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Research Article

FORMULATION, EVALUATION AND CHARACTERIZATION OF ACECLOFENAC MODIFIED RELEASE MICROCAPSULES

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ABSTRACT

Aceclofenac is a drug from NSAID category used in the treatment of arthritis and for other pain problems. Because of its short half-life (~4 hrs) it needs frequent dosing which decreases patient compliance. In the present work the modified release microcapsules of aceclofenac were formulated using ethyl cellulose as coating material and study was carried out on micromeritic properties of microcapsules, encapsulation efficiency, and in-vitro drug release. Microcapsules were prepared using three different solvents (chloroform, dichloromethane, ethyl acetate) at varying drug: polymer ratios (1:1, 1:1.5, 1:2). Aceclofenac modified release microspheres formulated by solvent evaporation technique were spherical in shape with particle size in range of 112 to 171 µm and % encapsulation efficiency in the range of 62.58 to 79.56%. Microcapsules formulated using ethyl acetate as solvent and drug: polymer ratio of 1:1 showed higher release rate. From dissolution data modeling, Korsemeyer Peppas was found as the best fit model for all the tested formulations. Based on in-vitro drug release and characterization, optimized formulation was evaluated for FTIR, DSC, XRD and SEM. XRD and DSC studies showed that the nature of pure drug aceclofenac remains unaffected till the completion of process of microspheres formation. SEM photographs showed that the microcapsules were spherical in nature with smooth surface and uniform distribution of the drug within the microcapsules. The aceclofenac microspheres were able to withstand the ICH accelerated stability test conditions for the studied duration of 3 months. The results clearly indicate the promise of microspheres for oral delivery of aceclofenac.

Keywords: Aceclofenac, Encapsulation Efficiency, Microspheres, Model Fitting

INTRODUCTION

The microparticles system has become an indispensable part of the controlled drug delivery fields for the past few decades since it can readily be adapted for various administration methods. In particular, biodegradable polymeric microparticles can provide a number of advantages over conventional formulations. Drugs from many different pharmacological classes have been microencapsulated, particularly analgesics, antibiotics, antihistamines, cardiovascular agents, iron salts, tranquilizers and vitamins. Aceclofenac is a non-steroidal anti-inflammatory, analgesic and antipyretic agent. It has short biological half-life (4- 4.3hours) which makes it a suitable candidate to be fabricated as sustained release formulation. Among the many techniques used for modulating the drug release profile, the rapidly expanding technology is microencapsulation. By encapsulating a drug in a polymer matrix, which limits access of the biological fluid into the drug until the time of degradation, microspheres maintain the blood level of the drug within a therapeutic window for a prolonged time period.

In this study, emulsion solvent evaporation technique is selected for the preparation of microspheres because of its ease, feasibility and scale-up compatibility with the industrial production process.

In emulsion solvent evaporation method, the polymer is dissolved in a volatile organic solvent such as methylene chloride. Drugs or diagnostic agents, either in soluble form or dispersed as fine solid particles, are added to the polymer solution, and then this mixture is emulsified in an aqueous solution that contains an emulsifying agent such as polyvinyl alcohol (PVA). The resulting emulsion is stirred until most of the organic solvent evaporates, leaving solid microparticles that may be washed with water and freeze-dried. To facilitate solvent evaporation, the emulsion is often heated slightly above the boiling point of the solvent. For example, when methylene chloride (boiling point: 39.8^{0}C) is used as an organic solvent, the emulsion is heated to 40^0 C.

The main objective of the present work is to develop sustained-release microcapsules of aceclofenac, and to study the effect of solvent system on properties of microcapsules. Three solvents were selected namely chloroform, dichloromethane and ethyl acetate. Microcapsules were prepared using three different solvents at three different drug: polymer ratios (1:1, 1:1.5, and 1:2).

The prepared microcapsules were evaluated for Average size, Surface morphology, Drug encapsulation efficiency, and Drug release.

MATERIALS AND METHODS

Aceclofenac [Curex Pharma Products, Jalgaon], Ethyl Cellulose [Wockhardt Limited, Aurangabad], Polyvinyl Alcohol, Dichloromethane, Chloroform, Ethyl Acetate, Sodium hydroxide, Potassium dihydrogen phosphate[Loba chem, Mumbai].

Formulation of Microcapsules[1, 2, 3]

The formulations were prepared by using different solvents (chloroform, dichloromethane, ethyl acetate) and different drug: polymer ratio (1:1, 1:1.5, 1:2) in each solvent.

