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RESEARCH PAPERS

Effect of Formulation Variables on Dissolution Profile of Diclofenac Sodium from Ethyl- and Hydroxypropylmethyl Cellulose Tablets

Sarat C. Chattaraj[1,*] and Sudip K. Das[2]

[1]*Rhodes University, School of Pharmaceutical Sciences, Grahamstown, South Africa*
[2]*Nova Southeastern University, College of Pharmacy, North Miami Beach, Florida, USA*

ABSTRACT

The effects of formulation variables on the release profile of diclofenac sodium from ethyl cellulose (EC) and hydroxypropylmethyl cellulose (HPMC) matrix tablets were investigated. With increase in viscosity of ethyl cellulose used in nonaqueous granulation, a decrease in drug release from the tablets was observed, while the percentage of fines (particles passed through 60 mesh) in the granulation had a significant effect on the dissolution profile. Granules containing 15% fines exhibited slow release of the drug in comparison to those containing 30% fines with EC matrices. An analysis of kinetics of drug release from hydrophobic EC matrix showed Fickian diffusion regulated dissolution. Drug release from HPMC tablets followed an apparent zero-order kinetics.

INTRODUCTION

Diclofenac sodium is a nonsteroidal anti-inflammatory agent which has been proven therapeutically more effective than indomethacin at a lower dose and causes fewer CNS side effects and gastrointestinal problems in rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis (1). It has been reported to be valuable in long-term therapy in oral administration. In healthy human volunteers, mean plasma clearance of diclofenac is 16 liter/hr and mean elimination half-life of the terminal phase is 1.2 to 1.8 hr (2,3). In order to make this drug devoid of gastrointestinal irritation, which is a common problem with all nonsteroidal anti-inflammatory agents,

*Present address: Nova Southeastern University, 1750 N.E. 167th Street, North Miami Beach, FL 33162.

effective enteric coated forms have been developed (4,5). However, it was previously reported that food effectively delays the absorption of the drug; this gives rise to a nonreproducible pharmacokinetic profile, and the drug has no immediate therapeutic effect (6). In order to have an uniform plasma level of diclofenac, Lee et al. (7) studied the drug release profile from suspension of glassy poly(hydroxyethyl methylacrylate) beads. Glassy cellulose ethers have been used to develop controlled-release delivery systems. Hogan (8) thoroughly reviewed the use of hydroxypropylmethyl cellulose in development of controlled-release systems. The effect of formulation variables on release rate of phenylpropanolamine hydrochloride from hydroxypropyl cellulose and ethyl cellulose has been reported (9). The pH, added salts, and viscosity grades of the hydrogel were reported to have effects on diclofenac release from hydroxypropylmethyl cellulose matrix tablets (10).

A number of reports described controlled-release diclofenac formulations with hydrogels (7), tablets made of spray-dried enteric coated microcapsules (11) and chitosan (12). In order to eliminate the gastrointestinal adverse effects, effective enteric coated products have been developed and commercialized (13). The present study describes the preparation of hydrophobic and hydrophilic matrices of diclofenac and analysis of dissolution profile of the drug from matrices. Drug release from hydrogel matrices is dependent on factors like swelling and true dissolution of the polymer, giving rise to mass erosion of the system, concomitantly with dissolution and diffusion of drug. Initially the matrix thickness increases due to polymer swelling and then due to polymer dissolution as well as dissolution of drug and fillers; the matrix thickness decreases and finally disappears when all polymer is swollen. This phenomenon has been referred to as "swellable-soluble matrix" (14). In the case of swellable-soluble matrices, three moving fronts play an important role in drug release: (a) matrix-water boundary (dissolution front), (b) solid drug-solution boundary (diffusing front), and (c) glass-rubber boundary (swelling front). The relative movements of these fronts determine the kinetics of drug release. The swelling and dissolution moving fronts tend to synchronize and when this is achieved the drug release rate appears to be independent of drug solubility at the same loading value. Finally, when swelling front becomes inactive, the drug release is due to synchronization of diffusing and eroding front movements (14).

This paper reports the effect of different viscosities of ethyl cellulose (EC) and degree of fineness of granules of ethyl cellulose matrix on the in vitro dissolution profile of the controlled-release matrix of diclofenac, in comparison to the hydrophilic matrix prepared with hydroxypropylmethyl cellulose (HPMC) and a commercial sustained-release dosage form of diclofenac sodium.

