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RESEARCH PAPER

Studies on Controlled-Release Formulations of Diclofenac Sodium

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ABSTRACT

The effects of various polymers on the release of diclofenac sodium from their matrices have been evaluated. In vitro release profiles of diclofenac sodium from ethylcellulose and hydroxypropylmethylcellulose (HPMC) K4M matrices showed that decreasing the concentration of ethylcellulose and increasing the concentration of HPMC K4M resulted in an increase in the release rate of diclofenac sodium. An increase in the amount of lactose in matrix resulted in an increase in the release rate of diclofenac sodium. It is suggested that the use of ethylcellulose or Precirol containing relatively large percentage concentrations of lactose in matrices will not provide zero-order release of diclofenac sodium from matrices. The best-fit release kinetics with the highest correlation coefficients was achieved with the Higuchi's plot followed by the zero-order. A straight line relationship was established between the $T_{50\%}$ and the ratio of HPMC K4M to diclofenac sodium.

INTRODUCTION

Diclofenac sodium is a nonsteroidal anti-inflammatory agent useful in the treatment of rheumatic disorders. Due to its rapid elimination, a sustained-release dosage form that would maintain therapeutic diclofenac blood concentration for a longer period of time is desirable. The matrix system also appears to be a very attractive approach from process development and scale-up points of view (1). The use of polymers in controlling the release of drugs has become important in the formulation of pharmaceuticals.

Hydroxypropylmethylcelluloses (HPMC) are cellulose ethers that can be used as the basis for hydrophilic ma-

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trices for controlled-release oral delivery. Prolonged release from HPMC matrices has been described from which it was concluded that a gelatinous layer, formed when the polymer hydrated on contact with water, controlled the release of drugs by two mechanisms. Water-soluble drugs were released by diffusion out of the gelatinous layer and by erosion of the gel, whereas poorly soluble drugs were released solely by erosion (2).

The rate of release through hydrogel matrices is governed by the rate and extent of swelling of the polymer; consequently, ionic strength and pH value of the surrounding medium affect the release rates from such matrices (3). Hydrophobic polymers do not have these drawbacks and have been used widely for fabrication of controlled-release matrices (4).

The aim of this study is to attempt to achieve a zero-order release of diclofenac sodium from matrices containing hydrophobic polymers (ethylcellulose and Precirol) and a hydrophilic polymer (HPMC K4M), and to determine under which circumstances and to what extent the polymer-to-drug ratio could be of assistance in controlling drug release.

MATERIALS AND METHODS

Materials

Diclofenac sodium (Chemo S.A., Switzerland), HPMC K4M (Dow Chemicals) polyvinylpyrolidone (PVP) with molecular weight of 35,000 (Merck, Germany), Precirol (Gattefosses, France), and ethylcellulose (EC) 10 cP (Dow Chemical) were used.

Methods

Formulation of Diclofenac Sodium Matrices Using EC, Precirol, or HPMC K4M

Diclofenac sodium matrices were produced by mixing diclofenac sodium with lactose, PVP, and ethylcellulose, granulating with the ethanol, then passing the mixture through a no. 14 sieve. The sieved fractions were dried in an oven for 2 hr. The granules were sieved again and mixed with magnesium stearate for 5 min. The granules were compressed on a 10-mm punch and die using a single-punch machine (formulations F1, F2, F3, F4, and F5).

Formulations F6 and F7 were prepared by mixing diclofenac sodium with lactose, PVP, and Precirol, granulating with water, then passing the mixture through a no. 14 sieve. The sieved fractions were dried in an oven for one day, and then made into tablets as mentioned.

Formulations F8, F9, F10, F11, F12, and F13 were prepared in a similar manner to formulations F6 and F7, and Precirol was replaced by HPMC K4M (Table 1).

