RESEARCH ARTICLE

Preparation and evaluation of delayed release aceclofenac microspheres

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Delayed release microspheres of aceclofenac were formulated using an enteric polymer, cellulose acetate phthalate (CAP) prepared by solvent evaporation technique. The effects of various other modern enteric polymers such as hydroxyl propyl methyl cellulose phthalate (HPMCP), Eudragit L 100, and Eudragit S -100 on the release of aceclofenac from the CAP microspheres have been evaluated. The microspheres were characterized for particle size, scanning electron microscopy (SEM), percentage yield, drug entrapment, and for *in-vitro* release kinetics. The shape of microspheres was found to be spherical by SEM. The drug entrapment efficiency of microspheres was found to be ranging from 75.65 to 96.52 %w/w. The study was designed in the form of a factorial design in which the effects of HPMCP, Eudragit L 100, and Eudragit S 100 on the release rate of drug from CAP delayed release microspheres were evaluated. The results revealed that the HPMCP exhibits positive influence whereas Eudragit L 100 and Eudragit S 100 exhibits negative effect on the drug release rate of CAP microspheres. *In vitro* drug release from all formulations followed the first order release kinetics and erosion plot. Formulation with drug: CAP : HPMCP ratio of 1:8:2 was considered best because it showed delayed release.

Key words: *Aceclofenac, cellulose acetate phthalate, delayed release microspheres, non-steroidal anti-inflammatory drugs*

INTRODUCTION

Microspheres are defined as homogeneous, monolithic particles in the size range of about 0.1-1000 μm and are widely used as drug carriers for controlled release. These systems have significant importance in biomedical applications. Microspheres can be produced for protection of core material, reduction of gastric irritation decrease in volatility, conversion of liquid to pseudo-solid, cell microencapsulation and for designing pulsatile drug delivery systems. Administration of the drug in the form of microspheres usually improves the treatment by providing the localization of the active substances at the site of action and by prolonging release of drugs.[1]

Aceclofenac is a newer non-steroidal anti-inflammatory drug (NSAID). Aceclofenac is a phenyl acetic acid derivative showing effective anti inflammatory and analgesic properties mainly used in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Aceclofenac is rapidly and efficiently absorbed after oral administration but has a short half life of 3-4 h and requires multiple dosing for maintaining therapeutic effect throughout the day.[2] The most frequent adverse side effects occurring with aceclofenac are gastrointestinal (GI) disturbances, peptic ulceration and GI bleeding, hence there is a potential need for an enteric coated dosage form for this drug to minimize gastric erosion side effect. Its biological half-life on the other hand is very short, sustaining its anti-inflammatory activity only for a few hours. The aim of the present study was to formulate a delayed release microspheres dosage form of aceclofenac.

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MATERIALS AND METHODS

Aceclofenac, CAP, HPMCP was obtained as a gift sample from Cee Gee Pharmaceutical Pvt–Ltd Pondecherry. Eudragit L100, Eudragit S100, liquid paraffin and *n*-hexane were obtained from Nice chemicals, Cochin. Acetone and methanol were of analytical grade.

Method of preparation

Delayed release aceclofenac microspheres were prepared by dissolving the drug (100 mg) in a 10%w/v solution of cellulose acetate phthalate (in acetone:methanol 8:2 solvent mixture). The solution was then emulsified into liquid paraffin and the system was stirred continuously and the solvent was allowed to evaporate at room temperature.[3] The microspheres were collected by filtration, washed with *n*-hexane and dried at room temperature.[4,5]

Eight different batches were formulated according to the factorial design and their composition is presented in Table 1. The surface morphology of the microspheres was examined by SEM. Particle size analysis was carried out by using sieving method to determine the size distribution of microspheres. The drug content in microspheres was determined (by taking 3 samples from each batch) and the entrapment efficiency was calculated from the delayed release aceclofenac microspheres.[6]

