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Preparation and Evaluation of Aceclofenac Ethyl cellulose Micro particles using Aerosil as dispersing carrier

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ABSTRACT

Aceclofenac ethyl cellulose micro particles prepared by emulsion solvent evaporation technique were evaluated for various characteristic properties such as encapsulation efficiency, particle size & size distribution, surface morphology and drug release pattern. The optimized formulation parameters were used to prepare porous, spherical micro particles (438 µm to 665 µm) with high entrapment efficiency (74 to 86%). Drug release over a period of 12 hrs ranged from 81.2 % to 94.4 %. Aerosil was used as an inert dispersing agent to retard drug release rate from the micro particles and acetone was used to control the particle size.

Key words: Aceclofenac, Ethyl cellulose, Aerosil, micro particles, sustained release.

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INTRODUCTION

Microencapsulation is one of the techniques used to prepare sustained release formulation. The techniques of microencapsulation employing various polymers and their applications are described in standard text books. They are widely used techniques to achieve sustained, oral & parenteral controlled release products and for drug targeting [5, 8, 9]. They are also used to modify drug release and to target a drug to specific site. Microencapsulation offers greater effectiveness, lower toxicity, improved stability & bioavailability over conventional formulations [1, 10]. Microcapsules additional advantages like constant drug blood level with minimal fluctuations, steady state drug concentration within therapeutic window range, absence of therapeutic non-occupancy period, reduced dose size & dosage frequency, improved patient compliance and better and safer therapeutic management [3,6, 12].

A popular method for microencapsulation of water insoluble drug is emulsion solvent evaporation technique. Generally, the entrapment efficiency of water soluble drug is low due to drug loss from the organic emulsified polymeric phase before solidification of polymer in the microspheres [2, 7, 15]. Therefore, optimization of the process may be advantageous for the efficient entrapment of water soluble drugs.

In this present study authors made an attempt to prepare Aceclofenac ethyl cellulose micro particles by emulsion solvent evaporation technique using aerosol as a dispensing carrier to extend the period of drug release by retarding the release rate. The prepared microparticles were evaluated for drug entrapment efficiency, various micromeritic properties, surface morphology and *in-vitro* drug release pattern.

MATERIALS AND METHOD

Aceclofenac was purchased from Sigma Chemical Co., Mumbai, India. ethyl cellulose (EC) (ethoxy content: 48-49.5% w/w, viscosity:18-22cps) was obtained from Loba chemie pvt Ltd, (Mumbai, India); Dichloromethane (DCM) AR, Acetone AR, Acetonitrile HPLC and tween 80 were from Qualigenas (Mumbai, India); potassium dihydrogen ortho phosphate AR, sodium chloride and sodium hydroxide were received from SD fine chemicals (Mumbai, India). All other reagents used were of analytical grade.

Preparation of Micro Particles

Emulsion-solvent-evaporation technique [16] with some modifications was used to prepare micro particles containing. Aceclofenac Five different batches of micro particles were prepared, keeping Polymer to drug and dispersing agent ratio constant and varying the ratio of organic phase to oil phase and composition of oil phase (Table1). Ethyl cellulose and Aceclofenac were dissolved in oil phase (4% w/v EC dissolved in DCM- acetone containing 1% Aerosil); this solution was dispersed in aqueous phase (purified water containing 0.02 % w/v tween 80) and agitated at 550 rpm for 1 hour using a medium duty mechanical stirrer

(Universal motor Type-ROT-134H, Mumbai, India). The micro particles were recovered by filtration, washed with distilled water, air dried and stored in a desiccators containing fused calcium chloride as desiccant.