Table 1: Schematic representation of formulation of microcapsules

Sr. No.	Formulation code	Drug : Polymer Ratio	Internal Organic Phase
1	A1	1:1	Chloroform
2	A2	1:1.5	
3	A3	1:2	
4	B1	1:1	Dichloromethane
5	B2	1:1.5	
6	B3	1:2	
7	C1	1:1	Ethyl Acetate
8	C2	1:1.5	
9	C3	1:2	

Method of Preparation

In the O/W Emulsion solvent evaporation method, the polymer ethyl cellulose was dissolved in internal organic phase or solvent. The accurately weighed 1 g aceclofenac was dispersed or dissolved in the polymer solution. This resulting mixture was poured slowly into stirring 100 ml of a 0.25% w/v aqueous solution of poly vinyl alcohol. The emulsion was stirred continuously at 700 rpm for 1 hr to evaporate the solvent. The microcapsules were recovered by vacuum filtration, washed with 200 ml of deionized water and dried at room temperature.

Table 2: Formula for Preparation of Aceclofenac Microcapsules using Chloroform, Dichloromethane and Ethyl Acetate as solvent

Sr. No.	Ingredients	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	Aceclofenac IP	1g	1g	1g	1g	1g	1g	1g	1g	1g
2	Ethyl Cellulose (50cps)	1g	1.5 g	2 g	1g	1.5 g	2 g	1g	1.5 g	2 g
3	Chloroform	10 ml	10 ml	10 ml	-	-	-	-	-	-
4	Dichloromethane	-	-	-	10 ml	10 ml	10 ml	-	-	-
5	Ethyl Acetate	-	-	-	-	-	-	10 ml	10 ml	10 ml
6	Water (External Phase)	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml
7	Polyvinyl Alcohol	0.025% w/w	0.025% w/w	0.025% w/w	0.025% w/w	0.025% w/w	0.025% w/w	0.025% w/w	0.025% w/w	0.025% w/w

Estimation of Drug Loading and Encapsulation Efficiency[4, 5]

For determination of drug content, microcapsules equivalent to 100 mg were weighed and dissolved in 100 ml methanol. Suitable dilutions were done with phosphate buffer pH 6.8. The resulting solution was analyzed spectrophotometrically at 274 nm.

$$\text{Encapsulation Efficiency}(\%) = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

$$\text{Drug loading}(\%) = \frac{\text{Weight of the drug}}{\text{Weight of microcapsules}} \times 100$$

$$\text{Percentage Yield} = \frac{\text{Weight of microcapsules}}{\text{Total expected weight of drug and polymer}} \times 100$$

Micromeritic Properties of Microspheres and Determination of Particle Size and Particle Size Distribution:

Determination of particle size[6, 7]

The particle size was determined using stage micrometer. The diameters of about 300 microspheres were measured and the average particle size determined.

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The microcapsules were allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. It forms a pile of microcapsules on the paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation

$\text{Tan}\ \theta = H/R$

$\therefore\ \theta = \text{Tan}^{-1}(H/R)$

Bulk Density

Bulk density of all batches of microcapsules was determined by pouring gently 2 g of sample through a glass funnel into a 10 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated as per given formula.

$$\text{Bulk Density} = \frac{\text{Weight of sample}}{\text{Volume occupied by the sample}}$$

Tapped Density

The tapped density was determined by pouring 2 g of microcapsules through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping was recorded .The values for tapped density was calculated as per given formula.

$$\text{Tapped Density} = \frac{\text{Weight of sample}}{\text{Volume occupied by the sample}}$$

Compressibility Index

The compressibility indices of the formulation blends were determined using Carr's compressibility index formula:

$$\text{Carr's Index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

In Vitro Dissolution of sustained release Microcapsules of Aceclofenac[8, 9, 10]

The study was carried out using dissolution apparatus USP Type-I (Rotating Basket type)

Dissolution Medium : Phosphate buffer pH 6.8, 900ml.

Speed of Paddle : 100rpm.

Temperature of Dissolution Medium : 37^0C ±0.5^0C

Accurately weighed microcapsules equivalent to 200 mg of aceclofenac were taken in muslin cloth and it was kept in baskets. Dissolution study was carried out in phosphate buffer pH 6.8 at 100 rpm at temp 37 ºC ± 0.5^0C. During dissolution study 10 ml aliquot was withdrawn at a time intervals of 1 to 12 hrs and same was replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatmann filter paper and absorbances were measured at 274 nm. Drug concentration in the samples was determined from the standard calibration curve. Cumulative percent of drug dissolved was found out at each time point.

