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Improvement of Absorption Rate of Indomethacin and Reduction of Stomach Irritation by Alginate Dispersions

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Abstract—The dissolution rates of indomethacin from low molecular weight (mol. wt) alginate dispersions were significantly enhanced in comparison with that of indomethacin alone. The dispersion with lower mol. wt alginate exhibited more rapid dissolution rate than that of dispersion with higher mol. wt alginate. These enhanced dissolution rates of indomethacin by alginate may be due to the improvement of wettability and the decrease of crystallinity and crystal size. The absorption rate from alginate dispersions was enhanced in comparison with that from indomethacin alone, and enhanced only the rate of bioavailability in beagle dogs and volunteers. In addition, indomethacin-induced gastric lesions were reduced by dispersing indomethacin in alginate.

Alginate has received much attention in the formation of sustained-release dosage forms (Badwan et al 1985; Yotsuyanagi et al 1987) and in stabilizing suspension dosage forms (Kawashima et al 1989). It has been clinically confirmed as a useful anti-ulcer agent based on the protection of the mucosal surface of the stomach (Daigo et al 1981).

In a previous paper, we reported that the hydrolysate of alginate, a so-called low molecular alginate (low mol. alginate), enhanced the dissolution rate of poorly water-soluble drugs (Shiraishi et al 1990). These observations led to the expectation that the absorption rate of drug may be enhanced, and that drug-induced ulcers can be reduced, by dispersing the drug in low mol. alginate.

In this study, the effects of low mol. alginate on the absorption of indomethacin and gastric damage induced by the same drug were studied.

Materials and Methods

Materials

Indomethacin (γ-form) was donated by Sumitomo Pharmaceutical Co. Ltd (Osaka, Japan). The fraction that passed through a 100 mesh sieve was used for all experiments. Low molecular alginates (low mol. alginates) were supplied by Kimitsu Chemical Industries Co. Ltd (Tokyo, Japan). The physicochemical properties of low mol. alginates are shown in Table 1. All other reagents and solvents were of analytical grade, and deionized double-distilled water was used throughout the study.

Preparation of indomethacin-low mol. alginate dispersion and mixtures

Indomethacin and low mol. alginate in a weight ratio of 1:1, 1:2 or 1:3 were placed in a mortar and the mixtures were kneaded with 2 volumes of water for 1 h by hand. Drying was carried out in-vacuo at room temperature (20°C) for 48 h. The fraction that passed through a 100 mesh sieve was used in the following experiments.

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The physical mixture of indomethacin with low mol. alginate was prepared by mixing of the powders (< 100 mesh) in a mortar.

Dissolution studies

The dissolution behaviour of indomethacin and its low mol. alginate dispersions was examined according to the paddle method (JP XI). Indomethacin or its low mol. alginate dispersions (equivalent to 7 mg indomethacin, < 100 mesh) was filled into gelatin capsules (size No. 2). A single capsule was placed into 500 mL of water (37°C) using a sinker. The dissolution medium was stirred at 100 rev min^{-1}, and 3 mL of sample was taken out at appropriate intervals. The percent of indomethacin dissolved in the medium was determined spectrophotometrically at 265 nm.

Powder X-ray diffraction studies

The powder X-ray diffractometer (Geiger-Flex RAD-1A; Rigaku Denki Co. Ltd, Tokyo, Japan) was operated under the following conditions: X-ray, Ni-filtered Cu-Kα radiation; voltage, 40 kV; current, 30 mA; time constant, 1 s; scanning speed, 1° min^{-1}.

Wettability

Wettability measurements were by the compressed disk method (Zografi & Tam 1976). The sample powder was compressed into a cylindrical tablet (diam. 1·3 cm) using a single-punch tableting machine (Riken Seiki Co. Ltd, Tokyo) at a pressure of 100 kg cm^{-2} for 1 min. A 25 μL drop of water was placed on the flat tablet surface using a microliter syringe. The drop was photographed at appropriate intervals, and the contact angle was measured from the photographs.

