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Formulation and In-vitro Evaluation of Aceclofenac Microcapsules

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Abstract: Aceclofenac was formulated as novel enteric microcapsules for improved delivery to the intestine using the polymer ethyl cellulose as the retardant material. Micro encapsulation of aceclofenac was done to achieve a controlled drug release profile suitable for per oral administration. Aceclofenac was used as core and microcapsules were prepared by an emulsion solvent evaporation method. The prepared microcapsules were evaluated for size analysis, drug content, encapsulation efficiency, wall thickness, optical microscopy and drug release characteristics. All microcapsules obtained were discrete, large sized, free flowing and spherical in shape. Aceclofenac release from microcapsules followed higuchi model and influenced by the size of the microcapsules. Slow release of aceclofenac from ethyl cellulose microcapsules over 12 hours was observed.

Keywords: Aceclofenac, micro encapsulation, first order kinetics.

Introduction:

Aceclofenac is Nonsteroidal anti-inflammatory drug (NSAID). It is phenyl acetic acid derivative, showing effective anti-inflammatory and analgesic properties mainly used in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. [1] Aceclofenac is rapidly and effectively absorbed after oral administration but has short half life of 4h.[2] Gastrointestinal side effects such as bleeding; ulceration and perforation of intestinal wall are common with aceclofenac therapy like other NSAID's.

The main objective of any drug therapy is to achieve desired concentration of drug in blood or tissue which is therapeutically effective and nontoxic for extended period of time. This goal can be achieved by proper design of sustained release dosage regimen.[3, 4]

Microencapsulation is a common technique used in the production of sustained release dosage forms. Microcapsule based drug delivery system has received considerable attention in recent years. Numbers of methods have been devised to prepare microcapsules of desired size, shape and surface properties.[5]

Ethyl cellulose microcapsules have been extensively studied for controlled release. [6, 7, 8] Ethyl cellulose being insoluble in water serves as good candidate for sustained release of drug. The study was previously carried out using diclofenac sodium as a core drug, employing three different solvents such as chloroform, dichloromethane and ethyl acetate to study the effect of solvent on drug release. The solvent employed in the preparation of microcapsules is likely to influence both the permeability and drug release from the microcapsules.[9]

In present paper the study was carried out with a view to extend the release of aceclofenac to prolong its action. The marketed SR preparation of aceclofenac was used to compare the release of drug from microcapsules. Microcapsules were prepared by an emulsion solvent evaporation method, using chloroform as a solvent.[9] After evaporation of solvent ethyl cellulose encapsulates the drug to form microcapsules of various size ranges. In a few reports the permeability coefficient of ethyl cellulose microcapsules prepared by different coacervation methods and relationship between physical properties such as size and density on the permeability and drug release from the microcapsules has been studied.[10]

The aim of this study was to prepare ethyl cellulose microcapsules containing aceclofenac to achieve a controlled drug release profile suitable for per oral administration.

Materials and Experimental Methods

Materials:

Aceclofenac was obtained as a gift sample from Ajanta Pharmaceuticals, Mumbai. Ethyl cellulose with a viscosity of 18.22 CPS and containing 48-49.5% ethoxyl group content was purchased from Loba Chemie, Mumbai. All other ingredients used were of an analytical grade.

Preparation of Microcapsules:

Aceclofenac microcapsules were prepared by Emulsion Solvent Evaporation method [9, 11]. Chloroform was used as solvent with coat: core ratio of 3:7. The polymer (1.5 g) was dissolved in polymer solvent (25 ml) to form a

homogenous polymer solution. Core material, aceclofenac (1.4 g) was added to the polymer solution (10 ml) and mixed thoroughly. The resulting mixture was added in continuous phase made up of 0.1N HCl and sodium carboxy methyl cellulose in a 500 ml beaker while overhead stirring at 200 rpm to emulsify added droplets. Stirring was done for 5-10 minutes and then continued further with magnetic stirrer to evaporate the solvent. Microcapsules were obtained by decantation and washing with water. The product was then dried at 40°c for 4 h to obtain discrete microcapsules.

