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Dissolution of diclofenac sodium from matrix tablets

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Summary

Several parameters were studied for their effect on the dissolution of diclofenac sodium from Voltaren SR and hydroxypropylmethylcellulose (HPMC) based matrix tablets. The results indicate that addition of sodium or potassium chloride to the dissolution medium decreases the solubility of the drug and slows the dissolution rate, with the effect of sodium chloride being greater. The dissolution of the drug was studied in a medium which simulates the changing pH of the pathway followed by the drug as it passes from the stomach to the intestine. Dissolution was found to be inversely related to the rate at which the pH was changed. This may be caused by the deposition of an insoluble drug layer when contact is made with an acid medium. When higher viscosity grades of HPMC are used, slower release rates result. Drug release from Voltaren SR is best described as non-Fickian in an aqueous medium irrespective of whether salt is added; however, a zero-order dependence became evident in pH-changing media. The release of diclofenac sodium from the hydrophilic HPMC matrices follows a non-Fickian transport in all media.

Introduction

The release of drugs from a hydrophilic matrix can depend on several factors such as both the rate and extent of moisture penetration, and the rate of gelation, dissolution and erosion (Bamba et al., 1979). HPMCs are cellulose ethers frequently used in controlled release oral delivery systems. Hogan (1989) thoroughly reviewed the use of HPMC in pharmaceuticals. According to Ford et al. (1985a–c), the most important factor affecting the rate of release from such matrices is the drug/HPMC ratio. The aforementioned researchers considered the effect of compressional force to be minor, and stated that the drug particle size was important only in the case of insoluble drugs, e.g., indomethacin. In another study, Ford et al. (1987) investigated the effects of soluble (lactose) and insoluble (calcium phosphate) diluents and tablet shape on the dissolution of promethazine HCl. Shah et al. (1989) reported the use of a special HPMC that results in a bimodal release pattern.

In spite of all the efforts directed at the use of HPMC, the effect of pH on release rates has largely been ignored. However, the influence of

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pH cannot be disregarded. Pagay (1988) determined that nearly 40% of a weakly basic drug was released from HPMC within the first hour, Doherty et al. (1989) demonstrated the effects of microenvironmental pH on dissolution, and Wilder et al. (1991) reported that the release of diclofenac sodium from controlled release preparations is strongly dependent on the medium used. This paper reports on the effects of the media (salts and changing pH) on the release rate of diclofenac sodium from Voltaren SR and from two different viscosity-grade HPMC matrices.

Materials and Methods

Raw material of diclofenac sodium was obtained from Yong-Shin Pharmaceuticals (Taiwan, R.O.C.) and Voltaren SR (MFD 04881) is a commercially available sustained release product of Ciba Geigy (Switzerland). Standard samples of diclofenac sodium and HPMC (100 cps, no. H-9262, lot 87F-1048; 4000 cps, no. H-7509, lot 117F-0582) were supplied by Sigma. All other reagents were analytical grade and the water used was deionized by reverse osmosis.

Preparation of HPMC matrix tablets

A wet granulation method was used to prepare HPMC tablets containing diclofenac sodium. Diclofenac sodium and HPMC were mixed and passed through a no. 40-mesh siever. The material was placed in a Hobart mixer. Water was sprayed gradually onto the mixture until granules of satisfactory size for tableting had been formed. The granules were dried in an oven at 60 ° C for 2 h, passed through a no. 20-mesh siever, and then mixed with magnesium stearate for 5 min in a plastic bag. A rotary tableting machine with 9 mm flat round punches was used to compress the tablets with a hardness of about 8 kg. Both 100 and 4000 cps grades of HPMC K series were used.

Dissolution studies

The USP paddle method was used to measure dissolution rates at 37 ° C. A 5 ml sample was withdrawn and replaced with fresh medium at fixed time intervals. The sample was diluted and its diclofenac sodium content was determined from the absorbance at 276 nm. The cumulative fraction of drug released was calculated, and the mean value for six tablets was used in analyzing the data. In evaluating the effect of salts (NaCl and KCl) on dissolution rate, a total of 900 ml of deionized water, containing the corresponding salt (pH 5), was used and stirred at a rate of 50 rpm.

Studies in changing pH medium

Dissolution of tablets was performed in a changing-pH medium. One tablet was placed in 600 ml of 0.1 N HCl and five 40-ml volumes of 0.2 N trisodium phosphate were added at equal time intervals over a 2, 3, or 4 h period. One of six dissolution vessels was run simultaneously with the same trisodium phosphate addition schedule, but with no tablet present. The medium in this vessel was used to replace that of the other vessels when samples were withdrawn for analysis. In these studies, the mean of five tablets was used in data analysis. The effect of two stirring rates (50 and 100 rpm) was examined.