Characterization of Microcapsules:

IR Analysis[11, 12]

The spectral analysis was done using FT-IR (Schimadzu 8400 SCCE).The dry sample of Aceclofenac, Ethyl cellulose, physical mixture, optimized formulation (C1) was mixed by triturating with dry potassium bromide (A.R. Grade) and placed in sample cell.

X-Ray Diffraction[13, 14]

The X-Ray powder diffraction patterns were obtained by using Philips PW 1700 with Cu K α (λ=1.54056A^0) radiation and a crystal monochromator, voltage: 45 kV and current 20 mA. The diffraction patterns run at 5-10^0 / min in terms of 2θ angle. The graph was plotted in 2 theta angle Vs intensity count.

Surface Morphology[15]

This study was performed at SAIF Department, IIT, Powai, Mumbai by Scanning Electron Microscopy (SEM) using JSM 6380 A(JOEL, Japan).The microspheres were coated with Platinum by ion sputtering using Autofine coater JFC-1600 (JOEL, Japan) The microspheres were kept on the sample holder and the scanning electron micrographs were taken.

Effect of Temperature on Formulation[16, 17]

The optimized formulation was subjected to study the effect of temperature. The study was carried out by storing the microcapsules in glass bottle at 4^0C, 25^0C, 37^0C, and 45^0C for 42 days. These samples were collected on 7th, 14th, 21st, 28th, 35th, 42nd day and checked at regular intervals for changes in physical properties (angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio). Drug content was estimated spectrophotometrically at 274 nm.

RESULTS AND DISCUSSION

Micromeritic Properties

Angle of repose

All the formulations show angle of repose value in the range of 15.69±0.754 - 20.48± 0.755. These values for angle of repose (< 30) indicated good flow properties.

Bulk density and Tapped density

Bulk density depends upon particle size, shape, and tendency of particles to adhere together. The values for bulk density were found to range from 0.323±0.063 to 0.429±0.035. The values for tapped density were found to range from 0.38±0.047 to 0.534±0.024.

Compressibility Index

These values were found in the range of 12.13±0.075 to 14.41±0.013 respectively. These values for compressibility index (12-16) indicated good flow properties of microcapsules.

Hausner's ratio

It was ranging from1.13±0.023 to 1.19±0.045, i.e., all the preparation showed that they had good flow Properties.

Table 3: Data for evaluation of Microcapsules

Formulation code	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Compressibility Index (%)	Hausner's Ratio
A1	15.69±0.754	0.427±0.039	0.505±0.064	15.44±0.024	1.18±0.067
A2	15.72±0.534	0.404±0.024	0.472±0.036	14.40±0.032	1.16±0.064
A3	16.31±0.633	0.391±0.024	0.445±0.014	12.13±0.075	1.13±0.023
B1	18.29±0.644	0.429±0.035	0.496±0.064	13.5±0.075	1.15±0.046
B2	19.46±0.352	0.323±0.063	0.38±0.047	15.02±0.035	1.17±0.067
B3	19.81±0.656	0.457±0.062	0.534±0.024	14.41±0.013	1.19±0.045
C1	20.72±0.353	0.359±0.044	0.410±0.042	12.43±0.064	1.14±0.025
C2	20.48±0.755	0.433±0.023	0.505±0.045	14.25±0.034	1.16±0.052
C3	20.32±0.353	0.45±0.035	0.51±0.074	11.76±0.042	1.13±0.025

n=3

Determination of Particle Size

By keeping drug ratio constant and varied polymer ratio as the polymer concentration increases viscosity increases which influences the interaction between disperse phase and dispersion medium that affects the size distribution of particle. If there was increase in the amount of polymer concentration, there was increase in relative viscosity so as a result increases in mean particle size. The average particle size of microcapsules is found to be within 112.546± 1.42 to 171.342± 1.36 µm.

