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SPREADING OUT OF ACECLOFENAC SUSTAINED RELEASE MICROCAPSULES BASED ON HPMC 50 CPS BY EMULSION SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT: Sustained released Aceclofenac microcapsules based on synthetic hydrophilic polymer hydroxypropyl methylcellulose (HPMC) were developed in this study in an attempt to design a dosage form that would manifest desirable release profile. W/O emulsion solvent evaporation technique was employed. Various release retarding agents were used to provide the analgesic and anti-inflammatory action of aceclofenac for prolong period of time. Microcapsules were prepared at a fixed stirring rate of 1000 rpm. Polymeric solution containing aceclofenac was emulsified by light liquid paraffin (LLP) which was initially emulsified by 1% (w/w of the continuum) lipophilic surfactant Span 80. The formulated microcapsules were evaluated for drug-polymer drug loading efficiency, micromeritic properties, surface morphology study, *in-vitro* drug release kinetics. It was found that all formulations showed satisfactory flow behavior. The maximum loading efficiency of was found to be 87.42%. SEM study showed that the microcapsules were discrete and spherical shaped. Efficacy of the dosage forms were evaluated in terms of *in-vitro* dissolution studies which showed statistically significant difference among the drug release profile from different polymeric blend as well as their increasing concentration. However, by increasing the polymer concentration, the rate of drug release from the microcapsules decreases dramatically. Drug release from all formulations followed Korsemeyer-Peppas kinetics and release mechanisms followed non-Fickian or anomalous type release.

INTRODUCTION: Aceclofenac, is a non-steroidal anti-inflammatory drug (NSAID) used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is an effective analgesic and anti-inflammatory agent with a good tolerability profile.

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Through its analgesic and anti-inflammatory properties, Aceclofenac provides symptomatic relief in a variety of painful conditions.

Aceclofenac is a newer derivative of diclofenac having less gastrointestinal complication which acts by blocking the action of cyclo-oxygenase, which is produced by prostaglandins. The usual therapeutic dose and dosing frequency of conventional Aceclofenac tablets is high (100 mg twice daily), because of the short biological half-life of the drug (3-4 h); makes it an ideal candidate for modified release dosage forms.

To reduce the frequency of administrations and to improve patient compliances, once-daily sustained release dosage forms of Aceclofenac is desirable [1].

The development of sustained release dosage forms through microspheres has received more attention, now days. Some of the advantages of controlled release microspheres as drug delivery devices include reduced dosage, decrease in systemic side effects, reduced frequency of administration, and, therefore, increased patient compliance [2].

Microspheres are one of the multiparticulate drug delivery systems prepared to obtain prolonged and controlled drug delivery, to improve bioavailability or stability and to target specific sites. Microspheres can be defined a solid, approximately spherical particles ranging from 1 to 1000 µm, containing dispersed drug in either as solution or as microcrystalline form [3, 4].

The commonly employed methods for the preparations of microspheres are, emulsion solvent evaporation method [5], phase-separation method and spray drying method [6]. The choice of the method depends on many factors such as the drug solubility, partition co-efficiency, polymer composition, molecular weight etc. For instance, emulsion solvent evaporation technique may be a method of choice for the preparation of microspheres of water insoluble drugs [7, 8].

In the emulsion solvent evaporation method, the water insoluble drug and polymer are dissolved in an organic phase, emulsified to form W/O emulsion, evaporated the organic phase and the microspheres so formed are filtered and dried.

Since, Aceclofenac is a water insoluble drug; emulsion solvent evaporation technique is selected for the preparation of sustained release microspheres.

The focal objective of this experiment was to investigate the possibility of obtaining sustained release formulation of Aceclofenac microcapsules by emulsion solvent evaporation technique.

The prepared microcapsules were evaluated for various physicochemical properties and *in-vitro* release rates from these formulations.

MATERIALS AND METHODS:

Materials: Aceclofenac was received as a gift sample SQUARE Pharmaceuticals Ltd., Bangladesh. HPMC 50 cps (Colorcon Asia, India), Kollidon SR (BASF, Germany), Ethyl cellulose 14 cps (BDH Laboratories Supplies, England), Eudragit RS-100 (EVONIK, Germany), Eudragit RL-100 (EVONIK, Germany), HPMC 15 cps (Colorcon Asia, India), Light Liquid Paraffin (MERCK, Germany), Span 80 (S. D. Fine Chemical Limited, Mumbai, India), Ethanol (MERCK, Germany), Acetone (MERCK, Germany), Cyclohexane (MERCK, Germany) of laboratory grade were purchased from the local market.