Dissolution Studies

The USP basket method was used for all the in vitro dissolution studies. In this method distilled water con-

Table 1

The Different Formulations of Diclofenac Sodium Matrices and their Composition (%)

Formulation Code	Matrix Composition						
	DNA[a]	EC[b]	Precirol	HPMC	Lactose	PVP	MgS[c]
F1	25	21.5	—	—	50	2	1
F2	39.2	37.2	—	—	18.6	3	2
F3	55	40	—	—	—	3.5	1.5
F4	50	45	—	—	—	3.5	1.5
F5	45	50	—	—	—	3.5	1.5
F6	38	—	38	—	18	4	2
F7	50	—	45	—	—	3.5	1.5
F8	55	—	—	40	—	3.5	1.5
F9	50	—	—	45	—	3.5	1.5
F10	45	—	—	50	—	3.5	1.5
F11	45	—	—	52	—	2.5	0.5
F12	40	—	—	55	—	3.5	1.5
F13	37	—	—	60	—	2.5	0.5

[a]Diclofenac sodium.
[b]Ethylcellulose.
[c]Magnesium stearate.

taining 0.02% polysorbate 80 (Tween 80), which simulated gastric fluid (pH 1.2), and intestinal fluid (pH 6.8) without enzyme were used as dissolution media. The rate of stirring was 100 ± 4 rpm. The amount of diclofenac sodium was 100 mg in all formulations with the exception of F1. The matrices were placed in 900 ml of gastric fluid and maintained at 37 ± 0.1 °C for 2 hr. At appropriate intervals, 5 ml of each sample was taken and filtered through a 0.45-μm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. After 2 hr, the dissolution medium pH was increased from 1.2 to 6.5 using phosphate buffer to simulate intestinal fluid. The samples were then analyzed at 275 nm by UV-visible spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulations.

RESULTS AND DISCUSSION

All formulations were relatively robust in terms of friablity and hardness with the exception of F12. Fig. 1 shows the dissolution characteristics of matrices prepared with different amounts of ethylcellulose. In vitro release profiles of diclofenac sodium containing ethylcellulose showed that a reduction in percent of lactose from 50% (F1) to 18.6% (F2) resulted in a reduction in the release rate of diclofenac sodium (Fig. 1). The explanation for this was that lactose caused a decrease in the tortuosity of the diffusion path of the drug. Fig. 2 shows the dissolution characteristics of matrices prepared with different percentages of Precirol. An increase in percent of Precirol from 38% (F6) to 45% w/w (F7) or a reduction in percent of lactose from 18% (F6) to 0% w/w (F7) resulted in a reduction in the release rate of the drug. Fig. 3 shows the dissolution properties of matrices prepared with different percentages of HPMC K4M. Matrices of the batch F13 showed the least release among all the formulations of matrices due to the high percentage of HPMC K4M (Fig. 3). Although the percentage of magnesium stearate in the matrices is different, it has been reported that the release rate was not modified by the presence of magnesium stearate (5).

The effect of pH on dissolution rate was investigated at pH 1.2 and 6.8. Figs. 1–3 show that release from all formulations is extremely slow at pH 1.2, with a maximum of 1% of drug dissolution at 2 hr for all formulations. Faster dissolution rates are displayed by all formulations at pH 6.8. All matrices are similarly affected by pH changes, and thus it can be concluded that drug dissolution is a function of drug solubility at the various pHs. Indeed, the pH-dependent solubility of diclofenac sodium is well known (6).