Evaluation of Microcapsules:

% Yield:

The total amount of microcapsules obtained was weighed and the percentage yield calculated taking into consideration the weight of the drug and polymer.

$$\%\text{Yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Particle size analysis:

For size distribution analysis, different sizes in a batch were separated by sieving; using a set of standard sieves (IP).[12] The amounts retained on different sieves were weighed.

Encapsulation efficiency:

Encapsulation efficiency was calculated using the formula:

$$\text{Encapsulation efficiency} = \frac{\text{Estimated \% drug content in microcapsules}}{\text{Theoretical \% drug content in microcapsules}} \times 100$$

The encapsulation efficiency of microcapsules of various size ranges was determined which is showed in Table 1.

Estimation of Drug Content:

Aceclofenac drug content in the microcapsules was calculated by UV spectrophotometric (Shimadzu 1700) method. The method was validated for linearity, accuracy and precision. A sample of microcapsules equivalent to 100 mg was dissolved in 25 ml ethanol and the volume was adjusted upto 100 ml using phosphate buffer of pH 6.8. The solution was filtered through Whatman No. 1 filter paper. Then the filtrate was assayed for drug content by measuring the absorbance at 275 nm [13] after suitable dilution. The amount of aceclofenac estimated from different samples and sizes are depicted in Table 1.

Wall thickness:

Wall thickness of aceclofenac microcapsules was determined by the method of Luu. et. al. [14] using equation:

$h = r (1-p) d_1 / 3[pd_2 + (1-p) d_1]$

where as:

h = wall thickness of microcapsules

r = arithmetic mean radius

d_1 = density of core material

d_2 = density of coat material

p = proportion of medicament in microcapsules

The values of wall thickness are depicted in Table 1.

Micro photographic Studies:

The prepared microcapsules were characterized optically in terms of morphology, by using computer microscope (model Qx3).

In vitro Drug release Studies:

Drug release was studied by using USP type II dissolution test apparatus (LABINDIA DISSO 2000) in Phosphate buffer of pH 6.8 (900 ml). The paddle speed at 100 rpm and bath temperature at 37 ± 0.5°c were maintained through out the experiment. A sample of microcapsules equivalent to 100 mg of aceclofenac was used in each test. Aliquot equal to 5ml of dissolution medium was withdrawn at specific time interval and replaced with fresh medium to maintain sink condition. Sample was filtered through Whatman No. 1 filter paper and after suitable dilution with medium; the absorbance was determined by UV spectrophotometer (SHIMADZU 1700) at 275 nm. All studies were conducted in triplicate (n=3). The release of drug from marketed SR tablet was also studied to compare with release from microcapsules.

Data analysis:

The data obtained from in vitro drug release study was fitted into models of data treatment as: zero order kinetics, first order kinetics, Higuchi square root model and Hixson-Crowell cube root model. [15]

Table 1: % encapsulation efficiency, % yield and wall thickness of ethyl cellulose coated microcapsules

Sr. No.	Particle Size (μm)	% Entrapment Efficiency	% Yield	Wall thickness
1	1350	24.56% (1.23) *	29.69 (1.03)*	168.32
2	855	32.54% (1.16)	30.55 (0.8)	123.45
3	532.5	41.45% (1.34)	40.34 (1.45)	66.32

*Figures in parentheses are coefficients of Variation (CV) values.