Table1. Composition of Aceclofenac ethyl cellulose (EC) micro particles using aerosil as dispersing Agent

Ingredients	Formulation				
	$EAAF_1$	$EAAF_2$	$EAAF_3$	$EAAF_4$	$EAA\ F_5$
Aceclofenac (g)	0.1	0.1	0.1	0.1	0.1
Ethyl cellulose(g)	0.4	0.4	0.4	0.4	0.4
Aerosil (g)	0.1	0.1	0.1	0.1	0.1
Dichloromethane (ml)	10	15	20	10	10
Acetone (ml)	10	10	10	15	20
Aqueous Phase (ml) (Purified water containing 0.02 % w/v Tween 80)	150	150	150	150	150

Evaluation of Aceclofenac micro particles

Assessment of viscosity of oil phase

The viscosities of oil phase were evaluated using an Ostwald viscometer at room temperature (30 ± 2ºC. The absolute viscosities of that solution were expressed in mPa.s.

Entrapment efficiency

Aceclofenac was extracted from micro particles after dissolving the polymer of micro particle using acetonitrile and sonicated for 2hours.filtered the resultant solution through what man Filter No41. Absorbance of the resultant solution was recorded by UV-VIS spectrophotometer (Lambda 25, Perkin Elmer, and Germany) at 275nm.
Microencapsulation efficiency was determined using the following relation:

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated practical percentage drug content}}{\text{Theoretical percentage drug content}} \times 100$$

Particle size analysis and surface morphology of micro particles

Surface morphology of Aceclofenac ethyl cellulose was studied using a scanning electron microscope (ISM 5610 LV SEM, JEOL, Datam Ltd, Tokyo, Japan). Samples were prepared on a 10 × 10 mm brass stub and coated with gold using a sputter coater (Joel auto fine coater, Japan) at accelerating voltage of 20kv at the high vacuum mode. Particle size analysis of the micro particles was carried out using a Malvern particle size analyzer (Malvern instruments, Mastersizer 2000, U.K.). Approximately 10mg of micro particles was suspended in 5ml of MilliQ water and analyzed with an obscuration index of ~5 % (measure of amount of light lost due to induction of sample against light path).

Drug release study

In vitro release study of Aceclofenac micro particles was carried out in 900ml of phosphate buffer (pH 7.2) maintained at 37±0.5ºC, with stirring speed 100rpm, using auto sampling US dissolution apparatus type 1(rotating basket) [DS8000 Disso Sr.No:0826533 Lab India]. Micro particles, equivalent to 50 mg of Aceclofenac were used for the study. 10 ml samples were withdrawn at pre-determined time intervals, filtered through a 0.45µm membrane filter, diluted suitably and analyzed using a UV spectrophotometer at 275nm.

Release kinetics

In order to understand the mechanism and kinetics of drug release, the results of the in vitro release equations like zero order (%release vs. time), First order(log% unreleased vs. time) Higuchi matrix(%release vs. square root of time), and Hixson Croswell matrix(cum% release vs. square root of time, [18].In order to define a model which will represent a better fit for the formulation ,drug release data further analyzed by Peppas equation, $Mt/M\infty=ktn$, where Mt is the amount of drug release at time t and $M\infty$ is the amount released at time∞,the $Mt/M\infty$ fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent measure of the primary mechanism of drug release.R^2 values were calculated for the linear curves obtained by regression analysis of the below plots.

RESULTS AND DISCUSSION

Aceclofenac ethyl cellulose micro particles containing aerosil as dispersing agent could be prepared by an emulsion solvent evaporation technique by using drug and polymer solvent in various ratios. Ethyl cellulose was selected as polymer because it is non-toxic, biocompatible, good film former and a good retarding agent to control the release rate. Aerosil, an inert solid dispersing carrier, was included in the formulation to extend the period of drug release [17]. Aerosil act as a retardant by reducing porosity and thus drug permeability by virtue of its hydrophobic nature. The micro particles were found to be smooth and spherical in nature.