Methods:

Preformulation studies: Preformulation study is one of the important prerequisite in development of any drug delivery system. It gives the information needed to define the nature of the drug release is either dissolution or diffusion. The release profile from microcapsules depends on the nature of the polymer used in the preparation as well as the nature of the drug. Hence, preformulation studies on the drug Aceclofenac for identification including solubility analysis, melting point determination and compatibility studies were performed.

Identification: The sample Aceclofenac was examined by Fourier Transform Infrared (FTIR) spectroscopic analysis and compared the spectrum with the reference standard FTIR spectrum of Aceclofenac.

Solubility analysis [1, 9]: An excess quantity of Aceclofenac was added to various solvents such as 10 ml of distilled water, acetone, 0.1 N HCl, phosphate buffer pH 6.8, phosphate buffer pH 7.0 and subjected to ultrasonication for 24 hours at room temperature. The solution was then filtered through Whatmann filter and after making suitable dilutions the amount of drug dissolved in various solvents was analyzed spectrophotometrically.

Melting point determination: Melting point determination is a good first indication of purity of the drug. The presence of relatively small amount of impurity can be detected by a lowering as well

as widening in the melting point range. Melting point of Aceclofenac was determined by using capillary tube method.

Compatibility study: Compatibility of Aceclofenac with different polymeric blend was confirmed by Fourier transform infrared (FTIR) spectroscopic analysis. The spectra were recorded for pure Aceclofenac alone and Aceclofenac loaded microcapsules using FTIR to observe whether any change appear in the chemical constitution of Aceclofenac after combining it with the excipient. Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The mixtures got were taken in a diffuse reflectance sampler and FTIR spectra recorded by scanning in the wavelength region of 400 to 4000 cm^{-1} in a FTIR Spectrophotometer (FT-IR8400S, Shimadzu, Japan).

Formulation studies:

Preparation of Aceclofenac microcapsules: Aceclofenac microcapsules were prepared by W/O emulsion solvent evaporation technique which is a slight modification of the Tsai technique [10]. 100 ml Light liquid paraffin (LLP) containing 1% span 80 was taken in a beaker (external phase). Aceclofenac was then suspended in the LLP with the help of a high speed stirrer (WisdStir HS-30D, LabTech, Korea).

The internal phase of polymeric solution was prepared by dissolving polymer (according to **table 1**) in combination of ethanol and acetone at a ratio of 5:5 with the help of a vortex mixer (VM-2000, Digisystem Laboratory Instruments Inc., Taiwan).

Previously prepared polymeric phase was added drop wise to the external phase with continuous stirring at 1000 rpm. After 2.5 hours of stirring, hard and spherical shaped microcapsules were found.

Formulated microcapsules were then filtered and washed with cyclohexane for several times until complete removal of the oil phase from the microcapsules and allowed to dry in natural air to obtain free-flowing microcapsules.

TABLE 1: FORMULATIONS OF ACECLOFENAC MICROCAPSULES

Formulation Code	Core: Polymer Ratio	Polymer Composition (1: 1)
F1	1:1	HPMC 50 cps: Kollidon SR
F2	1:1	HPMC 50 cps: Ethyl cellulose 14 cps
F3	1:1	HPMC 50 cps: Eudragit RS-100
F4	1:1	HPMC 50 cps: Eudragit RL-100
F5	1:1	HPMC 50 cps: HPMC 15 cps
F6	1:2	HPMC 50 cps: Kollidon SR
F7	1:2	HPMC 50 cps: Ethyl cellulose 14 cps
F8	1:2	HPMC 50 cps: Eudragit RS-100
F9	1:2	HPMC 50 cps: Eudragit RL-100
F10	1:2	HPMC 50 cps: HPMC 15 cps