In-vivo absorption studies

Four male beagle dogs, 11-12·5 kg, were fasted for 24 h before drug administration. Indomethacin or its low mol. alginate dispersion (equivalent to 2 mg kg^{-1} indomethacin) was filled in a gelatin capsule (size No. 2), and administered orally together with 20 mL water. One mg kg^{-1} of indomethacin, dissolved in phosphate buffer (pH 8), was administered

Table 1. Physicochemical properties of low mol. alginates.

	AL-I	AL-II
Molecular weight	4400	9600
Melting point (decomp.) (°C)	206	204
Viscosity (cp)*	1·5	2·9
pH*	6·88	6·89
Solubility (g mL^{-1})**	>0·1	>0·1

* 1% solution at 25°C. ** Measurements at 25°C.

intravenously. At appropriate intervals, a 3 mL blood sample was withdrawn into heparinized syringes from the forefoot vein and immediately centrifuged at 3000 rev min^{-1} to obtain plasma samples. One mL of plasma was used for the measurement of indomethacin in the plasma.

Four healthy male volunteers (23–38 years, 60–63 kg) received orally gelatin capsules filled with indomethacin or its low mol. alginate dispersion (equivalent to 0·4 mg kg^{-1} indomethacin) together with 100 mL water. Subjects were fasted for 12 h before drug administration, and received a standard meal at 6 h after drug administration. At appropriate intervals, 6 mL of blood was withdrawn and 2 mL serum was used for determination of indomethacin concentration.

The concentration of indomethacin in plasma or serum samples was determined using HPLC. Indomethacin was extracted with 6 mL of ethyl acetate after adding 0·5 mL of phosphate buffer (pH 3) and 1 mL of water to 1 mL of the plasma or 2 mL of serum. Five mL of ethyl acetate phase was transferred to a new tube, with a methanolic solution (0·5 mL) of mefenamic acid (10 $\mu g\ mL^{-1}$) as an internal standard. The residue on evaporation of the organic phase was redissolved in 0·2 mL of mobile phase, 10 μL of which was injected for determination of indomethacin. The HPLC conditions were as follows: pump and detector, Hitachi L-6000 type equipped with 655A-21 UV monitor (Tokyo, Japan); column, LiChrospher 100, RP-18 (5 μm, 4 mm i.d. × 150 mm, Merck); mobile phase, methanol: 1% acetic acid (3:1); flow rate, 1 mL min^{-1}; detection, 265 nm.

Pharmacokinetic analysis

The concentration-time data after oral administration were fitted to the equation derived from a one-compartment open model with first order absorption. The rate constant for the absorption phase (k_a) and that of the terminal phase of elimination (k_e) were calculated using the MULTI program (Yamaoka et al 1981). The area under the plasma concentration-time curve (AUC) was calculated by means of the trapezoidal method. The absorption rate was obtained by the deconvolution method (Yamaoka & Tanigawara 1983) using the plasma concentration after intravenous injection and after oral administration of the drug preparation. The intravenous injection data reported by Kwan et al (1976) were used for the calculation of the absorption rate for volunteers.

Gastric mucosal damage

The evaluation of indomethacin-induced ulcer was examined according to the method of Kasuya et al (1979). Male Wistar rats (180–200 g, 8 weeks old) were fasted for 24 h before the experiment, but allowed free access to water. Indomethacin or its low mol. alginate dispersion (equivalent to 10 mg kg^{-1} indomethacin) was filled in mini capsules (size 2·4 mm i.d. × 7·3 mm, Japan Elanco Co. Ltd, Osaka, Japan). During administration, a capsule was fixed into one end of a teflon tube into which a wire was fitted. The teflon tube was then inserted into the stomach, and the capsule was pushed out from the tube by a wire into the stomach. A further, 0·5 mL of water was orally administered by sonde. The animals were killed 5 or 7 h after oral administration, the stomach removed and inflated with 1% formalin and immersed in 1% formalin solution for 30 min. The stomach was then incised

