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Development of polyethylene glycol and hard fat-based mucoadhesive tablets containing various types of polyvinyl alcohols as mucoadhesive polymers for buccal application

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Summary

Topical drug application has the advantage of avoiding systemic side effects. We attempted to develop a long-acting matrix-type tablet containing indomethacin (IM) with low physical stimulus and potent mucoadhesive force to treat pain caused by oral aphtha. A mixture of polyethylene glycol (PEG) and hard fat was used as the tablet base. Ethylcellulose was added to the base in an attempt to control drug release. Tablets with PEG as a base were also prepared for comparison. Polyvinyl alcohols (PVAs) with various degrees of saponification were added to increase the mucoadhesive force. From the optical microscopic observations, formulations using PEG and hard fat exhibit PEG/hard fat dispersions caused by the stabilizing effects of PVA. Although the tablets using PEG and hard fat showed sufficient adhesiveness and sustained drug release, those using PEG as the base did not. Drug release was controlled by the amount of hard fat and the saponification degree of PVA. The drug release rate was most increased in a tablet containing PVA with an intermediate degree of saponification, PEG and hard fat. From differential scanning calorimetry and powder X-ray diffraction, IM was considered to exist in the molecular phase. From the results of buccal administration of tablets to rats, highest tissue concentrations were observed in the tablet containing PVA with the intermediate degree of saponification using PEG and hard fat, and the plasma concentrations were sufficiently low in comparison.

Keywords:

Mucosal delivery, buccal, formulation, solid dosage form, controlled release, indomethacin

Introduction

Oral mucositis is a common complication of chemotherapy and is often accompanied by erythema, ulceration, pain, weight loss, and delayed remission.[1)] Chemotherapy-induced mucositis occurs in 40%–70% of patients and can limit the anticancer effects of chemotherapy, thus extending the therapeutic period and potentially decreasing patient survival.[2)] The treatments for oral mucositis are mainly palliative.[3)] Oral aphtha is associated with pain that is treated by coadministration of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid pain relievers.[4-6)] However, the systemic administration of NSAIDs is limited because it can cause thrombocytopenia as a side effect. Renal dysfunction may be exacerbated by concomitant treatments of NSAIDs and drugs with renal toxicity, such as cisplatin. Topical administration to the oral mucous membrane is an alternative route that aims to avoid systemic side effects, which also has the advantage of effectively treating local lesions.[7-9)] No topical preparations to be applied to the oral cavity for relieving pain caused by oral mucositis are commercially available. Topical preparations containing NSAIDs to relieve pain such as sprays, gels and solutions have been formulated in hospital preparations[5-6)] and previous studies have developed mucoadhesive films.[10-13)] However, there are limitations in the sustained application of film preparations to the oral mucosa. We have been developing a matrix-type mucoadhesive tablet consisting of hard fat with a low physical stimulus and long drug release properties.[14)] Indomethacin (IM) was used as an active drug to treat the pain of oral aphtha. Ethylcellulose (EC) was added as the base in an attempt to control drug release. Drug release from the matrix-type tablet consisting of hard fat and EC was sustained, and the release was controlled by the addition of polyethylene glycol (PEG). Although this matrix-type mucoadhesive tablet has good potential as a newly designed preparation to treat oral aphtha pain, the *in vitro* adhesive force was moderate compared with a commercially

available drug, Aftach Adhesive Tablet (TEIJIN PHARMA LIMITED, Tokyo, Japan). In the present study we attempted to develop a long-acting matrix-type tablet with low physical stimulus and potent mucoadhesive force. A mucoadhesive polymer was added to the tablets to increase the mucoadhesive force. Polyvinyl alcohol (PVA) has been used as a carrier polymer in drug delivery devices, a surfactant for forming polymeric drug carriers and as a mucoadhesive carrier.[15,16] We selected PVA as a mucoadhesive polymer based on these properties. PVAs with various degrees of saponification were compared to estimate the appropriate characteristics of PVA as a mucoadhesive polymer. A mixture of PEG4000, hard fat, and EC4 (viscosity = 4 mPa·s) was used as the base of the mucoadhesive tablets. Tablets with PEG4000 as a base were also prepared for comparison. Glycerol was added to aid PVA dissolution. The preparation properties, such as the breaking strength, adhesive force, drug release properties, and the crystal form of IM, were investigated. Drug absorption and drug permeation to buccal tissue after buccal administration of PEG-based tablets and PEG and hard fat-based tablets were evaluated *in vivo* using rats.

Materials and Methods

Materials

Hard fat (Witocan® H) was supplied by Mitsuba Trading Co. (Tokyo, Japan). PVAs (KL-03, NK-5R, LL-810) were supplied by The Nippon Synthetic Chemical Industry Co., Ltd. (Osaka, Japan). EC4 was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). IM, PEG4000 (average molecular weight = 3000), glycerol, carboxymethyl cellulose sodium salt (CMC-Na), and D(−)-sorbitol were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Mucin from porcine stomachs was purchased from Sigma-Aldrich Co. (MO, USA). All other chemicals were obtained commercially at the purest grade available.

Preparation of mucoadhesive tablets

The characteristics of the PVAs used are shown in Table 1. The degree of saponification and viscosity values are those stated by the supplier. The chemical structure of PVA is shown in Fig. 1. The following equation is the formula for calculating the degree of saponification (1),

$$\text{Saponification degree} = n / (n+m) \times 100 \quad (1)$$

where m and n denote the degree of polymerization of vinyl acetate and vinyl alcohol, respectively.

The saponification degrees of the PVAs from highest to lowest were KL-03 (A) > NK-05R (B) > LL-810 (C) (Table 1). The compositions of the mucoadhesive tablets are shown in Table 2. The preparation charts for tablets using PEG as the base and using PEG and hard fat as the base are shown in Fig. 2. The preparation method for tablets using PEG as the base was as follows. PVA (A or B) was dissolved in 70% (v/v) ethanol solution. PVA (C) was dissolved in ethanol. PEG and glycerol were mixed and heated to 60 °C until melted. PVA solution was added to the PEG and glycerol and agitated. Ethanol and water were evaporated from the mixture under a vacuum in the presence of desiccating silica gel for 48 h. The dry solid was melted and stirred for 15 min at 70–80 °C under an aluminum foil cover. Samples (0.2 mL) were then poured into tablet molds (bore diameter = 10 mm). The solidified tablets were removed from the molds after standing at room temperature for 5 h. The preparation method for tablets using PEG and hard fat as the base was as follows. PVA (A or B) was dissolved in water. EC4 was dissolved in ethanol. PVA (C) and EC4 were combined and dissolved in ethanol. PEG, glycerol, and hard fat were mixed and heated to 60 °C until melted. PVA solution was added to the mixture of PEG, glycerol, and hard fat, then the EC solution was added for formulations with PVA A or B. The mixture was agitated

in a mortar and spread thinly on the mortar wall. Ethanol and water were evaporated from the mixture under a vacuum in the presence of desiccating silica gel for 48 h. Further processing was the same as that for the tablets using PEG as the base.

The compositions of the mucoadhesive tablets containing IM are shown in Table 3. The preparation charts for tablets containing IM using PEG as the base and using PEG and hard fat as the base are shown in Fig. 3. The preparation method for formulations containing IM using PEG as the base was as follows. PVA (A or B) was dissolved in water. IM was dissolved in ethanol. PVA (C) and IM were dissolved together in ethanol. PEG and glycerol were mixed and heated to 60 °C until melted. PVA solution and IM solution were added to the mixture of PEG and glycerol and agitated. Ethanol and water were evaporated from the mixture under a vacuum in the presence of desiccating silica gel for 48 h. Tablet preparation was the same as that for formulations without IM. The preparation method for tablets containing IM using PEG and hard fat as the base was as follows. PVA (A or B) was dissolved in water. IM and EC4 were dissolved in ethanol. PVA (C), EC4, and IM were dissolved together in ethanol. PEG, glycerol, and hard fat were mixed and heated to 60 °C until melted. PVA solution was added to the mixture of PEG, glycerol, and hard fat, followed by the IM and EC4 solution. The mixture was agitated in a mortar and thinly spread on the mortar wall. Ethanol and water were evaporated from the mixture under a vacuum in the presence of desiccating silica gel for 48 h. Tablets were prepared as above.

Breaking strength of mucoadhesive tablets

The diameter, thickness, and hardness of the mucoadhesive tablets were measured. The diameter and thickness were measured with Vernier calipers. The hardness of the tablets was measured with a FUDOH Rheometer (Fudoh Kogyo Co., Ltd., Japan). A tablet was placed

upright on the rheometer tray, and an adapter (No. 13, a tooth-shaped stick) was mounted on the rheometer. The tray was raised at a speed of 2 cm/min. The stress when the tablet was cut in the direction of the diameter was measured as the hardness. The tablet-breaking strength was calculated using the following equation (2) [17-20)]

$$\text{Breaking strength (N/mm}^2\text{)} = F/dt \quad (2)$$

where F, d, and t denote the hardness, diameter, and thickness, respectively.

In vitro adhesive force

The *in vitro* adhesive force of the mucoadhesive tablets was determined using the FUDOH Rheometer (Fudoh Kogyo Co., Ltd., Japan). A tablet was fastened to a slide grass and the slide grass was fastened to an adapter (No. 3, diameter of the disk; 10 mm) mounted on the rheometer using double-stick tape. A mucin disk was used as a mucosa model to evaluate mucoadhesive properties. The mucin disk was prepared according to the method of Tsuchiya et al.[21)] 400 μL of mucin solution (10% (w/v)) was spread on filter paper with a diameter of 25 mm. The filter paper was dried at room temperature for 24 h and then used as the mucin disk. The mucin disk was fastened to a fluorine resin board heated at 37 °C and the fluorine resin board was fastened to the tray of the rheometer. 50 μL of artificial saliva solution consisting of 1% (w/v) CMC-Na, 3% (w/v) D-sorbitol, 0.12% (w/v) KCl, 0.084% (w/v) NaCl, 0.015% (w/v) $CaCl_2$, 0.005% (w/v) $MgCl_2$, and 0.03% (w/v) K_2HPO_4 was placed on the mucin disk, and the tablet was attached to the mucin disk with a force of 5 N for 30 s. The tray was lowered at a speed of 2 cm/min. The stress of the separation of the tablet from the mucin disk was measured. The *in vitro* adhesive force of a commercially available drug, Aftach Adhesive Tablet, was also determined. A tablet was fastened to an adapter (No. 3) mounted on the rheometer using double-stick tape. The Aftach Adhesive Tablet was measured

using the same method as that for our mucoadhesive tablets.