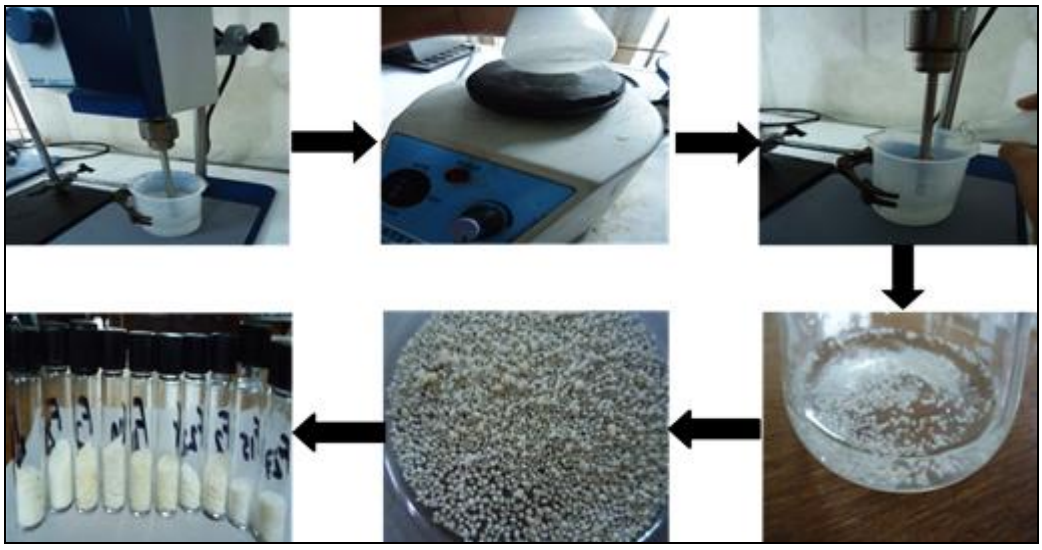

FIGURE 1: ILLUSTRATION OF STEPS INVOLVED IN PREPARATION OF ACECLOFENAC MICROCAPSULES

Evaluation of Formulated Microcapsules:

Quantitative analysis of Aceclofenac: Aqueous solutions of Aceclofenac (0 to 20 µg/ml) in phosphate buffer (pH 6.8) were prepared and the absorbance was measured at 274 nm by a SHIMADZU UV-VIS Spectrophotometer (UVmini-1240, Shimadzu Corporation, Japan). A linear line was obtained while absorbance values were plotted against concentrations ($R^2 > 0.997$).

Drug loaded microcapsules of each batch were finely powdered in a glass mortar and 20 mg powder was taken in a volumetric flask. A clear solution was made using the same buffer (pH 6.8) after proper sonication (POWER SONIC 410, Hwashin Technology Co., Korea). The solution was then filtered through 0.45 µm filter and analyzed spectrophotometrically for drug content.[11]

The weight of Aceclofenac theoretically contained in the microcapsules was compared with the weight actually obtained from the drug content studies, i.e., the quantity loaded into the microcapsules formulated. To get the Aceclofenac loading efficiency, following equation was used for the calculation.

Drug loading efficiency (%) = (Actual drug content/Theoretical drug content) x 100

Micromeritic Properties [12, 13]**:**

Angle of Repose: Flow properties of microcapsules were studied by measuring angle of repose of the prepared formulations by employing fixed funnel method. Microcapsules were passed through the funnel, which was kept at a height 'h' from the horizontal surface.

So, the passed microcapsules formed a pile of a height 'h' above the horizontal surface and the radius 'r' of the pile was measured and the angle of repose was determined for all formulations.

Angle of repose, $\theta = \tan^{-1} (h/r)$

Where, h = Height of the pile and r = Radius of the pile

Surface Morphology Study: To observe the surface morphology of the microcapsules, a Scanning Electron Microscope (SEM) (JEOL, JSM-6490 LA, Japan) was used. SEM image at different magnification was taken for comparative study.

***In-Vitro* Dissolution studies:** *In-vitro* dissolution was carried out in a USP XXX apparatus 2 (Paddle Apparatus) in 900 ml of phosphate buffer (pH 6.8) of 37 $\pm$ 0.5°C at a rotational speed of 100 rpm. Dissolution Samples were withdrawn at predetermined intervals and were filtered through 0.45 µm filters. The drug content was determined in the filtrate either directly or after appropriate dilution with the dissolution media.

