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In-vitro and In-vivo Studies of the Diclofenac Sodium Controlled-release Matrix Tablets

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Abstract

Controlled release matrix tablets for diclofenac sodium were developed in this study.

Five matrix-tablet formulations were prepared by granulating two viscosity grades of HPMC (hydroxylpropylmethylcellulose) in varying ratios with water in the planetary mixer. The in-vitro dissolution tests indicate that all five matrix formulations prolong the release of diclofenac sodium. The main factors controlling drug release were the HPMC viscosity grade and the amount of HPMC used. The larger the amount of high viscosity grade HPMC used, the slower the resultant release rate of diclofenac sodium. There was no significant degradation of diclofenac sodium or change in drug release rate in any of the five formulations during a three-month period of stability testing. The sustained release ability of four formulations was further demonstrated in an in-vivo study in six healthy subjects.

There were in-vitro/in-vivo correlations between C_{max}, AUC_{0-14}, and the time for 50 or 80% drug to be released.

The research of controlled-release dosage forms is an important field in pharmaceutics. Diclofenac sodium is one of a class of non-steroidal drugs which has as potent an anti-inflammatory, analgesic and antipyretic action as indomethacin. Diclofenac sodium is a phenylacetic acid derivative with a pK_a value of 4·0. As a result, diclofenac sodium is practically insoluble in acidic solution but dissolves in intestinal fluid and water. It is generally known that diclofenac sodium migrates into blood within 30 min and reaches the maximum blood concentration (C_{max}) within 1·5 to 2·5 h following oral administration of a 50 mg enteric coated tablet. The maximum average concentration in blood is between 0·7 and 1·5 mg L^{-1}. The oral bioavailability is around 60% with an excretion half-life of between 1·1 and 1·8 h (Todd & Sorkin 1988). The benefits of administering diclofenac sodium in a controlled release way have been demonstrated (Fowler et al 1983). Vyas et al (1989) used a high viscosity grade of hydroxypropylmethylcellulose (HPMC, 1000 and 1500 cP s) to prepare matrix tablets by a dry granulation method. Bain et al (1991) employed low-viscosity grade HPMC (15 cP s) and cetostearyl alcohol as matrix materials to produce the tablets by direct compression. Romero et al (1991) utilized polyvinyl chloride with ethylcellulose as the controlling matrix. Wilder et al (1991) filled Eudragit RL and cellulose acetophthalate-coated pellets into hard gelatin capsules. Hydrogel beads of diclofenac sodium have been studied in healthy humans by Thakker et al (1992). A long-acting diclofenac sodium preparation produced by enteric coating tablets with a mixture of methacrylic acid copolymer S and glycerin fatty acid ester was reported by Sawayanagi & Otani (1990). Voltaren SR, a commercial product of diclofenac sodium manufactured by Ciba-Geigy, is a hydrophobic matrix tablet consisting of a cetyl alcohol matrix.

HPMC is the material most widely used as the matrix to control drug release. The influence of technological variables on drug release from HPMC matrices has been reviewed by Vazquez et al (1992). However, due to the poor flow of the powder blend, it is common to use less desirable methods such as direct die-filling or double compression. Wet-granulation with water as a simple binding aid has not been employed, probably because of the tendency of HPMC to gel and form lumps in the presence of water. In previous studies (Liu 1992; Liu et al 1993), it was shown that HPMC granules suitable for compression into matrix tablets could be produced by spraying the powder blend with water and granulating in the planetary mixer. Employing the same granulation process in this study, the combination of high and low viscosity grades of HPMC at various ratios was used as the matrix base to prepare diclofenac sodium sustained-release tablets. Both in-vitro dissolution tests and in-vivo pharmacokinetic studies were performed to evaluate the control characteristics of these matrix tablets.

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Materials and Methods

Materials

Diclofenac sodium (lot no. 0100951) was obtained from Yung Shin Pharm. Co. (Taiwan, Republic of China). Two viscosity grades of hydroxypropylmethylcellulose (HPMC, Metolose 60-SH, 50 and 4000 cP s) were supplied by Shin-Etsu Chem. Co. (Tokyo, Japan). All other reagents were analytical or pharmaceutical grade.

