DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 2, pp. 151–161, 2004

RESEARCH PAPER

Development of Patient-Friendly Preparations: Preparation of a New Allopurinol Mouthwash Containing Polyethylene(oxide) and Carrageenan

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ABSTRACT

Stomatitis is a harmful side effect induced by high and/or multiple dosing of cytotoxic drugs such as 5-fluorouracil. Allopurinol mouthwash has been used to prevent stomatitis induced by cancer chemotherapy. In the present study, the pharmaceutical utility of allopurinol mouthwash (Alkox-mw), which consists of polyethylene(oxide) (Alkox®) and iota-carrageenan (INA), was investigated as a possible material for a new oral dosage preparation for improving the adhesiveness onto the oral mucosa. From the observation of the gel formation, which was studied as a function of the variety of the added Alkox® and/or INA, the preferential compositions of Alkox®-mw (Alkox®:INA % ratio) seemed to be 1.0:(0–1.0) and (0–3.0):0.4, respectively. The adhesiveness and the spinnability of various allopurinol mouthwashes were also investigated using a creep meter. The adhesiveness of Alkox-mw increased with the increase in the amount of added Alkox®. Furthermore, the adhesion force of Alkox®-mw was greater than that of allopurinol mouthwash consisting of sodium carboxymethylcellulose (CMC–Na). From the in vitro assessment of mimicking the effusion of the allopurinol mouthwashes from the surface of the oral mucosa, the effusion of Alkox®-mws was retarded by the added Alkox®. The results obtained in the present study suggest that Alkox-mws may be useful as a new dosage form that adheres to the oral mucosa.

Key Words: Polyethylene(oxide); Iota-carrageenan; Adhesiveness; Stomatitis; Mouthwash; Allopurinol.

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DOI: 10.1081/DDC-120028710
0363-9045 (Print); 1520-5762 (Online)

INTRODUCTION

Although in recent years there have been significant developments in cancer chemotherapy, various side effects induced by an antineoplastic agent are still unavoidable.[1] Stomatitis is a harmful side effect induced by high and/or multiple dosing of cytotoxic drugs such as 5-fluorouracil. Stomatitis may cause pain in the oral cavity, impaired swallowing or loss of appetite, and a lowering of the quality of life (QOL) of patients. With respect to stomatitis, it has been reported that cryotherapy using an ''ice ball'' or a ''mouthwash'' containing povidone iodine prevents the import of the antineoplastic agent into the oral mucosa or the removal of the free radicals induced in the oral cavity.[2–4]

Clark and Slevin[5] demonstrated that allopurinol mouthwash diminished the mucositis resulting from the 5-fluorouracil administration in colorectal cancer. Dozono et al.[6] also reported that allopurinol mouthwash showed a marked effect on stomatitis induced by chemotherapy. Usually, allopurinol mouthwash was prepared at 1 mg/mL in a 3% methylcellulose, 1% sodium carboxymethylcellulose (CMC–Na) or 0.1–0.2% sodium polyacrylate, which acts as a suspending or viscosity-increasing agent.[4] However, patients have reported the taste and smell of allopurinol mouthwash to be disagreeable. The salty taste due to the sodium contained in the CMC–Na or sodium polyacrylate, as well as the odor of methylcellulose, were disliked by patients.[7,8]

In a previous study, we prepared the allopurinol gel consisting of iota-carrageenan and polyethylene (oxide) (Alkox®). Iota-carrageenan has been used as a texture modifier and as a gelling agent in the food industry,[9] whereas polyethylene(oxide) is obtained by the ring-opening polymerization of ethyleneoxide, which has a high viscosity and spinnability.[10] Inasmuch as both compounds are tasteless and odorless, it is thought that these compounds are suitable as additive agents. From the in vitro assessment of the adhesiveness of allopurinol gels, the adhesiveness of the allopurinol gel increased with an increase in the amount of added Alkox®. On the other hand, as the gelation behavior of the gel containing various amount of Alkox® and iota-carrageenan was investigated, the concentration domain in which the gelation does not take place was also observed.

In the present study, we attempted to prepare an allopurinol mouthwash consisting of iota-carrageenan (INA) and Alkox® (Alkox-mw) by focusing attention on the concentration domain in which gelation did not take place. The goal of this study was to investigate the effect of the mixing ratio of INA and Alkox® on the physicochemical properties of the allopurinol mouthwash in vitro compared with allopurinol mouthwash consisting of CMC–Na as a dispersion medium (CMC–Na-mw) and evaluate the feasibility of its pharmaceutical utility.

