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DESIGN AND EVALUATION OF MUCOADHESIVE MICROCAPSULES OF ACECLOFENAC BY SOLVENT EMULSIFICATION METHOD

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Abstract:
The main objective of this investigation was to prepare and characterize different concentration and different combination of rate retarding polymer ethylcellulose, Eudragit L100 and mucoadhesive polymer Carbopol 940 by solvent emulsification method to increase the residence time and controlled the drug release. The prepared microcapsules was found to be discrete, spherical and free flowing .The percent yield was found to be between 78.61% to 88.60% and encapsulation efficiency was found to be 90.78% to 97.84%. The microcapsules showed good mucoadhesive property in in vitro wash off test. The drug release was found to be followed first order release pattern and fit into Higuchi model. Hence the prepared mucoadhesives microcapsules was suitable to control the drug release and increase the residence time at target site specifically.

Key Words: Aceclofenac, mucoadhesive microcapsules, Higuchi model, emulsification method.

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INTRODUCTION:

The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible. Among the various approaches for controlled systems, microencapsulation process have gained good acceptance as a process to controlled release and drug targeting [1]. The Gastric residence time is very short, the drug transit small intestine within 3hr and in fasting it is 1 hr, hence it is very difficult to control the drug release and this gastric residence time phenomenon leads to reduction in absorption of drugs. Mucoadhesion, an interfacial phenomenon is based on two materials, one of which is mucus layer of mucosal tissue to which the drug is held together by means of interfacial forces for prolonged period of time [2, 3]. Aceclofenac is a nonsteroidal anti-inflammatory used in the treatment of osteoarthritis, rheumatoid arthritis, post-traumatic pain, spondylitis etc. Aceclofenac is rapidly and efficiently absorbed after oral administration but has short biological half life of 4-4.3 hrs [4, 5, 6], hence an attempt was made to formulate aceclofenac mucoadhesive microcapsules which will increase the residence time due to its mucoadhesive property

MATERIALS AND METHODS:

Aceclofenac was obtained from Research Lab Mumbai, Eudragit RL100 from Degussa India Pvt Ltd., Ethyl Cellulose, Petroleum ether, Acetone, Liquid Paraffin, Magnesium Stearate were obtained from SD Fine Chemicals, Mumbai, Materials and excipients used in preparing microcapsules were of Pharma grade.

Formulation of Aceclofenac Mucoadhesive Microcapsule

Aceclofenac was prepared by solvent Emulsification method. Different concentration of release rate retarding polymer like Ethyl cellulose & Eudragit RL100 and Mucoadhesive polymer Carbopol 940 was dissolved in acetone separately by using a magnetic stirrer .Pure Aceclofenac and magnesium stearate were dispersed in the polymeric solution. The resulting mixture was then poured into beaker containing the mixture 300ml of liquid paraffin light and 30ml n-hexane, while stirring. Stirring was continued for 3to 4h, until acetone evaporated completely. After evaporation of acetone, the microcapsules formed were filtered using Whatmann no.1 filter filter paper. The residue was washed with 4-5 times in 50ml petroleum ether (40^0 C- 60 ^{0} C) each. Microcapsules were dried at room temperature for 24 h under vacuum [7].

Aceclofenac mucoadhesive microcapsules were prepared by using different concentration of polymer given in Table No 1.

Table 1: Formulations of the Mucoadhesive Microcapsules of Aceclofenac

Formulation	Drug (mg)	Ethyl Cellulose (mg)	Eudragit RL100 (mg)	EC + Eu RL100 (mg) 1:1	Carbopol 934 (10% of polymer wt) mg	Magnesium Stearate (mg)	Drug: Polymer
1	100	200	-	-	20	100	**1:2**
2	100	300	-	-	30	100	**1:3**
3	100	400	-	-	40	100	**1:4**
4	100	-	200	-	20	100	**1:2**
5	100	-	300	-	30	100	**1:3**
6	100	-	400	-	40	100	**1:4**
7	100	-	-	100 + 100	20	100	**1:2**
8	100	-	-	150 + 150	30	100	**1:3**
9	**100**	-	-	**200 + 200**	**40**	**100**	**1:4**

Evaluation of Mucoadhesive Microcapsules:

Percent Yield:
Microcapsules dried at room temperature were than weighed and the yield of microcapsules was calculated using the formula [8]:

$$\text{Percent yield} = \frac{\text{The amount of microcapsules obtained (g)}}{\text{The theoretical amount (g)}} \times 100$$

Determination of Particle Size:
The microcapsules were separated into different size fractions by sieving for 15min using standard sieves having aperture of 250 µm, 325µm , 430µm.The particle size distribution of the microcapsules for all formulations determined and mean particle size of microcapsules were calculated. Results of particle size shown in table no2

Efficiency of the Microcapsules:
Microcapsules were crushed and powdered by using a mortar. Accurately weighed 10mg of this powder was extracted in 10ml of methanol. 1ml of this solution is diluted up to 100ml with phosphate buffer & assayed spectrophotometrically [9] at 276 nm to determine the aceclofenac content of the microcapsules.

