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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASED INDOMETHACIN MICROCAPSULES

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Abstract

Indomethacin, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1 *H* -indole-3-acetic acid is a non-steroidal anti-inflammatory drug used in the treatment of rheumatoid arthritics, ankolysing spondylitis, oesteo arthritis and acute gout and it is poorly soluble in water and aqueous fluids and its absorption is dissolution rate limited. Further indomethacin has a side effect like dizziness, rash, nausea, abdominal pain etc. The prolonged contact of indomethacin with the gastric mucosa causes severe gastric ulceration and bleeding. Hence the aim of present work to prepare and evaluation of sustained release microcapsules to release drug for prolong time to maintain a constant plasma concentration and reduce gastric irritation in stomach. The solvent-evaporation method was used first for its simplicity. This method had been developed for lipophilic drug. Encapsulation of hydrophilic drugs also possible if the method of preparation is slightly adapted to reduce the diffusion of the drug in the continuous phase. In solvent evaporation technique first preparation of solid dispersions by common solvent, these micronised the drug at molecule and adhere to the surface of hydrophilic drug carriers. This method enhances the solubility and bioavailability of indomethacin. Once a solid dispersion was prepared it coated with ethylcellulose for sustained release in small intestine. The half-life of indomethacin is also short (4.5 hrs) which makes it suitable candidate for sustained release formulation, moreover it reducing side effects, decreasing dosing frequency and improve patient compliance. In the present work has been made to prepare indomethacin microcapsules by emulsion solvent evaporation technique by using PVP, MCC, pectin and ethylcellulose and were evaluated by using various evaluation studies. Digital photography was used for morphological observation. The micromeritics data showed

that there was showed good flow ability in term of angle of repose, bulk density and porosity. Size distribution by sieve analysis and microscopic method showed not much significant difference in formulations F_1, F_2, F_3 and F_4, while formulations F_5 having small particle size than remaining formulation. The compatibility studies were done by FT IR spectroscopy and DSC analysis. Both the studies imply that there was no interaction between drug and polymers and they are compatible with each other. In vitro studies showed that F_1, F_2, F_3 and F_5 were able to release the drug up to 18 hrs, but only formulation F_4 followed the release up to 24 hrs, and follows the first order release kinetics. Furthermore the result of formulation F_6 , F_7 shows the release rate up to 6 hours only witch was prepared by solid dispersion method, that the microencapsulation by Emulsion solvent evaporation technique was superior to simple solid dispersion method.

Introduction

Microencapsulation [3,4] is a process by which small particles or droplets are surrounded by a coating to produce capsules in the micrometer to millimeter range known as microcapsules. Generally the spherical particles ranging in size from 1to1000 μm. The idea of controlled release from polymers dates back to the 1960s through the employment of silicone rubber and polyethylene. The lack of degradability in these systems implies the requirement of eventual surgical removed and limits their applicability. The idea of polymer microcapsules as delivery systems was prepared as early as the 1960s (Chang, 1964) and degradation was incorporated by Muson et al. (1976) through the employment of a degradable polymer coating.

The successful formulation of poorly-water soluble drugs is one of the major problems in pharmaceutical manufacturing. Poorly water-soluble drugs, such as indomethacin and nifedipine, may show low and erratic oral bioavailability due to poor dissolution of the drug in the fluids of the gastrointestinal tract .The dissolution rate of a drug can be increased by several approaches including conversion of the crystalline drug into the amorphous state and by dispersion in a hydrophilic polymer In addition, the presence of the polymer may increase the physical stability of the amorphous drug, which often limits application of the amorphous state in dosage form design

1.1 Materials and Methods

The following materials that were AR grade were used as supplied by the manufacturer, analyzed and tested as per the pharmacopoeias specifications.