Solubility measurement

Excess drug was dispersed in a jacketted beaker (37 ° C) containing a particular dissolution medium. The medium with a specific pH was prepared by mixing 0.1 N HCl solution (pH 1.08) with an appropriate volume of 0.2 N trisodium phosphate solution. The media containing three concentrations (0.5, 1.0 and 1.5% w/v) of either sodium or potassium chloride were dispersed by dissolving the appropriate amount of the corresponding salt in deionized water. The dispersions were stirred at 300 rpm and samples of the supernatant were withdrawn at 12, 24, and 36 h for analysis. Drug concentrations were measured by UV absorbance (276 nm) after dilution of the samples, and the mean value for triplicate samples was used in data analysis.

Results and Discussion

Regulations regarding bioequivalence and bioavailability promulgated by the FDA in 1977

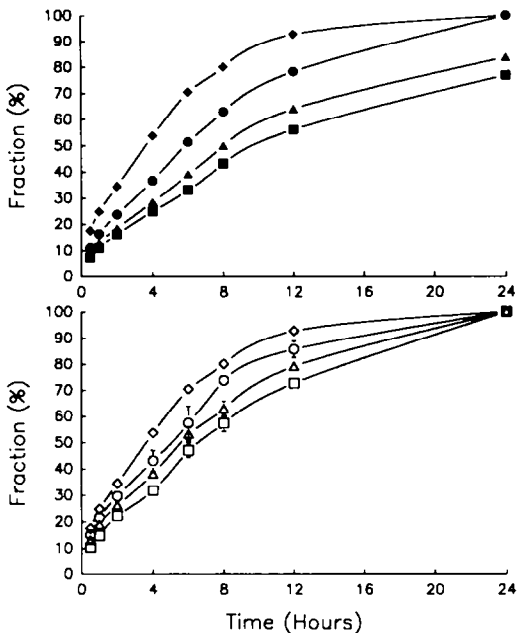

Fig. 1. Cumulative fraction of diclofenac sodium released from Voltaren SR matrix tablets as a function of time at 37 °C using different dissolution media containing deionized water and either sodium chloride or potassium chloride, each at three different concentrations. (Upper panel) (◆——◆) H_2O alone; with NaCl at (●——●) 0.5%, (▲——▲) 1.0%, and (■——■) 1.5%; (lower panel) (◇——◇) H_2O alone; with KCl at (○——○) 0.5%, (△——△) 1.0%, and (□——□) 1.5%.

(Anonymous) have stimulated an interest in establishing an in vivo/in vitro correlation for drugs in delivery systems. This often results in the attempt to identify a discriminating dissolution methodology for a drug in a solid dosage form. This study was designed to provide baseline parameters upon which a dissolution test that simulates the in vivo environment could be developed.

Effect of electrolytes on dissolution

The solubility of a drug has a major impact on the rate of solution. When the rate of accumulation of diclofenac sodium was measured in the tablets made with Voltaren SR using dissolution media containing either NaCl or KCl, the rate of solution was found to be inversely proportional to the salt content (Fig. 1) with sodium chloride having a greater effect. When the solubility of

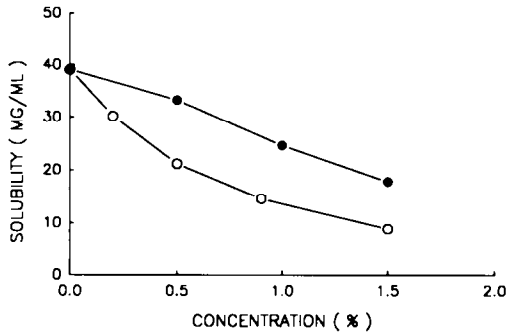

Fig. 2. Solubility (mg/ml) of diclofenac sodium at 37 °C as a function of concentration of (○——○) NaCl and (●——●) KCl.

diclofenac sodium was measured in the presence of these salts, the solubility decreased as the salt concentration was increased. Sodium chloride, again, demonstrated a greater effect (Fig. 2). A similar effect by KCl on the solubility of triamcinolone has been reported (Block et al., 1973). Parrott and co-workers (1955) examined the solubility of benzoic acid in the presence of salts and dextrose, using the empirical Setschenow equation to linearize the observed effect:

$$\log(S_0/S) = KC \qquad (1)$$

where S_0 denotes the solubility of a non-electrolyte in pure solvent, S is the solubility in the presence of an electrolyte at concentration C, and K represents a 'salting-out' coefficient. Application of this approach to diclofenac sodium

