation of clinical efficacy and preference of foam formulations in patients receiving cancer chemotherapy would be of value.

Conclusion

In this study, we prepared 12 different foams from different concentrations of three viscosity grades of methylcellulose. There was a significant relationship between the foam drainage ratios at 5–15 min and the disappearance time in the oral cavities of healthy volunteers. A significant relationship of foam densities to the foam disappearance time and overall palatability in the clinical study was observed. Thus, the foam density is considered an important parameter and reflects these clinically important properties. Our clinical study indicated that the foam from 2% SM-4 had the best palatability and preference of the foams. We also prepared foam formulations containing benzydamine, dexamethasone, allopurinol and rebamipide for use as a prevention and treatment of oral mucositis. Our results suggested that these formulations had pharmaceutically acceptable properties.

The drug contents in the foam formulations was likely because of the higher soluble component of the drug and sustained dispersion of the undissolved drugs in the foaming mixture suspensions. Thus, these results suggested that 4% SM-4 in the foaming solution would be more suitable in the case of a suspension, although 2% SM-4 showed the best palatability. The rebamipide foam formulation with 4% SM-4 could not be prepared because the mixture became stuck in the foam pump.

Table 4 indicates pharmaceutical properties of drug-containing foam formulations. There was no appreciable difference of foam density and foam drainage ratios at 5–15 min between almost all the drug-containing foam formulations and the corresponding foam shown in Fig. 1. Only the foam drainage ratio of the dexamethasone foam formulation with 1% SM-4 was lower than that of the placebo foam. The drug contents in the foam formulations of drugs represented 104–112% of the loaded drug contents (Table 4). The minimum values of the R.S.D. of the drug contents among the foam formulation of each drug were c<2.23, which suggests that these formulations had pharmaceutically acceptable properties (Table 4).

In the preparation of foam formulations in this study, benzydamine was dissolved in a 2% SM-4 solution, whereas the other three drugs existed as a suspension in the mixtures. The variation of drug content in benzydamine foam formulation showed the smallest in tested formulations. It was suggested that improved solubility of drugs in the foam mixture could reduce the content variation. For dexamethasone and allopurinol, we prepared foam formulations using 1 and 4% SM-4 in addition to 2% SM-4. The R.S.D. of the drug contents in the foam formulations of dexamethasone and allopurinol decreased as the content of SM-4 increased (Table 4). The mixtures with 4% SM-4 showed higher viscosity compared with the 1 and 2% mixtures. The lower variance (R.S.D.) of
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Conflict of Interest   The authors declare no conflict of interest.