Available online at www.ijpsdr.com
International Journal of Pharmaceutical Sciences and Drug Research 2009; 1(2): 71-73

Research Article

ISSN 0975-248X

Formulation Development and Evaluation of Sustained Release Aceclofenac Suppository

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ABSTRACT
The aim of this study was to prepare sustained release (SR) suppositories containing Aceclofenac microspheres. In the first part of the study, Aceclofenac microspheres were prepared by solvent evaporation method employing ethyl cellulose as a microsphere forming polymer. The effect of drug: polymer ratio and stirring rate on microspheres formation, average particle size, incorporation efficiency, micromeritic properties and in vitro Aceclofenac release were investigated. The highest drug loading capacity was found with 1:1 drug- polymer ratio stirring rate caused insignificant effect on drug loading capacity. In the second part, SR suppositories were formulated by incorporating Aceclofenac microspheres having the highest drug loaded. The bases used were PEG 4000, PEG 6000 and stearic acid. The drugs released were evaluated by in vitro dissolution tests. Comparative results of SR suppositories containing Aceclofenac microspheres with that of conventional ones showed that the former has sustained effect up to 8 h *in vitro*.

Keywords: Sustain release, suppository, microspheres, rectal route.

INTRODUCTION

The advantages of administration of drugs through suppositories over other dosage forms are reduction of side effects mainly gastrointestinal irritation and the avoidance of unpleasant taste. When administered through rectal route, hepatic first pass elimination of high clearance drug is partly avoided. [1] The prime aim in designing suppositories with sustained release (SR) is to obtain a desirable blood concentration of the drug, to maintain such a concentration at a nearly constant level for a appropriate period of time. [2] Aceclofenac (ACF) is a non-steroidal drug having potent analgesic, anti-inflammatory and antipyretic activities due to its prostaglandin synthatase inhibitory action. Since it produce serious gastrointestinal complication such as ulcer, severe bleeding and perforation resulting in hospitalization and even death, so rectal administration is used as an alternative to oral route. The aim of this study was to formulate SR suppositories containing ACF microspheres. Release of ACF from SR suppositories was evaluated by in vitro dissolution tests and the data was compared with that of conventional suppositories.

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MATERIALS AND METHODS

ACF and ethyl cellulose were purchased from Welable Pharmaceutical, Gujarat. PEG 4000, PEG 6000, Stearic acid were procured from S.D. Fines Chem. Mumbai. All other reagents and chemicals were of analytical grade.

Preparation of ethyl cellulose microspheres containing ACF

Ethyl cellulose microspheres containing ACF were prepared by emulsification solvent evaporation technique in an oily phase (o/o). [3] Accurately weighed ethyl cellulose 1 % (w/v) was dissolved in 10 ml of acetone to form a homogenous polymer solution. Drug was separately suspended in a continuous phase consisting of 70 ml of liquid paraffin and 1 % (w/w) of span 80. The solution-containing polymer was added into continuous phase with variable stirring, i.e. 800, 1000, 1200 rpm using a variable speed propeller stirrer to form a uniform emulsion. About 5-10 ml of acetone was added to the external continuous phase to produce a stable o/o emulsion. Stirring was continued (3-4 h) until residual acetone evaporated. The microspheres formed were separated by filtration, washed 3 to 4 times with n-hexane to remove adhering liquid paraffin and dried for 48 h in a vacuum desiccator. Three batches were prepared with different proportions of core to coat materials (drug: polymer = 1:1,

1:1.5 and 1:2 (w/w)). From the study, 1:1 drug: polymer ratio was selected for further study.