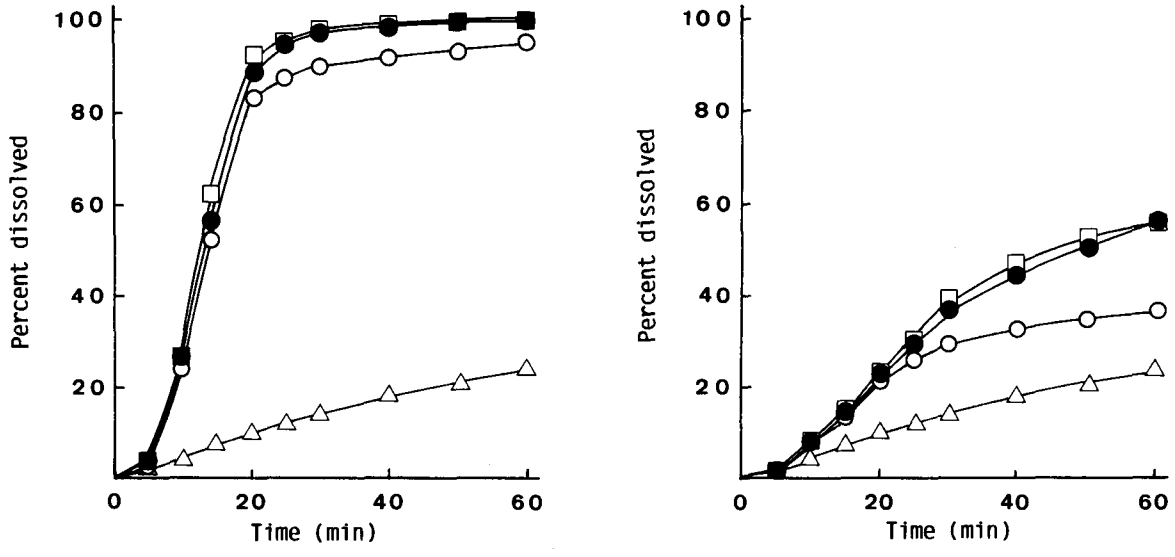

FIG. 1. Dissolution profiles of indomethacin-AL-I dispersions (left) and indomethacin-AL-II dispersions (right) in water at 37°C. △, indomethacin alone; ○, 1:1 w/w; ●, 1:2 w/w; □, 1:3 w/w.

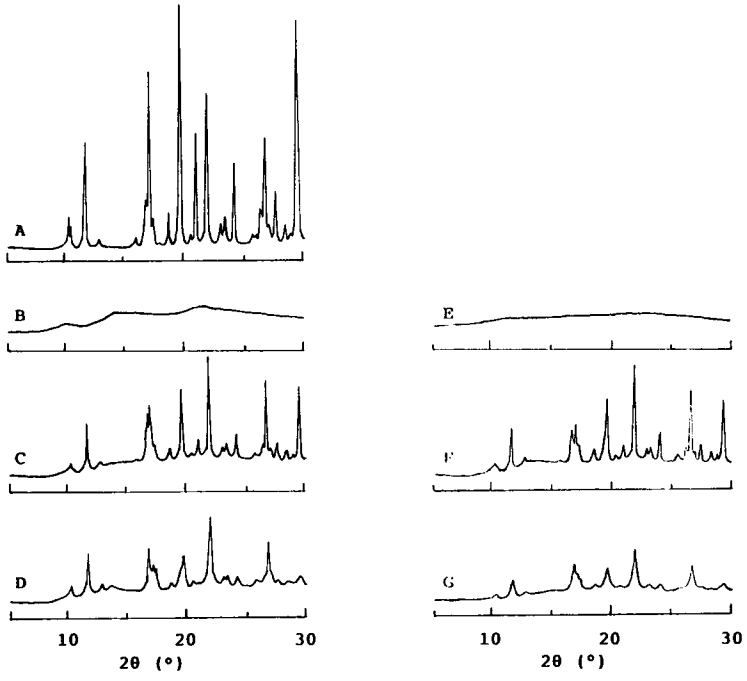

FIG. 2. Powder X-ray diffraction patterns of indomethacin-low mol. alginate systems. A, indomethacin alone; B, AL-I alone; C, indomethacin-AL-I physical mixture (1:2 w/w); D, indomethacin-AL-I dispersion (1:2 w/w); E, AL-II alone; F, indomethacin-AL-II physical mixture (1:2 w/w); G, indomethacin-AL-II dispersion (1:2 w/w).

along the greater curvature and the length of each mucosal ulcer was measured under a microscope. The sum of the lengths of all mucosal ulcers per rat was used as the ulcer index.

