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Short Communications

Preliminary study on sustained-release particles prepared with hydrogenated soya phospholipid and cholesterol

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Summary

Granules prepared with hydrogenated soya phospholipid and cholesterol caused the sustained release of indomethacin in a medium of pH 6.8, and a release of apparent zero-order kinetics was observed. However, the release of indomethacin seemed to occur by the leaching mechanism, proposed by Higuchi (1963). In the scanning electron micrographs, holes on the granule surface were observed, and the numbers and size of these holes increased with immersion time. Thus, the increase of the volume of the infiltrated solvent into the matrix along with the immersion time may result in the release of indomethacin from the granules in zero-order kinetics.

Sustained-release formulation seems to be a plausible dosage form to avoid a transient high drug concentration in plasma and to maintain the effective drug concentration. There have been many efforts to develop the sustained release formulation (Chang et al., 1986). Osmotic pump system tablets of indomethacin are one example (Theeuwes, 1975).

Recently, we have reported the sustained release of sodium diclofenac from suppositories and tablets, which were prepared with hydrogenated soya phospholipids (Nishihata et al., 1985 and 1986; Nishihata, 1987). Administration of these dosage forms could avoid the transient high drug concentration and maintain the plasma drug concentration in healthy human subjects (Nishihata et al. 1986; Nishihata, 1987). It was supposed that release of drug from the suppository and the tablets seemed to occur by the leaching mechanism proposed by Higuchi (1963). According to the leaching mechanism, release of drugs from the formulation should be dependent on the solubility of drugs in the infiltrated solvent.

In the present study, we investigated the release of indomethacin from granules prepared with hydrogenated soya phospoholipids and cholesterol as diluents. Further, scanning electron micro-

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scopic study was performed to investigate the change of granule surface during release of drug.

Indomethacin was supplied by Sumitomo Pharmaceutical Industry (Osaka, Japan), and hydrogenated soya phospholipids (phospholipid), which was supplied by Nikko Chemicals Co. (Tokyo, Japan), contained 30% phosphatidylcholine and 70% phosphatidylethanolamine with iodine value was less than 3%. Cholesterol (99% grade) was obtained from Sigma (St. Louis, U.S.A.). Other reagents used were of analytical grade.

All constituents (0.50 g indomethacin, 4.75 g phospholipid and 4.75 g cholesterol) were dissolved in 250 ml of mixture of dichlorethan and trichloroethan (50% : 50%). After evaporation of organic solvent under reduced pressure, the residue was pulverized by mortar and pestle. The granules, 150–350 μm, were collected for the release study. The content of indomethacin in granules from 4 preparations was 50.5 ± 1.1 mg in 1 g of the granule ($n = 4$), which was measured after extraction with 0.001 N NaOH. Thus, the content of indomethacin in the granule in each preparation is reproducible. However, amounts of granules (150–350 μm) collected in each preparation were 68.5%, 66.2%, 64.7% and 59.1%; i.e., these low yields in the preparations are due to the process of pulverization.

About 0.5 g of granules containing 25 mg indomethacin was wrapped with polyethylene net (multitype polyethylene with pore size of about 10–30 μm, Kanebo Co., Osaka, Japan), and then immersed in 250 ml of 0.1 M sodium phosphate buffer (pH 6.8) under shaking at 50 cycles/min. Then, 200 μl aliquots were collected at designated time intervals through a Millipore filter (pore size: 0.45 μm).

Platinum coating on granules was performed to investigate the change of granule surface by using scanning electron microscopy (Hitachi S-800 type). After the release study granules were dried under reduced pressure before this study.

Assay of indomethacine was performed by using high-performance liquid chromatograpy (Yaginuma et al., 1981).

The complete dissolution of 25 mg of indomethacin powder in 250 ml of the buffer was observed within 2 h (Fig. 1A). The release of indomethacin from the test granules delayed significantly and occurred apparently in zero-order kinetics for 2–32 h. Indomethacin was released in about 75% at 32 h.

When the amounts of indomethacin released were plotted against the square root of time (h), a good straight line was obtained up to about 16 h. However, the release obtained of a later stage was greater than that expected from the solid straight line in Fig. 1B.

