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Sustained release of indomethacin from chitosan granules in beagle dogs

SHOZO MIYAZAKI, HIDEKI YAMAGUCHI, CHIZUKO YOKOUCHI, MASAHIKO TAKADA, WEI-MIN HOU*. *Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University, Ishikari-Tohbetsu, Hokkaido 061-02, Japan and *Department of Dosage Form, Shanghai Institute of Pharmaceutical Industry, 1320 Beijing Road West, Shanghai, China*

Abstract—The potential of chitosan granules as an oral sustained-release dosage form of indomethacin has been compared with conventional capsules in beagle dogs. When a commercial capsule was administered orally, the plasma concentrations reached the maximum level in 30 min. The granules did not give a sharp peak to the plasma concentration, but produced a sustained plateau of the drug. This may be due to the slow rate of release and a longer residence time in the stomach. Thus, in terms of reducing the peak in plasma concentration and maintenance of drug concentration in plasma, the chitosan granules were superior to conventional capsules.

Chitin is a naturally occurring polymer of *N*-acetyl-D-glucosamine, and chitosan is easily prepared from the chitin of crabs and lobsters by *N*-deacetylation with alkali.

Recently, chitosan has been reported to have some useful applications in the pharmaceutical field. We have previously described the use of chitosan as a vehicle for sustained release preparations (Miyazaki et al 1981). It was useful for the preparation of granules exhibiting the sustained release of indomethacin (Hou et al 1985). A unique characteristic of the chitosan granules was that they gradually swelled and floated on acid medium (pH 1·2). A sustained release orally administered product was achieved by using a formulation that floats on the gastric medium (Sheth & Tossounian 1984). The floating property of the chitosan granules on the acid medium can be applied to the formulation of sustained release preparations of various drugs.

In the present study, an in-vivo study on indomethacin release after oral administration of a capsulated product containing the granules was investigated in beagle dogs.

Materials and methods

Materials. Chitosan, Flonac N for chromatography use, was kindly supplied by Kyowa Yushi Co., Tokyo, and used after being passed through 42 mesh screen. Indomethacin was obtained from Sigma Chemical Co., St Louis. Conventional indomethacin capsules were a product of Banyu Pharmaceutical Co., Tokyo.

Preparation of the chitosan granules. The chitosan granules containing indomethacin were prepared by the method of Hou et al (1985). Indomethacin was dissolved in 5 mL of methanol at 60°C and chitosan was added to the drug solution. After evaporation of the solvent at 60°C, the residue was dissolved in 10% acetic acid. The gelatinous chitosan-drug mixture was into a glass syringe, and extruded onto a glass plate. After drying overnight at room temperature (20°C), the chitosan gel cord was cut into pieces and dried for an additional 8 h at 80°C in a vacuum. The final granules were 0·5–0·7 mm in diameter and 1–3 mm in length. The drug-chitosan ratio was calculated from the weight of drug and chitosan used.

Correspondence to: Shozo Miyazki, Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University, Ishikari-Tohbetsu, Hokkaido 061-02, Japan.

Measurement of release rate. Drug release from the granules was determined by a JP XI dissolution apparatus. Method 1 (rotating basket method). The temperature was maintained at 37 ± 0·5°C. The drug concentration of the sample was determined with a spectrophotometer at 265 nm. All experiments were in triplicate and average values were plotted.

Animal experiment. Three male beagle dogs, 12–18 kg, were used under non-fasted conditions. Chitosan granules, equivalent to 50 mg of indomethacin, were encapsulated in hard gelatin capsules (JP-XI, no.0), and administered orally. Immediately after swallowing the capsule, the dogs were given 30 mL of water. Conventional commercial indomethacin capsules were used as a control and administered to dogs in a similar manner.

At given intervals, a 5 mL blood sample was taken from the forefoot vein. The plasma samples were separated by centrifugation and assayed for indomethacin using an HPLC technique (Skellern & Salole 1975) with slight modifications (Miyazaki et al 1986).

Results and discussion

The rate of drug release from the chitosan granules was measured for 6 h in pH 7·2 phosphate buffer–water (1:4) and compared with that of the commercial capsule (Fig. 1). To study

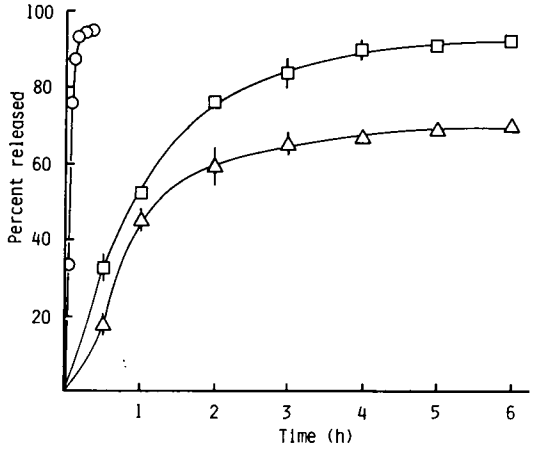

FIG. 1. Comparison of indomethacin release from chitosan granules and commercial capsules at 37°C: ○, commercial capsules; □, chitosan granules with 1:0·5 mixture; △ chitosan granules with 1:2 mixture.