Preparation and characterization of matrix tablets

The two grades of HPMC (Total 375 g) at five different ratios (Table 1) were mixed with 375 g diclofenac sodium in a planetary mixer (KitchenAid, Model K45SS). While stirring, water was added using a spray system (nozzle size 0·012 inches). After the measured amount of water (approx. 120 mL) was added, the wet granules were discharged and tray-dried for 12 h at 50°C in a hot air oven. All granule batches had Loss On Drying values of less than 2% (measured with an Ohaus moisture determination balance, model MB-200). The dried granules were passed through a No. 20 mesh screen, then thoroughly mixed with 1% Aerosil-200 and 0·5% magnesium stearate. Tablets were compressed using a rotary tableting machine (Jenn-Chiang Machinery Co., Ltd, Feng-Yuan, Taiwan) with 9-mm flat round punches. A constant compression force was obtained by using the same distance between the upper and lower punches. Each tablet contained 100 mg diclofenac sodium. Three batches were prepared for each formulation.

The weight variation of the tablets was evaluated on 20 tablets using an electronic balance (Sartorius, Type 1801). Tablet hardness was obtained on 10 tablets using a hardness tester (Erweka, TBH 28). Friability was determined on 10 tablets in a Roche friabilator for 5 min at a speed of 25 rev min^{-1}. The thickness of the tablets was measured on 10 tablets with a Vernier Caliper (made by Mitutoyo, Japan).

Dissolution studies

The USP paddle method (USP XXII) was used to measure the dissolution rate of diclofenac sodium from HPMC matrix tablets at 37°C. The dissolution of drug was conducted in a medium of changing pH by starting with a tablet in 500 mL water for 1 h. Then 400 mL phosphate buffer was added to raise the pH to 6·8. The phosphate buffer was prepared by dissolving 17·1 g $Na_3PO_4 \cdot 12H_2O$ and 5·6 mL concentrated HCl in 400 mL water and adjusting the pH to 6·8 ± 0·1 with HCl or NaOH solution if necessary. The stirring speed was set at 100 rev min^{-1}. At predetermined time intervals up to 24 h, a 5 mL sample was withdrawn and replaced with fresh dissolution medium. After the appropriate dilution, the sample solution was analysed for diclofenac sodium by UV absorbance at 276 nm. Cumulative percentage of drug release was calculated and the mean of six tablets was used in data analysis.

Stability study

A stability test was conducted by storing tablets in amber bottles at ambient temperature, 31, 37 and 43°C. (The relative humidity was controlled at 75%, except at ambient temperature.) The content of diclofenac sodium and the dissolution of drug from tablets were tested monthly for three months. The assay of diclofenac sodium and the dissolution study followed the same procedure as previously described.

In-vivo study

Six healthy male volunteers with a mean age of 23·8 ± 1·5 years (ranging from 22 to 26 years), a mean body weight of 70·5 ± 9·9 kg (ranging from 60 to 83 kg), and a mean height of 175·5 ± 7·2 cm (ranging from 167 to 185 cm) were included in this cross-over study. Their health was confirmed by physical examination, medical history and clinical laboratory tests. All subjects were free from other drugs before and during the study. Only four formulations of diclofenac sodium (R1, R3, R4 and R5) were tested in random order. R2 was excluded as it had a similar dissolution rate to that of R1. A one-week wash-out period was employed between each treatment. All doses were administered with 200 mL water in the morning following at least a 10-h overnight fasting period. Blood samples were obtained from the forearm veins at 0, 0·5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 and 24 h after dosing. Plasma was separated immediately and stored at −20°C until assay.

Assay method

The concentration of diclofenac in plasma samples was determined by a modified HPLC method (Said & Sharaf 1981). A Hitachi HPLC system with Linear 206 PHD detector was used. The chromatographic conditions were: column, Nucleosil C-18, 3·9 mm × 15 cm; mobile phase, acetonitrile : 0·01 M potassium dihydrogen phosphate (pH 6·3) = 35 : 65 v/v; flow rate, 1·0 mL min^{-1}; internal standard, mefenamic acid. A wavelength of 278 nm was used to monitor the drug and the diclofenac to mefenamic acid peak-area ratio was taken as the basis of quantification. The sensitivity of this method was 10 ng mL^{-1}. The accuracy of the analysis was checked daily using samples to which had been added known amounts of analyte, and both the

Table 1. Components and physical properties of diclofenac sodium matrix tablets.