EXPERIMENTAL

Materials

Allopurinol was purchased from Sigma (St. Louis, MO). Inagel F13 (INA) and Alkox E-30 (Alkox®) were generously supplied by the Ina Food Co. (Nagano, Japan)

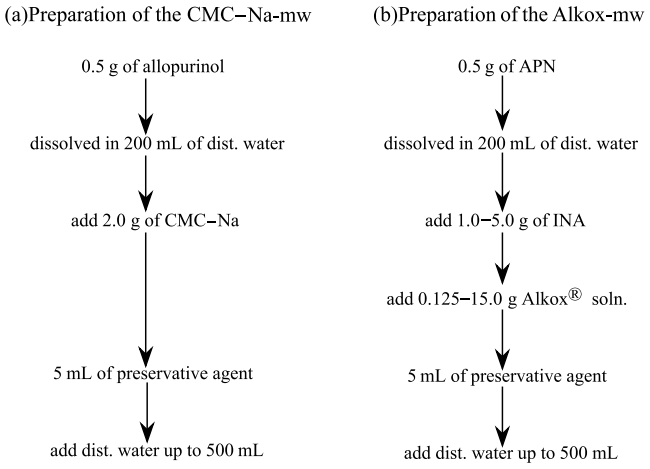

Figure 1. Schematic side view of the measurement of the adhesiveness of Alkox-mouthwash.

and Higuchi Inc. (Tokyo, Japan), respectively. Carboxymethylcellulose sodium (CMC–Na) was purchased from Wako Pure Chemical Industries (Osaka, Japan).

Preparation of Allopurinol Mouthwashes

A fixed weight (0.5 g) of allopurinol crystals, various weights (1–5 g) of INA, various weights of Alkox® (0.125–15 g), and 5 mL of a preservative agent composed of ethyl- and propyl-p-hydroxybenzoate were added and dissolved in 500 mL of distilled water at 70°C. The allopurinol mouthwash was stored at room temperature (25±1°C). We called this mouthwash Alkox-mw. The allopurinol mouthwash prepared using CMC–Na alone was called CMC–Na-mw (Fig. 1).

Confirmation of Gelation Behavior

A fixed volume (5.0 mL) of solution was placed in a 10-mL, flat-bottomed cylindrical vial (diameter: 21 mm). The vial was tilted at definite time intervals, and gelation was defined as the time at which the solution formed a gel just strong enough to retain its shape in position.[11]

Measurement of the Viscosity of the Mouthwashes

The viscosity of the mouthwashes was measured using a Toki RE-80U Viscometer (Tokyo, Japan) equipped with a cone and plate fixture (14 mm diameter, 3° angle). All measurements were performed at a temperature of 25±0.2°C, 30±0.2°C, 35±0.2°C, or 40±0.2°C.

Table 1. Component of the artificial saliva.

Component	
Sodium carboxymethylcellulose	10.0 g
D-sorbitol	30.0 g
Potassium chloride	1.20 g
Sodium chloride	0.84 g
Calcium chloride dihydrate	0.15 g
Magnesium chloride hexahydrate	0.05 g
Dipotassium hydrogenphosphate	0.30 g
Add. dist. water	1,000 mL

In Vitro Assessment of Mimicking the Effusion of the Allopurinol Mouthwashes from the Surface of the Oral Mucosa

In order to evaluate the effect of saliva secreted onto the oral mucosa on the effusion properties of the adhered allopurinol mouthwashes, we attempted to investigate the in vitro effusion using the falling liquid technique of Ranga and Buri.[12] The apparatus of this investigation is schematically illustrated in Fig. 2. The sample support was prepared as follows: the body of a disposable syringe (volume: 1 mm) was vertically cut off and set at an acute angle of 2°. A definite weight (0.8 g) of allopurinol mouthwash containing 0.1% brilliant blue was placed on the sample support. Artificial saliva, the constituents of which are listed in Table 1, was then added dropwise onto the sample support at the rate of 1 mL/min. Portions of the fluid that effused from the sample support were collected at suitable intervals. The brilliant blue concentration was determined using a UV spectrophotometer (Shimadzu UV-240, Kyoto, Japan) at 630 nm.

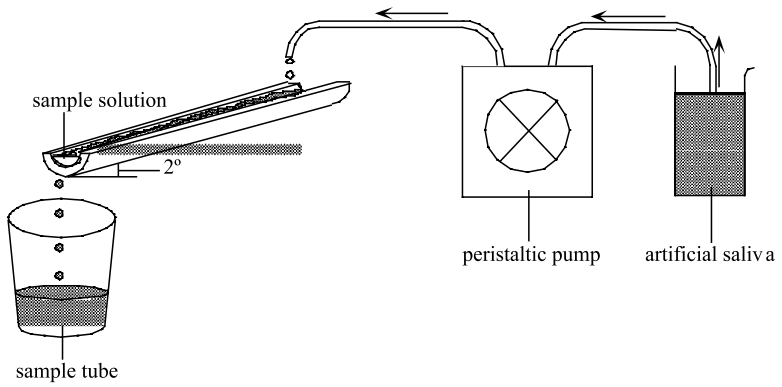

Figure 2. Schematic view of release study mimicking the release behavior on the oral mucosa.