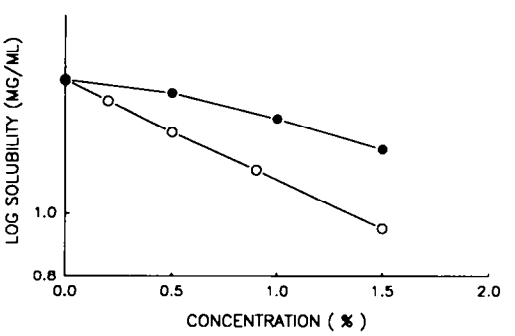

Fig. 3. Setschenow plot (see text) of the relationship between solubility and salt concentration for diclofenac sodium at 37 °C. (○——○) NaCl, (●——●) KCl.

TABLE 1

Solubility of diclofenac acid and its sodium salt in water at 37 °C and different pH values

pH	Acid form		Salt form	
	(Mean/ml)	S.D.	(Mean/ml)	S.D.
1.08	3.55 μg	0.27		
2.50	3.78 μg	0.81		
6.27			14.70 mg	0.31
7.50			26.06 mg	0.32
H_2O	11.59 μg	0.55	39.09 mg	0.62

Adjustment of pH refers to the description in Materials and Methods.

resulted in the data shown in Fig. 3. Although good linearity is observed for NaCl, and to a lesser extent for KCl, the use of Eqn 1 is not appropriate because diclofenac sodium is a salt. However, the equation does provide a way to determine semi-quantitatively the salt effect. On the other hand, further suppression on the solubility of diclofenac sodium by a common ion effect due to Na^+ would be operative, resulting in a slower dissolution rate compared to that of potassium chloride.

Effect of pH on dissolution

The solubility of diclofenac sodium ($pK_a = 4.0$) is markedly dependent on pH (Table 1). Its rate of solution from a tablet matrix will therefore depend on the pH of the medium. As a tablet passes from the stomach into the intestine, it encounters a change in pH from about 1 to 7. Consequently, the residence time of the tablet in a particular hydrogen ion environment affects the availability of the drug from the tablet. In order to simulate the in vivo environment, experiments were run using a pH-changing medium. Fig. 4 illustrates the effect on the total accumulation of diclofenac sodium in solution from Voltaren SR matrices when acid is neutralized over a 2, 3, or 4 h period: the slower the rate of neutralization, the lower the overall accumulation over time. The reproducibility of the method used to produce a pH-changing environment has been validated. A 3 : 1 final volume of acid to base regardless of the total volume results in a pH of approx. 7. Fig. 4 indicates that even at a rate of neutralization occurring over a 2 h period (the shortest simulated residence time in the stomach), almost no drug is in solution. These observations suggest that a precipitate formed on or in the matrix.

Effect of stirring rate in changing pH medium studies

Fig. 5 shows that doubling the stirring rate from 50 to 100 rpm has only a slight effect on the rate of accumulation of the drug in solution. Statistical differences do not appear evident and the small differences observed in the dissolution rate at stirring rates of 50 and 100 rpm are not likely to translate into significant bioavailability sequelae.

Effect of HPMC matrix on availability

A successful hydrophilic matrix system requires a polymeric substance that will wet and hydrate rapidly to form a gelatinous barrier. The rate of release is likely to depend on permeation through the barrier for water-soluble drugs, and on erosion of the matrix for water-insoluble drugs. In either case, the viscosity of the preparation is important. In this study, three formulations were made (Table 2) using the two viscosity grades of HPMC in the K series (100 and 4000 cps) that

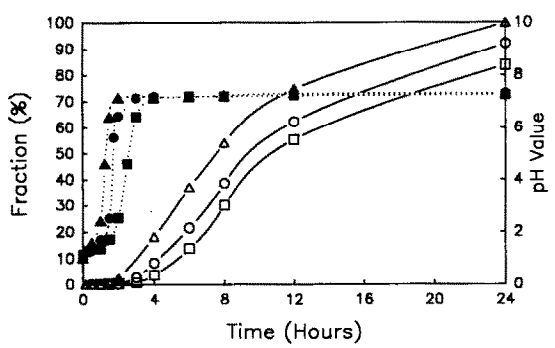

Fig. 4. Cumulative fraction of diclofenac sodium released (left *y*-axis) from Voltaren SR matrix tablets as a function of time at 37 °C using dissolution media where the pH was changed at three different rates over a period of (△ ——— △) 2 h, (○ ——— ○) 3 h, and (□ ——— □) 4 h. Filled symbols refer to the time dependence for the pH changes (right y-axis) over the same periods of (▲ ····· ▲) 2 h, (● ····· ●) 3 h, and (■ ····· ■) 4 h.