In terms of the release of indomethacin from the granules during the first 16 h, it may be considered that the release occurs by a leaching mechanism, proposed by Higuchi (1963), with the following equations:

$$Q = kt^{1/2} \tag{1}$$

$$Q' = SQ \tag{2}$$

$$k = (ADC_s i/j)^{1/2} \tag{3}$$

Where Q = the amount of drug released after time t per unit of exposed area; Q' = the amount of drug released after time t from the granule containing 25 mg of indomethacin; S = the total surface area of granules; A = the total amount of drug in the matrix per unit volume; D = the diffusivity of drug in the infiltrated solvent; C_s = the solubility of drug in the infiltrated solvent; i = the porosity of the matrix and j = the tortuosity factor of the capillary system. The k may be an apparent total control factor for the release of drug from formulation.

In the scanning electron micrographs of granules, changes of the exposed surface of granules were observed by the immersion of granule in the buffer. After the immersion, holes had appeared on the granule surface, and the numbers and size of holes increased with immersion time (compare Fig. 2B with Fig. 2C; although scanning electron micrographs at 16 h and 24 h were also investigated, the micrograph exhibited holes on the surface which were larger than those at 8 h and smaller than those at 32 h). These results seem to indicate that both the porosity, relating to the volume of the infiltrated solvent, and the tortuos-

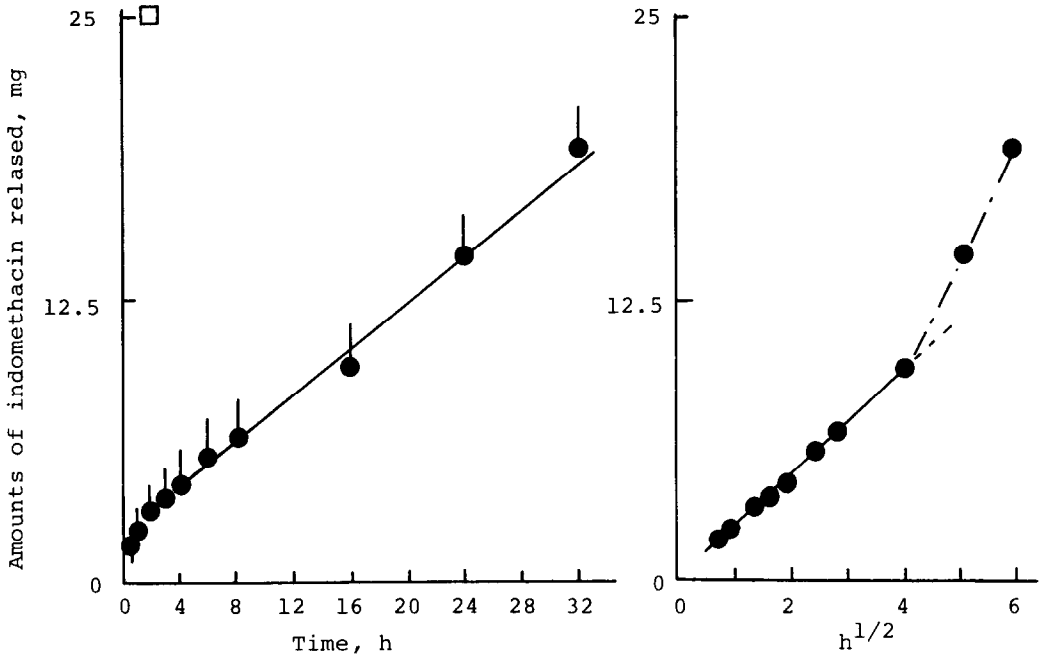

Fig. 1. Release of indomethacin from granules prepared with hydrogenated soya phospholipid and cholesterol (closed circles). The symbol of open square represents the dissolution of indomethacin powder in the buffer. The amount of indomethacin used was 25 mg. A: profile of the amounts released against time (h). The slope is 0.514 ± 0.023 ($r > 0.990$). B: profile of the amounts released against the square root of time (h). The slope shown in the solid line was $8.6 + 1.1$ ($r > 0.992$). Each value represents the mean $\pm$ S.D. ($n = 4$).