S.No	Material used	Grade	Manufacturer
1	Indomethacin	USP	Micro labs Ltd., Pondicherry.
2	Povidone	LR	Loba chemie Pvt. Ltd. Mumbai.
3	Microcrystalline	LR	S.d.fine-chem Ltd. Mumbai.
4	cellulose	LR	S.d.fine-chem Ltd. Mumbai.
5	Pectin (pure)	LR	Loba chemie Pvt. Ltd.Mumbai.
6	Ethylcellulose	GR	Loba chemie Pvt. Ltd. Mumbai.
7	Methanol	LR	Merck Limited, Mumbai.
8	Dichloromethane	LR	Universal laboratories Pvt.Ltd, Mumbai.
9	Acetone	LR	S.d.fine-chemie Ltd, Mumbai.
10	Liquid paraffin	LR	S.d.fine-chemie Ltd, Mumbai.
11	(Light)	AR	Reachem laboratory chemicals, Pvt.Ltd,
	Petroleum ether		Chennai.
	(60^o-80^oC)		
	Sodium hydroxide		
	(Pellets)		

1.2. Preparation of Indomethacin microcapsules

The microcapsules were prepared by emulsion solvent evaporation technique [15,16,17,18] In first stage prepared solid dispersion of indomethacin with different polymers ratio of povidone,[10] microcrystalline cellulose [14] (MCC) and pectin such as 1:1:2.5:05; 1:1:2:1; 1:1:1.5:1.5; 1:1:1:2; 1:1:0.5:2.5 which is shown in the Table 1. All ingredients are transferred to a china dish added 6 ml of methanol and 12ml of dichloromethane in a ratio of (1:2) to the china dish containing drug and different polymers. The china dish was heated on a water bath to evaporate the solvent. Now 1.5 gm of ethyl cellulose[13] was accurately weighted and dissolved in 25ml of acetone to form a homogenous polymer solution. To this solid dispersion containing indomethacin [7,8,9,11,13] was added and dispersed thoroughly. The resulting mixture was added drop wise by glass syringe to light liquid paraffin (100ml) contained in a 250ml beaker under stirring about 500rpm to disperse the added mixture to form fine droplets. The system was stirred for further 2 hrs in order to evaporate the solvent at room temperature and to form small uniform microcapsules. The microcapsules were separated from oil phase by filtration, and washed with petroleum ether to remove the adhering liquid paraffin. The microcapsules were kept in a desiccator for 24hrs. The ethyl cellulose [12] was used as coating

polymer (1.5g) constant in each formulation. The formulation F_6 and F_7 was prepared by simple solid dispersion [5,6] without emulsion solvent evaporation technique by using same drug, polymers as mentioned.

Table1: Formulation design of Indomethacin microcapsules[20].

S.no	Formulation Code	Drug: polymers ratio (mg)	Indomethacin (mg)	Povidone (mg)	MCC (mg)	Pectin (mg)
1	F_1	1:1:2.5:0.5	500	500	1250	250
2	F_2	1:1:2:1	500	500	1000	500
3	F_3	1:1:1.5:1.5	500	500	750	750
4	F_4	1:1:1:2	500	500	500	1000
5	F_5	1:1:0.5:2.5	500	500	250	1250
6	F_6	1:1:1:2	500	500	500	1000
7	F_7	1:1:1:2.5	500	500	500	1250

2. Characterization of indomethacin microcapsules.

2.1. Fourier transforms infrared spectroscopy:

Infrared (IR) spectrum of indomethacin was obtained by liquid paraffin mull method and PVP, MCC ethyl cellulose and pectin spectra were obtained by KBr disk method using mediated Fourier transformed infrared spectroscopy (Model - FT/IR - 4100 type A).

2.2. Differential scanning calorimetry:

Differential scanning calorimetry (DSC) thermo grams of indomethacin, PVP, MCC, pectin and ethylcellulose were obtained on Perkins Elmer Thermal Analysis. The samples were sealed in the aluminium pan and measurement was performed at a heating rate of 10^0C/min from 50^0 to 300^0C. An empty pan was used as a reference.