EXPERIMENTAL

Materials

Diclofenac sodium was obtained from Sigma Chemical, USA. Ethyl cellulose (7, 10, and 18 cps, Dow Chemical Corp, USA) was sieved through a #150 mesh (105 μm) screen. Hydroxypropylmethyl cellulose (K100M, nominal viscosity of 2% in water 100 cps) was from Dow Chemical. Microcrystallin cellulose (AVICEL PH101) was from FMC Corp., USA. Magnesium stearate and dibasic calcium phosphate were of USP grade. All other reagents were of analytical grade and water used was deionized by reverse osmosis.

Methods

Preparation of Hydrophilic Matrices of Diclofenac Sodium Granules Containing HPMC and Microcrystalline Cellulose

A nonaqueous granulation process was adopted to prepare diclofenac sodium tablets. Drug was mixed with microcrystalline cellulose (MCC) and hydroxypropylmethyl cellulose (HPMC, K100M) according to the composition shown in Table 1, passed through #40 mesh sieve, and uniformly wetting with a spray of 5% w/w isopropyl alcohol while mixing. The wet mass was forced through a #8 sieve (2.36 mm). The granules were dried in a fluid bed drier at minimum flow capacity and 50–60°C inlet temperature. The dried granules were sieved and separation of the particle size ranges was performed using a sieve shaker. Granules were lubricated with 1.8–1.9% w/w magnesium stearate, and compression was performed using a single punch press (Manesty, England) at 6–8 kg/cm^2, using 11.28 mm flat punches. Weight and hardness of the tablets were monitored periodically.

Preparation of Hydrophobic Matrices of Diclofenac Sodium Granules with Ethyl Cellulose and Dicalcium Phosphate

The same method was followed for the hydrophobic matrix (Table 1), using dicalcium phosphate for micro-

Table 1

Composition of the Tablets

	Formulations	
	Hydrophilic Matrix	Hydrophobic Matrix
Diclofenac sodium	100 mg	100 mg
Microcrystalline cellulose	82 mg	—
Hydroxypropylmethyl cellulose	32 mg	—
Dicalcium phosphate	—	94 mg
Ethyl cellulose	—	6 mg
Magnesium stearate	4 mg	4 mg

crystalline cellulose and ethyl cellulose for hydroxypropyl methyl cellulose.

Compression Parameters

Values listed are the average of 20 tablets.

Diameter	9.0 mm
Thickness	3.8 mm
Hardness	6–8 kg/cm^2 for hydrophobic matrix
	3–4 kg/cm^2 for hydrophilic matrix
Friability	less than 1%
Moisture	4.18%

Effect of Formulation Parameters

To determine the effect of formulation factors on drug release from hydrophilic and hydrophobic matrices, the following studies were conducted: (a) effect of viscosity grades of ethyl cellulose on drug release profile, (b) effect of degree of fineness of the granules, and (c) comparison of dissolution profile of tablets prepared with HPMC and EC and a commercial product.

In Vitro Dissolution Studies

Tablets of each formulation were subjected to dissolution testing using a USP XXII paddle-type dissolution apparatus, in 900 ml distilled water at pH 5.5–6, maintained at 37 ± 1°C, at 100 rpm. At each sampling interval, an aliquot of the dissolution medium was withdrawn and an equal volume of fresh dissolution medium was replenished. Diclofenac content was determined at 276 nm using an ultraviolet/visible (UV/VIS) spectrophotometer. Experiments were done in triplicate and mean values obtained.

Analysis of Dissolution Data

Dissolution data were analyzed using the equation proposed by Ritger and Peppas (15) to describe the relative availability of drugs from matrix systems:

$$Mt/M\infty = Kt^n$$

where Mt corresponds to the amount of drug release in time t, $M\infty$ is the total amount of drug release after infinite time, K denotes a constant, and n is the release exponent indicating the type of drug release mechanism. As described by Ritger and Peppas, the drug release kinetics could follow: (i) Fickian diffusional release occurring by the usual molecular diffusion of drug due to a chemical potential gradient, or (ii) case II relaxational drug release where the drug transport is associated with stresses and state transition in hydrophilic glassy polymers which swell in water, or (iii) anomalous non-Fickian transport.