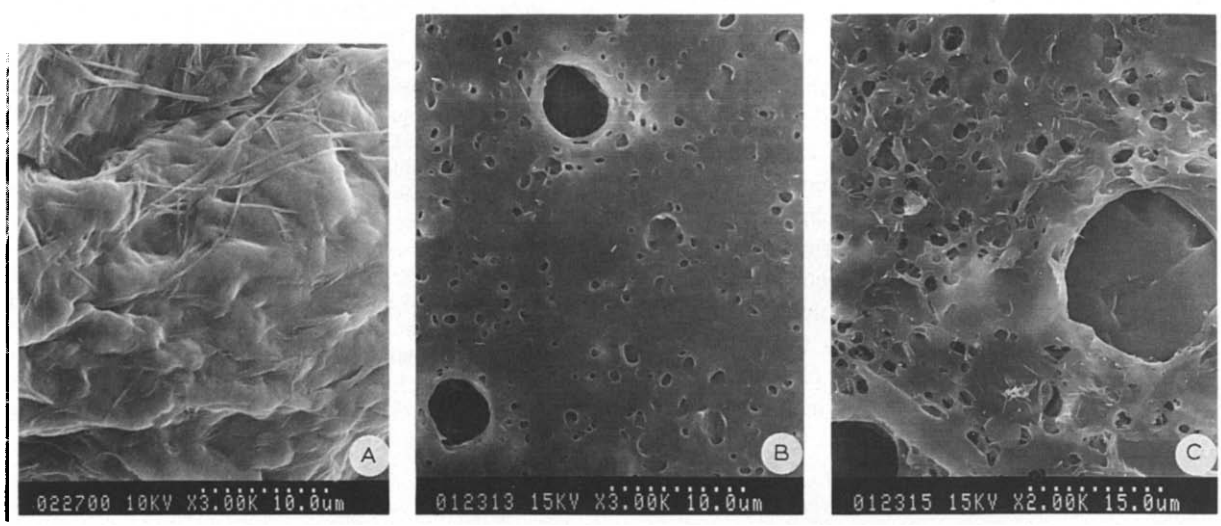

Fig. 2. Scanning electron micrographs of the granule surface. A: the surface after rinsing with ethanol for 1 min to remove the small particles adsorbing on the granule surface. B: the surface 8 h after the immersion in the buffer. C: the surface 32 h after the immersion in the buffer.

ity in the matrix changed during the immersion in the buffer; i.e., the value of i/j in Eqn. 3 increases by the increase of numbers and size of holes in the matrix, and with immersion time.

From findings obtained in the present study, it is considered that the release of indomethacin from the test granules occurs by the leaching system mechanism. But the value of i/j in equation 3 increases along with the immersion time; i.e., the increase of the value may occur slowly in an early stage but is accelerated after about 16 h. Since it has been reported (Nishihata et al., 1987) that gel formation of phospholipid in the buffer was observed, marked characteristic changes of the granule matrix may occur after a long immersion time. Thus, the increase of the value of i/j with a long immersion time causes the release of indomethacin in an apparent zero-order kinetic. It is difficult to estimate the degree of porosity from the present study with only a single prescription of granule. But it is estimated that apparent value of i/j after 16 h is about 2 times greater than that up to 16 h (slopes in Fig. 1B).

Since the appearance of holes on the granule surface was also observed in granules which did not contain indomethacin (data not shown), appearance of these holes occurs when the solvent (the buffer) infiltrates into the matrix, probably through the phospholipid layer. Since it has been reported that phospholipids as surfactant can hydrate in spite of the poor solubility (Lunberg et al., 1978) and gel formation of phospholipids in the buffer was observed (Nishihata et al., 1987), part of the phospholipid in the matrix may be rinsed out by the infiltrated solvent, resulting in the holes. Because the phospholipids used are cationic as described in the experimental section, the release profile may be changed in the acidic medium. However, the low solubility of indomethacin in the acidic medium should delay a release of indomethacin. Thus, to characterize the phospholipid–cholesterol granule in the release of drug in media of various pH, a neutral compound should be employed as the model compound. Although release of indomethacin from the matrix is also involved in the change of the value of i/j in Eqn. 3, a phospholipid in the matrix seems to promote the appearance of these holes.

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