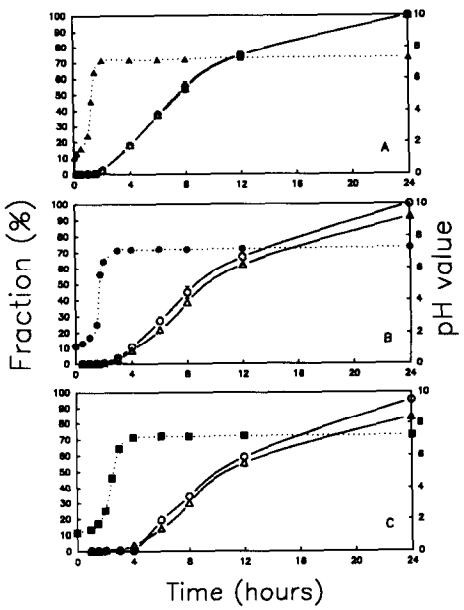

Fig. 5. Effect of stirring rate [stirring rate in all three panels: (△——△) 50 rpm and (○——○) 100 rpm] on the cumulative fraction of diclofenac sodium released (left y-axis) from Voltaren SR matrix tablets as a function of time at 37 °C using a dissolution medium where the pH was changed at three different rates over a period of: (A) 2 h, (B) 3 h, and (C) 4 h. Filled symbols refer to the time dependence for the pH changes (right y-axis) corresponding to each of the above rates: (▲·····▲) 2 h, (●·····●) 3 h, and (■·····■) 4 h.

had the fastest hydration rates. Fig. 6 shows the effect of the various formulations and that of Voltaren SR on the rate of drug release into a pH-changing system. As expected, the higher the viscosity grade, the slower the release rate.

TABLE 2

Composition of the tablets used to form hydrophilic matrices of HPMC

	Formulation		
	F_1	F_2	F_3
Diclofenac sodium (mg)	100	100	100
HPMC K100LV [a,c] (mg)	195	97.5	–
HPMC K4M [b,c] (mg)	–	97.5	195
Mg stearate (mg)	5	5	5

[a] Nominal viscosity 2% in water 100 (type 2208).
[b] Nominal viscosity 2% in water 4000 (type 2208).
[c] Methoxyl 19–24%; hydroxypropyl 7–12%.

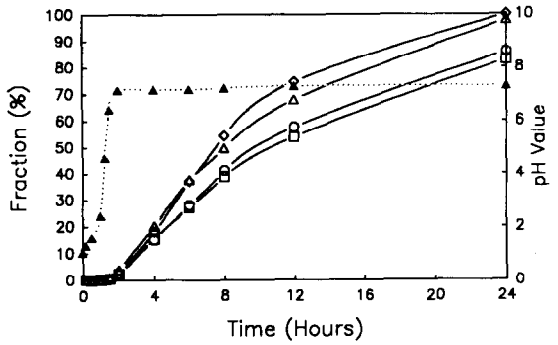

Fig. 6. Cumulative fraction of diclofenac sodium released (left y-axis) from different formulations using 100 and 4000 cps HPMC as defined in Table 2 and from a Voltaren SR matrix tablet as a function of time at 37 °C into a dissolution medium where the pH was changed over a 2 h period. (◇——◇) Voltaren SR, (△——△) F_1, (○——○) F_2, (□——□) F_3. The filled symbols (▲·····▲) show the time dependence for the pH change (right y-axis).

Voltaren SR, containing cetyl alcohol which is relatively hydrophobic, reacts similarly to the low-viscosity HPMC formulation. This may be due to the type of medium used in which the residence of the tablets, at an initially low pH, may cause precipitation of the drug at the surface of the tablet.

Characterizing release mechanism

A simple release equation (Eqn 2) was proposed by Ritger and Peppas (1987b) to describe the relative availability of drugs from matrix systems:

$$M_t/M_0 = Kt^n \qquad (2)$$

where M_t corresponds to the amount of drug released in time t, M_0 is the total amount of drug released after infinite time, K denotes a constant and n is a number ranging from 0.5 to 1 which indicates the type of release mechanism. Eqn 2 can be used with systems that swell, provided the swelling does not exceed 25% (Ritger and Peppas, 1987b), and the approach can be modified to analyze coupled diffusion/relaxation systems (Peppas and Sahlin, 1989). When this equation is applied to the first 60% release of diclofenac sodium from Voltaren SR into aqueous media, the value for n is 0.53; when applied to the first