Optical microscopic observations

An optical microscope (OLYMPUS BX51, Olympus Corporation) equipped with a microscope digital camera (DP71, Olympus Corporation) was used to characterize the morphologies of the preparations. An objective lens (UplanApo, Olympus Corporation) with 10 times magnification was used. Before the melted preparation was poured into the mold, some was placed on a slide glass and covered with a cover glass. After the preparation solidified, the slide glass was observed under an optical microscope.

Drug release properties

The drug release experiments were performed according to a modified method of the dissolution test for IM capsules in the Pharmacopoeia of Japan (JP) 16. A dissolution tester (NTR-VS6P, Toyama Sangyo Co., Ltd.) was used and the paddle method of the dissolution test was applied. Water : 50 mM phosphate buffer (KH_2PO_4-NaOH, pH 7.2) (4 : 1) was used as the dissolution medium. A tablet was placed in a sinker and immersed in 500 mL of dissolution medium pre-warmed at 37 ± 0.5 °C, and the paddle was then rotated at 60 rpm. 5 mL samples of the dissolution media were taken and filtered with a membrane filter (0.45 μm pore size) at 2, 5, 10, 15 and 20 min for the tablets using PEG as the base and at 0.5, 1, 2, 3, 4 and 6 h for the tablets using PEG and hard fat as the base. 5 mL of fresh medium was added immediately after each sampling. The filtrate was analyzed using an UV spectrophotometer (UV-1800, Shimadzu corporation) at 320 nm to determine the amount of the drug released. Calibration curves were obtained by a linear regression analysis of concentrations plotted against absorbance. The linearity of the method was verified within the range of 5–50 μg/mL

(R^2 = 0.999). Hard fat and the polymers had no influence on the determination of IM concentrations in the drug release tests performed.

Drug release data were fitted to various kinetic models to analyze the release pattern from the tablets using PEG and hard fat as the base. The zero order, Korsmeyer–Peppas and Higuchi models given by equations (3)–(5), respectively, were fitted to the individual fractional release profiles calculated as the ratio between the cumulative amounts of drug released at time t (M_t) and infinite time (M_∞).

Zero order model:

$$M_t/M_\infty = k_0 \times t \qquad (3)$$

where k_0 is the zero order release constant.

Korsmeyer–Peppas model:[22-24)]

$$M_t/M_\infty = a \times t^n \qquad (4)$$

where a is a constant depicting structural and geometric characteristics of the drug, and n is the release exponent indicative of the drug release mechanism. A value of n less than 0.45 suggests Fickian diffusion, while n = 0.89 is related to a mechanism of case-II transport and values between 0.45 and 0.89 are a superposition of both phenomena (anomalous transport). A value of n > 0.89 suggests super case II transport.[25)]

Higuchi model:[26,27)]

$$M_t/M_\infty = k_H \times t^{0.5} \qquad (5)$$

where k_H represents a release rate constant incorporating the design variables of the system. The model assumes Fickian diffusion is the rate limiting step and the predominant release mechanism.

Differential scanning calorimetry

The thermal properties of materials and tablets with formulations A20H40IM, B20H40IM, C20H40IM, and A20IM were determined using differential scanning calorimetry (Thermo plus EVO□ DSC8230, Rigaku Corporation). Samples weighing approximately 2 mg were heated in a sealed aluminum pan at a constant heating rate of 10 °C/min from 25 to 290 °C under a nitrogen purge (100 mL/min).[28)]

X-ray diffraction

X-ray diffraction (XRD) patterns of materials and tablets (A20H40IM, B20H40IM, C20H40IM, and A20IM) were obtained using a 9 kW SmartLab Rigaku diffractometer with a rotating anode at room temperature. The voltage and amperage were set at 45 kV and 200 mA, respectively. Each sample was scanned between 3° and 40° in 2θ with a step size of 0.02 and scan speed of 2°/min.[29)]

***In vivo* experiments**

Male Sprague-Dawley strain rats weighing 220–280 g were purchased from Tokyo Laboratory Animals Science Co., Ltd. (Tokyo, Japan). The experimental protocol was approved by the Ethics Review Committee for Animal Experimentation of Hoshi University, which is accredited by the Ministry of Education, Culture, Sports, Science, and Technology, Japan, as conforming to the Guide for the Care and Use of Laboratory Animals (Approval No. 28-048).

The A20H40IM, B20H40IM, C20H40IM and A20IM formulations were used for drug absorption and drug permeation experiments. A consistent IM dosage of 6 mg/kg was administered to the rats and the tablets were portioned according to the required dose. Rats

were anesthetized with 20% (w/v) ethyl carbamate solution (1 g/kg, ip) and the cut tablet was administered on the buccal mucosa. For drug absorption experiments, blood samples were collected at 1, 2 and 5 h from the jugular vein after buccal administration and centrifuged immediately at 3,000 rpm (1,000×*g*) for 15 min. Plasma samples were stored at −80 °C until IM levels were assayed. For drug permeation experiments, the animals were euthanized at 5 h after buccal administration by an overdose of ether anesthesia and the buccal mucosa was excised. Tissue samples were washed with 75% (v/v) methanol in water, and then homogenized with 2 mL of 75% (v/v) methanol in water.[30] Homogenates were centrifuged at 3,000 rpm (1,000×*g*) for 15 min and the supernatants were filtered with a membrane filter (0.45 μm pore size). The extract was stored at −80 °C until the IM level was assayed. For further drug permeation experiments, the animals were euthanized at 1 and 2 h after buccal administration by an overdose of ether anesthesia and the buccal mucosa was excised. The tissue samples were treated in the same manner as with the rats administered for 5 h.

Drug determination

The concentration of IM was determined using an HPLC system consisting of a LC-6AD pump and a C-R7A chromatopac (Shimadzu, Kyoto, Japan) equipped with a Capcell Pak C18 MG II column (4.6 × 250 mm, Shiseido Co., Ltd., Tokyo, Japan) and a SPD-20AV UV detector (Shimadzu). Chromatography was carried out at 40 °C. The mobile phase consisted of 60% (v/v) acetonitrile in 0.02 M sodium acetate buffer and was adjusted to pH 3.6 using orthophosphoric acid. The flow rate was 1 mL/min and the detection wavelength was 250 nm. Mefenamic acid was used as an internal standard. Calibration curves were obtained by a linear regression analysis of concentrations plotted against peak area. Each 200 μL plasma sample was dispensed into a centrifuge tube and 160 μL of methanol and

mefenamic acid in methanol (10 μg/mL, 40 μL) was added. The samples were agitated for 4 min and then centrifuged at 3,000 rpm (1,000×*g*) for 15 min. The supernatant was transferred to a clean centrifuge tube and concentrated under nitrogen flow. A further 200 μL of methanol was added to the residue, the mixture was agitated for 4 min then centrifuged at 3,000 rpm (1,000×*g*) for 5 min. The supernatant was filtrated and 20 μL of filtrate was injected for HPLC. To analyze buccal tissue extracts, 20 μL of the extract was injected for HPLC.

Statistical analysis

A one-way analysis of variance with Tukey's multiple comparison test and Dunnett's multiple comparison test were performed to compare formulations. Data were considered significantly different when the *p*-value was less than 0.05.

Results

Physical-mechanical properties of mucoadhesive tablets

The breaking strength of the tablets is shown in Fig. 4. The breaking strengths of the tablets using PEG as the base were significantly lower than those of tablets consisting of PEG only, except for B10, C10, C20 and C30. Tablets containing PEG, a high concentration of hard fat, and PVA (B) could not be prepared as a homogeneous formulation. Of the tablets using PEG and hard fat as the base, A20H40, B20H40, and C20H40 had significantly higher breaking strength values that those with hard fat only. However, formulations A20H56 and C20H56 indicated that the breaking strength decreased with increasing amounts of hard fat. The *in vitro* adhesion of the tablets is shown in Fig. 5. Increases in adhesiveness were observed for the tablets using PEG as the base with the addition of PVA and glycerol compared with PEG, except for C10. The highest value was obtained for formulation B20. In

the tablets using PEG and hard fat as the base, increases in adhesiveness were observed in all formulations compared with those using hard fat alone. Furthermore, a significant increase in adhesiveness was observed in all formulations using PEG and hard fat as the base compared with B20.

Physical-mechanical properties of mucoadhesive tablets containing IM

The weights of tablets containing IM are shown in Table 3. The variation of the tablet weights was small. The breaking strength of tablets containing IM is shown in Fig. 6. C10IM was not prepared because good adhesiveness was not achieved with C10. The breaking strengths of tablets using PEG as the base were significantly lower than those of tablets consisting of PEG only, and were further decreased by the addition of IM. Regarding the breaking strength of tablets using PEG and hard fat as the base, C20H40IM showed a significantly higher value than that with hard fat only. The breaking strengths of tablets using PEG and hard fat as the base were decreased by the addition of IM. The *in vitro* adhesiveness of each tablet formulation is shown in Fig. 7. In the tablets using PEG as the base, the highest value was observed for A20IM. In the tablets using PEG and hard fat as the base, higher values were observed in all formulations compared with the formulations using only PEG as the base, and a significant increase in adhesiveness was observed in all formulations using PEG and hard fat as the base compared with A20IM.

Release pattern analysis of tablets containing IM

The drug release properties of A20IM, which had the highest *in vitro* adhesiveness in the formulations using PEG as the base, and all the formulations using PEG and hard fat as the base were investigated. The release profiles of IM from tablets are shown in Fig. 8.

A20IM dissolved quickly and over 95% of IM was released from the formulation at 10 min. Tablets using PEG and hard fat as the base showed sustained release, with drug release more sustained from A20H40IM than from C20H40IM. B20H40IM showed relatively rapid drug release among the tablets using PEG and hard fat as the base. Drug release was sustained for longer as the amount of hard fat increased. The release data of the tablets using PEG and hard fat as the base were fitted to various kinetic models. The parameters obtained from various kinetic models are shown in Table 4. From values of the coefficient of determination, it was considered that the drug release from A20H40IM, A20H56IM, C20H40IM and C20H56IM followed the Korsmeyer–Peppas equation and the drug release from B20H40IM followed Higuchi's equation.