The effect of the drug-polymer-aerosil ratio

Generally, highly sticky droplets were produced in the early period of the preparation and resulted in the droplets gathering together. Silica has tremendous surface area, high porosity and unique adsorption property [16]. It is an inorganic material which is insoluble in any organic solvents. During the preparation process of micro particles, silica commixed with the drug-polymer uniformity. The viscosity of the droplets was so reduced, which could prevent conglunation occurred between emulsified droplets and could improve the solidification of the droplets. It is a good anti-adhesion agent against the viscous characteristic of polymers [11]. What is more, it was considered to be helpful to promote the dispersibility of the drug in the microparticles. Therefore, and it would accelerate the drug release rate.

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The effect of the dichloromethane-acetone ratio

The acetone was used as a good solvent, which can dissolve drug and polymer, and can mix with bridging liquid. In the preparation process of the micro particles, the diffusion of the good solvent from the emulsion droplets into the poor solvent promoted the co precipitation of the drug and the polymer in the droplets, and the residual dichloromethane lined the sediments together to from micro particles [4]. An unsuitable ratio of dichloromethane to acetone would affect the preparation processes, and the micro particles would not be produced successfully.

Table 2 shows the influence of composition and volume of polymer solvent on particle characteristics. Polymer solvent phases (Phase O) with the following composition were investigated. Dichloromethane/Acetone: 1:1, 1.5:1, 2:1, 1:1.5 & 1:2. Phase O contained fixed amount of ethyl cellulose (400 mg) irrespective of the volume. Aqueous phase (Phase W) contained 0.02 % tween 80. Volume of Phase W was kept constant (150 ml) in all the batches.

Table 2. Characteristic properties of micro particles

Formulation code	Polymer solvent ratio (DCM/AC)	Viscosity (m ps)	Angle of Repose (°)	Percentage of compressibility Index (%)	Particle size (µm)	Drug Entrapment Efficiency (%)
EAAM $_1$	1:1	0.5444	30.850.50	22.42 ± 1.1	665.051	85.64
EAAM $_2$	1.5:1	0.5216	24.94 0.75	17.65 ± 1.2	636.203	83.84
EAAM $_3$	2:1	0.5005	22.91±0.32	15.84 ± 1.1	520.573	79.72
EAAM $_4$	1:1.5	0.4210	23.48±0.66	12.67 ± 1.2	438.774	86.04
EAAM $_5$	1:2	0.4176	21.90±0.45	14.61 ±1.2	444.978	74.90

Micro particles obtained from various composition of Phase O were all smooth, spherical and well individualized. It was observed that size of the particles reduced while the total volume of Phase O was increased, either by increasing the proportion of dichloromethane or acetone. However, particle size reduction rate was found to be higher with increasing proportion of acetone than with dichloromethane. Drug loading and drug entrapment efficiency was found to be reduced while proportion of acetone was increased.

The microencapsulation efficiency was in the range of 64.7% -86.04% (Table-2).Low values of standard deviation in percentage drug content indicate the uniformity of drug content in each batch of micro particles. The encapsulation efficiency increased with decreased the proportion of polymer solvent [13]. The low yield in some cases could be attributed to looses occurring during various steps of processing such as sticking of polymeric solution to glass container and due to washing steps) by optimizing the drug to polymer solvent ratio, stirring speed (5.5×10rpm), viscosity of emulsion phase and homogenization 550rpm for 1hrs), the particle sizes were brought down to 438.7 µm to 665µm.