RESULTS AND DISCUSSION: Aceclofenac microcapsules were prepared by emulsion solvent evaporation technique. Effect of different polymeric blend on Aceclofenac microcapsules was successfully examined.

Identification: The FTIR spectrum of the sample Aceclofenac complied with the reference standard FTIR spectrum of Aceclofenac, which indicates that the obtained sample is Aceclofenac (Figure 2).

Solubility analysis: The solubility study was carried out to determine the most suitable dissolution medium for in-vitro drug release study. Aceclofenac was found to be practically insoluble in distilled water, poorly soluble in 0.1 N HCl, moderately soluble in phosphate buffer pH 6.8, phosphate buffer pH 7.0 and freely soluble in acetone. Aceclofenac showed optimum solubility in phosphate buffer pH 6.8.

TABLE 2: SOLUBILITY OF ACECLOFENAC IN VARIOUS SOLVENT MEDIA

Solvent	Solubility (mg/ml)
Distilled water	0.81
0.1 N HCl	0.018
Phosphate buffer 6.8	6.329
Phosphate buffer 7.0	8.230
Acetone	9.138

Melting point determination: The melting point of Aceclofenac was found to about 151°C, which is within reported range (149°C to 153°C) that indicates the purity of sample.

Compatibility study: Fourier transform infrared (FTIR) spectroscopic analysis was carried out to study the compatibility of pure Aceclofenac with polymer. FTIR spectrum of pure Aceclofenac is shown in figure 2. It shows the characteristic peaks at 1770.65cm^{-1}, 1714.72 cm^{-1} are due to C=O stretching vibration, peak at 2970.64 cm^{-1} is due to stretching vibration of OH group, peak at 2937.85 cm^{-1} is due to C–H stretching vibration, peak at 3317.56 cm^{-1} is due to N–H stretching vibration, peaks at 667.37 cm^{-1} is assigned to C–Cl stretching vibration. These peaks can be considered as characteristic peaks of Aceclofenac and were not found affected and prominently observed in figure 3 and 4. This ruled out the drug-polymers interaction, hence, it can be said that the drug is stable in the formulations.