Formulations	R1	R2	R3	R4	R5
Components					
Diclofenac sodium	375·0[a]	375·0	375·0	375·0	375·0
HPMC (4000 cP s)	375·0	281·3	187·5	93·7	0·0
HPMC (50 cP s)	0·0	93·7	187·5	281·3	375·0
Properties[b]					
Weight (mg)	206·6 ± 3·8[c]	209·7 ± 3·3	205·6 ± 4·8	205·5 ± 4·8	207·7 ± 2·3
Hardness (Kp)	7·2 ± 1·0	8·4 ± 1·3	5·6 ± 1·0	6·1 ± 1·2	7·2 ± 1·3
Friability (%)	−0·1 ± 0·8	−0·6 ± 0·1	−0·8 ± 0·9	−0·4 ± 0·7	−0·4 ± 0·1
Thickness (mm)	3·97 ± 0·03	3·97 ± 0·04	3·97 ± 0·03	3·98 ± 0·05	3·99 ± 0·08

[a]Unit = g, [b]average of three batches, [c]mean ± s.d.

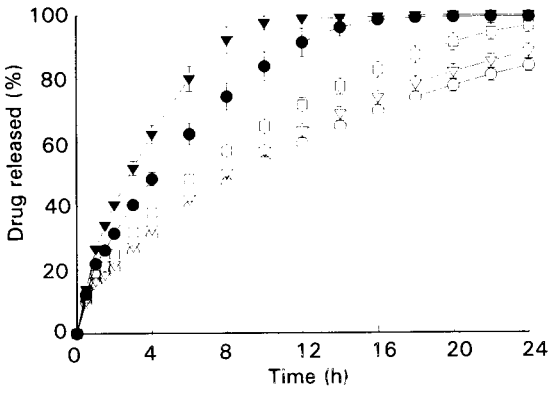

FIG. 1. Dissolution profiles of diclofenac sodium from five different matrix tablets prepared by mixing viscosity grades of HPMC. ○ R1, ▽ R2, □ R3, ● R4, ▼ R5.

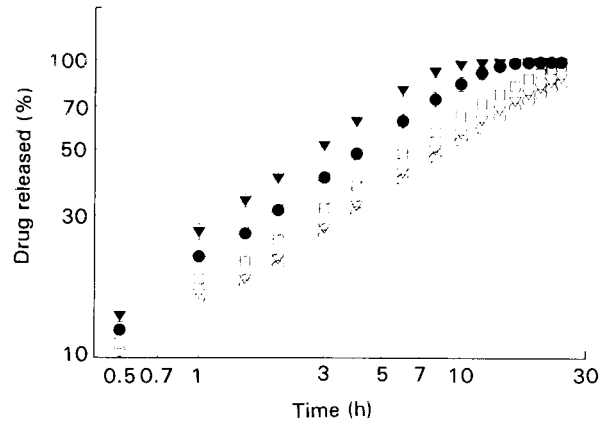

FIG. 2. Release of diclofenac sodium from five different matrix tablets. ○ R1, ▽ R2, □ R3, ● R4, ▼ R5.

intra-day and inter-day variations (standard error) were found to be less than 6%.

Data analysis

The pharmacokinetic parameters, including the area under the plasma drug concentration–time curve (AUC), clearance (CL/F), and mean residence time (MRT = AUMC/AUC), were evaluated by the LAGRAN-P computer program (Version 2.01, edited by Linyee Shum, Department of Pharmaceutics, SUNY at Buffalo). The peak concentrations (C_{max}) and times to peak concentration (t_{max}) were obtained from the observed values. Differences in pharmacokinetic parameters were tested statistically using one-way analysis of variance and Tukey's multiple range test ($\alpha = 0{\cdot}05$).