Results and Discussion

In-vitro studies

Fig. 1 shows the dissolution profiles of indomethacin from its low mol. alginate dispersion in water at 37°C. The dissolution rate of indomethacin from the alginate dispersions was significantly enhanced in comparison with that of indomethacin alone. The dissolution behaviour for each alginate dispersion was independent of the content of alginate, although 1:1 alginate dispersions showed slightly slower dissolution, compared with all other dispersions. The dispersion with AL-I, the lower mol. wt alginate, exhibited more rapid dissolution rate than that of dispersion with AL-II. The dissolution rates of indomethacin from the alginate dispersions in pH 1·2 medium were also enhanced in the order AL-I > AL-II > indomethacin alone, but were slower than those in water (not shown). These data indicate that the dissolution of indomethacin alginate dispersions are dependent on the mol. wt of low mol. alginate, and the lower mol. alginate may be superior to the higher mol. alginate as a carrier for increasing absorption rate. These enhanced dissolution rates may relate to some other factors such as the buffering effect of alginate, the reduction of particle size by kneading, increasing solubility and wettability of indomethacin, and decreasing crystallinity of indomethacin. The buffering effect is negligible, since the dissolution behaviour was independent of alginate content and dissolution in pH 1·2 was similar to that in water. The initial and final pH values of water as dissolution medium were almost the same, for example, the initial and final pH values for AL-I were 6·37 and 6·57, respectively. The average particle sizes of indomethacin, AL-I and AL-II dispersions were 44, 63 and 69 μm, respectively. Thus, enhanced dissolution rate of alginate dispersions could not be explained by particle size effect.

The solubility of indomethacin increased with increasing concentration of low mol. alginate, and the solubility curve can be classified as type A (Higuchi & Connors 1965). The solubility of indomethacin increased about 15- and 10-fold in the presence of 1% AL-I and AL-II, respectively. However, the solubility of indomethacin was scarcely increased at the concentration of low mol. alginates used in the dissolution test (< 0·004%). Therefore, it is difficult to explain the rapid dissolution rate of the low mol. alginate dispersion in terms of increased solubility.

Fig. 2 shows the powder X-ray diffraction patterns of the low mol. alginate dispersion, the physical mixture, indomethacin and low mol. alginate. The diffraction patterns of AL-I and AL-II showed halo patterns over the 2θ range, 5° to 30°, indicating the diffraction peaks in each physical mixture were characteristic of indomethacin. The diffraction peaks of indomethacin in each low mol. alginate dispersion were broader than those in the physical mixture. In addition, the diffraction peaks which were observed around 29·3° and 20·8° at 2θ in each physical mixture were not present in the low mol. alginate dispersions. Furthermore, the DSC endothermic peak based on the melting of indomethacin was decreased and shifted to lower temperature by dispersion in low mol. alginate. These data suggest that the dispersion of indomethacin in low mol. alginate causes a decrease of crystallinity and microcrystal size, and change of the crystal lattice and microcrystal shape (Alexander 1969), and that

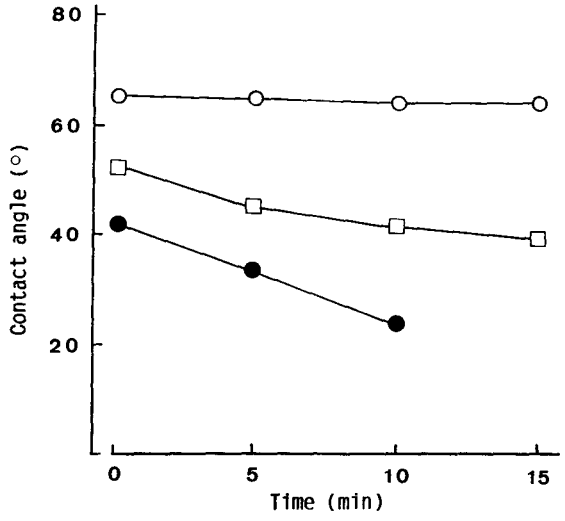

FIG. 3. Contact angle profiles of indomethacin and its low mol. alginate dispersions. ○, Indomethacin alone; ●, indomethacin-AL-I dispersion (1:2 w/w); □, indomethacin-AL-II dispersion (1:2 w/w).