Table 4: Data for average particle size

Sr. No.	Formulation Code	Average Particle size (µm)± SD
1	A1	112.546 ± 1.42
2	A2	128.743 ± 1.54
3	A3	133.787 ± 1.76
4	B1	132.256 ± 1.64
5	B2	148.347 ± 1.57
6	B3	159.112 ± 1.46
7	C1	151.263 ± 1.35
8	C2	162.424 ± 1.46
9	C3	171.342 ± 1.36

n=3

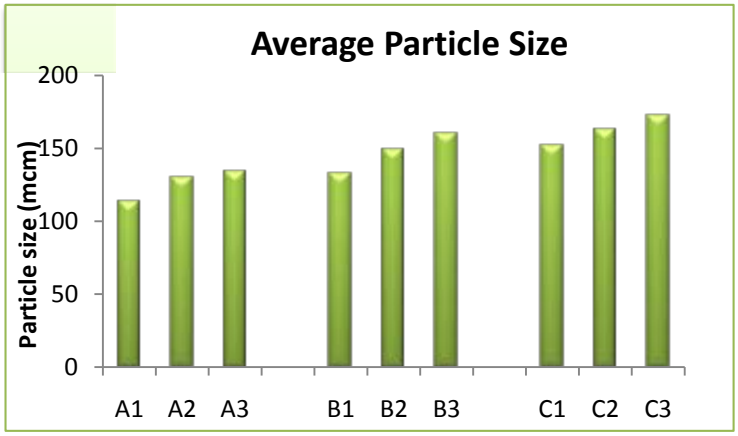

Fig. 1: Chart of average particle size

Analysis of drug content

The drug % encapsulation efficiency of ethyl cellulose microcapsules is shown in table 5. The drug: polymer ratio showed significant effect on the encapsulation efficiency of microcapsules.

The increase in concentration of polymer showed the increase in drug encapsulation efficiency. The microcapsules formulated using ethyl acetate as internal organic phase or solvent showed better encapsulation efficiency than other Formulations. The % encapsulation efficiency is found to be in the range of 62.58 to 79.56 %.

Figure 2 demonstrates the dissolution profiles of all formulations. From the results it can be concluded that formulation C1 showed the optimum cumulative % drug release of 94.127±0.24 % in 12 hrs. Although Formulation A3 showed cumulative % drug release of 68.77% in 12 hrs and B3 showed cumulative % drug release of 60.97% in 12 hrs, their release was insufficient. So formulation C1 is selected for the further study.

Table 5: Data for Percentage yield, percentage loading and encapsulation efficiency of Aceclofenac microcapsules

Formulation Code	Drug : Polymer	Theoretical loading (%)	Actual Drug Loading (%)	Encapsulation Efficiency (%)	Yield (%)
A1	1:1	50	32.68 ± 0.905	65.36 ± 1.81	78.95
A2	1:1.5	40	27.02 ± 0.455	67.55 ± 1.13	79.2
A3	1:2	33.33	25.81 ± 0.355	77.43 ± 1.06	81.96
B1	1:1	50	31.29 ± 0.35	62.58 ± 0.7	82.2
B2	1:1.5	40	27.77 ± 0.45	69.42 ± 1.13	83.6
B3	1:2	33.33	26.14 ± 0.44	78.42 ± 1.33	81.33
C1	1:1	50	36.52 ± 0.202	72.04 ± 0.405	86.24
C2	1:1.5	40	30.04 ± 0.53	75.1 ± 1.32	84.52
C3	1:2	33.33	26.52 ± 0.38	79.56 ± 1.14	84.03