2.3. Percentage yield:

Microcapsules were dried in dessicator for 24hrs after formulation, then weight and the yield of microcapsules preparation was calculated using the formula:

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

2.4. Determination of size and shape of microcapsules:

2.4. 1. Digital photograph of microcapsules:

The surface morphology and internal texture of indomethacin microcapsules were observed by digital photography.

2.4. 2. Measurement of microcapsules size distribution by microscopic method [17]

To study the shape of the microcapsules, the microcapsules were dispersed in liquid paraffin and observed under 45X magnification using an optical microscopy. The microscope eyepiece was fitted with an eyepiece micrometer, by which the size of the particles may be estimated. An average of about 200 particles were counted and determined.

$$\text{Log number mean diameter} = \frac{\Sigma nd}{\Sigma n}$$

2.4. 3. Measurement of microcapsules size distribution by sieve analysis: [1,2,19]

Particles having size range between 50-1500 μm are estimated by sieve analysis. The sieves are arranged in a nest with the coarsest at the top. A carefully weighed sample of the microcapsules was place on the top sieve, and shaken for a predetermined period of time, the microcapsules retained on each sieve are weighed and arithmetic mean of the sample is determined.

$$\text{\% of wt of microcapsules Retained} = \frac{\text{Weight of microcapsules retained}}{\text{Total weight of microcapsules}} \times 100$$

2.5. Micromeritics properties [17]

2.5. 1. **Bulk density (ρ_b) [19]**

Bulk density is defined as the mass of a powder divided by the bulk volume. Bulk density largely depends on participle shape, as the particles became more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. It is determined by accurately weight the sample and introduced into graduated cylinder. The cylinder is dropped on to hard wood surface about 200 times from a height of inch at 2-second interval.

$$\text{Bulk density } (\rho_b) = \frac{\text{Mass of microcapsules (W)}}{\text{Bulk volume } (V_b)}$$

2.5. 2. **True density(ρ)[19]**

True density, (ρ), is the density of the actual solid material. Method for determining the density of nonporous solids by displacement in liquids in which there are insoluble. It is the weight of the body divided by the weight of the liquid it displaces, i.e., the loss of weight of the body when suspended in a suitable liquid.

2.5.3. **Porosity (∈) [19]**

It is also called as voids. If the powder is nonporous, i.e. has no internal pores or capillary spaces, the bulk volume of the powder consist of the true volume of solid particles plus the volume of the spaces between the particles.

Void volume (v) = Bulk volume – true volume

$$\% \text{ Porosity } (\in) = 1 - \frac{\text{Bulk density } (\rho_b)}{\text{True density } (\rho)} \times 100$$

2.5.4. **Angle of repose (θ) [19]**

The flow characteristics are measured by angle of repose. It is defined as maximum angle possible between the surface of a pile of powder and horizontal plane. Angle of repose was determined by using funnel method; accurately weighed microcapsules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of blends. The blends were allowed to flow through the funnel freely on to the surface. The diameter of the microcapsules cone was measured and angle of repose was calculated by using the following equation:

$\theta = \tan^{-1} h/r$ Where θ = angle of repose

h = height of pile

r = radius of the base of pile

Values of angles of repose ≤ 30^o usually indicate a free - flowing material and angles ≥ 40^o suggest a poorly flowing material.