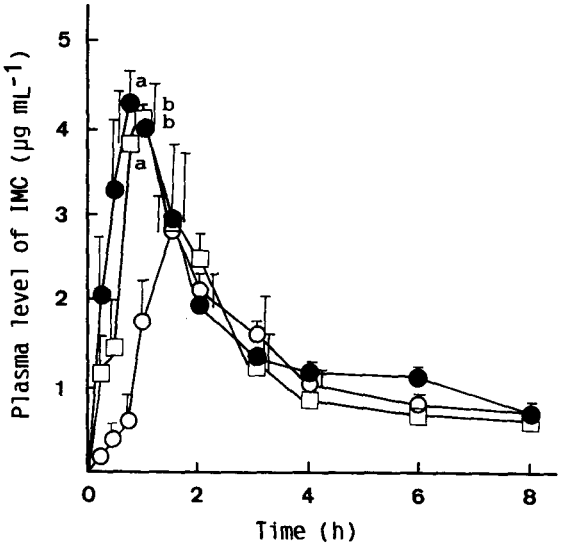

FIG. 4. Plasma levels of indomethacin after oral administration of indomethacin and its low mol. alginate dispersions (equivalent to 2 mg kg^{-1} indomethacin) to beagle dogs. ○, indomethacin alone; ●, indomethacin-AL-I dispersion (1:2 w/w); □, Indomethacin AL-II dispersion (1:2 w/w). Values represent the mean ± s.e. for 4 dogs. $^{a}P<0.01$ in the dispersion vs indomethacin alone, $^{b}P<0.05$ in the dispersion vs indomethacin alone.

indomethacin powder exists as separated crystals in the low mol. alginate dispersion. The decrease of crystallinity and crystal size of indomethacin in low mol. alginate dispersion may enhance dissolution rate. Recently, we reported that low mol. chitosan and low mol. alginate enhance the dissolution rate of drugs owing to the improvement of wettability (Shiraishi et al 1990). Thus, the effect of low mol. alginates on the wettability of indomethacin was examined. Fig. 3 shows the contact angle of the low mol. alginate dispersions and of indomethacin itself. The contact angle of indomethacin showed 65° initially, and was held at the same angle for 15 min. On the other hand, the contact angles of AL-I and AL-II dispersion were 41° and 53° initially, and significantly decreased with time; the enhanced dissolution rate of indomethacin by low mol. alginates may be due to the improvement of wettability and the decrease of the crystallinity and crystal size.

Table 2. The absorption rate constant (k_a), elimination rate constant (k_e) and area under the curve up to 8 h ($AUC_{0\text{-}8}$) after oral administration of indomethacin and its low mol. alginate dispersions (equivalent to 2 mg kg^{-1} indomethacin) to beagle dogs.

	k_a (h^{-1})	k_e (h^{-1})	$AUC_{0\text{-}8}$ ($\mu g\ mL^{-1} h$)
Indomethacin alone	0·77 ± 0·16	0·67 ± 0·11	9·44 ± 1·00
AL-I dispersion	2·14 ± 0·35*	0·98 ± 0·05*	13·00 ± 1·65
AL-II dispersion	1·41 ± 0·20*	1·01 ± 0·13*	10·65 ± 1·10

Values represent the mean ± s.e. for 4 dogs. *$P<0.05$ in the dispersion vs indomethacin alone.

In-vivo absorption studies

Low mol. alginate dispersions of indomethacin were expected to have good bioavailability after oral administration because of rapid dissolution rate. Absorption of indomethacin from its low mol. alginate dispersions was studied in beagle dogs and volunteers. Fig. 4 shows the mean indomethacin plasma concentrations after oral administration of indomethacin alone and its low mol. alginate dispersions to beagle dogs. After administration of indomethacin alone, indomethacin was absorbed slowly and the time to reach the maximum plasma concentration (t_{max}) was 1·5 h. For the low mol. alginate dispersions, the plasma concentrations rapidly increased, with the t_{max} values from AL-I and AL-II dispersions of 0·75 and 1·0 h, respectively. Moreover, the mean maximum plasma concentrations (C_{max}) from low mol. alginate dispersions were significantly higher than from indomethacin alone.