In Vitro Drug Release

Table 6: In-vitro Drug Release from All Formulations of Microcapsules

Time in Hrs	Cumulative Percent Drug Release ±SD								
	A1	A2	A3	B1	B2	B3	C1	C2	C3
1	21.80 ±0.23	18.55 ±0.46	11.12 ±0.34	16.16 ±0.35	12.42 ±0.46	6.66 ±0.35	23.31 ±0.84	20.85 ±0.57	15.17 ±0.75
2	30.95 ±0.35	24.71 ±0.75	18.53 ±0.65	25.35 ±0.46	19.92 ±0.24	12.92 ±0.57	33.28 ±0.35	33.86 ±0.28	23.87 ±0.36
3	39.86 ±0.42	31.45 ±0.23	25.52 ±0.34	33.85 ±0.24	26.74 ±0.57	18.49 ±0.35	42.53 ±0.68	40.16 ±0.34	30.71 ±0.63
4	45.65 ±0.46	37.79 ±0.64	32.11 ±0.76	42.82 ±0.87	32.69 ±0.18	25.38 ±0.13	51.31 ±0.46	48.81 ±0.44	39.35 ±0.22
5	51.83 ±0.68	44.03 ±0.42	40.66 ±0.54	50.27 ±0.57	39.91 ±0.49	32.50 ±0.45	60.13 ±0.92	54.27 ±0.25	47.12 ±0.95
6	58.68 ±0.24	50.27 ±0.57	47.15 ±0.78	59.80 ±0.35	47.06 ±0.36	38.21 ±0.52	69.45 ±0.46	61.01 ±0.55	54.64 ±0.31
7	65.89 ±0.64	56.55 ±0.32	54.10 ±0.43	66.20 ±0.24	52.42 ±0.16	44.74 ±0.36	75.34 ±0.24	68.75 ±0.36	62.70 ±0.65
8	72.65 ±0.52	63.64 ±0.57	59.39 ±0.78	72.34 ±0.75	58.25 ±0.35	50.08 ±0.79	81.07 ±0.57	74.94 ±0.24	69.97 ±0.24
9	77.73 ±0.31	71.79 ±0.35	63.02 ±0.34	78.42 ±0.24	63.78 ±0.57	55.53 ±0.35	86.78 ±0.64	81.92 ±0.57	74.21 ±0.65
10	82.86 ±0.36	74.63 ±0.24	65.69 ±0.65	81.69 ±0.64	68.44 ±0.42	57.79 ±0.57	90.65 ±0.24	85.64 ±0.42	77.45 ±0.96
11	85.08 ±0.57	76.05 ±0.68	67.65 ±0.28	83.37 ±0.24	70.06 ±0.86	59.75 ±0.24	92.57 ±0.65	87.36 ±0.74	79.84 ±0.38
12	86.379 ±0.24	77.367 ±0.23	68.772 ±0.58	84.771 ±0.74	71.882 ±0.23	60.973 ±0.36	94.127 ±0.24	88.981 ±0.24	81.606 ±0.75

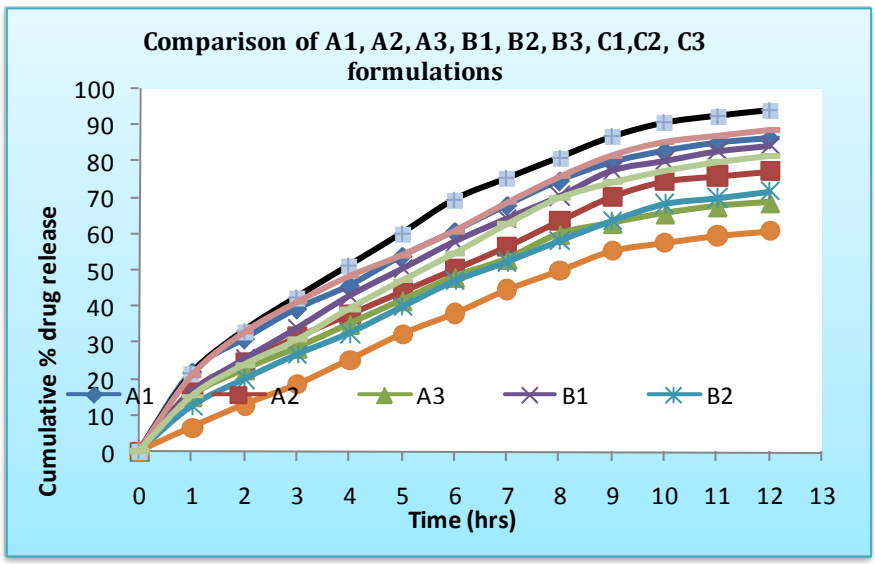

Fig. 2: Cumulative drug release of all formulations

Kinetic Treatment to Dissolution Data

Table 7: Values of rate constants (K) and correlation coefficients (R) for release of aceclofenac microcapsules

Batch	Zero Order		First Order		Matrix		Korsemeyer Peppas			Hixon- Crowel	
Code	(K)	(R)	(K)	(R)	(K)	(R)	(K)	(R)	(n)	(K)	(R)
A1	8.447	0.914	-0.166	0.994	24.71	0.994	22.68	0.995	0.539	-0.042	0.990
A2	7.257	0.950	-0.120	0.993	21.09	0.988	17.06	0.996	0.600	-0.033	0.992
A3	6.432	0.966	-0.975	0.992	18.62	0.980	14.14	0.996	0.629	-0.028	0.994
B1	7.708	0.981	-0.139	0.977	22.19	0.968	14.77	0.994	0.692	-0.037	0.992
B2	6.526	0.984	-0.109	0.993	18.76	0.965	11.48	0.997	0.734	-0.028	0.996
B3	5.725	0.984	-0.081	0.989	16.43	0.959	9.042	0.996	0.785	-0.024	0.996
C1	9.244	0.891	-0.206	0.985	27.14	0.996	25.75	0.998	0.524	-0.050	0.993
C2	8.511	0.931	-0.166	0.991	24.84	0.993	19.69	0.998	0.615	-0.043	0.995
C3	7.633	0.968	-0.133	0.994	22.08	0.978	15.51	0.997	0.668	-0.036	0.994