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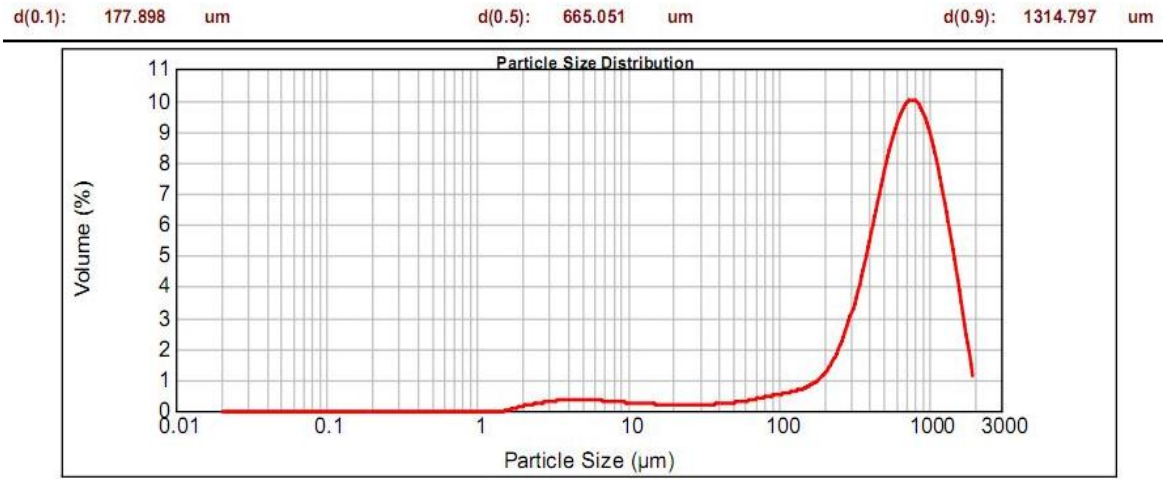
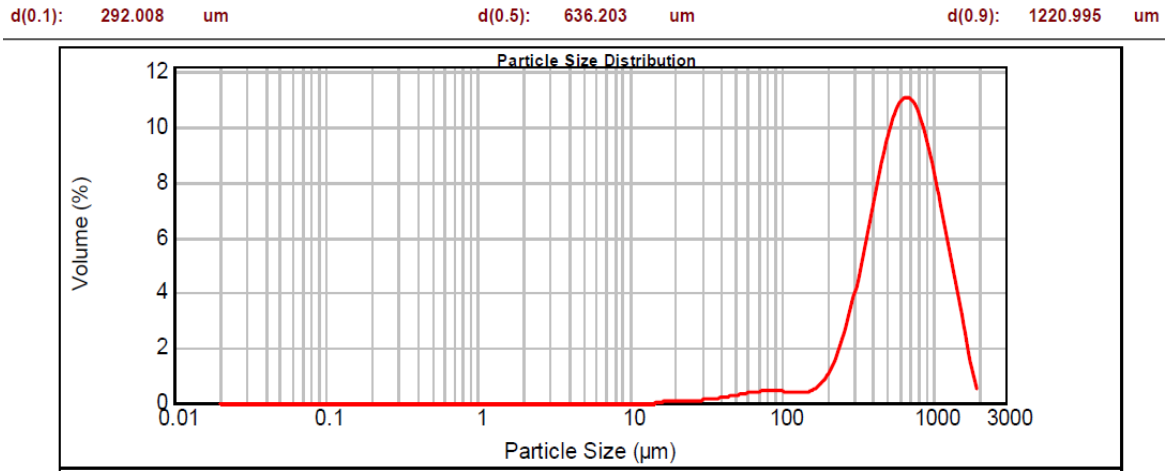
The particle size distribution grape obtained from Malvern particle sizer (U.K) shows a sharp and steep peak, indicating that the range of particle size distribution of uniform and narrow (fig 1.a,b, c, d, and e).The micro particles were found to be discrete, free flowing, spherical, smooth and were of the matrix type. The micro particles were with very narrow size range (146µm to 292µm).