Evaluation of ACF microspheres

The prepared microspheres were evaluated for their particle size and particle size distribution, incorporation efficiency, micromeritic properties, surface morphology and in vitro drug release study. [4]

***In-vitro* release studies of ACF microspheres**

Dissolution of ACF microspheres was carried out using USP XXII basket method. [4] Microspheres containing 100 mg of ACF were dispersed in the dissolution medium (900 ml, pH 6.8 phosphate buffer solution, 37 ºC ±0.5, 100 rpm). At appropriate times, 10 ml of the test solution was removed and 10 ml of the same fresh fluid was added to maintain the steady volume. The amount of ACF was assayed spectrophotometrically at 275 nm. [5]

Preparation of SR suppositories containing ACF microspheres

SR suppositories composed of ACF microspheres were prepared by using melting method. PEGs 4000, PEGs 6000 and stearic acid were used as different suppository bases. Homogenous dispersions were formed in melted bases with microspheres of highest drug loading capacity (49.16 %) within the particle size range of 115- 165 µm and then moulded. [6] Comparative studies were run with conventional ACF suppositories.

Evaluation parameters of SR suppositories

Melting time and ACF content

SR suppositories of ACF microspheres were analyzed for their weight variation, melting time and ACF content. Melting time is determined by using disintegration apparatus USP at 37°C in a 900 ml distilled water, and time taken by suppository to disintegrate completely is observed. [7] For ACF content, suppository is allowed to dissolve in a methanol and after filtration absorbance is taken at 275 nm.

***In-vitro* dissolution of SR suppositories**

In vitro drug release from SR suppositories was determined using the USP XXII paddle method (900 ml, pH 6.8 phosphate buffer solution, 37ºC±0.5, 100 rpm). [7-8] At appropriate intervals (0.5 to/8 h), 10 ml samples were taken and the content of ACF was assayed spectrophotometrically at 275 nm.

Table 1: Formation of SR suppositories of ACF with different bases

Ingradients	S_1	S_2	S_3	S_4
ACF microspheres	0.203	0.203	0.203	
PEGs 4000	1.297	-	-	Conventional
PEGs 6000	-	1.297	-	suppository
Stearic acid	-	-	1.297	
Total weight (gm)	1.5	1.5	1.5	1.5

(S_1: Suppository with PEGs 4000; S_2: suppository with PEGs 6000; S_3: suppository with stearic acid; S_4: plain suppository. The amounts are given in grams)

Table 2: Influence of process variables on ACF micropsheres (n=3)

Drug: polymer ratio	Stirring rate (rpm)	Average particle size (µm)	Drug loading capacity (%) ± SD
1: 1	800	150-200	48.10± 0.28
1: 1	1000	115-165	49.16 ± 0.34
1 :1	1200	105-138	44.58 ± 0.56
1: 1.5	1000	112 -160	35.01 ± 0.21
1: 2	1000	125 - 170	30.69 ± 0.39

RESULTS AND DISCUSSION

Table 2 indicates the influence of process variables as drug: polymer ratio and stirring rate on average particle size and drug loading capacity. Increase in polymer ratio resulted in decrease in the amount of drug encapsulated. Variations in stirring rate caused no significant difference with respect to drug loading capacity. Higher mixing rate led to the formation of microspheres with smaller sizes. The highest loaded drug was found with 1:1 drug: /polymer ratio at 1000 rpm with 89.52 % practical yield. Insignificant effect was obtained between particle size and drug loading capacity. According to the morphological analysis ACF micropsheres were spherical and porous in respect to their shape and surface.

The results of drug released from ACF microspheres are shown in Fig. 1. This shows that SR behavior of formulation. The percentage of ACF released from microspheres within 8 h was approximately 98 %. No significant effect of particle size on released amount of ACF was observed.

Weight variation and melting time of SR suppositories prepared from ACF microspheres were similar to those of the standards. Content uniformity was found within the expected values (Table 3).