***In Vitro* Wash-Off Test for Mucoadhesion:**
The mucoadhesive property of the microcapsules was evaluated by an *in vitro* adhesion testing method known as wash-off method. The mucoadhesiveness of these microcapsules was compared with that of non-bioadhesive material, ethylene vinyl acetate microcapsules. Pieces of intestinal mucosa (2x2 cm) were mounted on to glass slides (3x1 inch) with cyanoacrylate glue. About 100 microcapsules were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of a USP tablet disintegrating test machine the tissue specimen was given a slow regular up and down moment in a test fluid at 37^0 taken in a 1 Liter vessel of the machine. At the end of 30 min., 1 h and later at hourly intervals up to 12 h, the machine was stopped and the number of microcapsules still adhering on to the tissue was counted [10-13]. The test was performed in Phosphate buffer of pH 7.4 shown in table no 4.

Scanning Electron Microscopy: Shapes and surface characteristics of the microcapsules were investigated and photographed using scanning electron microscope.

***In vitro* Drug Release Studies Of Microcapsules:**

In vitro drug release studies of microcapsules of Aceclofenac were carried out using USP XXVI dissolution test apparatus type-I (rotating basket method), in Phosphate buffer of pH 7.4 (900 ml). The basket was rotated at 100 rpm. The temperature was maintained at 37 ± 0.5^0C.A quantity of microcapsules equivalent to 100 mg of aceclofenac were tied in a muslin bag and kept in the basket. 5 ml samples of dissolution fluid were withdrawn at regular intervals. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution fluid to maintain sink condition. The samples were filtered, diluted and analyzed by UV-Spectrophotometer at 276nm .For all the formulations, the dissolution were carried out for triplicates.

RESULTS AND DISCUSSION:

Evalution of Mucoadhesive microcapsules of Aceclofenac

Particle Size Distribution:
The sieve analysis results of all formulation of microcapsules were shown in Table No 2 .The major fraction in all the microcapsules having a size range of 250-325 µm .Percentage of microcapsules passed through sieve no 44 & retained on sieve no 60 were 39.01%, 48.19%, 48.50%, 48.35%, 44.49%, 48.65%, 48.46%,48.88%,49.11% for F1, F2, F3, F4, F5, F6, F7, F8, F9, .As shown in fig No1. Higher conc. of polymer which produced a more viscous dispersion & consequently larger microcapsules. Thus as the polymer conc. Increases the microcapsules size also get increased.

Table 2: Particle Size Distribution of Microcapsules

Formulation	below 60	44/60	25/44	above25
1	2.22	39.01	34	**9.22**
2	2.40	48.19	35.11	**9.45**
3	3.11	48.50	34.99	**9.90**
4	2.13	48.35	33.89	**9.45**
5	2.43	48.49	34.75	**9.88**
6	3.04	48.65	35	**9.89**
7	2.22	48.46	34.58	**9.66**
8	2.55	48.88	35	**10**
9	**3**	**49.11**	**35.28**	**10.33**