a) $EAAM_1$- Average, Saturday, March 13, 2010 9:42:47 AM



b) $EAAM_2$- Average, Saturday, March 13, 2010 12:2 2:47 AM

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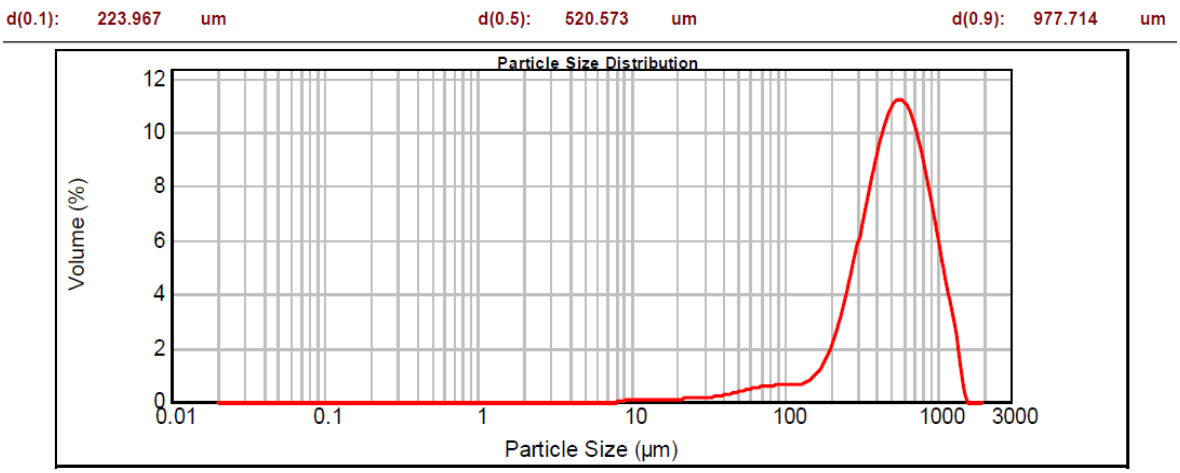
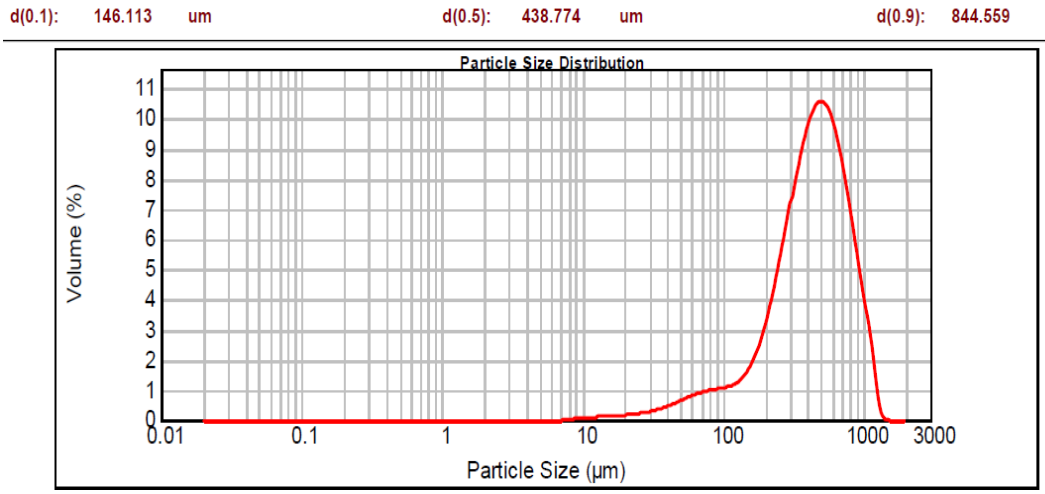
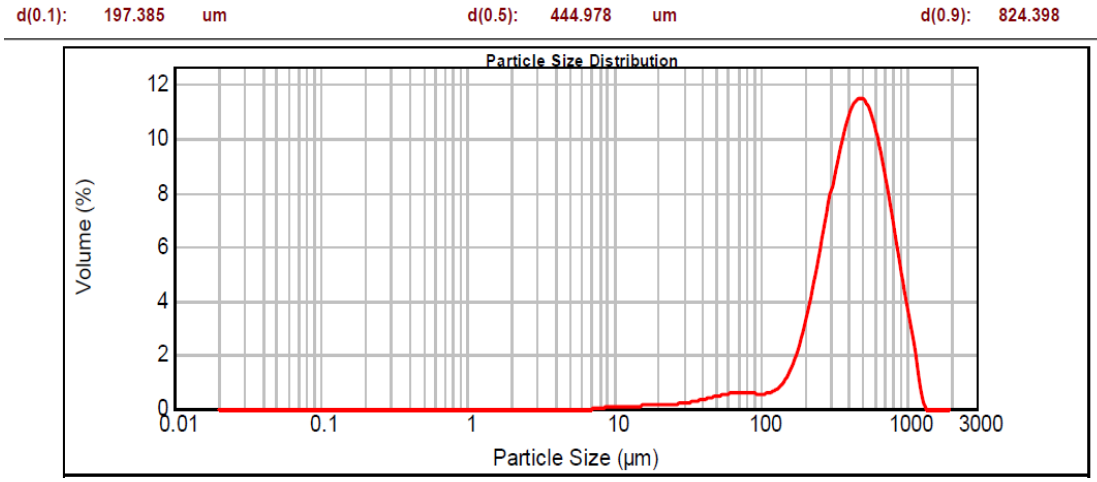