the effect of chitosan content on the drug release kinetics, the release of indomethacin from the granules of different weight ratios of drug and chitosan (1:0·5 and 1:2) was measured. The release of indomethacin from the chitosan granules was slower than that from the commercial capsule. The effect of increasing the chitosan content in the granule was to cause a decrease in the release rate of drug. In contrast with the rapid release of indomethacin from the commercial capsule, sustained but almost complete release from the chitosan granules was observed in the 1:0·5 mixture. The in-vitro release of indomethacin from the chitosan granules with a 1:2 mixture continued for longer than the 6-day test period. The total amount of indomethacin released during the period was 95·4 and 71·3% of the dose for the granules with 1:0·5 and 1:2 mixture, respectively. The results indicate that the chitosan gels serve as a rate controlling barrier.

The potential of chitosan granules as an oral sustained release dosage form was studied by comparing the bioavailability parameters following oral administration of a conventional commercial capsule and the granule formulation with 1:0·5 and 1:2 mixture of drug and chitosan. Fig. 2 shows the mean plasma level profile of indomethacin obtained. Table 1 summarizes the parameters of bioavailability obtained from Fig. 1, where the area under the plasma concentration curve (AUC), up to 8 h post-administration, was calculated by moment analysis (Yamaoka et al 1981).

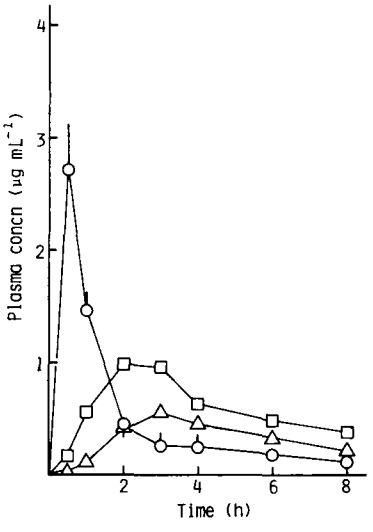

FIG. 2. Plasma concentration of indomethacin after oral administration to beagle dogs: key, see Fig. 1. Mean values and standard errors for 3 dogs are shown.

Table 1. Comparison of T_{max}, C_{max}, and AUC values between chitosan granules and commercial capsules in 3 non-fasted beagle dogs

Preparation	Drug-chitosan ratio	C_{max} ($\mu g\ mL^{-1}$) ±s.e.	T_{max} (h)	AUC[a] ($\mu g\ h\ mL^{-1}$) ±s.e.
Commercial capsules	—	2·72±0·41	0·5	4·00±0·36
Chitosan granules	1:0·5	1·04±0·05*	2–3	4·77±0·13
Chitosan granules	1:2	0·58±0·01**	2–3	2·70±0·15**

[a] Up to 8 h post-administration.
* Significantly different ($P < 0·02$) from the commercial capsule.
** Significantly different ($P < 0·05$) from the commercial capsule.

It was evident that there was a distinct difference in plasma concentration response between the commercial capsules and chitosan granules. The absorption of indomethacin from commercial capsules was rapid, and the mean maximum plasma concentration (C_{max}) was 2·72 $\mu g\ mL^{-1}$ at 0·5 h, which was higher than concentrations from the chitosan granules. Then indomethacin was eliminated rapidly from the plasma. On the other hand, the chitosan granules did not give a sharp peak of plasma concentration, but produced a sustained plateau. In the case of the granules with 1:2 mixture of drug and chitosan, a low and plateau plasma concentration of indomethacin was maintained for over 8 h. As shown in Table 1, however, the granule with 1:2 mixture is unfavourable because its AUC value was only 67% of the commercial capsules. This was probably due to the slow rate of release (see Fig. 1) and the gel-forming property of chitosan granules at low pH. The mean AUC value after administration of 1:0·5 mixture (4·77 $\mu g\ h\ mL^{-1}$) was slightly larger than that of the commercial capsule (4·00 $\mu g\ h\ mL^{-1}$). Therefore, no significant difference in the extent of bioavailability could be seen between the two. This indicated that chitosan granules composed of 1:0·5 mixture might be an effective sustained release preparation with good bioavailability. This may be due to the slow rate of release (Fig. 1) and the longer residence time in the stomach. Although the advantages of chitosan have been discussed elsewhere, one unique advantage of the granules is that they gradually swell and float on the acid medium at pH 1·2, as shown by Hou et al (1985). This ability may permit use of chitosan in the formulation of sustained release preparations of indomethacin.

In addition, chitosan granules have a gel-layer forming property in the low pH range, and chitosan has antacid and antiulcer activities (Hillyard et al 1964). These characteristics may be useful for preventing drug irritation in the stomach, since the clinical usefulness of indomethacin is restricted by gastrointestinal side effects.

These results suggest that sustained release chitosan granules containing indomethacin have potential as a method of drug delivery which prolongs drug action.

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