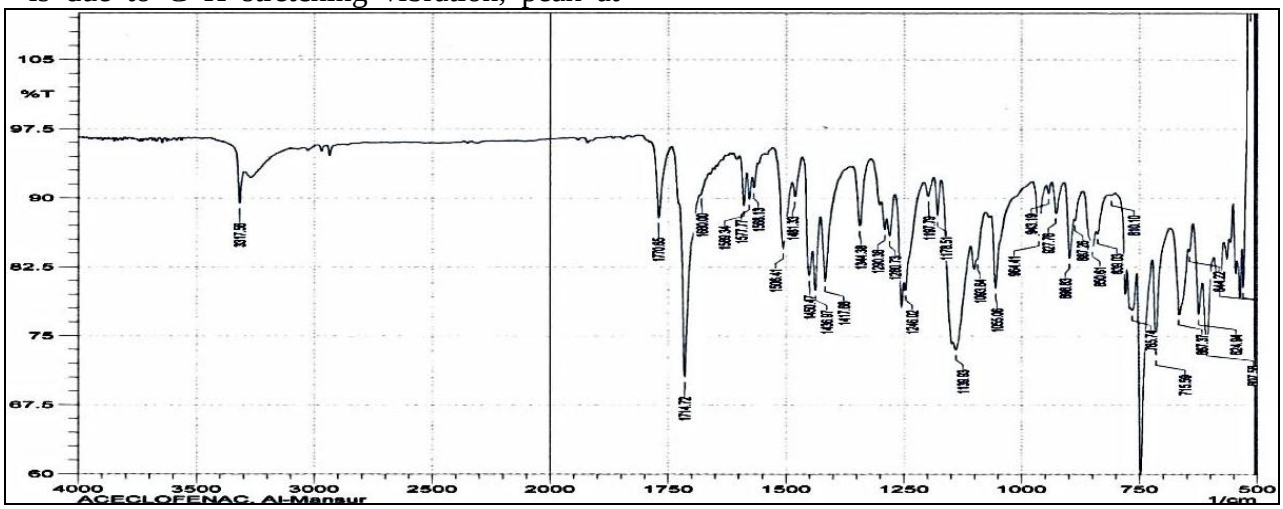

FIGURE 2: FTIR SPECTRA OF PURE ACECLOFENAC

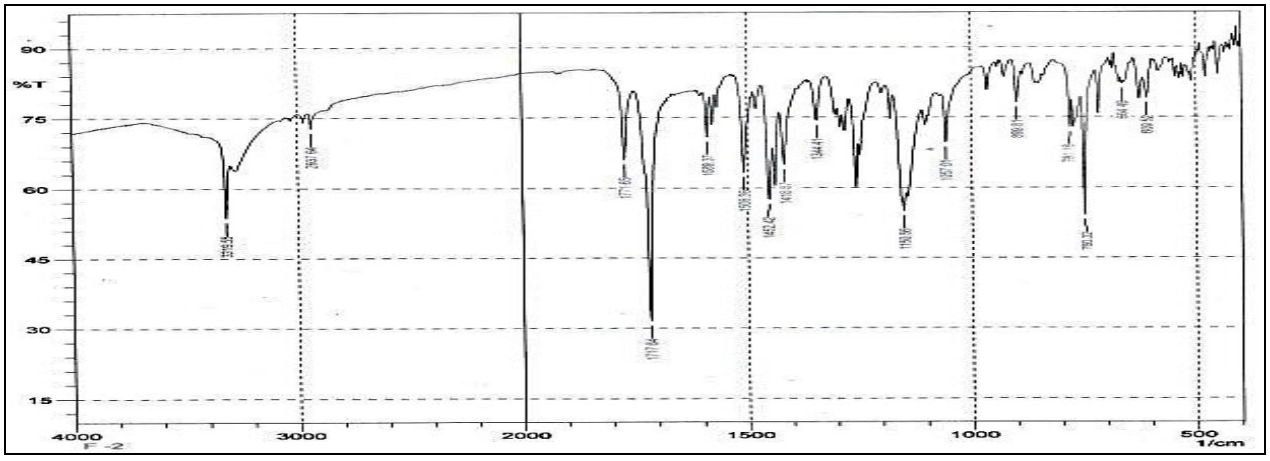

FIGURE 3: FTIR SPECTRA OF FORMULATION F2

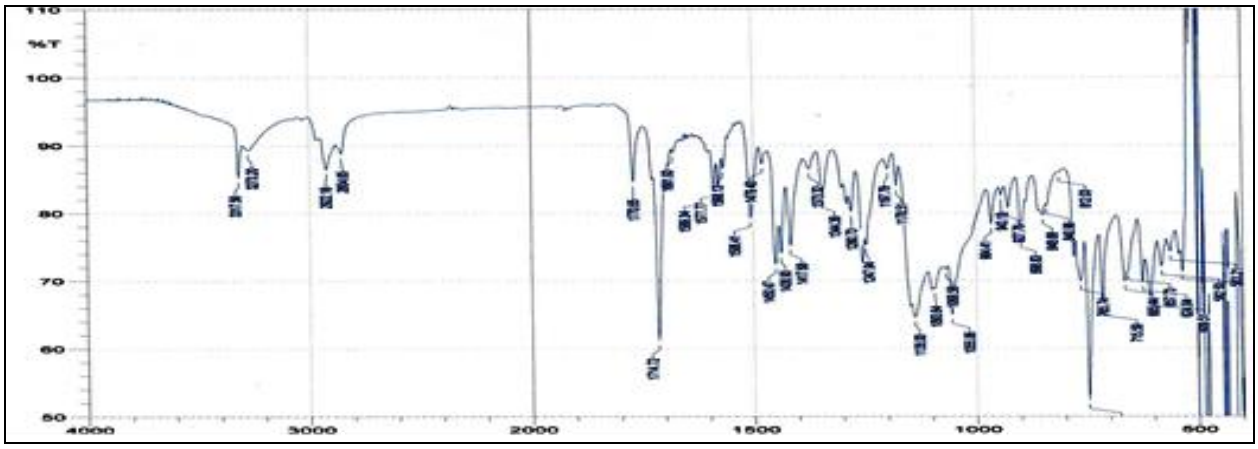

FIGURE 4: FTIR SPECTRA OF FORMULATION F8

Drug Loading Efficiency: Maximum drug loading efficiency was 87.42% for batch F8 and minimum drug loading efficiency was 54.36% for batch F1 (**Table 3**). Higher polymeric content entrapped higher amount of drug. Generally drug loading efficiency of a drug depends on the solubility of the drug in the organic solvent and continuous phase. But, an increase in the concentration of polymer in a fixed volume of organic solvent also results in an increase in loading efficiency [14].