Results and Discussion

Physical characterization of the matrix tablets

Tablet hardness, friability, thickness and weight variation of the prepared tablets are listed in Table 1. The weight variations of all matrix tablets were satisfactory due to good granule flowability for all the formulations. The tablet hardness values ranged from 5·6 ± 1·0 to 8·4 ± 1·3 Kp for R3 and R2, respectively. The friability of these matrix tablets was extremely low, indicating that the wet-granulation method is an acceptable technique for producing HPMC granules suitable for preparing matrix tablets.

Dissolution tests

Since diclofenac sodium has a pK_a value of 4, the solubility in acidic medium such as gastric juice is extremely low (Sheu et al 1992). Furthermore, drugs are usually taken with water during an in-vivo study. For this reason, the dissolution studies were conducted in water for the first hour. Thereafter, the pH of the dissolution medium was titrated to pH 6·8 by adding an adequate volume of phosphate buffer solution. Plots of the percent drug released vs time for the five matrix tablet formulations are shown in Fig. 1. Apparently, the release rate of diclofenac sodium is mainly controlled by the polymer viscosity. Specifically, the drug release rate is inversely proportional to the quantity of the higher viscosity polymer. Although compressing tablets at different compression forces gives different hardness, compression force usually has little influence on drug release from the HPMC matrix (Vazquez et al 1992). Likewise, tablet hardness shows minimal effect on drug release in our study. Basically, drug released from these types of systems results from hydration of the HPMC, which forms a gelatinous barrier through which drugs must diffuse. In addition, the resistance of such a gel layer is controlled by the viscosity grade of the HPMC. In this case, decreasing HPMC 4000 in the formulation would increase the release rate of diclofenac sodium.

Swelling and erosion of HPMC matrix may have occurred during dissolution; however, the release rates (% h^{-1}) were

Table 2. Values of kinetic constant (K), release exponent (n), and correlation coefficient (r) for the five matrix formulations.

Formulations	R1	R2	R3	R4	R5
K (% h^{-n})	1·1578	1·1828	1·2400	1·3252	1·4240
n	0·5650	0·5644	0·5653	0·5967	0·6085
r^2	0·9965	0·9961	0·9971	0·9983	0·9999
T50 (h)	10·8	8·1	7·0	5·2	3·4

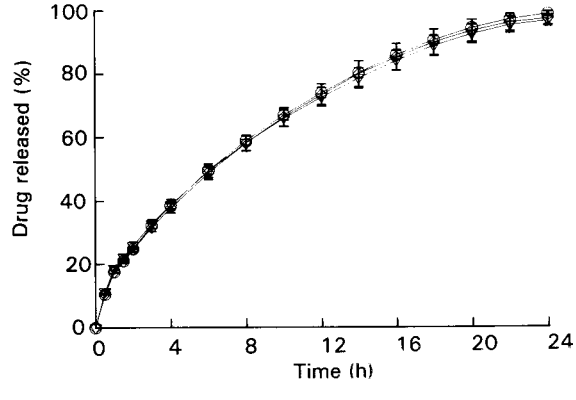

FIG. 3. Dissolution profiles of diclofenac sodium from the matrix formulations of R3 stored at 37°C for ◇ 0, ○ 1 and ▽ 3 months.

Table 3. Pharmacokinetic parameters for six volunteers after a single oral dose of four matrix formulations.

Parameters	R1	R3	R4	R5	F Value
t_{max} (h)	3·3 ± 0·8	3·5 ± 1·4	4·7 ± 3·0	4·0 ± 1·1	0·67
C_{max} (ng mL^{-1})	259·2 ± 112·6	318·7 ± 106·9	302·2 ± 87·3	354·8 ± 68·7	0·91
AUC_{0-14} (ng h mL^{-1})	1411·4 ± 664·7	1771·0 ± 524·9	2171·5 ± 496·6	2190·1 ± 456·6	2·81
CL/F (mL h^{-1})	81·6 ± 36·1	57·8 ± 20·2	44·6 ± 8·7	45·6 ± 8·3	3·84*
MRT (h)	6·0 ± 1·2	6·9 ± 0·6	7·6 ± 1·0	6·3 ± 0·8	3·43*

Mean ± s.d., *P < 0·05 (F = 3·10).