Differential scanning calorimetry thermograms and X-ray diffraction patterns

Differential scanning calorimetry (DSC) thermograms of materials and tablets are shown in Fig. 9. XRD patterns of materials and tablets are shown in Fig. 10. The DSC thermogram of IM (Fig. 9a) has a sharp peak at 161.8 °C corresponded to the melting temperature of the γ-crystalline form.[31] The diffraction peaks in the XRD pattern of IM (Fig. 10a) corresponds to those of the γ-crystalline form.[32,33] The peak corresponding to the melting temperature of IM was not observed in the DSC thermograms of the tablets containing IM (A20IM, A20H40IM, B20H40IM, and C20H40IM) (Fig. 9h–k). Furthermore, the obvious peak corresponding to the γ-crystalline form of IM was not observed in the XRD patterns of these tablets (Fig. 10h–k). The peaks at 36.2, 36.6, and 36.9 °C in the DSC thermograms of the tablets correspond to the melting temperatures of hard fat in A20H40IM, B20H40IM, and C20H40IM, respectively, and were shifted to a lower temperature than that of raw hard fat (40.1 °C). In A20IM, A20H40IM, B20H40IM, and C20H40IM, the peaks at

49.7, 50.0, 52.7, and 52.5 °C correspond to the melting temperature of PEG, which were shifted to a lower temperature than that of raw PEG (59.2 °C). Diffraction peaks corresponding to PEG and hard fat were observed in the XRD patterns of the tablets. The crystalline analysis of the tablets confirmed consistencies between DSC thermograms and XRD patterns.

***In vivo* study**

A formulation with sustained drug release properties is desirable for obtaining a long-acting therapeutic effect. The drug release from the tablets with PEG and with high amounts of hard fat were deemed too prolonged, and the *in vivo* study was carried out using the tablets with PEG and a low amount of hard fat. The A20IM formulation, which had the highest *in vitro* adhesiveness of the formulations using PEG as the base, was used for the *in vivo* study. The tissue concentration-time profiles and plasma concentration-time profiles after buccal administration are shown in Fig. 11. Although the tissue concentration at 1 h after buccal administration was highest for C20H40IM, this difference was not significant (Fig. 11a). The tissue concentration at 2 h after administration of B20H40IM was significantly higher than that after administration of A20H40IM. The plasma concentration after buccal administration of B20H40IM and A20IM was higher than that after buccal administration of A20H40IM and C20H40IM (Fig. 11b). However, significant differences between the formulations were not observed. Low plasma concentrations were observed compared with the high tissue concentrations.

Discussion

The breaking strengths of the tablets using PEG as the base were significantly lower than those of tablets consisting of PEG only. This was attributed to glycerol being dispersed into PEG. In the formulations C10, C20, and C30, the breaking strengths were not decreased by the addition of PVA (C), which has the lowest saponification degree and could have good affinity with PEG and glycerol allowing the PVA to expand in the base. In the breaking strength of the tablets using PEG and hard fat as the base, A20H40, B20H40, and C20H40, had significantly high values that those with only hard fat. This was attributed to the addition of PEG to hard fat. Although increases in adhesiveness were observed for the formulations using PEG as the base with the addition of PVA compared with PEG alone — except for C10 — the adhesiveness values were significantly lower than those of all formulations using PEG and hard fat as the base. This was attributed to PVA being dispersed inside the tablets using PEG as the base and less presented on the surface. The tablets using PEG and hard fat as the base had significant increases in adhesiveness in all formulations, and PVA could work effectively as an adhesive on the surface of these tablets. The optical micrographs of B20, C20H40 and C20H56 are shown in Fig. 12. A homogeneous mixture of components was observed in B20, and PEG/hard fat dispersion was confirmed in C20H40 and C20H56. A comparison of optical micrographs between C20H40 and C20H56 showed that hard fat existed as the dispersive medium and PEG as the dispersed phase. A previous study has suggested that hard fat and EC had affinity for each other and formed a fixed matrix.[14] Hence, EC was considered to disperse into hard fat and form a fixed dispersion medium. PVA has hydrophilic hydroxyl groups and hydrophobic acetic acid groups (Fig. 1), and is most commonly used to stabilize emulsions caused by the formation of relatively small-sized particles with uniform size distribution.[34,35] PVA could reside at the PEG and hard fat

interface and stabilize the PEG/hard fat dispersion, i.e., the tablets using PEG and hard fat as the base formed the PEG/hard fat dispersion because of the stabilizing effects of PVA at the interface. PVA at the interface should play an important role in the significant increase observed in adhesiveness of the tablets using PEG and hard fat as the base because PVA could be present at the surface of the tablet. Since no peak related to PVA was observed in the DSC analyses of the formulations it was considered that PVA existed in a molecular state.

The breaking strengths of tablets containing IM using PEG as the base were decreased by the addition of more IM. The intermolecular interactions of PEG might be weakened by IM. PEG is a non-ionic water-soluble polyether. Hydrogen bonds, associated with ether oxygen and hydroxyl groups, and hydrophobic interactions influence the intermolecular interactions of PEG.[36] The interposition of IM may decrease the intermolecular interactions between PEG molecules. The breaking strengths of the tablets using PEG and hard fat as the base were also decreased by the addition of IM. Although the breaking strengths of tablets containing IM were decreased by the addition of IM, friability may be overcome by applying a backing film to one side of the tablet. A significant increase in adhesiveness was observed for all tablet formulations containing IM using PEG and hard fat as the base. The adhesiveness of commercially available Aftach Adhesive Tablets is shown in Fig. 7. The diameters of Aftach Adhesive Tablets and the tablets prepared were 7 mm and 10 mm, respectively. The active ingredients of Aftach Adhesive Tablets and the tablets prepared were triamcinolone acetonide and IM, respectively. Although it is not possible to simply compare these tablets, the adhesive force of the tablets using PEG and hard fat as the base was approximated to that of the Aftach Adhesive Tablets. The drug release from the tablets using PEG and hard fat as the base was sustained compared with A20IM, which used PEG as the base. In our previous study, the partition property of IM between hard fat and PEG was

measured to investigate the affinity between IM and hard fat or PEG.[14] Hard fat and PEG were melted, poured into a glass container and IM was added. The partition of IM into the hard fat and PEG phases was allowed to equilibrate and the IM concentrations of the hard fat and PEG phases were measured. IM was distributed to the PEG phase with an approximately 4-fold higher concentration compared with the hard fat phase. Hence, in tablets using PEG and hard fat as the base, most of the IM was present in the dispersed PEG phase, and hard fat containing EC formed the dispersive medium. Since the dispersive medium was a fixed matrix, drug release from the dispersed phase needs to be sustained by the dispersive medium of the fixed matrix. Drug release was more sustained from A20H56IM and C20H56IM than from A20H40IM and C20H40IM, and this was attributed to an increase in the amount of hard fat that formed the dispersive media. Regarding the saponification degree of the PVAs, drug release was more sustained from A20H40IM than from B20H40IM and C20H40IM. The drug release from B20H40IM increased the most in the tablets using PEG and hard fat as the base. A PEG/hard fat dispersion was confirmed in A20H40IM, B20H40IM and C20H40IM (Fig. 12). The dispersive phase comprised of IM in PEG should be released through the PVA shell comprising the interphase between PEG and hard fat. The shell of PVA (A) will be hydrophilic in nature because this PVA has the highest saponification degree and many hydroxyl groups. IM is hydrophobic and hardly released through the hydrophilic PVA (A) shell. PVA (C) has the lowest saponification degree and may have a greater affinity with hard fat to construct a more fixed matrix. The drug release from C20H40IM was sustained compared with B20H40IM. In the tablets using PEG and hard fat as the base, the drug release data were fitted to the zero order, Korsmeyer–Peppas and Higuchi models. The drug release from B20H40IM followed Higuchi's equation related to drug diffusion from matrices, and a relatively good coefficient of determination was obtained. The drug release from A20H40IM,

A20H56IM, C20H40IM and C20H56IM followed Korsmeyer–Peppas's equation, based on the values of the coefficients of determination. The values of *n* for A20H40IM, A20H56IM, C20H40IM and C20H56IM were between 0.45 and 0.89, indicating the drug release is related to the anomalous transport in these formulations. PVA (B) may have appropriate balance at the interface between PEG and hard fat compared with PVAs (A) and (C), and the drug release from B20H40IM followed drug diffusion from a matrix. In the DSC thermograms of the tablets, the peaks corresponding to the melting temperatures of PEG and hard fat were shifted to lower temperatures. This is considered to be an influence of the glycerol contained within the tablets. IM was considered to exist in the molecular phase in the tablets based on the DSC thermograms and XRD patterns. A molecular phase of IM may improve drug solubility and increase permeability into buccal mucosa. From the results of the *in vivo* study, higher tissue concentrations were observed compared with plasma concentrations for all the formulations. In A20IM, the tablet became paste like within 1 h and spread to a wide area in the oral cavity. Although a higher tissue concentration in A20IM was observed after 1 and 2 h compared with A20H40IM, the plasma concentration was also increased. In the tablets using PEG and hard fat as the base, A20H40IM showed the lowest tissue concentration. This should be caused by a decrease in drug release from A20H40IM. Although the tissue concentration 1 h after buccal administration was highest for C20H40IM, the difference was not significant. The tissue concentration at 2 h after administration of B20H40IM was significantly higher than that after administration of A20H40IM, and the B20H40IM formulation maintained the highest tissue concentration until 5 h. The highest *in vitro* adhesiveness and the continuous higher tissue concentration were observed for B20H40IM, and the plasma concentrations were sufficiently low compared with the tissue concentrations. Hence, we suggest that PVA (B) has the optimum properties among three kinds of PVA tested

as a mucoadhesive for the mucoadhesive tablet using PEG and hard fat as the base.

We confirmed that mucoadhesive tablets using PEG and hard fat as the base and containing PVA as a mucoadhesive had a sustained drug release property and good adhesiveness. PVA (B) has the optimum properties among three kinds of PVAs investigated because B20H40IM showed the highest tissue concentration and relatively low plasma concentration. Mucoadhesive tablets using PEG and hard fat as the base and containing PVA (B) have good potential as a newly designed preparation to treat pain caused by oral aphtha.