c) $EAAM_3$- Average, Saturday, March 13, 2010 11:58:47 AM



d) $EAAM_4$- Average, Saturday, March 13, 2010 11:52:47 AM



e) $EAAM_5$- Average, Saturday, March 13, 2010 10:02:21 PM

Figure 1: Particle size(µm) volume (%) distribution curve of ethyl cellulose aceclofenac aerosol micro particles.(a) $EAAM_1$,(b) $EAAM_2$,(c) $EAAM_3$, (d) $EAAM_4$,(e) $EAAM_5$ Measured in a Malvern particle sizer

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Variation in the formulations with respect to the solvent composition (DCM/AC&AC/DCM) and volume as well as proportion (Table2) had influence in physiochemical characteristic of the product. The size of the micro particles increased with reduction in the proportion of polymer solvent phase which is likely due to increased viscosity. Micro particles were of relatively larger in size (mean diameter 438µm to 665µm) and wider size ranges (146µm to 977µm). Increasing the volume of O phase caused the mean microspheres size to shift towards a smaller size range (Fig-3).Increased volume of the O phase resulted a less viscous dispersion encouraging formation of smaller droplets and consequently smaller microspheres.

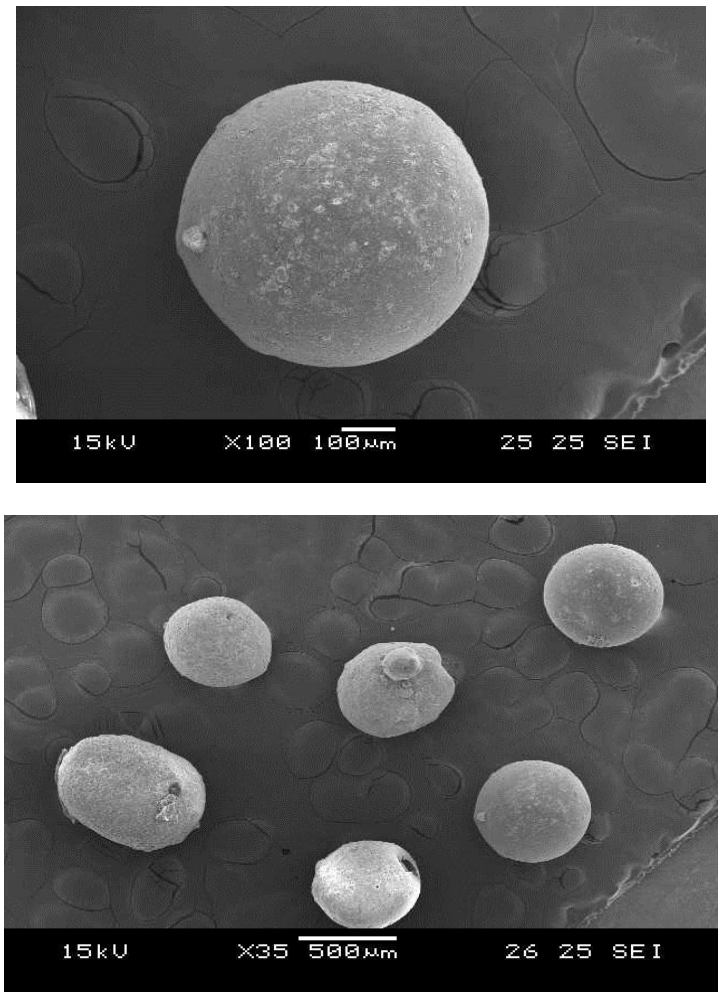

Figure 2: SEM photographs of Aceclofenac ethyl cellulose (EC) micro particles using aerosil a (EAAM), b (EAAM).

***Dissolution profiles*:**

The ultimate aim of this present work was to develop sustained release drug delivery system of Aceclofenac. It is observed from the dissolution study that concentration of ethyl cellulose offers sustained effect of the drug up to12hrs.The drug release from batches $EAAM_1$-$EAAM_5$ indicates that as the acetone ratio increased the release rate is decreased. The difference was

