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Simple formulation of sustained-release tablets of sodium diclofenac and examination in humans

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Summary

The sustained-release tablet of sodium diclofenac (SR-tablet) was prepared simply by mixing sodium diclofenac with hydrogenated soya lecithin without any other additive. The dissolution of sodium diclofenac from the SR-tablet occurred in an apparent zero-order kinetics process with 90% release at 24 h. The human subjects to whom the SR-tablet was administered excreted diclofenac in urine gradually up to 24 h. However, they excreted diclofenac rapidly and no more excretion of diclofenac was observed 9 h after administration of the conventional tablets.

Introduction

Drugs with narrow ranges between effective and toxic plasma concentrations may require a sustained-release (SR) formulation to avoid transient high drug concentrations in plasma. Recently it has been reported that addition of lecithin to a triglyceride base could control the release of sodium diclofenac from the suppository (Nishihata et al., 1985, 1986). Since lecithin can hydrate (Lundberg et al., 1978), the mechanism of drug release might be dependent on the infiltration of water into the suppository matrix; i.e. the infiltration of water was regulated by the content of lecithin. Thus, lecithin, which can form the infiltration route of water by its ability of hydration, seems to be an effective substance to form a SR vehicle. Since natural soya lecithin is liquid in form, addition of a solid substance with a high melting point such as a triglyceride is required to form the solid vehicle. However, hydrogenated soya lecithin, in powdered form, seems to be useful to prepare the solid vehicle without any concomitants.

In the present research, the release of sodium diclofenac from a SR tablet prepared with hydrogenated soya lecithin was examined. The absorption of sodium diclofenac in humans was also investigated by following the urinary excretion of diclofenac, after administration of a SR tablet and a conventional tablet of sodium diclofenac.

Materials and Methods

Materials

Sodium diclofenac and hydrogenated soya

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lecithin (lecithin) were supplied from Ciba Geigy Japan (Takarazuka, Japan) and Nikko Chemicals (Tokyo, Japan), respectively. Particle size for both substances were less than 74 μm. Conventional tablets of sodium diclofenac, with 25 mg of sodium diclofenac in a tablet (Ciba Gaigy) were obtained commercially. Other reagents used were of analytical grade.

Preparation of SR tablet

Four g sodium diclofenac and 16 g lecithin were mixed well. Ethanol was then added to the mixture to obtain a paste by mixing thoroughly after each addition. After drying the paste under reduced pressure, the solid mass obtained was pulverized with a mortar and pestle. Granules of 149–350 μm were collected to produce the SR tablet. The SR tablets produced, 8 mm in diameter with 3 mm thickness, weighed 251.2 ± 2.4 mg ($n = 52$) and contained 52.3 ± 1.1 mg sodium diclofenac per tablet ($n = 20$).

In vitro dissolution study

A SR tablet (or two conventional tablets) wrapped with gauze was immersed in 200 ml sodium phosphate buffer (0.1 M, pH 6.8) in a beaker kept at 37 °C. The beaker was shaken at 100 rpm and a 100 μl aliquot was collected through a Milipore filter (pore diameter 0.45 μm) at designated times. In another experiment, a SR tablet wrapped with gauze was immersed first in 0.01 N HC for 1 h and then immersed in the phosphate buffer.

Human study

Three healthy male human subjects after a breakfast at 07.00 h were employed. As a breakfast, 270 g boiled rice and 200 ml hot water were given. After administration of each tablet at 08.00 h urine was collected at the designated time to measure the diclofenac excreted.

Assay

The assay of diclofenac was carried out using the high-performance liquid chromatographic method described by Yaginima et al. (1981) with minor changes; i.e. 0.01 M citrate buffer (pH 5.5) was used instead of 0.01 M phosphate buffer (pH 7.0) to delay the retention time for complete separation of diclofenac from urine. The detection limit was 0.04 μg/ml with a coefficient of variation of 5.1%, and the correlation coefficient of the calibration curve (0.04 μg/ml to 1 μg/ml) was more than 0.99.