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Conflict of interest

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Fig. captions

Fig. 1 Chemical structure of PVA

Fig. 2 Preparation charts for tablets using PEG as the base (a) and using PEG and hard fat as the base (b)

Fig. 3 Preparation charts for tablets containing IM using PEG as the base (a) and using PEG and hard fat as the base (b)

Fig. 4 Breaking strengths of mucoadhesive tablets

Each column represents the mean±S.D. (n=5).

* $p<0.05$ and ** $p<0.01$, Dunnett's test was performed to compare the formulations with breaking strengths < PEG.

$p<0.01$, Dunnett's test was performed to compare the formulations with breaking strengths > Hard fat.

Fig. 5 *In vitro* adhesiveness of mucoadhesive tablets

Each column represents the mean±S.D. (n=5-6).

** $p<0.01$, Dunnett's test was performed to compare the formulations with adhesiveness > B20.

Fig. 6 Breaking strengths of mucoadhesive tablets containing IM

Each column represents the mean±S.D. (n=5).

** $p<0.01$, Dunnett's test was performed to compare the formulations with breaking strengths < PEG.

[#] $p<0.05$, Dunnett's test was performed to compare the formulations with breaking strengths > Hard fat.

Fig. 7 *In vitro* adhesiveness of mucoadhesive tablets containing IM

Each column represents the mean±S.D. (n=5-6).

* $p<0.05$ and ** $p<0.01$, Dunnett's test was performed to compare the formulations with adhesiveness > A20IM.

Fig. 8 Release profiles of IM from mucoadhesive tablets

Each point represents the mean±S.D. (n=3).

Fig. 9 DSC thermograms of (a) IM, (b) PEG4000, (c) hard fat, (d) EC4, (e) PVA (A), (f) PVA (B), (g) PVA (C), (h) A20IM, (i) A20H40IM, (j) B20H40IM, (k) C20H40IM

Fig. 10 XRD patterns of (a) IM, (b) PEG4000, (c) hard fat, (d) EC4, (e) PVA (A), (f) PVA (B), (g) PVA (C), (h) A20IM, (i) A20H40IM, (j) B20H40IM, (k) C20H40IM

Fig. 11 (a) Tissue concentration-time profiles and (b) plasma concentration-time profiles after buccal administration of mucoadhesive tablets

Each point represents the mean±S.E. (n=3-4).

* $p<0.05$ *vs*. A20H40IM, Tukey's test was performed to compare the formulations.

Fig. 12 Optical micrographs of preparations

Bar = 200 μm

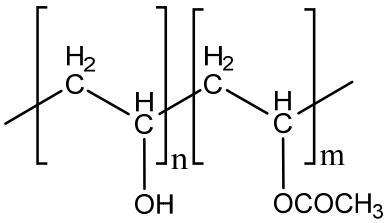

Fig. 1

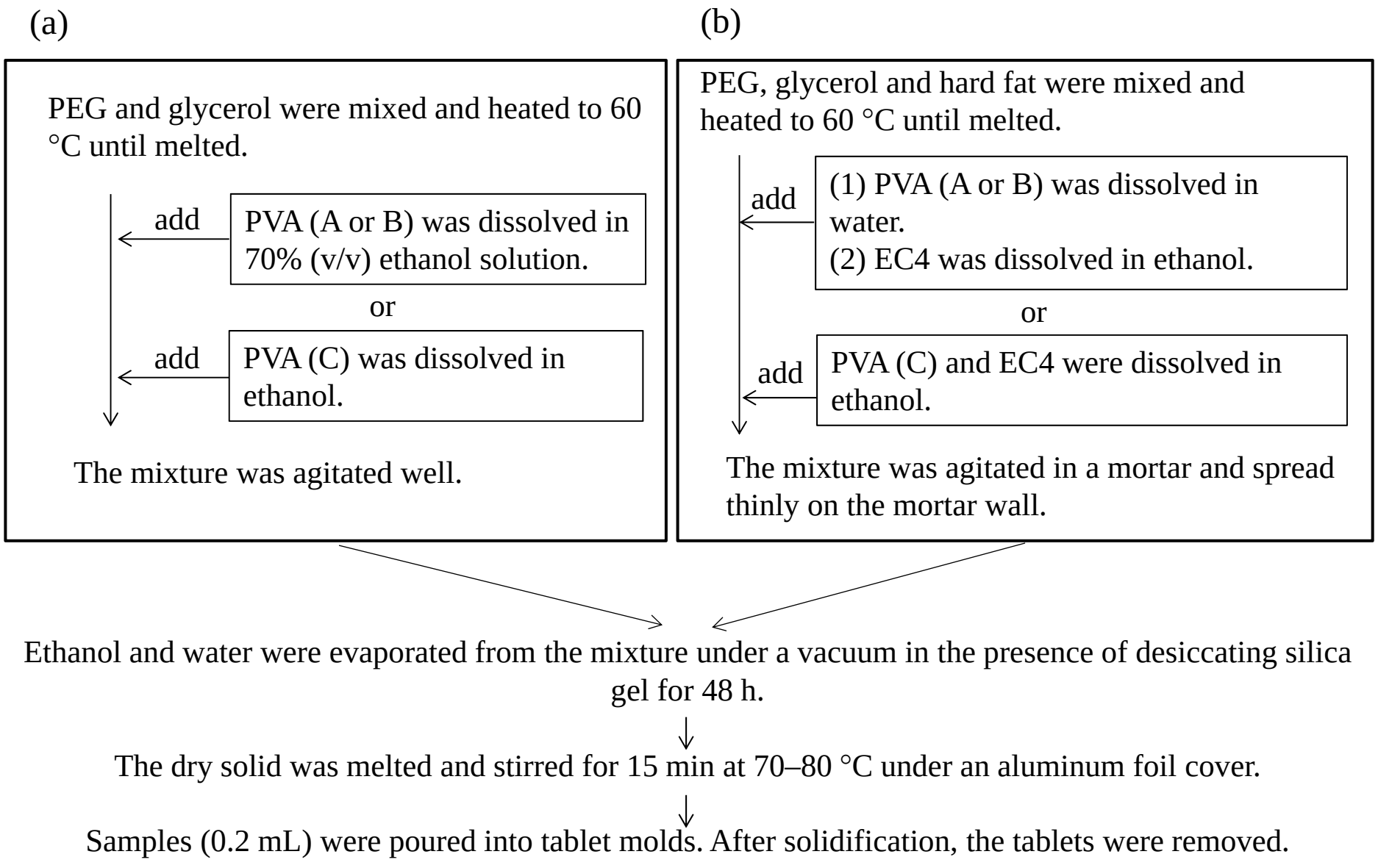
(a)
PEG and glycerol were mixed and heated to 60 °C until melted.
add
PVA (A or B) was dissolved in 70% (v/v) ethanol solution.
or
add
PVA (C) was dissolved in ethanol.
The mixture was agitated well.
(b)
PEG, glycerol and hard fat were mixed and heated to 60 °C until melted.
add
(1) PVA (A or B) was dissolved in water.
(2) EC4 was dissolved in ethanol.
or
add
PVA (C) and EC4 were dissolved in ethanol.
The mixture was agitated in a mortar and spread thinly on the mortar wall.
Ethanol and water were evaporated from the mixture under a vacuum in the presence of desiccating silica gel for 48 h.
The dry solid was melted and stirred for 15 min at 70–80 °C under an aluminum foil cover.
Samples (0.2 mL) were poured into tablet molds. After solidification, the tablets were removed.

Fig. 2

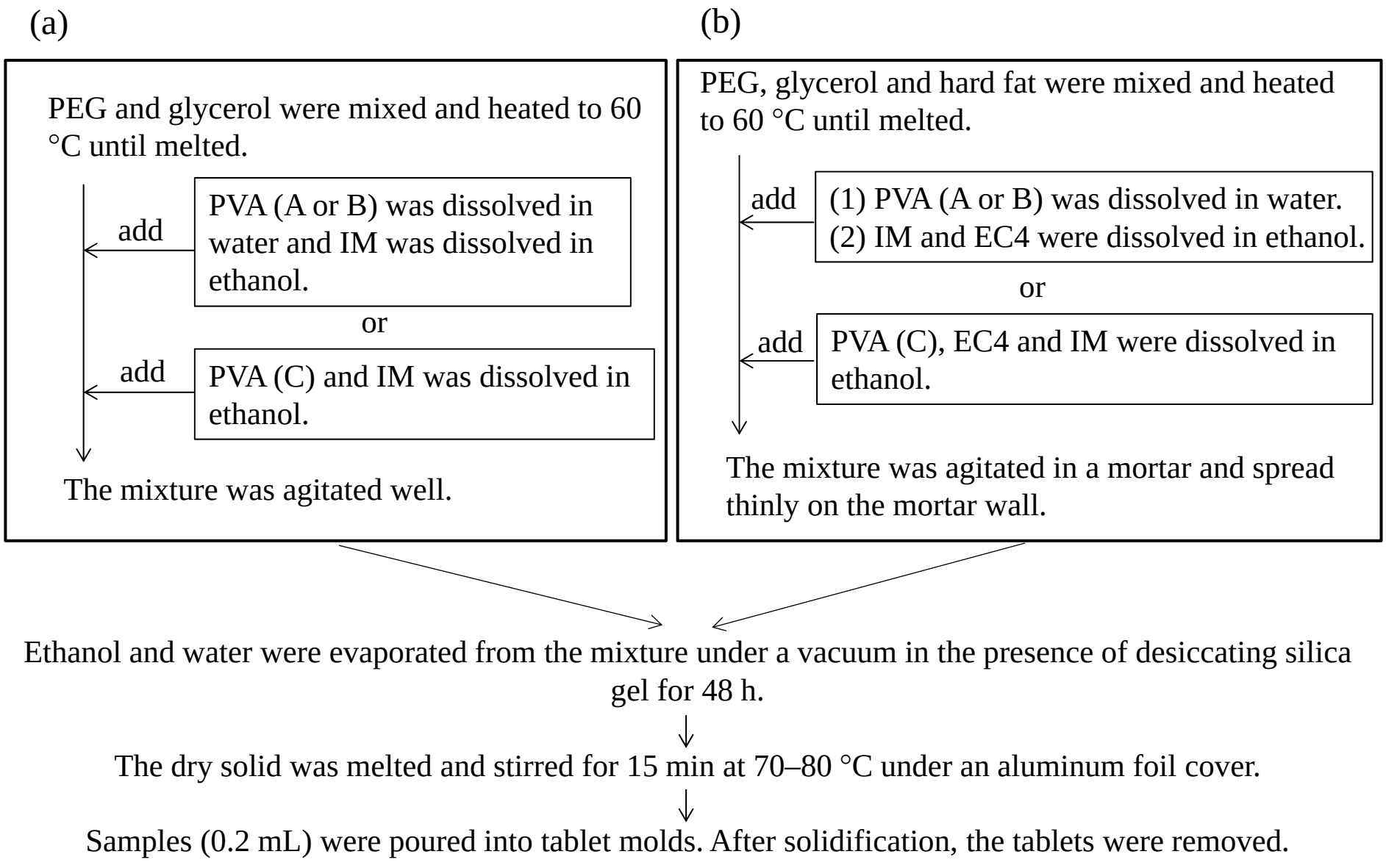
(a)
PEG and glycerol were mixed and heated to 60 °C until melted.
add
PVA (A or B) was dissolved in water and IM was dissolved in ethanol.
or
add
PVA (C) and IM was dissolved in ethanol.
The mixture was agitated well.
(b)
PEG, glycerol and hard fat were mixed and heated to 60 °C until melted.
add
(1) PVA (A or B) was dissolved in water.
(2) IM and EC4 were dissolved in ethanol.
or
add
PVA (C), EC4 and IM were dissolved in ethanol.
The mixture was agitated in a mortar and spread thinly on the mortar wall.
Ethanol and water were evaporated from the mixture under a vacuum in the presence of desiccating silica gel for 48 h.
The dry solid was melted and stirred for 15 min at 70–80 °C under an aluminum foil cover.
Samples (0.2 mL) were poured into tablet molds. After solidification, the tablets were removed.