Angle of repose: Flow property of the formulated microcapsules was characterized by measuring angle of repose. The angle of repose of microcapsule was found to be in range of 22.26 to 26.21 (Table 3). All the formulations showed excellent flow properties.

TABLE 3: DRUG LOADING EFFICIENCY AND MICROMERITIC PROPERTIES OF FORMULATED ACECLOFENAC MICROCAPSULES

Properties	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug Loading Efficiency (%)	54.36	63.13	79.38	66.23	70.87	62.24	70.24	87.42	73.63	76.19
Angle of repose (°)	22.26	25.11	26.21	25.39	24.66	26.32	26.93	28.19	27.03	26.21

Morphology of the Microcapsules: Surface morphology study of prepared microcapsules was done by Scanning Electron Microscope (SEM). SEM study showed that the prepared microcapsules were found to be discrete, spherical shaped and free flowing. The SEM photograph indicated that the microcapsules were completely covered with the coating polymer (**Figure 5**).

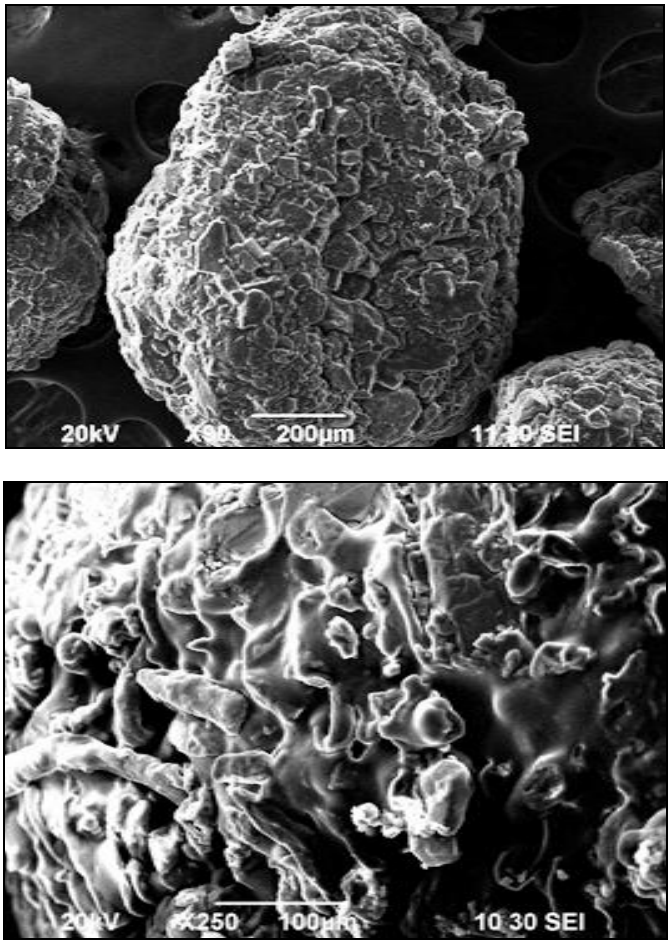

FIGURE 5: SEM IMAGE OF ACECLOFENAC MICROCAPSULE OF F8

***In-Vitro* Release Profile:** The drug release profile of all the formulations was studied in phosphate buffer (pH 6.8). The release profile for all formulations was shown in Figure 6. It is important to note that the dissolution behavior of granules and powders is greatly influenced by their wettability, surface area, and particle size distribution.[15] The release of drug takes place after complete swelling of the polymer and as the amount of polymer in the formulation increase the time required to swell also increase thereby decrease in the drug release.