In Vitro Assessment of the Adhesiveness of the Allopurimol Mouthwashes

The apparatus and the brief principles are schematically illustrated in Fig. 3. The adhesive measurements were carried out using a creep meter (Yamaden model 33005, Tokyo, Japan). A fixed volume (40 mL) of the allopurinol mouthwash was measured in a beaker (diameter: 45 mm, depth: 25 mm). In these assessments, we designated a Teflon® plunger to be the oral mucosa. The surface of the Teflon® plunger (diameter: 20 mm) and the surface of an allopurinol mouthwash came into contact with each other, and then the top of the Teflon® plunger was dipped to a depth of 1 mm. The Teflon® plunger was then pulled up at a rate of 1 mm/s and the adhesive force and the displacement were measured when the plunger was completely separated from the surface of the allopurinol mouthwash.

Sensory Test of Allopurinol Mouthwashes

In order to evaluate the texture of the allopurinol mouthwash, a sensory test was carried out. Ten healthy volunteers (males, 22–23 years) participated in the sensory test. The subjects received complete information on the study and gave informed consent. The sensory test was carried out for two kinds of allopurinol mouthwashes composed of 0.4% INA and 1.0% or 3.0% Alkox®, and CMC–Na-mw was used as the control solution. First, the subjects rinsed out their mouth with CMC–Na-mw and evaluated the taste, texture, adhesiveness, smoothness, and mouthfeel of the CMC–Na-mw. Next, Alkox-mws were tested after rinsing the oral cavity with 50 mL of distilled water. After rinsing, the subjects evaluated the taste, texture, adhesiveness, smoothness, and mouthfeel by the five stage evaluation method of each Alkox-mw compared to the CMC–Na-mw.

Statistical Analysis

All results are presented as the mean±S.D. The significance of difference was analyzed by the use of the paired *t*-test, and a significance level of less than 5% was considered significant.

RESULTS AND DISCUSSION

Gelation Behavior of the Allopurinol Mouthwashes Containing Various Amounts of INA and Alkox®

Table 2 shows the gelation behavior of the allopurinol mouthwashes containing various amounts of INA and Alkox®. When the concentration of INA

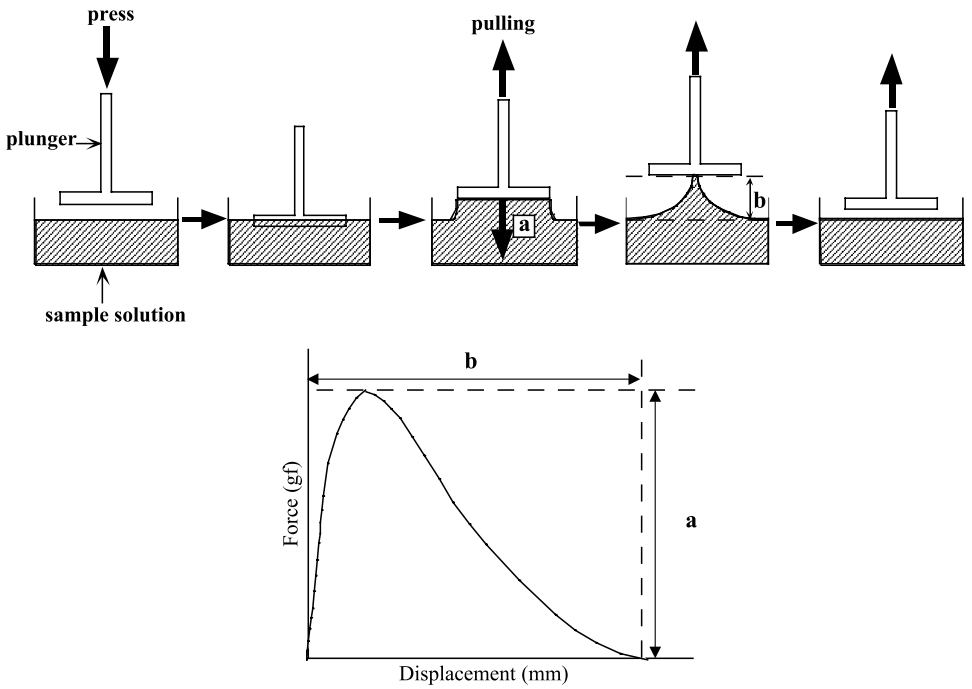

Figure 3. Schematic side view of the measurement of the adhesiveness of Alkox-mouthwash.

Table 2. Gelation behavior of the sample consisting of various amounts of Alkox® and INA (%).