Fig. 3

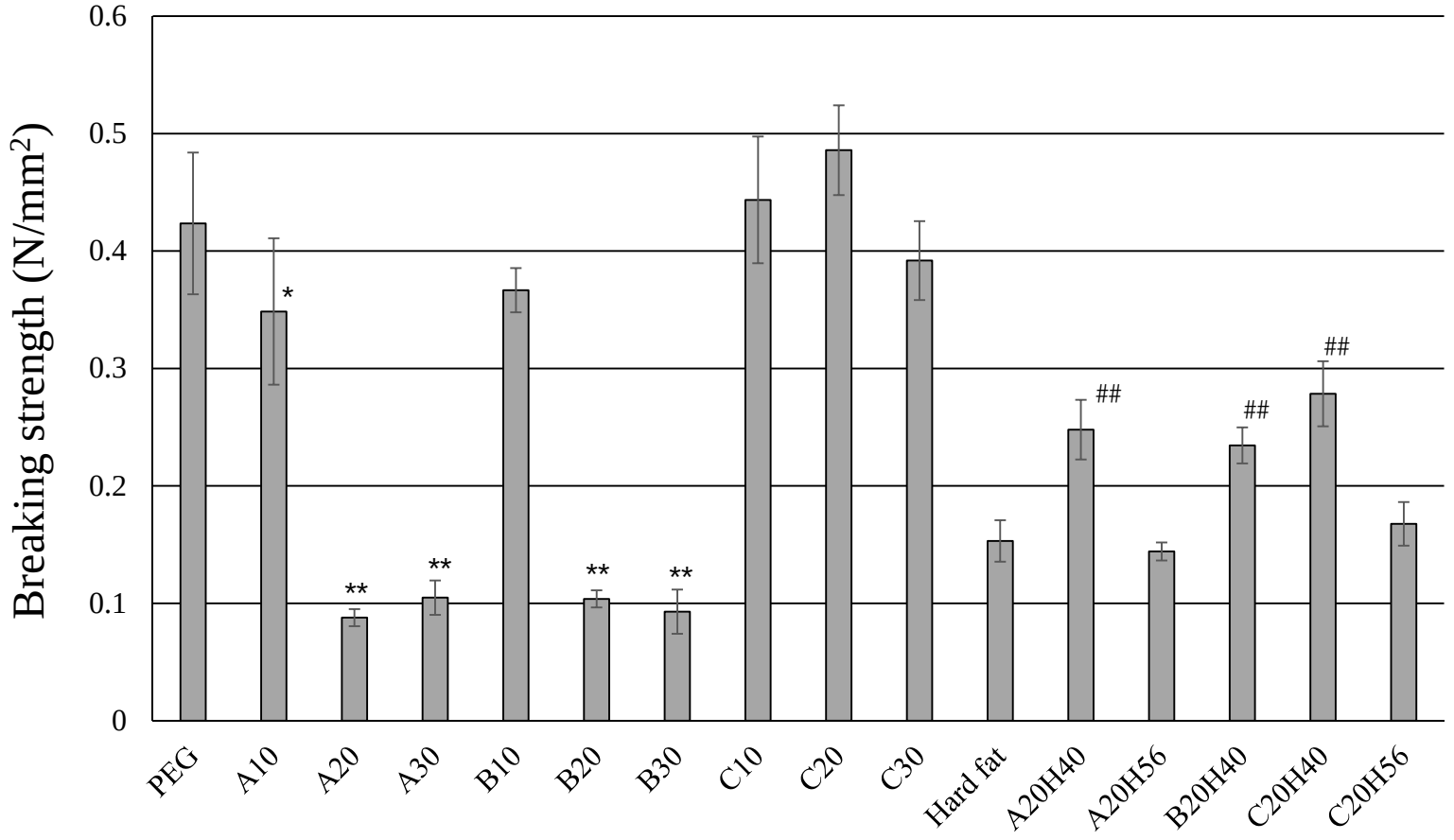
Breaking strength (N/mm2)
0.6
0.5
0.4
0.3
0.2
0.1
0
*
**
**
**
**
##
##
##
PEG
A10
A20
A30
B10
B20
B30
C10
C20
C30
Hard fat
A20H40
A20H56
B20H40
C20H40
C20H56

Fig. 4

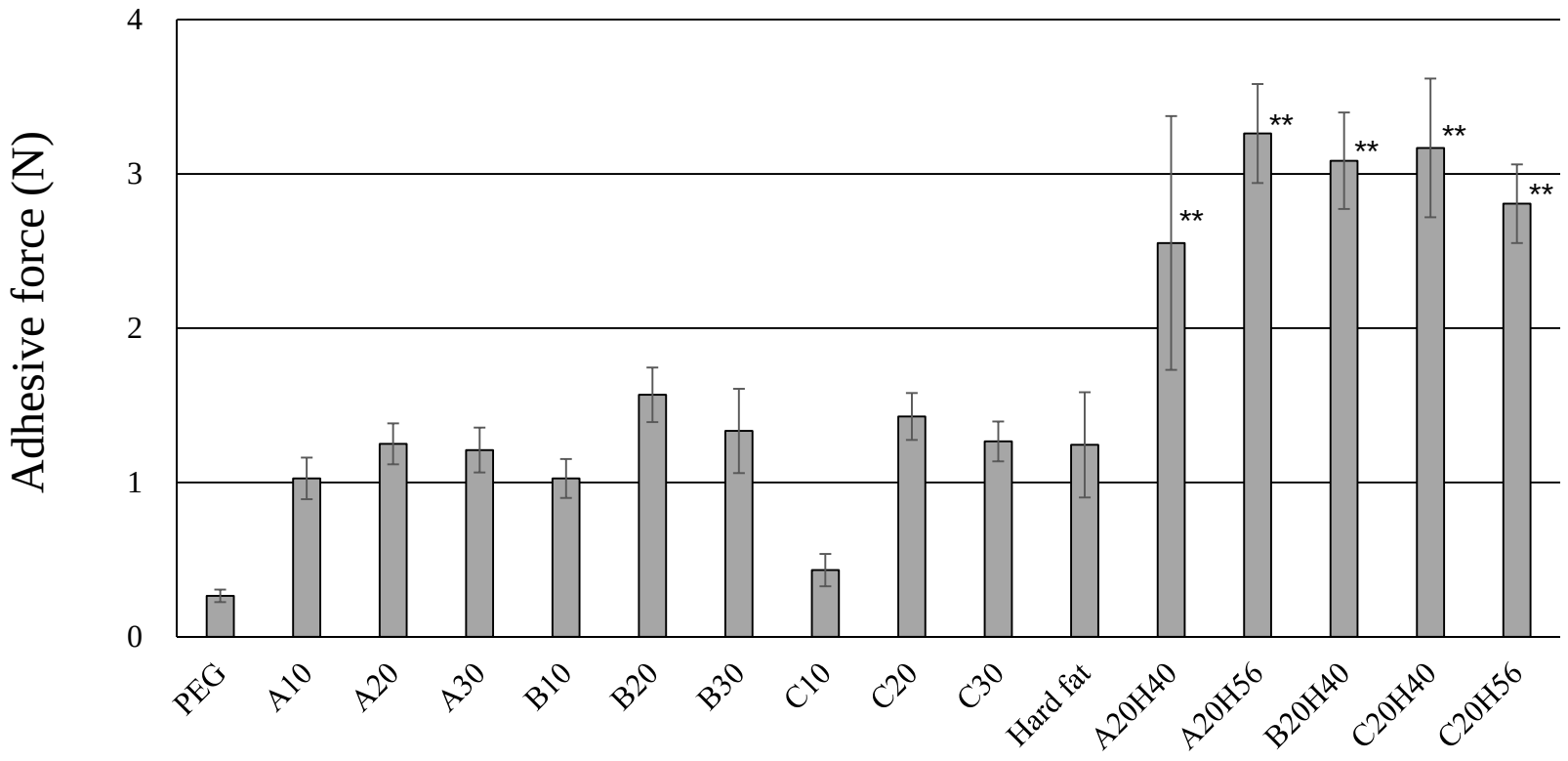
Adhesive force (N)
4
3
2
1
0
**
**
**
**
PEG
A10
A20
A30
B10
B20
B30
C10
C20
C30
Hard fat
A20H40
A20H56
B20H40
C20H40
C20H56