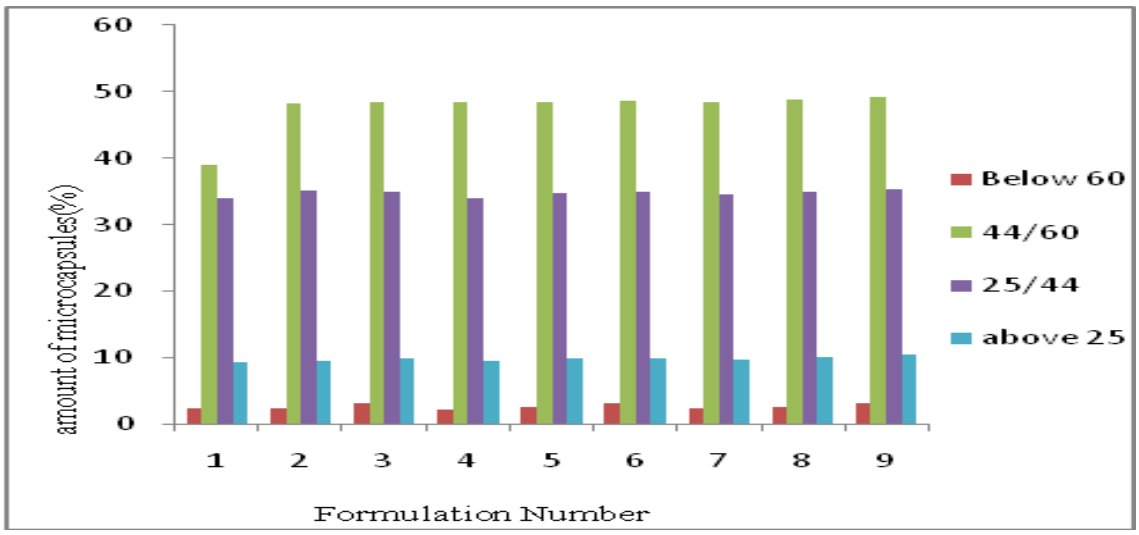

Fig.No.1 Particle Size Distribution

Encapsulation Efficiency and Percent Yield: The microcapsules were found to be discrete, large, spherical, free flowing. Encapsulation Efficiency in range of 97.84%, 92.72%, 90.78% for F1, F2, F3 formulation 97.75% 94.01% 90.84% for F4, F5, F6 formulations 97.81%, 93.53%, 91.90% for F7, F8,F9, formulations and Percent yield for F1, F2,F3 formulations were 82.89%, 78.61 %, 88.60%,For F4, F5, F6,formulations 81.93%, 68.91%, 87.49%, and 84.78% , 84.44%, 80.48%,for F7, F8, F9 formulations. The Percent yield & Encapsulation Efficiency were high for all the microcapsules obtained.

Table 3: Percent Yield and Percentage Encapsulation Efficiency

formulations	wt taken (mg)	%drug (mg) practical	%drug (mg) theoretical	%yield	%Encapsulation Efficiency
F1	100	30.16	25.00	82.89	**97.84**
F2	100	21.00	16.51	78.61	**92.72**
F3	100	17.20	15.24	88.60	**90.78**
F4	100	14.28	11.70	81.93	**97.75**
F5	100	22.10	15.23	68.91	**94.01**
F6	100	17.43	15.25	87.49	**90.84**
F7	100	29.98	25.42	84.78	**97.81**
F8	100	22.43	18.94	84.44	**93.53**
F9	**100**	**17.42**	**14.02**	**80.48**	**91.90**

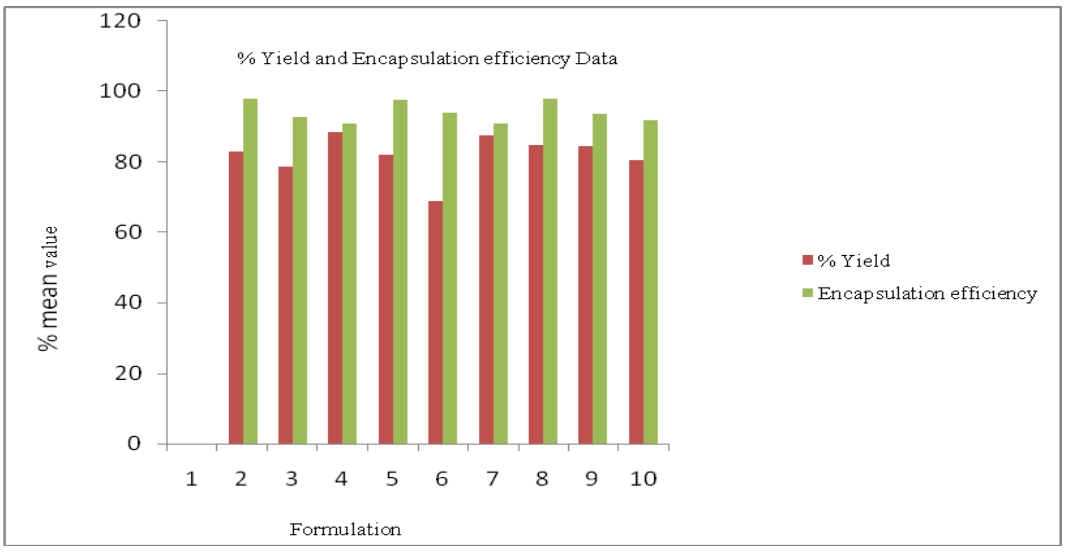

Fig 2: Percent Yield and Encapsulation Efficiency

In Vitro Wash off Test:

The wash-off was slow in the case of microcapsules containing coat of Carbopol 934 mucoadhesive polymer when compared to that of Ethylene vinyl acetate. As the concentration of Carbopol 934 is increased the mucoadhesion is also increased .The results of wash-off test as shown in Table No. 4, indicates that all the formulations has fairly good mucoadhesive property.