The dissolution data for formulations A1, A2, A3, B1, B2, B3, C1, C2, and C3 was fitted to various drug release kinetic models like Zero order, First order, Higuchi Matrix and Korsemeyer Peppas, Hixson-Crowell model. Rate constants (K), correlation coefficients (R) obtained for various models are listed in Table No. Release exponent (n) values obtained in Korsemeyer Peppas model are also given in Table 7. The model that gives high 'R' value is considered as the best fit model for the release data. It was found that as Korsemeyer Peppas best fit model for all the formulations tested.

All the formulations showed diffusion exponent (n) varying from 0.524 to 0.784. From the n values of all formulations it can be concluded that as the concentration and viscosity of polymer was increased the value of diffusion exponent also increases. This is because as the concentration of polymer increases, the rate of dissolution of disentangled chains decreases and diffusion path length of aqueous channel increases. This leads to increase in diffusion exponent value and results in shifting of the mechanism of drug release from fickian diffusion to anomalous transport thus overlapping of different types of phenomena, potentially including drug diffusion and polymer swelling.

Characterization of Microcapsules

FT-IR Analysis

The FT-IR spectra of pure drug - Aceclofenac, ethyl cellulose and physical mixture and formulation (C1) were taken by preparing KBr pellets. (Disk method) Scanning Range: 4000 – 500 cm^{-1}

Figure 3 shows IR spectra for aceclofenac, ethyl cellulose and formulation C1. Major functional groups of aceclofenac (di-substituted aromatic ring, ketone bond, C-Cl) can be seen in spectra of individual drugs as well as in spectra of formulation. So there is no interaction between aceclofenac and ethyl cellulose.

X- Ray Diffraction

X-Ray diffraction is a means of identifying crystalline compounds. It can be particularly useful when these compounds are very fine-grained components or mixtures. The X-Ray spectrum of aceclofenac, ethyl cellulose and Formulations were determined using X-Ray Diffractometer apparatus Philips PW 1700.