Fig. 5

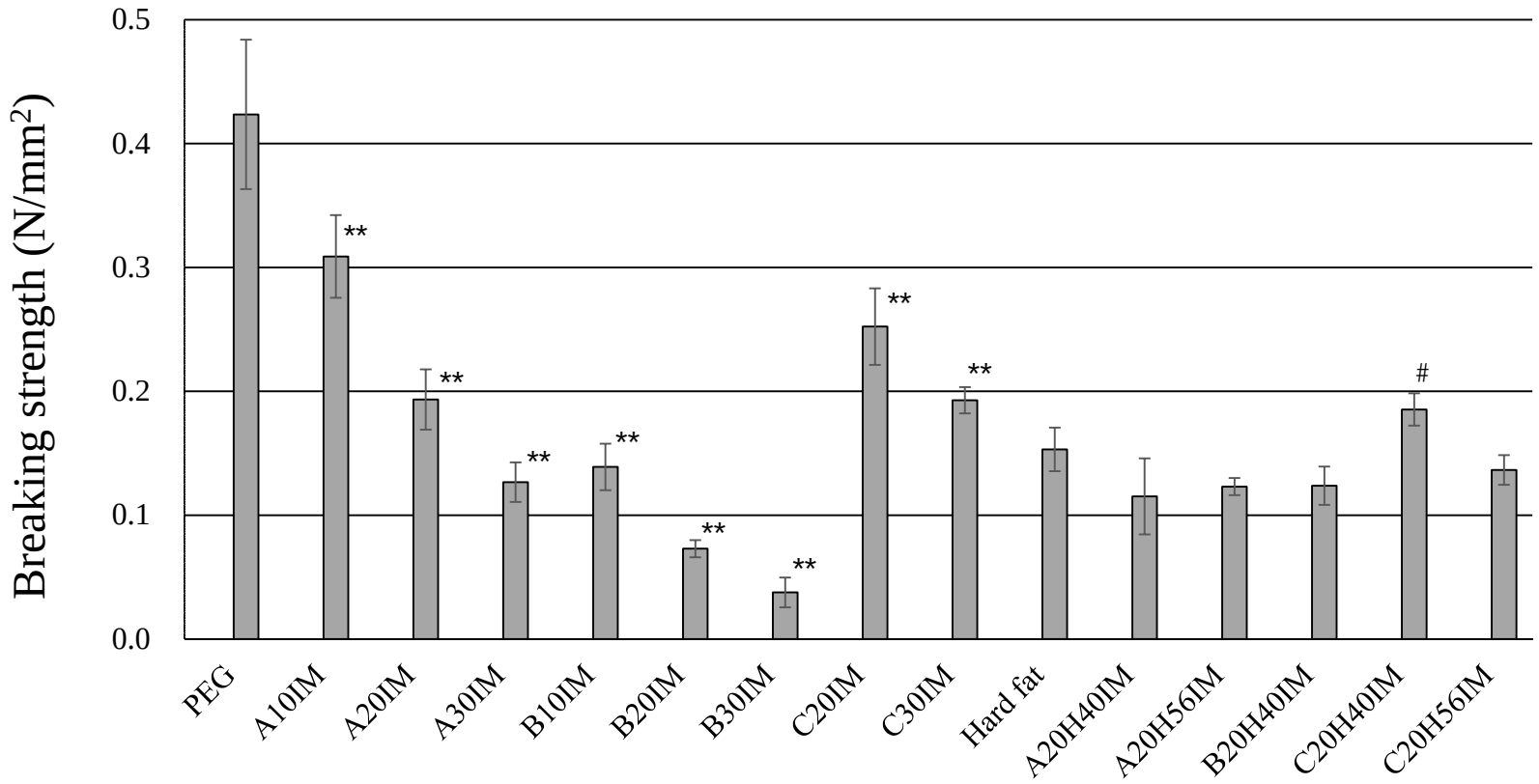
Breaking strength (N/mm2)
0.5
0.4
0.3
0.2
0.1
0.0
**
**
**
**
**
**
**
**
#
PEG
A10IM
A20IM
A30IM
B10IM
B20IM
B30IM
C20IM
C30IM
Hard fat
A20H40IM
A20H56IM
B20H40IM
C20H40IM
C20H56IM

Fig. 6

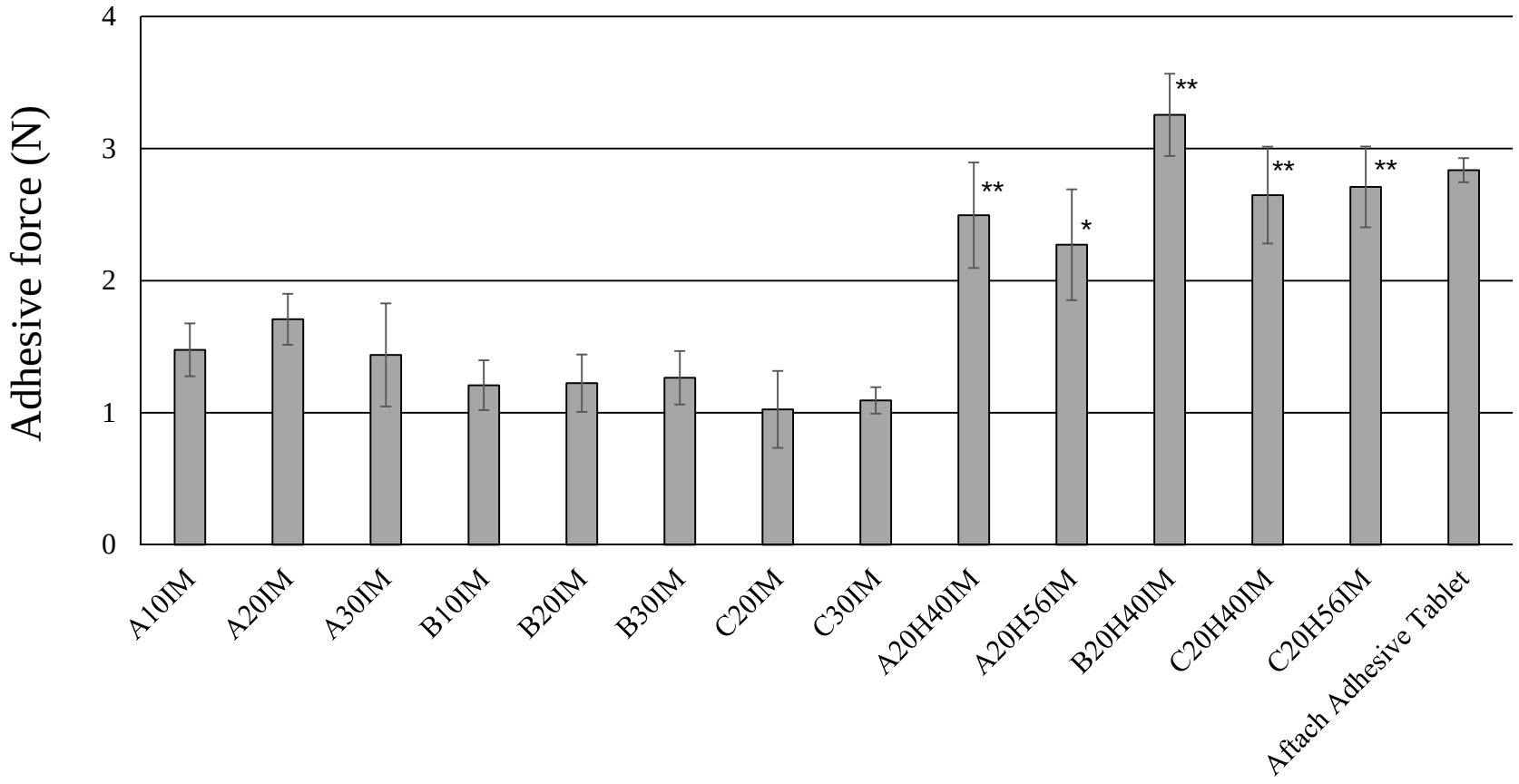
Adhesive force (N)
4
3
2
1
0
**
*
**
**
**
A10IM
A20IM
A30IM
B10IM
B20IM
B30IM
C20IM
C30IM
A20H40IM
A20H56IM
B20H40IM
C20H40IM
C20H56IM
Aftach Adhesive Tablet

Fig. 7

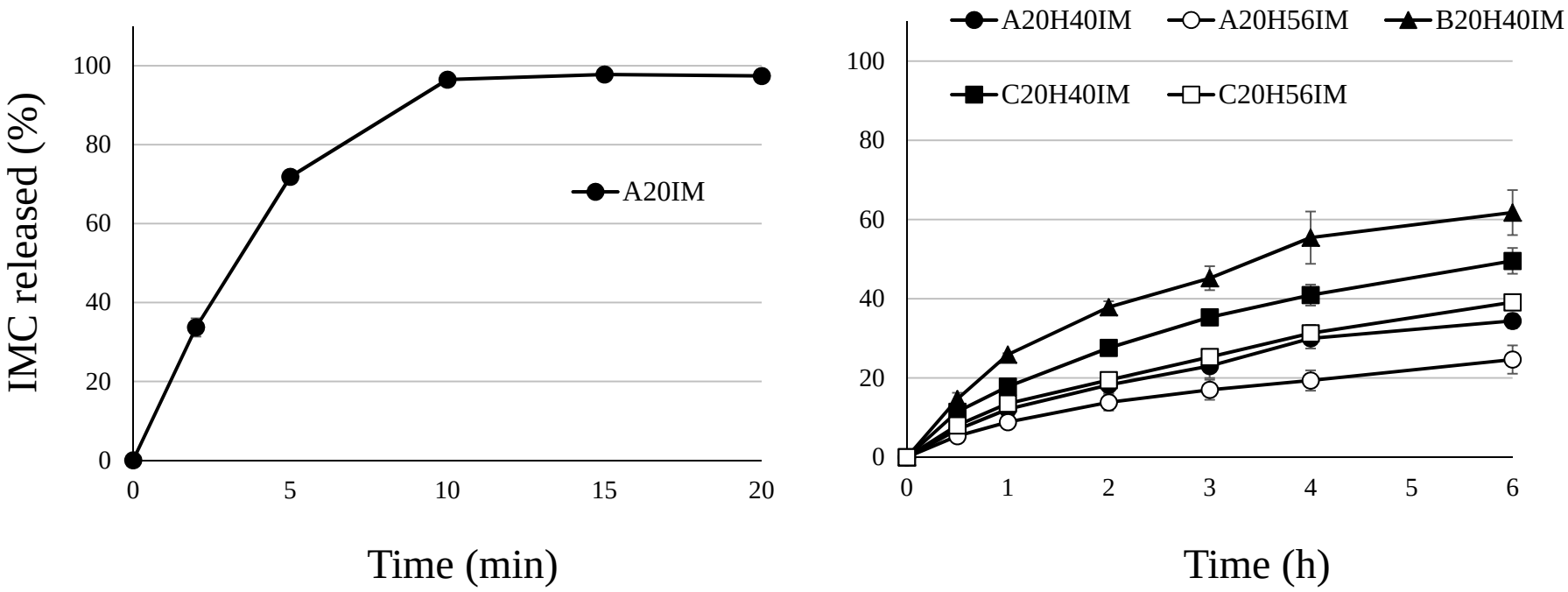
IMC released (%)
100
80
60
40
20
0
0
5
10
15
20
A20IM
Time (min)
A20H40IM
A20H56IM
B20H40IM
C20H40IM
C20H56IM
100
80
60
40
20
0
0
1
2
3
4
5
6
Time (h)