Table 2 lists the calculated pharmacokinetic parameters obtained from the plasma concentration profiles of indomethacin according to Fig. 4. The absorption rate constants (k_a) from each low mol. alginate dispersion were 2-3-fold greater than that from indomethacin alone. However, no statistically significant differences were recognized in the area under the plasma concentration-time curve ($AUC_{0\text{-}8}$). The absorption rates from the low mol. alginate dispersions were evaluated by means of a model-independent deconvolution method. Fig. 5 shows the profiles of the absorption rates calculated from the deconvolution of the plasma concentrations of indomethacin following intravenous injection and oral administration to beagle dogs. The absorption rate of indomethacin from its low mol. alginate dispersion was clearly higher than that of indomethacin alone in the initial absorption phase. The maximum absorption rates of AL-I, AL-II dispersions were observed at 0·38 and 0·63 h after oral administration, respectively, and the absorption of indomethacin from both low mol. alginate dispersions was almost complete at 1·75 h after administration. On the other hand, absorption rate from indomethacin alone reached its maximum at 0·88 h and the absorption was complete at 2·5 h. In addition, the maximum absorption rate from AL-I and AL-II dispersions were about 2·5-fold higher than that from indomethacin alone. These results indicate that the low mol.

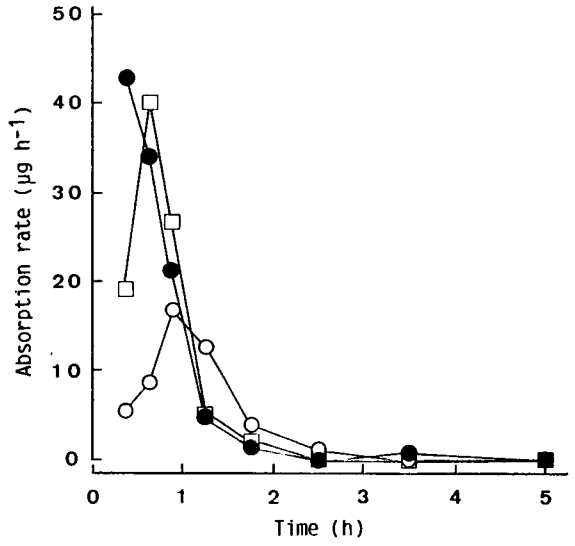

FIG. 5 Absorption rate profiles calculated from the deconvolution between the plasma concentration of indomethacin after intravenous injection of indomethacin and oral administration of its low mol. alginate dispersions to beagle dogs. ○, Indomethacin alone; ●, indomethacin-AL-I dispersion (1:2 w/w); □, indomethacin-AL-II dispersion (1:2 w/w).

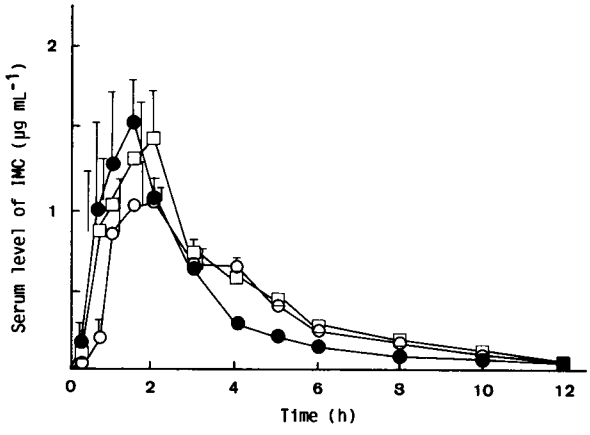

FIG. 6. Serum levels of indomethacin after oral administration of indomethacin and its low mol. alginate dispersions (equivalent to 0·4 mg kg^{-1} indomethacin) to volunteers. ○, indomethacin alone; ●, indomethacin-AL-I dispersion (1:2 w/w); □, Indomethacin-AL-II dispersion (1:2 w/w). Values represent the mean ± s.e. of 4 volunteers.

alginate dispersions enhanced the rate of bioavailability only in beagle dogs.