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significant for 12hrs with using auto sampling dissolution DS8000 apparatus. The release rate of Aceclofenac from the micro particles could be modulated with adjusting the ratio of acetone with ethyl cellulose to aerosil in the formulation with increasing release rate were in the following order $EAAM_5$< $EAAM_4$ < $EAAM_3$ < $EAAM_1$< $EAAM_2$ (Table 3, fig 3 release follows zero order kinetic after a long period of 1hrs up to 12hrs.

Table 3. Dissolution profile of Aceclofenac ethyl cellulose micro particles containing using aerosil

Time(h)	EAAM 1	EAAM 2	EAAM 3	EAAM 4	EAAM 5
0.5	0	0	0	0	0
1	4.9 ± 0.65	6.5 ± 0.29	5.8 ± 0.17	3.0 ± 0.94	3.0 ± 0.66
2	13.3 ± 1.37	13.7 ± 0.86	12.6 ± 0.92	10.2 ± 0.84	9.4 ± 0.96
3	19.7 ± 0.51	21.4 ± 0.94	20.8 ± 0.24	17.0 ± 0.66	14.8 ± 0.79
4	24.3 ± 1.08	27.1 ± 1.15	26.4 ± 1.36	21.4 ± 0.62	20.3 ± 0.94
5	32.6 ± 1.03	36.1± 1.04	34.7 ± 1.02	27.6 ± 1.12	25.4 ± 1.19
6	40.6 ± 1.15	44.6 ± 1.81	42.7 ± 1.56	34.6 ± 1.12	32.8 ± 1.66
7	44.8 ± 1.18	49.3 ± 1.06	47.9 ± 1.37	40.3 ±1.67	38.2 ±1.56
8	57.9 ± 0.72	64.7 ± 0.78	59.8 ± 1.63	53.8 ± 1.19	51.6 ± 1.13
9	65.6 ± 1.12	73.8 ± 1.55	68.2 ± 0.78	62.8 ± 1.82	59.8 ± 1.63
10	74.3 0.93	82.6± 1.45	78.3 ± 0.71	74.8 ± 1.88	69.6 ± 1.09
11	81.4 ± 1.51	87.4 ± 2.14	84.1 ± 1.74	82.7 ± 1.73	77.6 ±2.13
12	90.2 ± 0.83	94.4 ± 1.29	91.6 ± 2.18	85.6 ± 0.53	81.2 ± 1.32
T50	3.4	4.4	4.7	3.1	4.3