	Concn. of INA (%)					
Concn. of Alkox® (%)	0	0.2	0.4	0.6	0.8	1.0
0	−	−	−	−	+	+
0.25	−	−	−	−	+	+
0.5	−	−	−	−	+	+
1.0	−	−	−	±	+	+
2.0	−	−	±	+	+	+
3.0	−	±	±	+	+	+

Note: −, Gelation was not recognized; +, gelation was recognized; ±, although obvious gelation was not recognized, a small amount of jelly-like material was dispersed in the sol.

was adjusted beyond 0.8%, gelation was realized for all of the Alkox® concentrations used in this study, whereas when the concentration of INA was less than 0.4%, gelation did not occur. In the cases when the concentrations of Alkox® and INA (Alkox®–INA%) were (1.0–0.6), (2.0–0.4), and (3.0–0.2), despite the absence of obvious gelation, a small amount of jelly-like material was dispersed in the sol. Though the detailed mechanism of gelation for carrageenan is not fully understood, the gelation may be caused by the formation of the three-dimensional network promoted from the formation of the cross-linked region due to the helix-helix aggregation. In this observation, at the concentration domain in which the gelation was not observed, the helix-helix aggregation of INA may be interfered with due to the presence of the excess amount of Alkox®. From a practical point of view, the preferential compositions of allopurinol mouthwash (Alkox®:INA % ratio) for rheological study appeared to be 1.0:(0–1.0), and (0–3.0):0.4. Furthermore, the precipitation of allopurinol crystals in Alkox-mw was not observed visually throughout this study.

Viscoelastic Study of Allopurinol Mouthwashes

Figure 4 shows the flow curves for allopurinol mouthwashes prepared with various amounts of Alkox® or INA. Overall, the viscosity of the mouthwashes decreased with increase in the rate of shear;

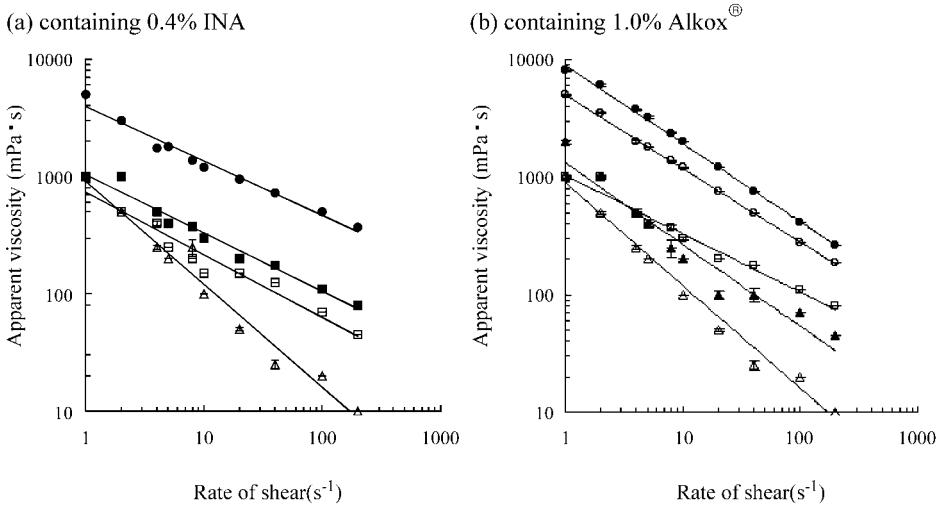

Figure 4. Flow curves of Alkox-mouthwashes prepared with various amounts of Alkox® or INA. Each point represents the mean±S.D. (n=3). (a) Containing 0.4% INA, △; CMC–Na-mw, Alkox® was added up to 0.5% (□), 1.0% (■) or 3.0% (○); (b) containing 1.0% Alkox®, △; CMC–Na-mw, INA was added up to 0.2% (σ), 0.4% (□), 0.8% (○) or 1.0% (●).

Table 3. The fluidity index of Alkox-mws prepared with various amounts of Alkox® or INA.

	Concn. of Alkox® (%)	Fluidity index
(a) containing 0.4% INA	0.25	0.362±0.005
	0.5	0.389±0.003
	1.0	0.503±0.001
	2.0	0.546±0.006
	3.0	0.537±0.003
	Concn. of INA (%)	Fluidity index
(b) containing 1.0% Alkox®	0.2	0.303±0.001
	0.4	0.503±0.001
	0.6	0.359+0.005
	0.8	0.373±0.004
	1.0	0.332±0.003

Note: Data are expressed as means±SD where n=3.

and typical shear thinning (but nonthixotropic) behavior was observed. The fluidity index was calculated using the relationship:[13,14]

$$\eta_{app} = m\dot{\gamma}^{n-1}$$

where η_{app}=apparent viscosity (mPa.s), m=coefficient of viscosity, $\dot{\gamma}$=shear rate (s^{-1}), and n=fluidity index. The fluidity index n characterizes the fluidity; the exponent takes the value of n=1 for Newtonian flow, and a value in the range of $0<n<1$ for nonNewtonian flow. The values of the fluidity index are listed in Table 3. All samples were observed as nonNewtonian flows.