Table 2: Drug Release Kinetics

Size Range	Zero order		First order		Higuchi Model		Hixson-Crowell	
Mesh No. (#)	Equation of Line	Reg. Coef (R^2)	Equation of Line	Reg. Coef (R^2)	Equation of Line	Reg. Coef (R^2)	Equation of Line	Reg. Coef (R^2)
10/16	y = 1.3602x + 4.7967	0.8905	y = - 0.0725x + 1.9543	0.9167	y = 50.92x + 3.9873	0.9337	y = - 0.0794x + 3.3163	0.8786
16/22	y = 1.2738x + 6.2689	0.8017	y = -0.0630x + 1.8717	0.9059	Y=51.255x + 5.3970	0.9251	y = -0.0895x + 2.9249	0.8874
22/44	y = 1.2934x + 5.7689	0.8812	y = -0.0543x + 1.1756	0.9267	y = 56.456x +4.6780	0.9432	y = - 0.0657x + 3.3312	0.8765

Results and Discussion:

Ethyl cellulose microcapsules containing Aceclofenac were prepared by an emulsion solvent evaporation method employing chloroform as solvent. The microcapsules were obtained in various size ranges and were found to be discrete, free flowing and spherical as evident from micro photographic study. The sizes could be separated and a more uniform size of microcapsules could readily be obtained. The size analysis of different microcapsules showed that generally about 16%, 34% and 40% were in the size range of -10+16 (1350 µm), -16+22 (855 µm), - 22+44 (532.5 µm) mesh size respectively. Aceclofenac release from microcapsules was studied in phosphate buffer pH 6.8 for a period of 12 hours. Aceclofenac release from pure drug was found to be in 5 minutes whereas Aceclofenac release from microcapsules was slow and spread over an extended period of time. The best fit with highest correlation coefficient was observed in Higuchi model indicating diffusion controlled principle. [16, 17] Equation of straight line and the 'r' values are given in Table 3.The drug release from microcapsules depends on the size of the microcapsules. The chloroform employed as a solvent serves as a promising solvent for preparing ethyl cellulose microcapsules for controlled release as slow, controlled and complete release of aceclofenac over a period of 12 hrs was obtained.

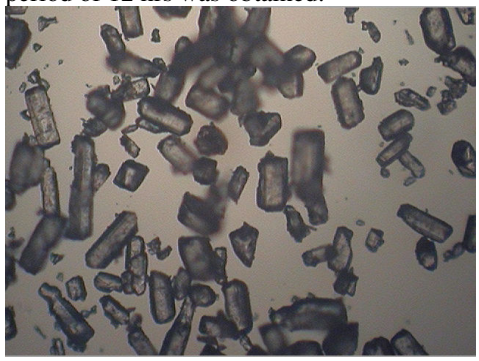

Fig. 1: Photomicrograph of Aceclofenac Magnification 200x.

Fig. 2: Photomicrograph of ethyl cellulose coated microcapsules, Magnification 200x.

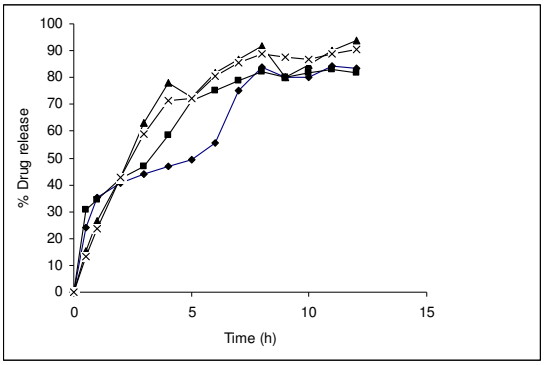

Fig. 3: Comparative Release profile
◆ # 10/16 ▲ SR
■ # 16/22 X # 22/44

Conclusion:

The present study illustrates the utility of microcapsules in extending the release of drug.

Microcapsules provide sustained release in localized areas and can be employed to reduce medication doses and its frequency. It was found that with decrease in particle size, Wall thickness of microcapsules also

reduced and therefore resulted in enhanced entrapment efficiency. Oral delivery is also desirable for medications that are effective upon intestinal absorption and can be administered with microcapsules that are unaffected by the stomach. Broad scope application of microcapsule systems requires testing on case-by-case studies and it may not always be clear how systems will perform during in vivo tests as compared to their controlled laboratory counterpart environment.

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