The values are Mean ± SD, for N=6

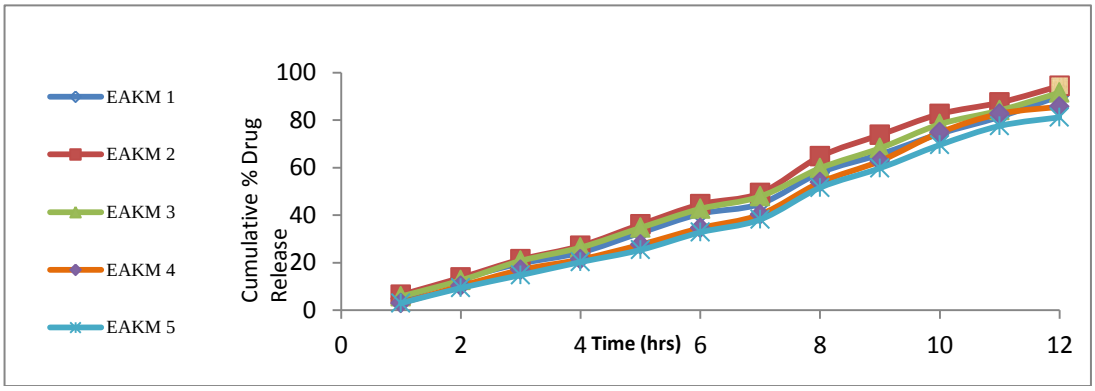

Figure 3: *In vitro* dissolution of Aceclofenac ethyl cellulose micro particles containing using aerosil

Release kinetic

The *in vitro* release profile was analyzed by various kinetic models. The kinetic models used were zero order, first order, Higuchi model, Hixson Croswell model equations (Table-4).The release constant were calculated from the slope of the respective plots. Higher correlation was observed in the Highchi equation. (R^2:0.936-0.962).To confirm the diffusion mechanism, the data were fitted into peppas equation [14]. The formulation showed good linearity (R^2:0.9950-0.9989), with slope (n) values ranging from 0.691-0.698, indicating that

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diffusion was the predominant mechanism of drug release from these formulations. The release profile of aceclofenac from all these formulation displayed very poor fitting with Hixson Crowell cube root model of drug release which were related with method of manufactured.

Table 4. Various parameters of the model equations on the in vitro release kinetics table

Batch	Zero- order		First- order		Higuchi Matrix		Hixson Croswell Matrix		Peppas Equation	
code	R^2	K_0	R^2	K_1	R^2	K_{hg}	R^2	K_{hx}	R^2	n
$EAAM_1$	0.994	17.343	0.888	-0.154	0.955	4.19	0.943	-0.154	0.9953	0.692
$EAAM_2$	0.996	17.343	0.816	-0.154	0.962	4.19	0.913	-0.425	0.9975	0.695
$EAAM_3$	0.996	18.350	0.894	-0.169	0.962	4.19	0.949	-0.460	0.9989	0.698
$EAAM_4$	0.984	18.252	0.902	-0.157	0.936	4.19	0.940	-0.438	0.9965	0.693
$EAAM_5$	0.986	17.255	0.921	-0.137	0.937	4.19	0.951	-0.394	0.9950	0.691

CONCLUSION

Micro particles of Aceclofenac were prepared by using an emulsion solvent evaporation technique by changing the drug to polymer ratio using combination of aerosil, an inert dispensing agent, and ethyl cellulose a release retardant by this method. The formulation factors, drug-polymer-aerosil and DCM –AC ratio were found to have an effect on the characteristics and release behavior of the micro particles. The drug could be incorporated into a suitable dosage form for oral application in the future. From the results of characterization and drug release studies of micro particles it is concluded that this method could simplify the manufacturing process for extended release microspheres. On the basic of release studies it was indicated that aerosil enhanced the release of Aceclofenac from microspheres. Hence the present method is suitable for preparing the extended release microspheres for poorly water soluble drug.

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