In order to clarify the effect of the addition of Alkox and/or INA on the rheological properties of Alkox-mw and to understand the dependence of fluidity on the surrounding temperature, the viscosity of Alkox-mw at various temperatures was investigated. Figure 5 shows the relationship between the apparent viscosity at the definite shear rate (200 s^{-1}) and the reciprocal of the absolute temperature. In accordance with this relation, a plot of log (η_{app}) vs. 1/T (273+t°C) is found to be linear. The dependence of the fluidity of a liquid on temperature is approximately expressed for many substances by Andrade's equation, which is the modified Arrhenius equation of chemical kinetics:

$$\ln \eta_{app} = \ln A + Ev/RT$$

where η_{app}=apparent viscosity, A=constant, R=gas constant, T=absolute temperature, and Ev=apparent activation energy required to initiate a flow between the molecules. Figure 6 denotes the relationship between the Ev and the concentration of Alkox® and/or INA added. In the case of Alkox-mws composed of various amounts (0–3%) of Alkox® and 0.4% INA, Ev decreased with increasing Alkox® content, whereas, for the allopurinol mouthwash composed of 1.0% Alkox® and various amounts (0–1.0%) of INA, Ev increased with increasing INA content. The increase in Ev appeared to be due to the gelation that was promoted by the increase in the concentration of INA, as shown in Table 2. That is, in order to break the gel

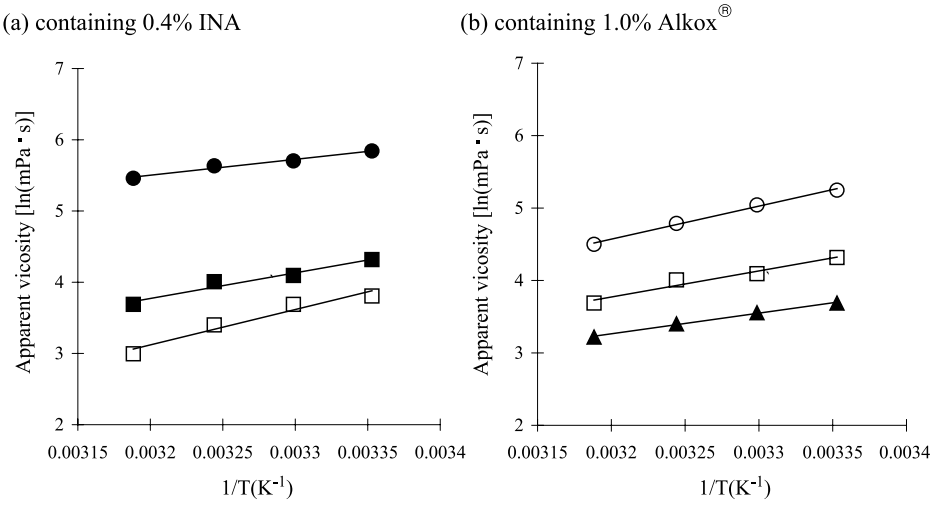

Figure 5. Andrade's plots of Alkox-mws prepared with various amounts of Alkox® or INA. Each point represents the mean±S.D. (n=3). (a) Containing 0.4% INA, Alkox® was added up to 0.5% (□), 1.0% (■) or 3.0% (●); (b) containing 1.0% Alkox®, INA was added up to 0.2% (σ), 0.4% (□) or 0.8% (○).

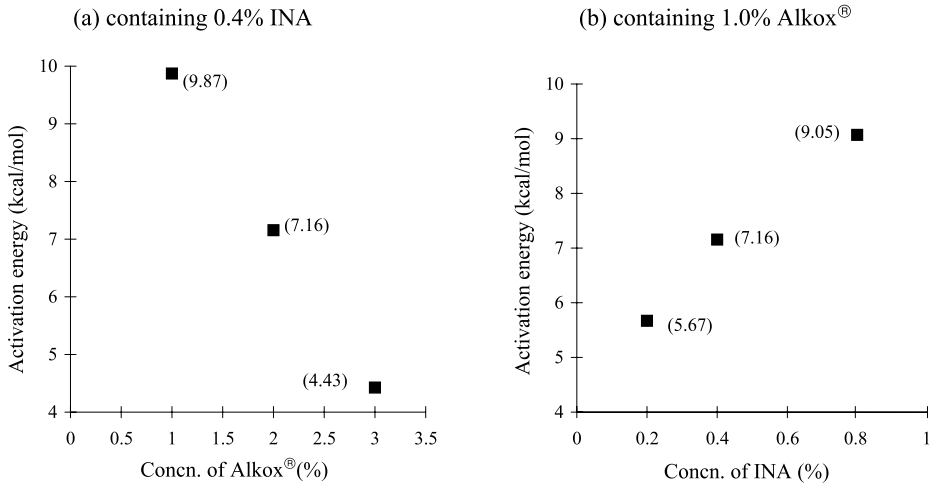

Figure 6. Activation energy of Alkox-mws prepared with various amounts of Alkox® or INA. *Values in parentheses show the activation energy. (a) Containing 0.4% INA; (b) containing 1.0% Alkox®.

structure progressed highly by gelation, it is considered that higher Ev is required.