The cumulative percentage drug release versus time data were assessed for the kinetics of drug release and dissolution using the program RELAN, based on least sum of squared errors, written by the authors.

RESULTS AND DISCUSSION

Effect of Viscosity of Ethyl Cellulose on the Dissolution Profile of Hydrophobic Matrix Tablets

Figure 1 shows the effect of viscosity of ethyl cellulose on dissolution profile. With higher viscosity of ethyl cellulose, significant prolongation of drug release was observed. Fast drug release was observed with 3% 7 cps EC while maximum retardation of drug release was obtained with 3% 18 cps of EC. A 3% 1:1 mixture of 10 and 18 cps EC showed an intermediate release

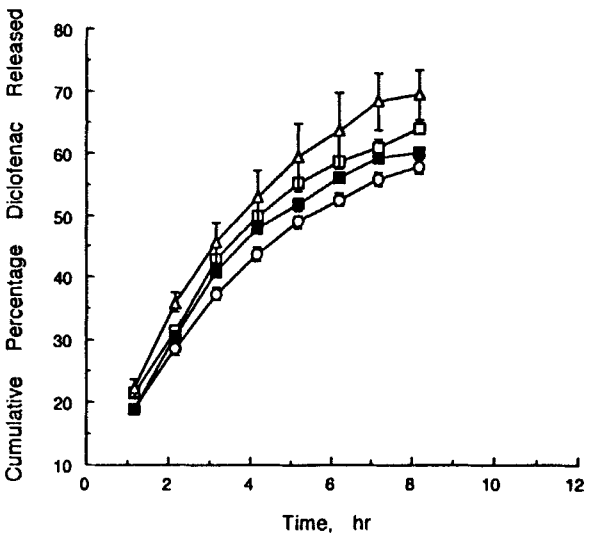

Figure 1. Effect of viscosity of ethyl cellulose on diclofenac release from matrices:
—Δ— 3% EC 7 cps; —□— 3% EC 10 cps;
—■— 3% 1:1 of EC 10 and 18 cps; —○— 3% EC 18 cps.

profile between those obtained with 10 and 18 cps EC, indicating the additive viscosity effect. The value of release exponents (n) of the equation, Table 2 reveals that the hydrophobic matrix tablets made with 10, 18, and 1:1 of 10 and 18 cps ethyl cellulose followed Fickian diffusion regulated dissolution of diclofenac. However, the tablets prepared with 7 cps EC exhibited marginal deviation from the Fickian kinetics, which could be due to coating of the tablet granules by EC and could show an inclination toward anomalous non-Fickian transport.

Effect of Degree of Fineness of Granules on Dissolution Profile

Figure 2 shows the effect of degree of fineness of the granules on the dissolution profile. Matrix granules were sieved through 40 mesh (425 μm) and the required quantity of the fines was added. As the degree of fineness was increased, the dissolution of tablet was promoted, which is evidenced from the profile exhibited by 15% and 30% fines. However, as the degree of fines increased to 50%, the degree of dissolution was de-

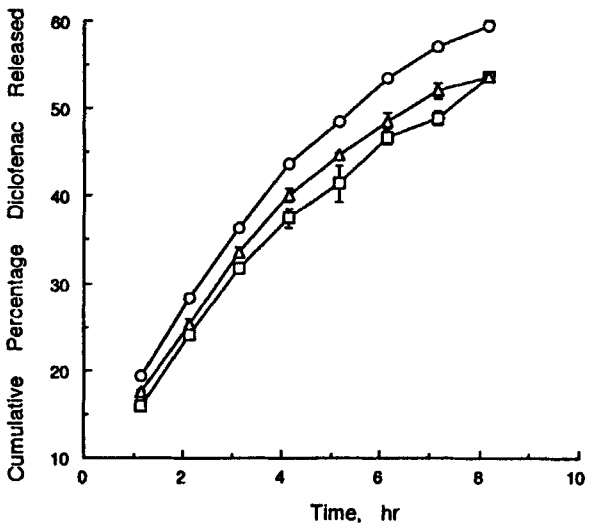

Figure 2. Effect of fines in granulation on diclofenac dissolution profile:
—□— 3% EC 20 cps 30% passed through 60 mesh; —○— 3% EC 20 cps 50% passed through 60 mesh; —Δ— 3% EC 20 cps 15% passed through 60 mesh.