Results and Discussion

The dissolution of sodium diclofenac from the conventional tablet in phosphate buffer pH 6.8 (0.1 M) occurred rapidly with 100% dissolution within 5 h (Fig. 1A). However, the dissolution of sodium diclofenac from the SR tablet occurred slowly in an apparent zero-order kinetics from 2 h (15% dissolution) to 20 h (90% dissolution). As shown in Fig. 1B, the amounts of sodium diclofenac dissolved from the SR tablet also showed the good linearity when plotted against square root of time up to 8 h. Even with naked-eye observation, SR-tablets were clearly disintegrated gradually from 8 h after the immersion. Thus, the dissolution of sodium diclofenac from the SR tablet up to 8 h seems to occur dominantly by the leaching mechanism which was suggested by Higuchi (1963). However, the dissolution profile of sodium diclofenac after 8 h seems to change along with an increase of surface area of the matrix resulting by disintegration. Thus, the observed apparent zero-order kinetics of diclofenac dissolution from the SR tablet may be due to complex mechanisms of a leaching system and disintegration; i.e. a gradual disintegration of the SR tablet accelerated the dissolution of diclofenac along with an increase of surface area. Since a disintegration of the tablet seemed to occur for the most part after 8 h, a dissolution of diclofenac from the SR tablet was accelerated gradually especially after 8 h, resulting in an apparent zero order kinetics process. The immersion of the SR tablet in acidic solution released diclofenac only slightly, due to its low solubility in acidic solution. The dissolution of sodium diclofenac from the SR tablet in the phosphate buffer (pH 6.8) was not affected by the pretreatment with acidic solution for 1 h.

After administration of two conventional tablets at a dose of 50 mg sodium diclofenac to human subjects, fast excretion of diclofenac in urine up to