Table 3: Weight variation, melting time and content uniformity of SR suppositories (n = 20)

Parameters	S_1 ± SD	S_2 ± SD	S_3 ± SD	S_3 ± SD
Weight variation	1.5 ± 0.02	1.5 ± 0.01	1.2 ± 0.02	1.55 ± 0.02
Melting time(mins)	21.10 ± 0.39	10.67 ± 0.45	49 ± 0.38	8.01 ± 0.23
Content uniformity	101.12 ± 0.34	100.42±0.62	98.77±0.43	98.08 ± 0.45

In-vitro dissolution tests showed that SR suppositories prepared with PEGs and stearic acid has SR effect (Fig. 2). The percentage of the drug dissolved within 8 hours was 88.0 % in SR suppositories composed of microspheres based PEGs - 4000 (S1). On the other hand 94 % of drug released in 8 hours from PEGs 6000 based ACF suppositories (S2). Suppositories containing ACF microspheres prepared with the base consisting of stearic acid (S3) released 39.12 % of drug in 8 h while plain conventional suppositories (S4) gave 99.0 % and 3 h, respectively.

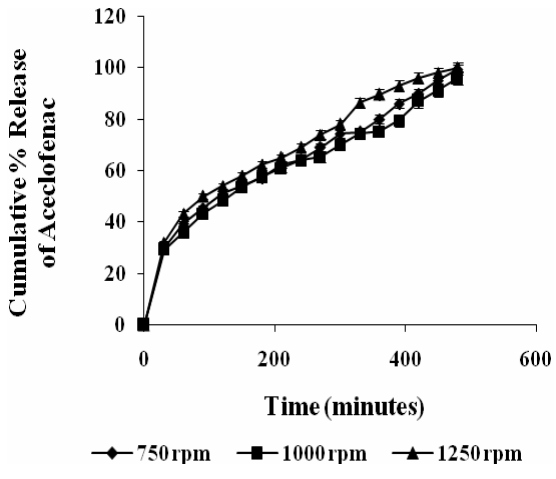

Fig. 1: Release profiles of ACF microspheres with different particle sizes. (0.2 M phosphate buffer solution, pH 6.8)

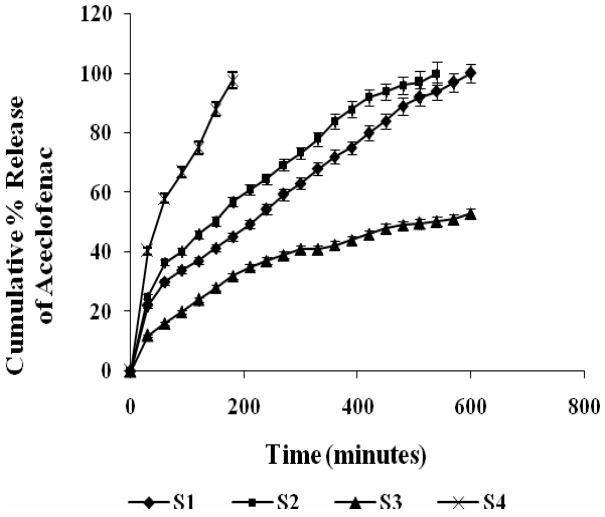

Fig. 2: Release profiles of ACF from the suppositories prepared with PEG 4000 (S1), PEG 6000 (S2), Stearic acid (S3) and Conventional suppository (S4)

Higher drug release from PEG 6000 and PEG 4000 containing suppositories can be attributed to high water solubility of PEG and probable formation of solid dispersion of drug in PEG during the melt-fusion stage of suppository preparation. Different from lipophilic bases, the drug is released from PEG system as a consequence of the progressive dissolution of PEG into the dissolution medium. PEG influenced in vitro drug availability considerably, by further increasing drug solubility and dissolution rate. This is probably due to the formation of micelles by PEG surrounding the drug molecule in molecular dimension, thereby making the drug undetectable by spectrophotometric measurement. Furthermore the osmotic effect of PEG, prominent on soluble drugs might also have reduced the availability of drug as reported previously.

Suppositories prepared with ACF loaded microspheres using PEG bases, stearic acid showed SR effect up to 8 h *in vitro*. PEGs based suppositories give the required release rate. From these results, it was concluded that reducing the frequency of drug administration provides more suitable therapy with less risk. Thus, the SR suppositories composed of ACF microspheres can be optional as an alternative way to conventional dosage forms.

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