further analysed based on a simple and effective method proposed by Ritger & Peppas (1987) to elucidate the possible release mechanism. This was calculated by using the dissolution data after 1 h to those values less than or equal to 60%, and fitting this data with equation 1. The plots of log percent released vs log time are shown in Fig. 2,

$$M_t/M_\infty = Kt^n \quad (1)$$

where M_t/M_∞ is the fraction of drug released at time t, K is the release-rate constant incorporating structural and geometric characteristics of the tablets, and n is the diffusional exponent indicative of release mechanism. The value of n for a cylinder is <0·45 for Fickian release, >0·45 and <0·89 for non-Fickian release, 0·89 for case II release and >0·89 for super II type release. The values of K, n and correlation coefficient (r) obtained from the dissolution data of the matrix tablets are given in Table 2. The times for 50% drug released (T50) for all formulations are also listed in Table 2. The values of n for these five tablet formulations ranged from 0·5650 to 0·6085, indicating a release mechanism very close to non-Fickian type when considering the shape of the matrix tablet to be cylindrical. The release rate of diclofenac sodium from the formulation R1 is the slowest with a K value of 1·157% $h^{-0.565}$ and a T50 value of 10·8 h, whereas the formulation R5 is the fastest with a K value of 1·424 $h^{-0.6085}$ and a T50 value of 3·4 h.

Lot reproducibility and stability test

Three batches of each formulation were prepared and the dissolution rate of the drug was evaluated under the same conditions. The resulting release profiles of diclofenac sodium from three different batches of each matrix formulation were constructed, but showed no significant difference among the release profiles for each set of three batches, indicating that this manufacturing process is reliable and reproducible.

The stability of diclofenac sodium in these matrix tablets was examined over three months. There was insignificant diclofenac sodium degradation in the five formulations of matrix tablets (Fig. 3). Apparently, the release of drug from the matrix tablets does not change after storage at an elevated temperature for this period of time, suggesting that diclofenac sodium is stable in the HPMC matrices, and the controlled-release ability of these matrix tablets is not influenced by the temperature range tested.

In-vivo studies

Table 3 summarizes the C_{max}, t_{max}, AUC and MRT values obtained from the in-vivo study of four tablet formulations including R1, R3, R4 and R5. Due to the closeness of the dissolution rate of R2 to both R1 and R3, R2 was excluded from this in-vivo study. The average plasma concentration vs time profiles are illustrated in Fig. 4. All four formulations demonstrate the prolongation of diclofenac sodium plasma concentrations to more than 14 h, indicating that the therapeutic effect of diclofenac sodium could be extended to a longer period of time.

By comparing the C_{max} and AUC_{0-14} with the in-vitro dissolution data of these four formulations, it was found that the slowest releasing formulation (R1) gave the lowest C_{max} and the least extent of absorption (AUC_{0-14}). In contrast, the fastest dissolver (R5) resulted in the highest C_{max} and AUC_{0-14}. However, the t_{max} values for these four formulations were similar. The results of the statistical analysis of various parameters using one-way analysis of variance are shown in Table 3; no significant differences were found in the values of C_{max}, t_{max} or AUC among these formulations, probably because the sample size is too small to detect any smaller but significant difference.

According to Thakker et al (1992), the AUC, C_{max} and t_{max} following administration of a hydrogel bead capsule containing 150 mg diclofenac sodium in the fasted state was 2511·3 ± 94·1 ng h mL^{-1}, 502·3 ± 216·0 ng mL^{-1} and 1·85 ± 0·96 h, respectively. In our study, R5 shows the fastest dissolution rate of diclofenac sodium, but the AUC (2190·1 ± 456·6) and C_{max} (354·8 ± 68·7) were comparable with the values obtained by Thakker et al (1992) after dose adjustment.