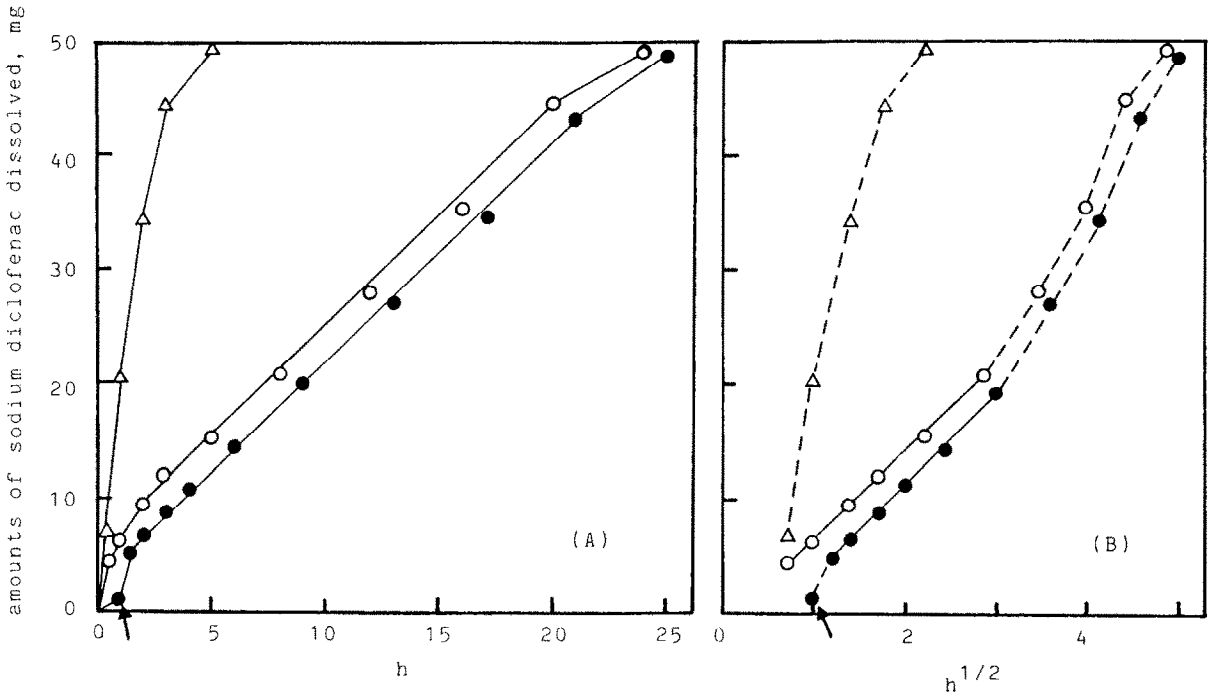

Fig. 1. Dissolution of sodium diclofenac from conventional tablets (△) and SR tablets (○ and ●) in phosphate buffer, pH 6.8 (0.1 M) and at 37 °C in (A). Closed circles represent the amount of sodium diclofenac dissolved in the buffer after treatment with 0.1 N HCl for 1 h; the arrow indicates the solvent changing time. B: Amounts of sodium diclofenac dissolved against the square root of time. (The regression for the square root plot with solid lines was as follows: open circles, $y = 8.7x - 8.1$, $r = 0.972$; and closed circles, $y = 7.9x - 4.2$, $r = 0.986$). Each value represents the mean of 3 experiments, and the standard error of each value was less than 5% of the mean.

5 h was observed and then the excretion slowed down (Fig. 2). The administration of one SR-tablet at a dose of 50 mg sodium diclofenac resulted in a slow excretion of diclofenac and its cumulative amounts increased up to 24 h.

The total excreted amounts of diclofenac in urine were 0.599 ± 0.035 mg ($n = 3$) after administration of the conventional tablets and 0.530 ± 0.056 mg after administration of the SR tablet ($n = 3$, no significant difference against conventional tablet, student's t-test). Thus, relative bioavailabilities of sodium diclofenac after administration of the SR tablet and conventional tablet seem to be similar. In the previous study (Nishihata et al., 1986), we investigated the relationship between plasma diclofenac excretion in humans after suppository administration. It was observed that the urinary excretion of diclofenac occurred relative to the plasma concentration of diclofenac at each time after an administration (Nishihata et al.,

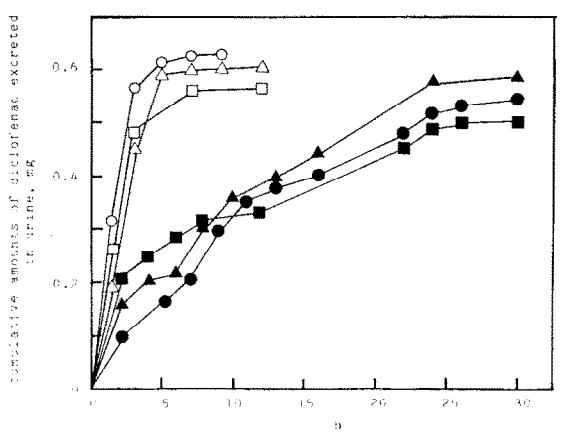

Fig. 2. Urinary excretion of diclofenac in 3 healthy human volunteers after administration of conventional tablets (open symbols) or SR tablets (closed symbols). The subject with circle symbols was a 37-year-old male weighing 73 kg; the subject with triangle symbols was a 25-year-old male weighing 58 kg; the subject with square symbols was a 34-year-old male weighing 62 kg.

1986); greater excretion of diclofenac was observed during a period when plasma diclofenac concentration was higher. In brief, when a SR suppository of sodium diclofenac was administered, a slow increase of plasma diclofenac concentration and a slow excretion of diclofenac in urine were observed, along with an avoidance of transient high diclofenac concentrations in plasma. Thus, the slow cumulative excretion profile of diclofenac after the administration of a SR tablet seems to indicate that the administration of a SR tablet avoid the transient high diclofenac concentration in plasma and maintains the diclofenac in plasma for a long time.

In an in vitro dissolution study, 90% dissolution of diclofenac was observed at 3 h for a conventional tablet and at 20 h for SR tablets. On the other hand, in an in vivo absorption study, 90% of total urinary excretion of diclofenac was observed at 3–5 h for conventional tablets and at about 20 h for SR tablets. It is advisable that the urinary excretion should be observed during some periods even after complete absorption, according to the half life of drugs. These observations seem to indicate that the dissolution profiles obtained in a present in vitro study is slower than those expected from urinary excretion of diclofenac after the administration. In spite of the above problem, the method of an in vitro dissolution study for SR tablets seems to be useful to dissolution rates among various tablets.

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