In Vitro Assessment of the Adhesiveness of Alkox-mw

In the present study, since Alkox-mw was prepared for the purpose of extending the residence time on oral mucosa, the effect of the differences in rheological properties of Alkox-mws on the adhesiveness was investigated in vitro.

Figure 7 shows the load–displacement curves of allopurinol mouthwashes. The value of the load, corresponding to part ''a'' shown in Fig. 3, indicates the tension of the Alkox-mws, and the area of the load–displacement curve indicates the adhesive energy

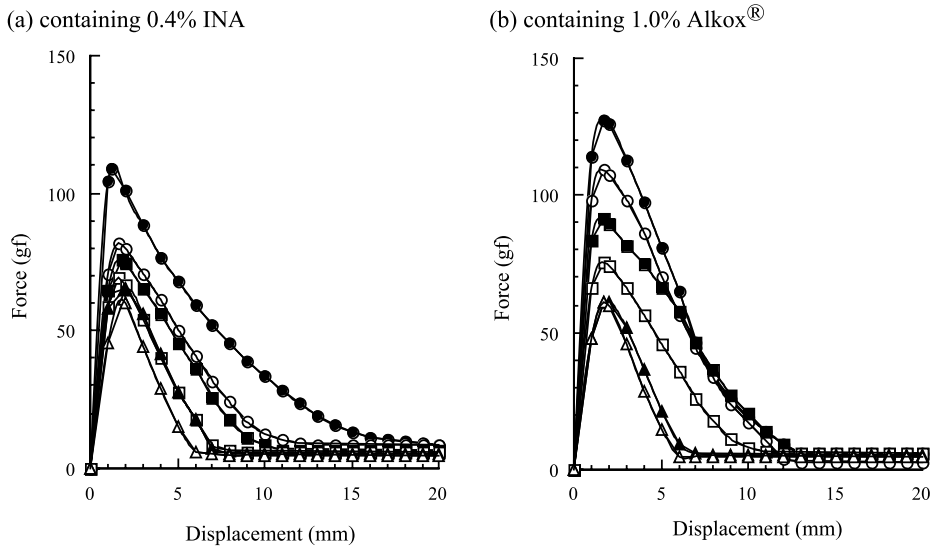

Figure 7. Adhesive force–displacement curves of Alkox-mws prepared with various amounts of Alkox® or INA. Each point represents the mean ± S.D. (n = 3). (a) Containing 0.4% INA, △; CMC–Na-mw, Alkox® was added up to 0.25% (σ), 0.5% (□), 1.0% (■), 2.0% (○) or 3.0% (●); (b) containing 1.0% Alkox®, △; CMC–Na-mw, INA was added up to 0.2% (σ), 0.4% (□), 0.6% (■), 0.8% (○) or 1.0% (●).

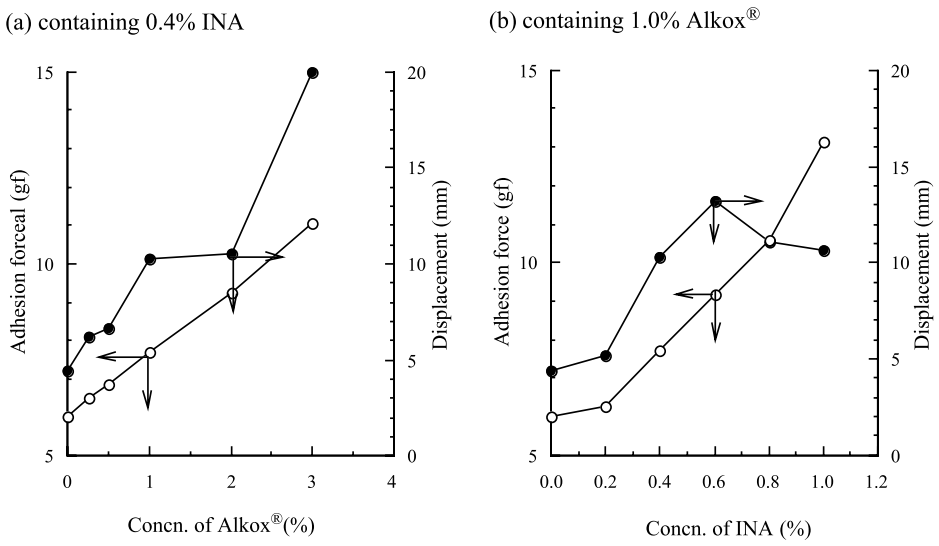

Figure 8. Adhesion force and displacement of Alkox-mws prepared with various amounts of Alkox® or INA. Each point represents the mean±S.D. (n=3). (a) Containing 0.4% INA, (b) containing 1.0% Alkox®, ○; adhesion force (gf) ●; displacement (mm).

between the surface of the plunger and that of the Alkox-mws; the larger the area of the load–displacement curve, the higher the adhesion energy of the Alkox-mw. At the same time, displacement, corresponding to part ''b'' shown in Fig. 3, indicates the spinnability of the Alkox-mw; the longer the displacement, the larger the spinnability of Alkox-mw. As shown in Fig. 8, the adhesion force and displacement increased with an increase in the added amount of Alkox® and/or INA. For Alkox-mw prepared with 1.0% Alkox® and various amounts of INA, however, the displacement decreased more than 0.8% of the concentration of the added INA. This seemed to be because the gelation occurred by adding the INA, similar to the viscoelastic study. Overall, both the adhesion energy and the spinnability of the Alkox-mws were higher than that of CMC–Na-mw (Table 4).