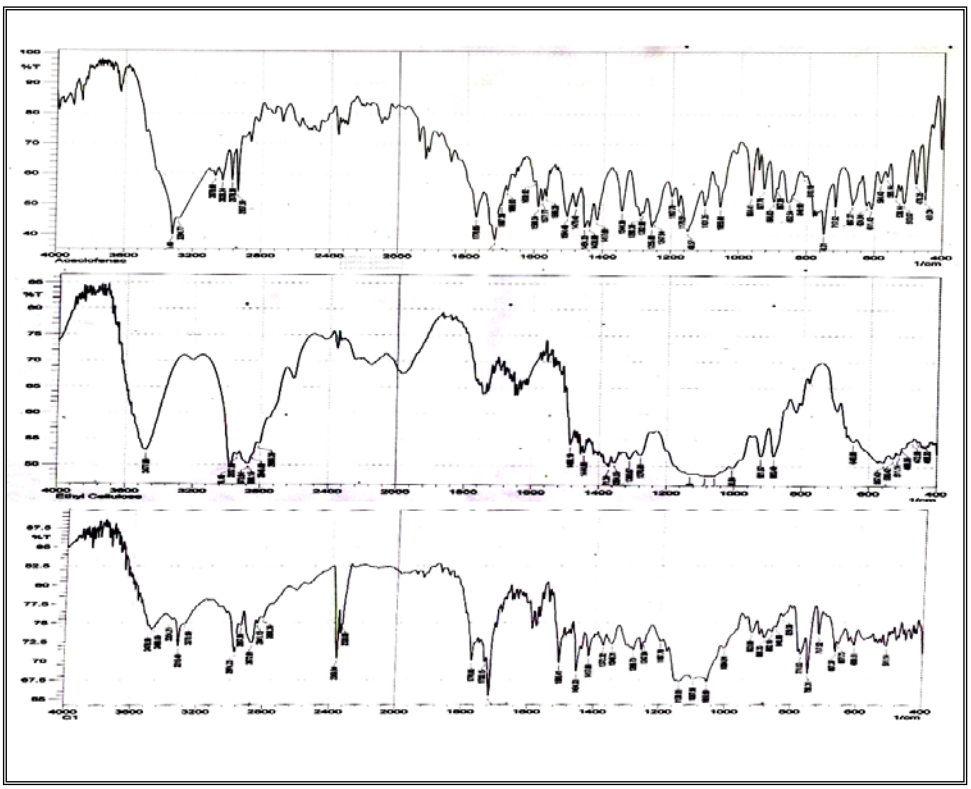

Fig. 3: FT-IR of Aceclofenac, Ethyl cellulose, Formulation C1

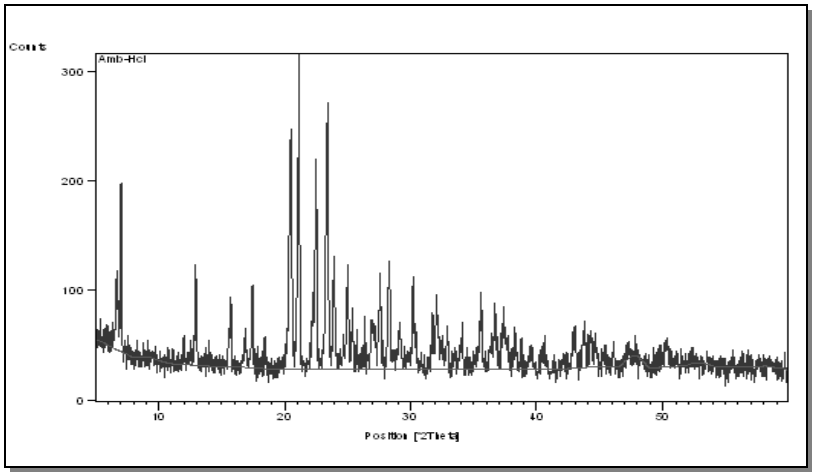

Fig. 4: XRD diffractogram of aceclofenac

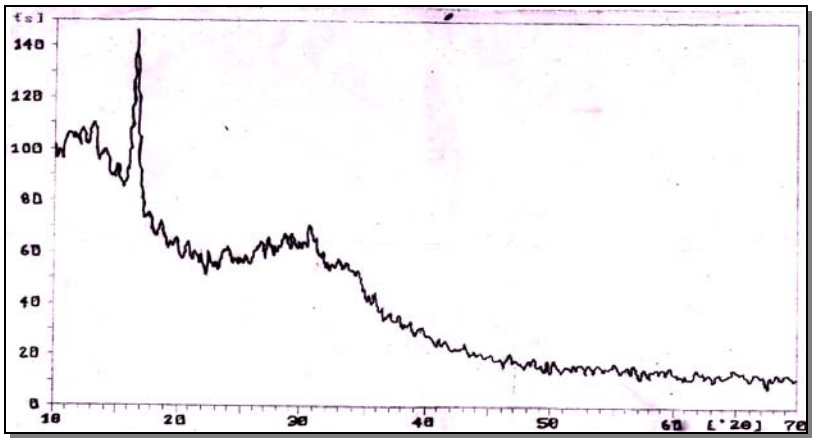

Fig. 5: XRD diffractogram of ethyl cellulose

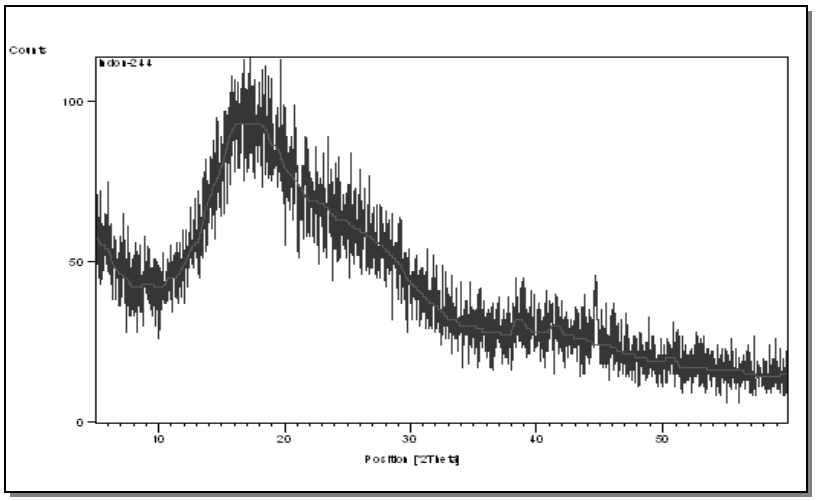

Fig. 6: XRD diffractogram of formulation C1

Figure 4, 5 and 6 report the XRD diffractogram of aceclofenac, ethyl cellulose and Formulation C1 respectively. The XRD scan of plain aceclofenac showed intense peaks of crystallinity. Diffractogram of aceclofenac showed high intensity peaks between 2θ of 20-30^0 values demonstrating the crystalline nature of drug. No intense peaks were observed in diffractogram of ethyl cellulose which indicates amorphous nature. The XRD pattern of formulation exhibited halo pattern with less intense and denser peaks compared to plain aceclofenac. This indicates that aceclofenac is dispersed at the molecular level in the blend polymeric matrix.