The *in-vitro* release profiles of aceclofenac from microspheres was examined in pH 1.2 buffer from 0-2 h and in phosphate buffer of pH 6.8 from 2-8 h by rotating basket method specified in the USP XXIII Tablet dissolution tester (TDT06P, Electro lab), following the procedure for enteric formulation. Delayed release microspheres equivalent to 100 mg of aceclofenac were accurately weighed, filled into capsules and used in this study. The dissolution medium is 0.1 N HCl for 2 h and phosphate buffer solution of pH 6.8 for the remaining period.[7] The temperature of the bath was maintained at 37 ± 0.5°C and the stirring speed at 100 rpm. Samples of the dissolution medium (5 ml) were withdrawn at various time intervals. The same volume of fresh fluid was added to the test medium to maintain the volume. The collected samples were analyzed by the UV double beam spectrophotometer at 276 nm.[8,9] Each experiment was carried out in triplicate. To characterize release of aceclofenac from microspheres, the *in-vitro* release data for all formulation was subjected to kinetic data treatment using mathematical models like zero order, first order, higuchi model, and erosion model.

RESULTS AND DISCUSSION

The delayed release microspheres of all batches were found to be spherical and free flowing [Figure 1]. The size range of different batches of microspheres was in the range of 8.40–14.60 µm [Table 2]. The drug entrapment efficiency analysis showed that the entrapment of drug within each batch of microspheres ranges from 75.65 to 96.52%w/w [Table 2]. The packing properties of the drug and the formulation widely depend upon bulk density. It has been stated that, bulk density values less than 1.2 gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow characteristic. It is seen from Table 2 that the bulk density values are less than 1.2 gm/cm^3 indicating good flow characteristics of the microspheres. Angle of repose less than or equal to 40° indicates free flowing properties of the microcapsules.[10] The angle of repose for all the formulations (F1-F8) is seen to be between 21°03' and 23°30' indicating good flow property.

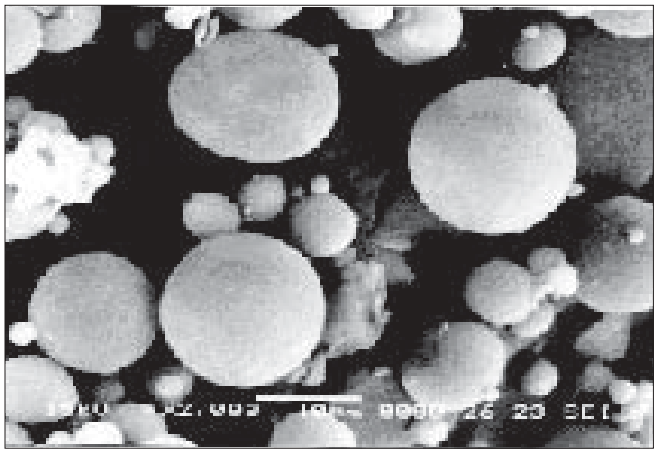

Figure 1: Scanning electron microscope of optimized formulation F2 (2000×)

Table 1: Composition of different formulation of delayed release microsphere of aceclofenac

Formulation	Drug (mg)	CAP (mg)	HPMCP (mg)	Eudragit L-100 (mg)	Eudragit S-100 (mg)
F1	100	1000	-	-	-
F2	100	800	200	-	-
F3	100	800	-	200	-
F4	100	800	-	-	200
F5	100	800	100	100	-
F6	100	800	-	100	100
F7	100	800	100	-	100
F8	100	800	66.66	66.66	66.66

CAP = cellulose acetate phthalate, HPMCP = hydroxy propyl methyl cellulose phthalate

Table 2: Physicochemical properties of different batches of delayed release aceclofenac microspheres