Different kinetic equations (zero-order, first-order, and Higuchi's equation) were applied to interpret the release rate from matrices at pH 6.8. The best fit with

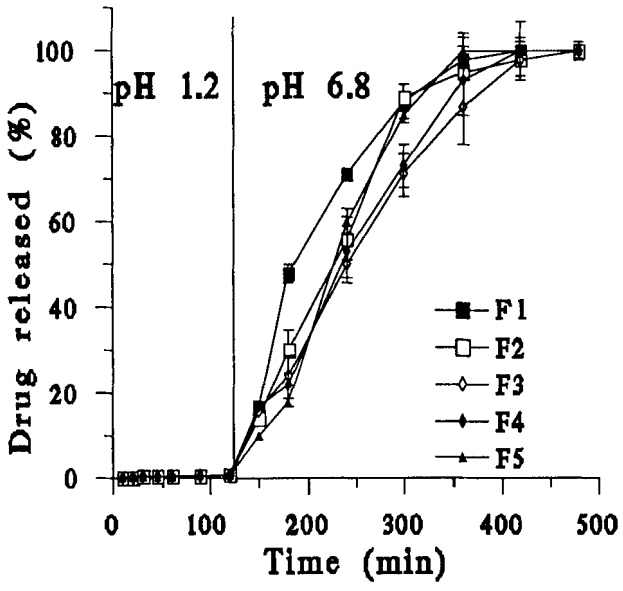

Figure 1. Release of diclofenac sodium from ethylcellulose matrices.

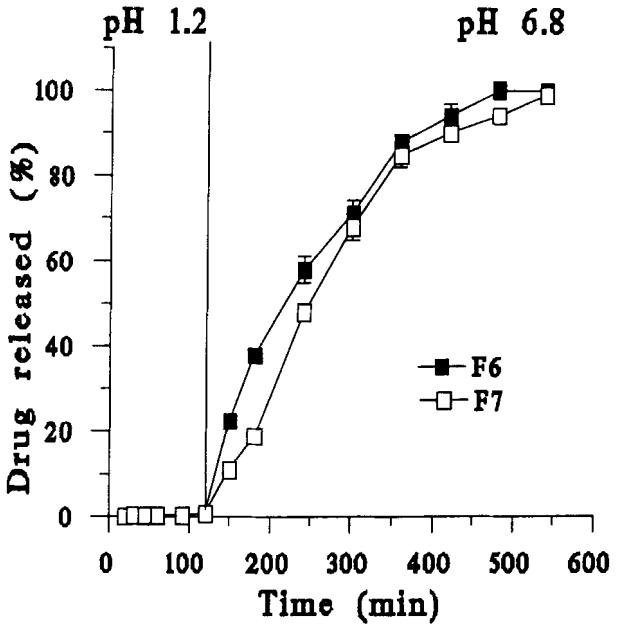

Figure 2. Release of diclofenac sodium from precirol matrices.

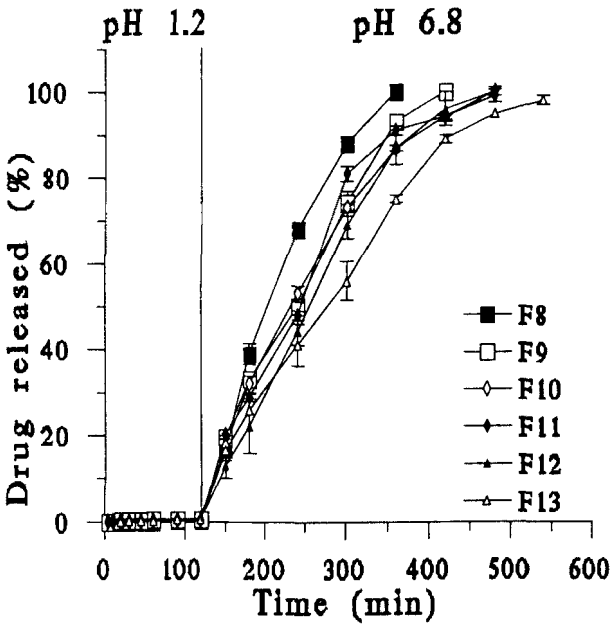

Figure 3. Release of diclofenac sodium from HPMC K4M matrices.

the highest correlation was achieved with the Higuchi's equation, with the exception of F2 and F5.