Plasma profiles showed multiple peaks for all subjects taking four different matrix formulations. This phenomenon has been investigated and thoroughly discussed by Chan

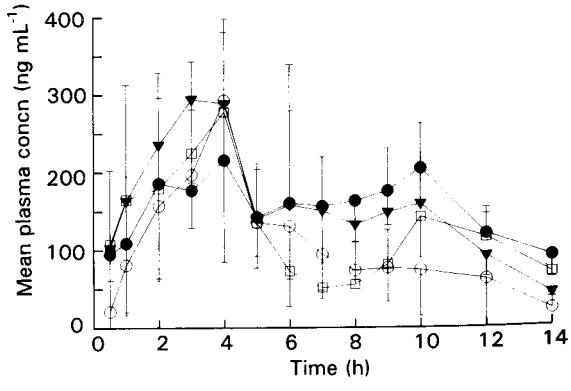

FIG. 4. Average plasma concentration profiles of diclofenac sodium after oral administration of four different matrix tablets. ○ R1, □ R3, ● R4, ▼ R5.

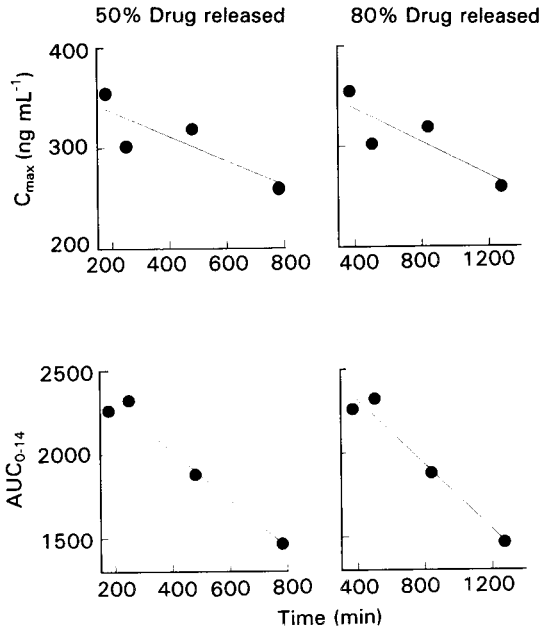

FIG. 5. In-vitro and in-vivo correlations of C_{max}, AUC_{0-14}, and the time for 50 or 80% drug release.

et al (1990), who concluded that when sustained-release formulations of diclofenac sodium were administered under fasting conditions, irregular patterns and multiple peaks with rapid onset and no lag time in the plasma profile were observed. However, a single peak with 2-h or 4-h lag time was observed when administering the drug with breakfast. We also observed this phenomenon, and suggest it might be due to the significant solubility difference of diclofenac sodium in gastric acid and either the intestinal fluid or the water taken with the tablet. Thus, depending on the ability of gastric acid to change the pH value of drinking water and on the time of emptying of the sustained release tablet core, irregular patterns and multiple peaks would be detected in the plasma profiles under fasting conditions.

In-vitro/in-vivo correlations

Due to multiple peaks in the plasma profiles, it was not easy to obtain accurate in-vivo dissolution rate profiles, which would be more appropriate for correlations of in-vitro parameters. Therefore, the attempts to relate in-vitro dissolution data and in-vivo parameters were tried. An inverse correlation was observed between C_{max} and the time for 50 ($r = 0{\cdot}86$) or 80% ($r = 0{\cdot}88$) of the drug to be dissolved. Also, the AUC_{0-14} is inversely correlated with the time for 50 ($r = 0{\cdot}99$) or 80% ($r = 0{\cdot}99$) of the drug to be dissolved. These results indicate that the dissolution process is the rate-limiting step during drug absorption. The appearance of the early peak in the plasma profiles may be due to that part of the drug released in the water which was taken with the tablets (Chan et al 1990). Therefore, the amount of drug in this portion, which in turn determines the value of C_{max}, depends on how fast the drug is released from the matrix tablet into the water. The dissolution test employed in this study was conducted in water for the first hour, and then the pH of the medium was brought to the intestinal pH and maintained for 24 h. It is expected that the faster the drug is released in water, the higher the peak plasma concentration. As a result, both the time for 50 and 80% drug release can be correlated with C_{max}, as shown in Fig. 5. Likewise, a correlation between AUC_{0-14} with the time for 50 or 80% of the drug to dissolve would be expected. From these correlations, controlled-release matrix formulations of diclofenac sodium could be designed to exhibit satisfactory controlled-release characteristics.

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