Table 4: Results of in *vitro* Wash off test

Formulation	% of Microcapsules Adhering to Tissue at 7 times (hr) Phosphate buffer pH 7.4				
	1	**2**	**4**	**6**	**8**
F1	20	25	22	15	12
F2	60	46	39	24	10
F3	70	59	47	32	25
F5	42	37	24	18	8
F6	49	33	20	12	10
F7	58	53	43	31	17
F9	55	41	27	12	10
EVA	23	11	3	-	-

Scanning Electron Microscopy:

SEM photograph of microcapsules as is free flowing, spherical in shape having smooth surface and uniformly coated with polymer**.**

***In vitro* Drug release:**

From the *in-vitro* dissolution data, it was found that the drug release studies from formulations containing Ethyl cellulose as polymer was 90.1%, 84.29%, 88.50%, in 720 min for F1, F2, F3 formulations, with Eudragit RL 95.21%, 95.41%, 95.61% in 420min and with combinations (EC + Eu RL 100) 97.25% in 540 min, 97.54% in 660 min, 97.69 % in 720min for M7, M8, M9 formulations. Percent of drug release shown in figure no 3.

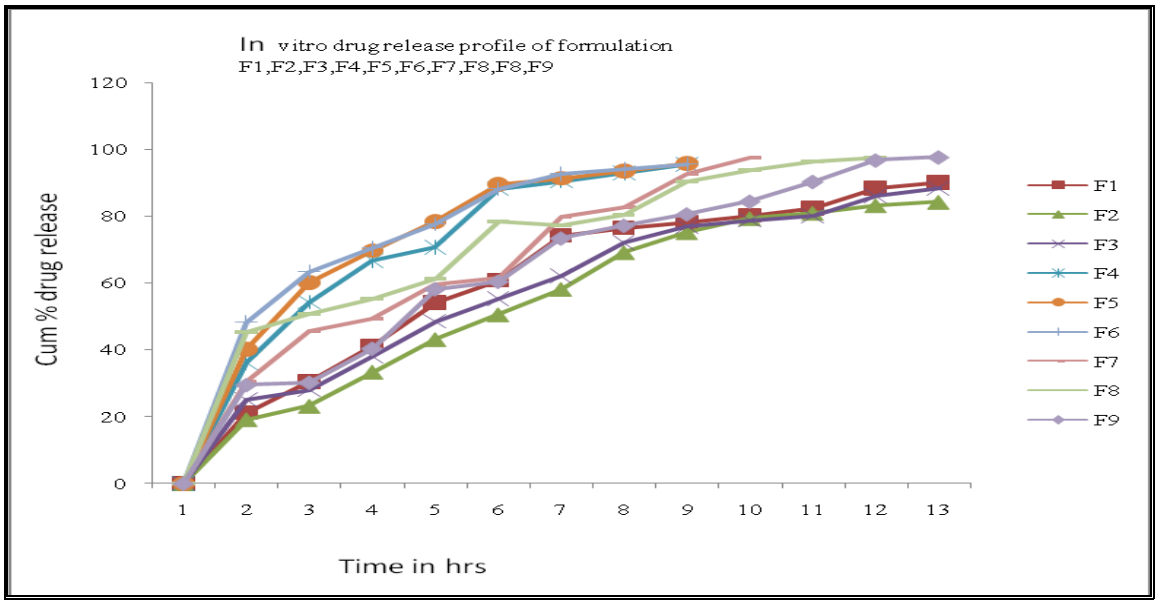

Fig 3: In vitro Drug Release Profile

CONCLUSION:

From the above investigation it was found as the concentration of polymer increases which intern increases the viscosity of dispersed phase and sphericity of microcapsules but optimization of stirring speed, polymer :drug ratio is important because increase in stirring speed reduces the microcapsules size. The drug release mechanism was found to be first order and nonfickian.Through this formulation maximum residence time of drug and dosage frequency can be achieved hence Mucoadhesive microcapsules of aceclofenac gives sustained release of drug.

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