Two factors, however, diminish the applicability of Higuchi's equation to all hydrophilic matrix systems. The model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. To account for these dual-release mechanisms, Korsemeyer et al. (7) used a simple empirical equation to describe general solute behavior from controlled-release polymeric matrices.

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

where M_t/M_∞ is the fractional release of the drug, t is the release time, K is a constant incorporating structural and geometric characteristics of the release device, and n is the release exponent indicative of the mechanism release. When n approximates to 0.5, a Fickian/diffusion-controlled release is implied, where $0.5 < n < 1.0$ non-Fickian transport and $n = 1$ for zero-order (case II transport). When the value of n approaches 1.0, phenomenologically one can conclude that the release is approaching zero-order (7).

Formulation of matrix tablets required the addition of excipients to alter the size of the tablet or to replace a portion of the polymer to modify drug released rate. Therefore the effects of partial replacement of the ethylcellulose and Precirol by lactose on release rates were examined. Replacement of ethylcellulose and Precirol by lactose increased the dissolution rates of diclofenac sodium and the values of n were changed. It was reported that the replacement of HPMC within matrices by as much as 75% w/w lactose resulted in increased release rate for promethazine HCl (8).

The n values calculated using Eq. (1) from dissolution data for all formulations were more than 0.7, with the exception of the matrix containing 38% Precirol and 18% lactose (F6, $n = 0.601$), suggesting a deviation from the Fickian/diffusion-controlled release toward zero-order. Although the values of n had no definite relationship with polymer content, comparing F1 (50% lactose, $n = 0.815$) with F2 (18.6% lactose, $n = 0.985$), and F6 (18% lactose, n = 0.601) with F7 (0% lactose, $n = 0.881$) showed that a reduction in the amount of lactose in formulations containing hydrophobic polymers (ethylcellulose or Precirol) resulted in an increase in values of n, indicating a mode of drug transport nearer to zero-order than Fickian at low lactose concentrations.

Comparing F3 (40% ethylcellulose, $n = 0.819$), F4 (45% ethylcellulose, $n = 0.853$), and F5 (50% ethylcellulose, $n = 1.17$) showed that an increase in the amount of ethylcellulose resulted in an increase in values of n, suggesting a deviation from the Fickian/diffusion-controlled release toward zero-order. It is clearly apparent for matrices containing ethylcellulose (0% lactose) that by increasing the ethylcellulose-to-diclofenac sodium ratio (F3, F4, and F5) from 0.72 to 1.11, the value of n increased from 0.819 to 1.17. On the other hand, the release kinetics from matrices consisting of HPMC K4M were very complicated. For instance, an increase in amount of HPMC K4M from 40 to 52% or an increase in the HPMC-to-drug ratio from 0.72 to 1.61 caused a decrease in n values from 0.849 to 0.691, whereas from 52 to 60% HPMC K4M or the HPMC-to-drug ratio from 1.23 to 1.61 there was no particular trend.

The influence of drug concentration within a matrix is of great importance. Generally, the greater the concentration of HPMC within a matrix, the slower the release of a drug (2,5,9). It has been demonstrated that HPMC-to-drug ratio is the major factor controlling release from HPMC matrices. In fact, varying the concentration of polymer is probably the most efficient way for a formulator to adapt the release characteristics. Attempts were made to determine other relationships between the time to release 50% of the drug and different HPMC K4M-to-diclofenac sodium ratios. The authors observed that there was a linear relationship (correlation coefficient of 0.995) between the time to release 50% ($T_{50\%}$) of the drug in vitro and the HPMC K4M-to-drug ratio in the matrix. Therefore, it is pos-

sible to predict the release rate of diclofenac sodium from matrices containing different percentages of HPMC K4M.

In conclusion, the results obtained in this study confirmed that the use of ethylcellulose or Precirol containing a large amount of lactose in matrices will not provide zero-order release of diclofenac sodium. Near zero-order release is only achieved with small amounts of lactose in matrices.

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