Table 4. Adhesion energy and displacement of Alkox-mws prepared with various amounts of Alkox® or INA.

	Concn. of Alkox (%)	Adhesion energy (J/m^3)	Displacement (mm)
(a) Containing 0.4% INA	0.25	6.49 ± 0.04^{c}	6.17 ± 0.29^{c}
	0.5	6.85 ± 0.09^{b}	6.63 ± 0.29^{c}
	1.0	7.74 ± 0.06^{c}	10.3 ± 0.00^{c}
	2.0	8.25 ± 0.28^{b}	10.5 ± 0.62^{c}
	3.0	7.55 ± 0.15^{c}	19.97 ± 0.21^{c}
	Concn. of INA (%)	Adhesion energy (J/m^3)	Displacement (mm)
(b) Containing 1.0% Alkox®	0.2	$6.55\pm0.25^{N.S.}$	5.17 ± 0.58^{c}
	0.4	7.74 ± 0.06^{c}	10.3 ± 0.00^{c}
	0.6	8.99 ± 0.36^{b}	13.23 ± 0.98^{c}
	0.8	10.28 ± 0.48^{c}	11.30 ± 0.50^{c}
	1.0	12.35 ± 1.27^{c}	10.50 ± 1.16^{c}
CMC–Na-mw		6.07 ± 0.02	4.40 ± 0.17

[a,b,c]Significantly different from CMC–Na-mw at $p<0.05$, $p<0.01$, and $p<0.005$, respectively.
Data are expressed as means±SD where n=3.

In Vitro Assessment of Mimicking the Effusion of the Allopurinol Mouthwashes from the Surface of Oral Mucosa

In the present study, the purpose of preparing allopurinol mouthwash was to retain allopurinol in the oral cavity. In practical use, however, the allopurinol mouthwash appears to be effused by saliva secreted onto the oral mucosa. We attempted to evaluate the effusion properties of allopurinol mouthwashes by using artificial saliva. Taking into account the fact that the Alkox-mw was rinsed out of the mouth, the adhesion properties of Alkox-mws seemed to be an indication of the retention of Alkox-mw. In order to reveal the effect of the constituent of Alkox-mw on the release behavior of drug, we selected brilliant blue as a model drug. Brilliant blue is used widely as a model drug for gel formulation,[15–17] and it is able to visually observe the effusion behavior of mouthwashes. Furthermore, in consideration of the possibility of the loading to Alkox-mw of drugs other than allopurinol, brilliant blue was used. The deposit of allopurinol crystals and the other physicochemical changes by addition of brilliant blue were not observed. Figure 9 and Table 5 show the release profiles and the percentage of released brilliant blue at 30 min the Alkox-mws, respectively. The data represents the average of three experiments. For the CMC–Na-mw, the dissolution of brilliant blue was completed within 10 min, whereas for the Alkox-mws prepared with various amounts of Alkox® or INA, the dissolution of brilliant blue was retarded with an increase in the added amount of Alkox® or INA. The differences observed between these Alkox-mws is considered to be attributed to the difference in the adhesiveness of the Alkox-mws. The slower release of brilliant blue corresponds to the adhesiveness of allopurinol mouthwash; the higher

Table 5. Percentage of released brilliant blue at 30 min from Alkox-mws prepared with various amount of Alkox® or INA.

	Concn. of Alkox® (%)	% Released at 30 min
(a) Containing 0.4% INA	0.5	99.59±0.57
	1.0	87.58±4.41
	2.0	85.78±2.64
	3.0	34.87±3.78
	Concn. of INA (%)	**% Released at 30 min**
(b) Containing 1.0% Alkox®	0.2	99.99±0.01
	0.4	87.58±4.41
	0.6	55.64±0.08
	0.8	46.55±0.14
	1.0	37.16±3.26

Note: Data are expressed as means±SD where n=3.