Fig. 8

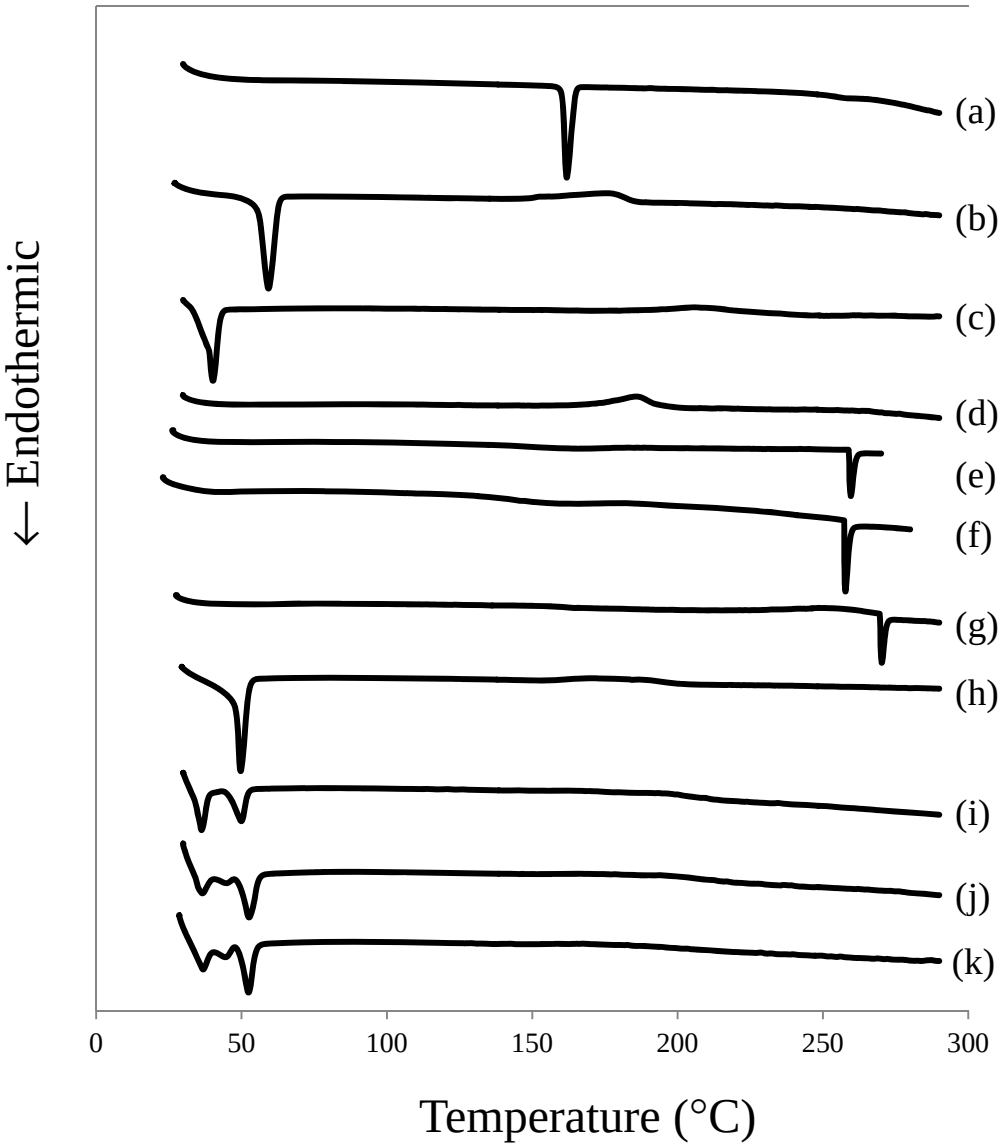
← Endothermic
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)
(j)
(k)
0
50
100
150
200
250
300
Temperature (°C)