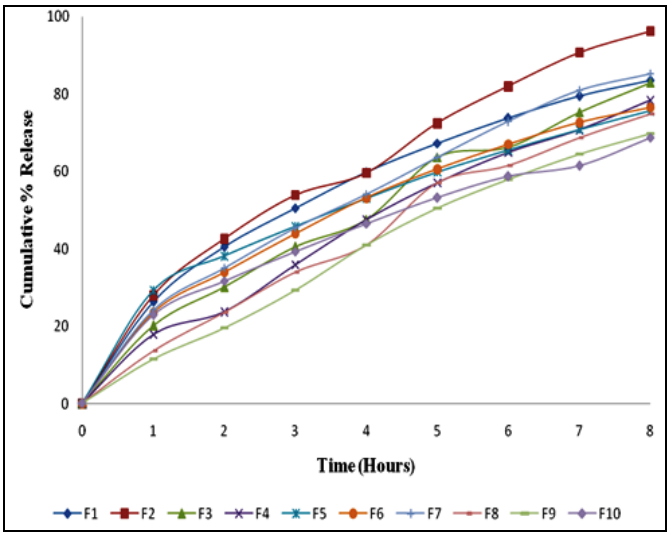

FIGURE 6: *IN-VITRO* DRUG RELEASE KINETICS OF ACECLOFENAC MICROCAPSULE FORMULATIONS

The initial burst release from formulation were F1-26.30%, F2-28%, F3-20.11%, F4-17.98%, F5-29.28%, F6-23.52%, F7-24.16%, F8-13.71%, F9-11.58% and F10-22.88%. In all formulations HPMC 50 cps was present. The hydration rate of HPMC depends on the nature of the substituent like hydroxypropyl group content.

However, decrease in drug release from microcapsule formulation with the increase of polymer concentration is a common incident. This can be explained by a decreased amount of drug present close to the surface and also by the fact that the amount of uncoated drug decreases with higher polymer concentration [16, 17]. The overall cumulative % release for formulations F1 to F10 were found to be 83.48%, 96.21%, 82.91%, 78.37%, 75.64%, 76.63%, 85.18%, 74.75%, 69.79% and 68.72% respectively. The drug release data obtained were extrapolated by Zero order, First order, Higuchi, Korsemeyer-Peppas equations to know the mechanism of drug release from these formulations (**Table 4**).[18, 19] *In-vitro* release profiles of drug from all these formulations could be best expressed by Korsemeyer-Peppas equation, at the plots showed highest linearity (R^2 = 0.982 to 0.998), where the slope value (n) ranged from 0.464 to 0.836. We know that a value of n = 0.45 indicates Fickian or case I release, 0.45 < n < 0.89 indicates non-Fickian or anomalous release, n = 0.89 indicates case II release and n > 0.89 indicates super case II release. So, the release of Aceclofenac was dominated by non-Fickian or anomalous type mechanism.

TABLE 4: RELEASE PARAMETERS OF ACECLOFENAC MICROCAPSULES

Formulations	Zero order		First order		Higuchi		Korsemeyer-Peppas	
	K_0	R^2	K_1	R^2	K_h	R^2	n	R^2
F1	9.612	0.925	-0.094	0.997	30.43	0.897	0.558	0.997
F2	11.17	0.955	-0.159	0.920	34.65	0.989	0.595	0.996
F3	9.875	0.976	-0.090	0.975	30.00	0.969	0.694	0.992
F4	9.593	0.983	-0.080	0.987	28.87	0.959	0.754	0.982
F5	8.265	0.908	-0.070	0.987	26.41	0.898	0.464	0.995
F6	8.943	0.942	-0.077	0.997	28.01	0.895	0.583	0.998
F7	10.07	0.965	-0.100	0.984	31.05	0.786	0.623	0.997
F8	9.374	0.985	-0.074	0.987	28.04	0.949	0.836	0.994
F9	8.919	0.990	-0.066	0.993	26.5	0.741	0.812	0.995
F10	7.643	0.932	-0.057	0.986	24.09	0.897	0.530	0.997

CONCLUSION: Emulsion solvent evaporation technique was found to be reproducible and may be an ideal method to prepare microcapsules of Aceclofenac. HPMC 50 cps based formulation F8 where 1:2 ratio of HPMC 50 cps and Eudragit RS-100 used, was found to be satisfactory in terms of higher drug loading efficiency (87.42%), excellent micromeritic properties (angle of repose 28.19°), 74.75% in-vitro drug release in a sustained manner with constant fashion over extended period of time 8 hours. Thus, the proposed formulation F8 can be successfully used for commercial production after an elaborate in-vivo study.

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