Table 2

Release Exponent (n) and Fitness into Equation (first 60%)[a]

Formulation	Exponent (n)[b]	Corr. Coeff.[2]
3% 7 cps EC	0.552 ± 0.007	0.998
3% 10 cps EC	0.497 ± 0.021	0.965
3% 18 cps EC	0.488 ± 0.012	0.983
3% 1:1 of 10 and 18 cps EC	0.453 ± 0.016	0.965
3% 20 cps EC 15% fine	0.561 ± 0.008	0.994
3% 20 cps EC 30% fine	0.531 ± 0.009	0.991
3% 20 cps EC 50% fine	0.523 ± 0.012	0.985
HPMC matrix (after lag time)	1.659 ± 0.049	0.984
Commercial (after lag time)	1.542 ± 0.049	0.982

[a]Based on Ritger and Peppas (15).
[b]Estimate + SE.

creased due to the fact that fine powders form more compact mass and give rise to less tortuousity of the matrices, resulting in fewer pores available for solute medium to enter into the tablet. An analysis of the kinetic data in Table 2 shows, with 15%, 30%, and 50% fines of 3% 20 cps EC matrix, the release exponent is significantly higher than 0.5, indicating anomalous (non-Fickian) drug release. It is also to be noted that as the degree of fineness increases, the release kinetics predominantly tends toward Fickian diffusion. This phenomenon explains the finding that the complete dissolution profile is more oriented toward a combination of diffusion and non-Fickian transport.

Effect of Hydrophilic Matrix

Figure 3 shows the dissolution profile of diclofenac from the HPMC matrix, revealing an apparent zero-order drug release with initial lag time. The release exponent in Table 2 reveals n greater than 1 with all the hydrophobic matrices prepared with HPMC and the commercial product which was known to be made of HPMC. Most hydrogels are glassy in the dehydrated state and the release of the drug from such matrices involves simultaneous absorption of water and desorption of drug through a swelling-controlled mechanism. Swelling and diffusion normally do not follow Fickian kinetics because of the existence of a slow macromolecular relaxation process in the swollen region. The commercial product of diclofenac also showed an apparent zero-order with lag time. A comparison of commercial product, hydrophilic matrix with HPMC, and hydrophobic matrix with EC revealed that the commercial product had an almost superimposable profile with the HPMC tablets while the tablets prepared with 3% 18 cps EC exhibited Fickian diffusion regulated dissolution.

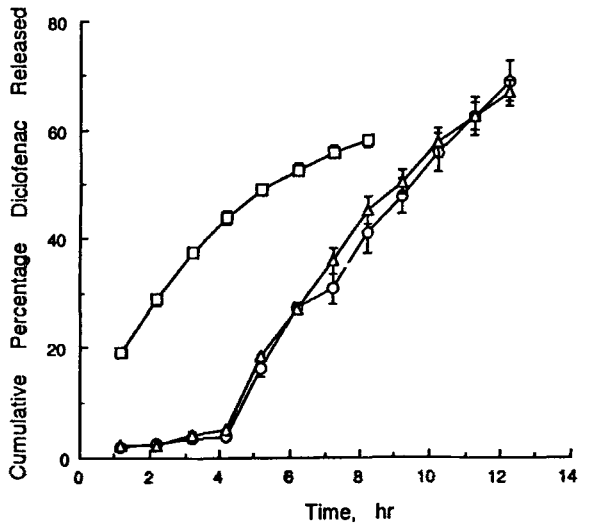

Figure 3. Comparison of dissolution profile of hydrophobic matrix, hydrophilic matrix, and a commercial product of diclofenac:
—□— 3% EC 18 cps; —○— HPMC matrix; —Δ— Commercial product.

CONCLUSION

A quantification of the release of diclofenac from both hydrophobic ethyl cellulose and hydrophilic hydroxypropylmethyl cellulose was dependent on the viscosities of the polymer used to form the matrix and also on the degree of fineness of granules. Release mechanism of diclofenac from the tablets was dependent on the composition of matrices used. The release of drug from ethyl cellulose matrices followed Fickian diffusion regulated dissolution while the drug release from hydroxypropylmethyl cellulose was essentially non-Fickian.

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