Fig. 6 and Table 3 show the mean indomethacin serum concentrations and pharmacokinetic parameters after oral administration of indomethacin and its low mol. alginate dispersion to volunteers. As expected from the results of animal experiments, absorption of indomethacin from both low mol. alginate dispersions exhibited more rapid absorption, compared with that from indomethacin alone. The k_a of AL-I and AL-II dispersions increased ~2·1- and 1·8-fold, respectively, in comparison with that from indomethacin alone. No statistically significant differences for AUC were found between administration of indomethacin alone and

Table 3. The absorption rate constant (k_a), elimination rate constant (k_e) and area under the curve up to 12 h ($AUC_{0\ 12}$) after oral administration of indomethacin and its low mol. alginate dispersions (equivalent to 0·4 mg kg^{-1} indomethacin) to volunteers.

	k_a (h^{-1})	k_e (h^{-1})	AUC_{0-12} ($\mu g\ mL^{-1}\ h$)
Indomethacin alone	0·85 ± 0·16	0·60 ± 0·09	4·33 ± 0·28
AL-I dispersion	1·78 ± 0·28*	0·83 ± 0·14	4·12 ± 0·18
AL-II dispersion	1·49 ± 0·20*	0·62 ± 0·13	4·97 ± 0·25

Values represent the mean ± s.e. for 4 volunteers. *$P < 0·05$ in the dispersion vs indomethacin alone.

low mol. alginate dispersions in volunteers. The maximum absorption rate according to the deconvolution method was exhibited at 0·8 h after administration of indomethacin alone, while it was at 0·5 h after administration of low mol. alginate dispersions (not shown). This indicates that indomethacin kneaded with low mol. alginates may enhance only the rate of bioavailability in volunteers, as well as in beagle dogs. These data suggest low mol. alginate is useful for enhancement of absorption rate of indomethacin.

Reduction of stomach irritation

It is well known that indomethacin, a non-steroidal anti-inflammatory agent, has a side effect of gastrointestinal irritation (Collier & Pain 1985). An erosion or ulcer occurs on gastric mucosa when indomethacin is given to rats (UD50 = 7·1 mg kg^{-1}) (Murakami et al 1988). Alginate has been clinically used as a haemostatic agent and protective agent for the mucous membrane of the upper-gastrointestinal tract. It is expected that indomethacin-induced ulcers would be reduced by low mol. alginates.

The frequency of occurrence of bleeding erosions in the stomach was 88% at 5 h and 75%, 7 h after administration of indomethacin alone and the ulcer index was 6·43 ± 1·24 and 5·73 ± 1·90 mm, respectively. On the other hand, the ulcer indices after administration of AL-I and AL-II kneaded mixtures were reduced remarkably in comparison with those of indomethacin alone, and were 2·04 ± 1·77 and 1·35 ± 0·72 mm, respectively, 5 h after administration. The frequency of occurrence of erosion was reduced to 50% for both AL-I and AL-II dispersions 5 h after administration. Furthermore, the ulcer index after administration of indomethacin with AL-II as a physical mixture was almost the same as that after AL-II dispersion.

It is known that indomethacin inhibits the synthesis of mucosal prostaglandin (PG) which protects the gastric mucosa by increasing mucosal blood flow (Cheung 1980), stimulating mucosal secretion and stabilizing the gastric mucosal cell (Miller 1983; Robert 1979), and consequently, the reduction of PG is accompanied by gastric lesions. Indomethacin directly enters the gastric mucosa during absorption (Frey & El-Sayed 1977) and later distributes to gastric mucosa from the systemic circulation, which causes the inhibition of mucosal PG synthesis. Thus, the shorter contact time of indomethacin with the gastric mucosa may decrease indomethacin-induced gastric lesions due to dispersal of indomethacin in the stomach by the low mol. alginate dispersion. However, the reduction of ulcer index of indomethacin by the physical mixture with AL-II without any

noticeable change in dissolution rate of the drug indicates that the alginate itself possesses some protective effect on stomach; alginate protects the gastric mucosa cell against hydrochloric acid or pepsin and increases gastric mucosa blood flow (Daigo et al 1981) and the reduction of ulcer index by low mol. alginate may be based on the protective effect of gastric mucosa and increasing gastric mucosal blood flow.

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