Formulation	Bulk density* (gm/cm^3)	Angle of repose*	% of drug entrapped* (%w/w)	Particle size (µm)
F1	0.592 ± 0.10	23°30'	77.39	8. 40–14.50
F2	0.624 ± 0.18	21°29'	96.52	8.78–14.31
F3	0.624 ± 0.12	21°17'	75.65	8.50–14.60
F4	0.596 ± 0.10	22°20'	79.13	8.49–14.30
F5	0.622 ± 0.18	29°24'	93.04	8.45–14.35
F6	0.610 ± 0.12	21°29'	84.34	8.60–14.32
F7	0.598 ± 0.15	21°03'	94.78	8.84–14.20
F8	0.622 ± 0.12	23°09'	91.30	8.65–14.00

*Average of three calculation (± standard deviation)

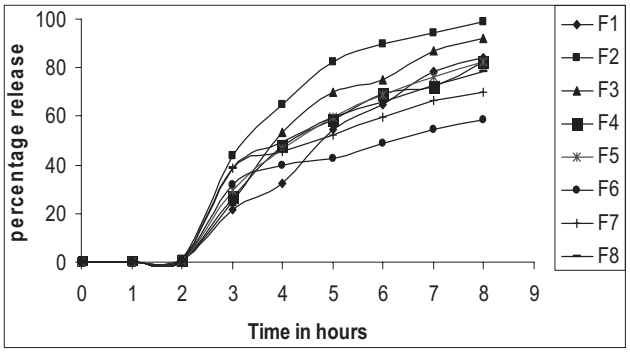

Figure 2: Release profiles of delayed release microspheres of aceclofenac for formulation F1 to F8

In-vitro drug release studies were carried out with formulations F1–F8. The gastro resistance of these formulations was confirmed to fit the USP XXIII specifications. Less than 0.5% of the drug content was released within 2 h in 0.1N HCl and more than 80% was released after 1 h in the phosphate buffer of pH 6.8. [Figures 1 and 2] shows the drug release pattern of microspheres prepared with CAP and other enteric polymers. It is evident from the figures that all formulations showed delayed release properties. The drug release in the acidic medium was found to be negligible. The drug release in the alkaline medium, which stimulated intestinal pH conditions, was found to be sustained. The *in-vitro* release data have been plotted according to the following models of data treatment, cumulative percent drug release versus time, log of cumulative drug retained versus time, and erosion plot of $(1\text{-}t/m)^{1/3}$ versus time.[11]

The *in-vitro* drug release from all formulations was found to follow first order release kinetics. The linearity of the first order plots was assessed by correlation coefficient values [Table 3]. The delayed release microspheres formulated in this study contain drug dissolved in a polymer matrix which is soluble in the dissolution medium (pH 6.8) considered as bioerodible device. The plot of $(1\text{-}Mt/M)^{1/3}$ versus time was found to the linear for all the eight formulations which indicates that the drug release occurs mainly by erosion. The linearity of the erosion plot was assessed by correlation coefficient values [Table 3].

It is seen that hydroxyl propyl methyl cellulose phthalate has an increasing effect on drug release rate, where as Eudragit L100, Eudragit S100 have decreasing effect on drug release rate. Among the eight formulation, the formulation F2 was considered best because it showed delayed release and the drug release in pH 6.8 buffer was found to be almost complete and sustained.

CONCLUSION

From the study, it was concluded that the aceclofenac loaded microspheres prepared with Eudragit L100 and Eudragit S100 showed decrease in the release rate of drug than the microspheres prepared by using CAP and HPMCP. The formulation with drug:CAP:HPMCP ratio of 1:8:2 (F2) was considered best because, it showed delayed release and the drug release in pH 6.8 buffer was found to be almost complete (99.91%) and uniform. Drug entrapment efficiency for formulation F2 was 96.52%w/w.

Table 3: *In-vitro* drug analysis for formulation of delayed release microspheres of aceclofenac

Formulation	First order kinetic model r^2	Erosion plot r^2
F1	-0.957	-0.970
F2	-0.955	-0.981
F3	-0.965	-0.977
F4	-0.976	-0.980
F5	-0.979	-0.982
F6	-0.972	-0.967
F7	-0.978	-0.972
F8	-0.982	-0.979

r^2 = correlation coefficient

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