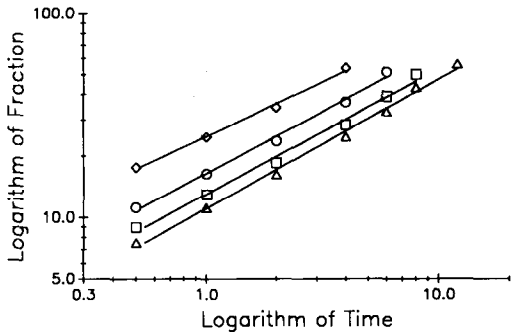

Fig. 7. A log-log plot of Eqn. 2 for the fractional release of diclofenac sodium as a function of time at 37 °C from a Voltaren SR matrix into deionized wate [(◇———◇), n = 0.53] and water containing three different concentrations of sodium chloride: NaCl present at (○———○) 0.5%, n = 0.60; (□———□) 1.0%, n = 0.61, and (△———△) 1.5%, n = 0.63.

60% of saline media of varying concentration, n takes on a value from 0.53 to 0.63 (Fig. 7 and Table 3). The drug's release into water and into solutions of low KCl concentration follows a nearly Fickian path. As the salt concentration increases, the release becomes even more non-Fickian. The effect of NaCl on increasing the value of n is greater than that of KCl, paralleling the results observed in the solubility studies. Whether or not this is due to the precipitation of drug on the tablet matrix remains speculative. A decrease in the intercept (log K) of the log-log plots, as shown in Fig. 7 (Table 3), is a reflection of the decrease in release rates with increasing salt concentration of the dissolution media. Treating the data under the assumption of coupled diffusion/relaxation mechanism was inconclusive.

TABLE 3

Exponent (n), intercept (log K) and correlation coefficient (r^2) found using Eqn 2 for the release of diclofenac sodium from Voltaren SR matrices into water and two salt solutions at different concentrations at 37 ° C and pH = 5

Concentration (%)	Log K	n	r^2
KCl			
0.5	1.329 ± 0.009 [a]	0.527 ± 0.019	0.996
1.0	1.272 ± 0.013	0.548 ± 0.027	0.993
1.5	1.178 ± 0.017	0.613 ± 0.029	0.991
NaCl			
0.5	1.126 ± 0.013	0.605 ± 0.026	0.996
1.0	1.113 ± 0.016	0.612 ± 0.028	0.992
1.5	1.043 ± 0.014	0.633 ± 0.021	0.995
H_2O	1.396 ± 0.009	0.533 ± 0.025	0.998

[a] Estimate ± S.E.

TABLE 4

Exponent (n), intercept (log K) and correlation coefficient (r^2) found using Eqn 2 for the release of diclofenac sodium from Voltaren SR and three HPMC formulations (Table 2) into a medium of changing pH at 37 ° C

	Formulation			Voltaren
	F_1	F_2	F_3	
log K	1.066 ± 0.033 [a]	0.943 ± 0.029	0.965 ± 0.022	0.960 ± 0.014
n	0.823 ± 0.055	0.835 ± 0.041	0.780 ± 0.031	1.002 ± 0.023
r^2	0.995	0.995	0.997	0.999

[a] Estimate ± S.E.

Table 4 demonstrates the results obtained when the logarithmic form of Eqn 2 was used to treat the data for the release rates observed beyond the initial lag phase into changing-pH systems. The release from the HPMC and Voltaren SR matrices is non-Fickian, and attempts to treat the release as a coupled diffusion/relaxation process were unsuccessful. Release from Voltaren SR is essentially a zero-order process. It is difficult to conclude that a relationship exists between the release rate and the viscosity of the matrix material when comparing the intercept values of the log-log plots (Table 4).

Conclusions

A quantification of the release of diclofenac sodium from both hydrophilic and hydrophobic matrix tablets is dependent on closely defining the type of release media used. Release is dependent on the concentration of salt in the medium, and both the relative rate and the mechanism are affected. The release of the drug into a system

which simulates the pH changes occurring in vivo during the passage of the drug from stomach to intestine shows a significant lag initially, during which time no drug appears in solution. The lag phase persists well beyond the time that the acid condition has become neutralized. This strongly suggests the occurrence of some kind of precipitation, since the phenomenon is observed in both hydrophilic and hydrophobic matrices and the solubility of the drug is significantly affected by both salt and hydrogen ion concentrations. Both the rate and the release mechanism, as analyzed by semi-empirical approaches, change as the dissolution medium changes.

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