Scanning Electron Microscopy

Figure 7 shows the SEM photographs of prepared formulations. SEM photographs showed that the microcapsules were spherical in nature and had a smooth surface. SEM photographs revealed the absence of crystals of drug on the surface of microcapsules and uniform distribution of the drug within the microcapsules.

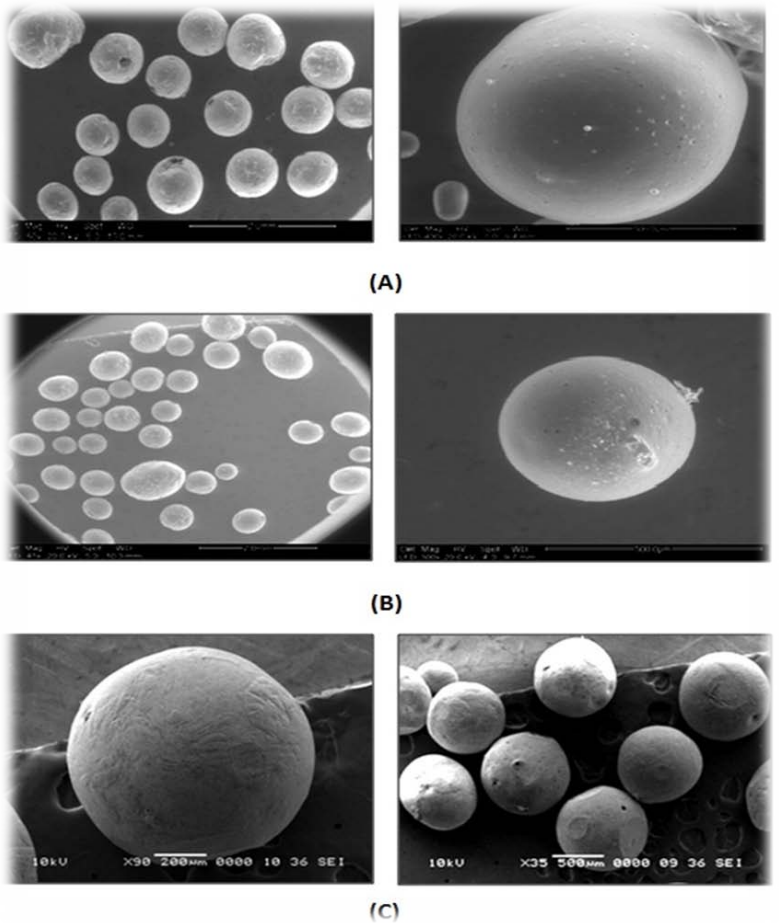

Fig. 7: SEM Photographs of Microcapsules formulated with (A) chloroform, (B) DCM, (C) Ethyl Acetate

Effect of Temperature:

The study conducted for observing effect of temperature on the formulation showed that there is no significant change in physical properties (angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio) and % drug content of the formulation and hence it can be concluded that formulation was stable for 42 days.

Table 8: Data for effect of temperature on drug content

Days	Drug Content (%)			
	4^{0}C	Room Temperature	37^{0}C	45^{0}C
0	99.78	99.78	99.78	99.78
7	99.59	99.65	99.63	99.14
14	99.47	99.56	99.51	99.04
21	99.34	99.45	99.38	98.88
28	99.21	99.38	99.23	98.72
35	98.96	99.25	99.11	98.61
42	98.84	99.13	98.89	98.52

CONCLUSION

The present study revealed that it is an appropriate method to encapsulate drug in to Ethyl cellulose because of good entrapment efficiency and sustained release behaviour among the formulations of the drug to polymer ratio employed. These results suggest the potential application of Ethyl cellulose microcapsules as a suitable sustained release drug delivery system and it decreases the frequency of dosing and improves the patient compliance in the treatment of arthritis and for other pain problems.

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