Fig. 9

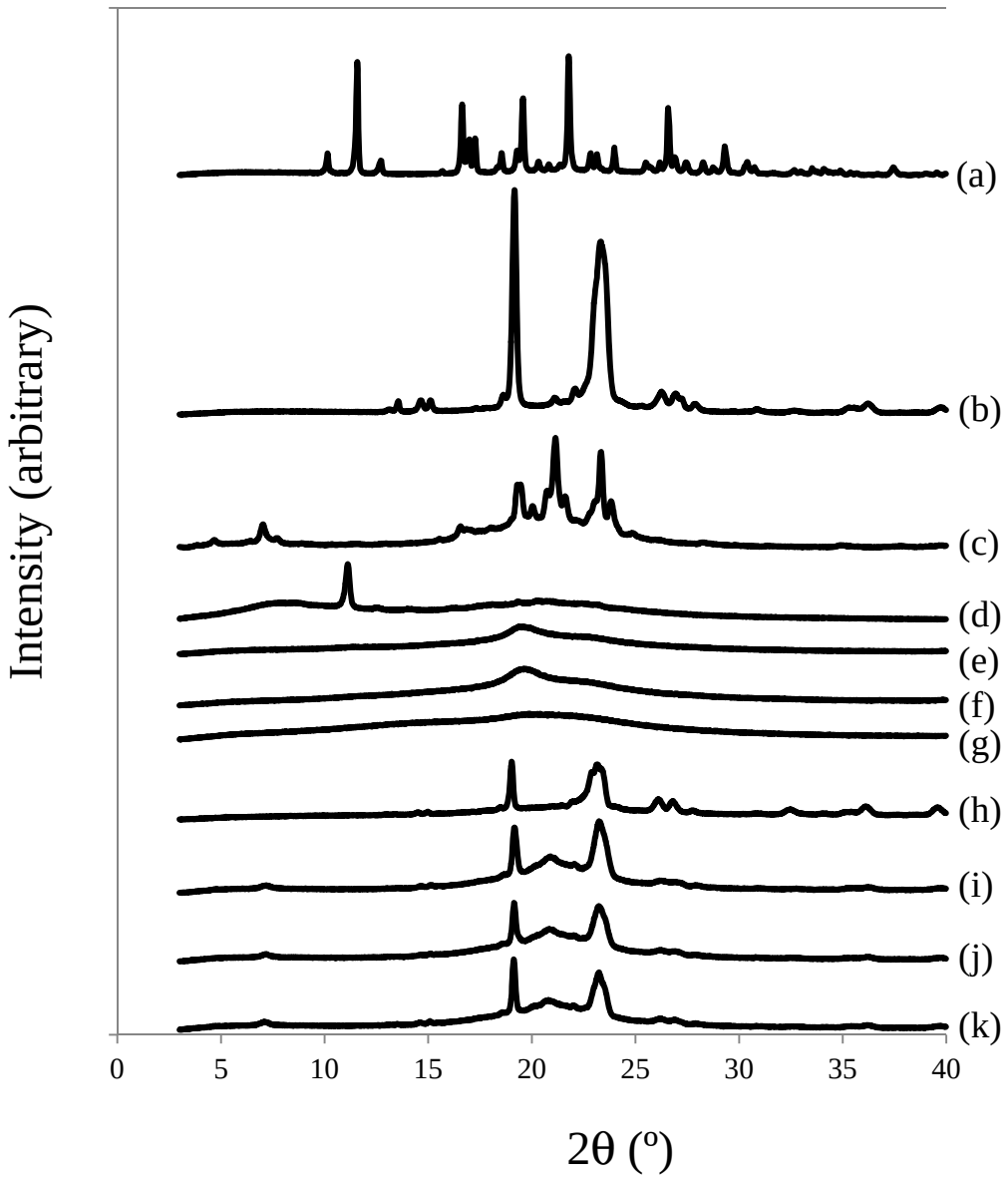

Fig. 10

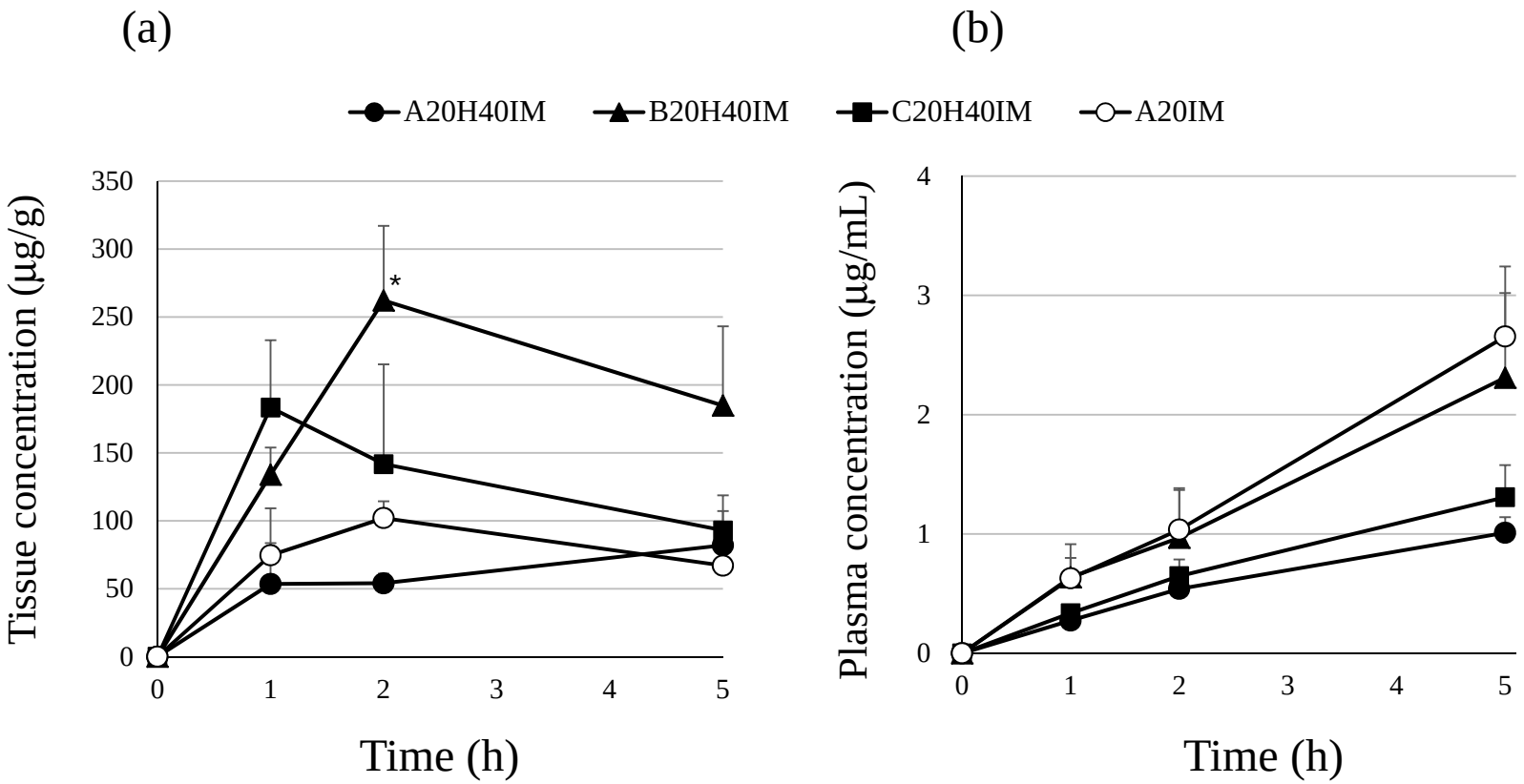
(a)
(b)
A20H40IM
B20H40IM
C20H40IM
A20IM
Tissue concentration (μg/g)
Plasma concentration (μg/mL)
Time (h)
Time (h)
*

Fig. 11

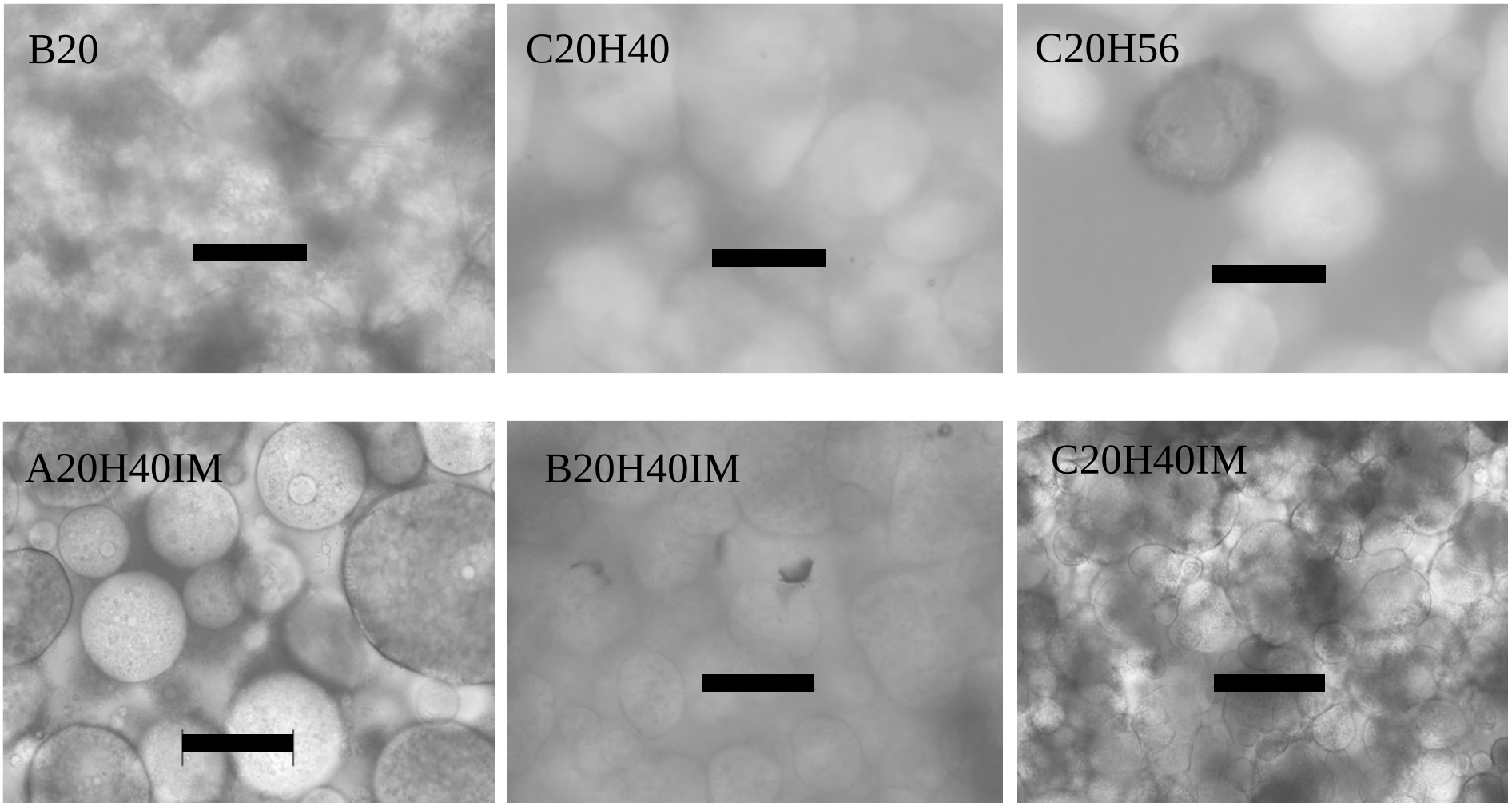

Fig. 12

Table 1 Characteristics of PVA

PVA (abbreviation)	Saponification degree (mol%)	Viscosity (mPa·s)
KL-03 (A)	79.7	3.2*
NK-05R (B)	72.4	4.8*
LL-810 (C)	48.7	7.7**

* : Viscosity of 4% (w/v) aqueous solution at 20 °C

** : Viscosity of 10% (w/v) water / methanol (50:50) solution at 20 °C

Table 2 Composition of mucoadhesive tablets

Formulation	PVA (A)	PVA (B)	PVA (C)	Glycerol	PEG4000	Hard fat	EC4
	% (w/w)						
A10	1.0	–	–	9.0	90.0	–	–
A20	2.0	–	–	18.0	80.0	–	–
A30	3.0	–	–	27.0	70.0	–	–
B10	–	1.0	–	9.0	90.0	–	–
B20	–	2.0	–	18.0	80.0	–	–
B30	–	3.0	–	27.0	70.0	–	–
C10	–	–	1.0	9.0	90.0	–	–
C20	–	–	2.0	18.0	80.0	–	–
C30	–	–	3.0	27.0	70.0	–	–
A20H40	2.0	–	–	18.0	39.0	40.0	1.0
A20H56	2.0	–	–	18.0	23.0	56.0	1.0
B20H40	–	2.0	–	18.0	39.0	40.0	1.0
C20H40	–	–	2.0	18.0	39.0	40.0	1.0
C20H56	–	–	2.0	18.0	23.0	56.0	1.0

Table 3 Composition and weight of mucoadhesive tablets containing IM

Formulation	PVA (A)	PVA (B)	PVA (C)	Glycerol	PEG4000	Hard fat	EC4	IM	Weight/tab * (mg)
	% (w/w)								
A10IM	0.95	–	–	8.55	85.50	–	–	5.00	237±10
A20IM	1.90	–	–	17.10	76.00	–	–	5.00	249±9
A30IM	2.85	–	–	25.65	66.50	–	–	5.00	248±4
B10IM	–	0.95	–	8.55	85.50	–	–	5.00	239±12
B20IM	–	1.90	–	17.10	76.00	–	–	5.00	239±10
B30IM	–	2.85	–	25.65	66.50	–	–	5.00	249±4
C20IM	–	–	1.90	17.10	76.00	–	–	5.00	231±5
C30IM	–	–	2.85	25.65	66.50	–	–	5.00	253±6
A20H40IM	1.90	–	–	17.10	37.05	38.00	0.95	5.00	210±7
A20H56IM	1.90	–	–	17.10	21.85	53.20	0.95	5.00	193±4
B20H40IM	–	1.90	–	17.10	37.05	38.00	0.95	5.00	205±3
C20H40IM	–	–	1.90	17.10	37.05	38.00	0.95	5.00	211±5
C20H56IM	–	–	1.90	17.10	21.85	53.20	0.95	5.00	199±3

* : Each value represents the mean ± SD (n = 5).

Table 4 Parameters obtained from various kinetic models

Formulation	Zero order		Korsmeyer-Peppas			Higuchi	
	r^2	k_0	r^2	a	Release exponent (n)	r^2	k_H
A20H40IM	0.872	6.756	0.992	11.466	0.649	0.979	13.756
A20H56IM	0.847	4.765	0.994	8.555	0.609	0.991	9.746
B20H40IM	0.771	12.632	0.982	23.939	0.578	0.990	26.076
C20H40IM	0.838	9.749	0.997	17.775	0.597	0.992	19.965
C20H56IM	0.893	7.431	0.997	12.823	0.629	0.982	15.09