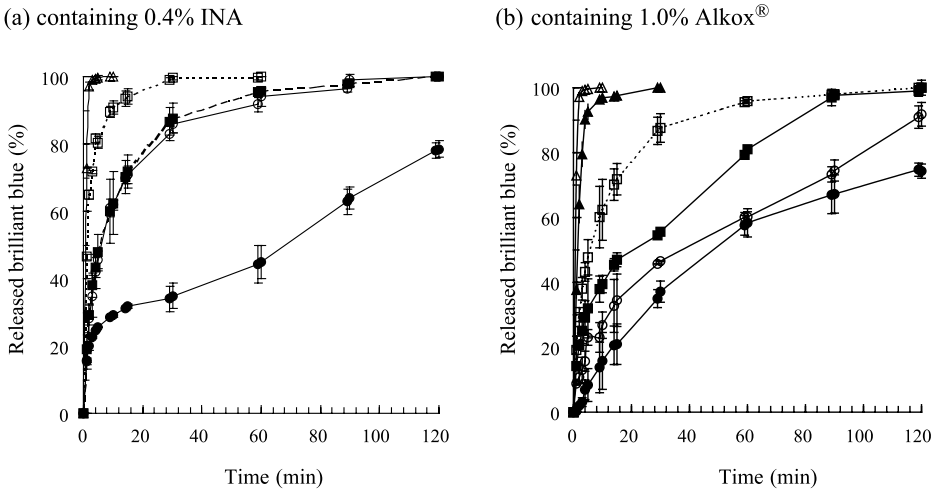

Figure 9. Release profiles of BB from Alkox-mws prepared with various amounts of Alkox® or INA. Each point represents the mean±S.D. (n=3). (a) Containing 0.4% INA, △; CMC–Na-mw, Alkox® was added up to 0.5% (□), 1.0% (■), 2.0%(○) or 3.0% (●); (b) containing 1.0% Alkox®, △; CMC–Na-mw, INA was added up to 0.2% (σ), 0.4% (□), 0.6% (■), 0.8% (○) or 1.0% (●).

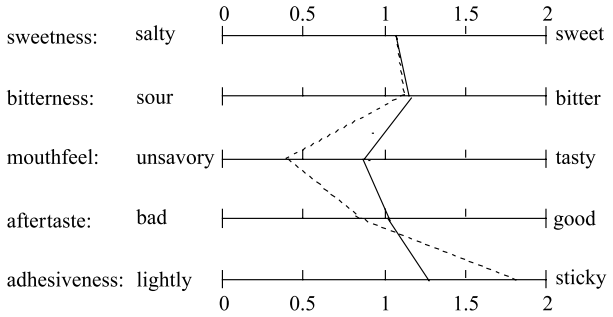

Figure 10. Sensory tests for Alkox-mws composed of 0.4% INA and 1.0 or 3.0% Alkox®. ——; APN-mw composed of 0.4% INA and 1.0% Alkox®. - - - -; APN-mw composed of 0.4% INA and 3.0% Alkox®.

the adhesion energy of the Alkox-mw, the slower the release of brilliant blue from the Alkox-mw. In practice, however, due to the chewing action and the movement of the tongue in the human mouth, the gelled Alkox-mw, such as that composed of 1.0% Alkox® and 0.8% or 1.0% INA, might be removed from the oral mucosa.

From these results, when taking into account the adhesion of an allopurinol mouthwash to the oral mucosa, the Alkox-mws consisting of 0.4% INA and 0.5–3.0% Alkox® seem to be favorable, since these Alkox-mws indicated not only a high adhesive energy and spinnability, but were able to exist in a liquid or sol form during storage.

Sensory Test of Alkox-mw

In order to evaluate the texture of Alkox-mws composed of 0.4% INA and 1.0% or 3.0% Alkox®, a sensory test was carried out (Fig. 10). As for the sweetness and aftertaste, both Alkox-mws were evaluated as having good character compared to the CMC–Na-mw. However, there was one subject who evaluated the Alkox-mw as having a bitter taste. Although Alkox®, INA, and allopurinol are tasteless and odorless, the methyl or ethyl p-hydroxybenzoate added to Alkox-mw as a preservative agent may have been responsible for the bitter taste. In the evaluation of the mouthfeel and adhesiveness of Alkox-mw containing 3.0% Alkox®, an unsavory quality and stickiness were reported. It seemed that the extremely high adhesiveness of Alkox-mw containing 3.0% Alkox® might produce an unsavory mouthfeel. From these results, in practical use, Alkox-mw containing 1.0% Alkox® is considered to be the favorite form for improving compliance and QOL.

CONCLUSION

As described in previous papers,[7,8] this quantitative and qualitative formula could be prepared as gel or sol form suitable to a patient's taste. In this study, we investigated the physicochemical properties and the utility as a mouthwash of the concentration domain in which the gelation does not take place. The addition of Alkox® resulted in an increased allopurinol mouthwash adhesiveness with increasing amounts of Alkox®. It was suggested that Alkox® can be utilized as an adhesion agent to the oral mucosa. Based on the confirmation of adhesiveness and sensory test results, when considering the adhesion of Alkox-mw to the oral mucosa, the Alkox-mw consisting of 0.4% INA and 1.0% Alkox® seems to be the most favorable. Although further detailed investigations of in vivo applications, an investigation into the administration of allopurinol to patients, and an evaluation of the practical therapeutic effect of Alkox® remain to be carried out, the results obtained in the present study suggest that the allopurinol mouthwash preparations containing Alkox® may be useful as new dosage forms that adhere to the oral mucosa.

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