2.6 Drug content analysis:

Accurately weight 25mg equivalent microcapsules contents and transfer to 100 ml volumetric flask, and add 50 ml of a mixture of equal volume of methanol and pH 7.5 phosphate buffer. Sonicate until the contents are dispersed dilute with the methanol and pH 7.5 phosphate buffer mixtures (1:1). Dilute a portion of the clear solution quantitatively, and stepwise with the methanol and pH 7.5 phosphate buffer mixture (1:1) to obtain a solution containing about 25 µg of indomethacin per ml Concomitantly determine the absorbance of this solution and a standard solution of USP indomethacin , in the methanol and pH 7.5 phosphate buffer mixture having a known concentration of about 25 µg/ml in 1-cm cell at the wave length of maximum absorbance at 318 nm, using the methanol and pH 7.5 phosphate buffer mixture as the blank. Calculate the quantity, in mg of $C_{19}H_{16}CINO_4$ in the microcapsules taken by the formula.

$$(TC/D)\ (Au/As)$$

Where *T* is the labelled quantity of indomethacin in mg, *C* is the concentration, in µg/ml, of USP indomethacin RS in the standard solution, *D* is the concentration in µg/ml of indomethacin test solution, and *Au* and *As* are the absorbance of the solution from the capsules contents and the standard solution, respectively.

2.7. In-vitro dissolution study

In vitro release profiles of Indomethacin microcapsules were determined by USP dissolution apparatus (apparatus 1) and followed test 3 which containing 750 ml of pH 6.8 phosphate buffer. The microcapsules were equivalent to 75 mg of drug were filled in a hard gelatine capsule and placed in dissolution medium at 37 ± 0.5^oC, the experiment was conducted up to 24 hours at 75 rpm. 5ml of the sample was withdrawn periodically at the interval of one hour and same volume of fresh medium was replaced into the beaker. The concentration of drug release at different time intervals were determined by measuring the absorbance using UV spectrophotometer at 318 nm with the help of standard graph. The percentage of the labelled amount of $C_{19}H_{16}CINO_4$ dissolved at the times specified conforms to acceptance table.

Time (hours)	***Amount dissolved***
1	Between 15% and 40%
2	Between 35% and 55%
4	Between 55% and 75%

6	Between 65% and 85%
12	Not less than 75%
20	Not less than 85%

Results and Discussion

The sustained release microcapsules of indomethacin were prepared by using natural polymer (pectin) and evaluated with an aim to prevent gastric irritation and increase bioavailability. It also leads to reduction in frequency of dosing which in turn improve patient compliance and reduce fluctuation in drug levels.

The prepared indomethacin microcapsules were subjected to various evaluation parameters such as FT IR characterisation, DSC analysis, size determination by sieve and microscopic method, shape and surface determination by digital photography, micrometrics properties like bulk density, porosity, and flow property by angle of repose, drug content determination and in-vitro dissolution studies.

3.1. **FT IR Spectroscopy:**

FT IR studied was done to detect the possible interaction between the drug and polymers. IR of indomethacin (Fig.1) The IR spectrum for indomethacin (γ -form) had peaks at 3,372.6 and 1,712.4 cm^{-1} , corresponding to carboxylic O−H and C=O stretch, respectively shows characteristic peaks at 1365.35cm^{-1} and 1702.84cm^{-1} in C-N stretching in aromatic ring, C=C stretching at 1594. 84cm,$^{-1}$ C=O stretching at and aromatic halogen (C-Cl) at 750cm^{-1}. PVP shows (Fig: 4) C-N aromatic stretching at 1361.5cm^{-1},C=O stretching at 1596.77cm^{-1}. MCC shows (Fig: 5) O-H bending at 1361.5cm^{-1}. Pectin shows (Fig:3) O-H bending (alkaline) at 1052.94cm^{-1}, C=O stretching at 1639.2cm^{-1} and C-H stretching at 2936.09cm-^{1}. Ethyl cellulose shows (Fig:2) C-O-C stretching at 1058.73cm^{-1} and methylene group stretching at 2923.56cm^{-1}. In the carbonyl frequency region, indomethacin showed strong peak at 1600-1900cm^{-1}, which were attributed to carboxylic C=O stretching, similar spectra that consisted of peaks corresponding to indomethacin, pectin and PVP were obtained in physical mixture formulation. This result demonstrated no molecular interaction among indomethacin and polymers used in formulation.

Fig: 1 IR Spectrum of Indomethacin.

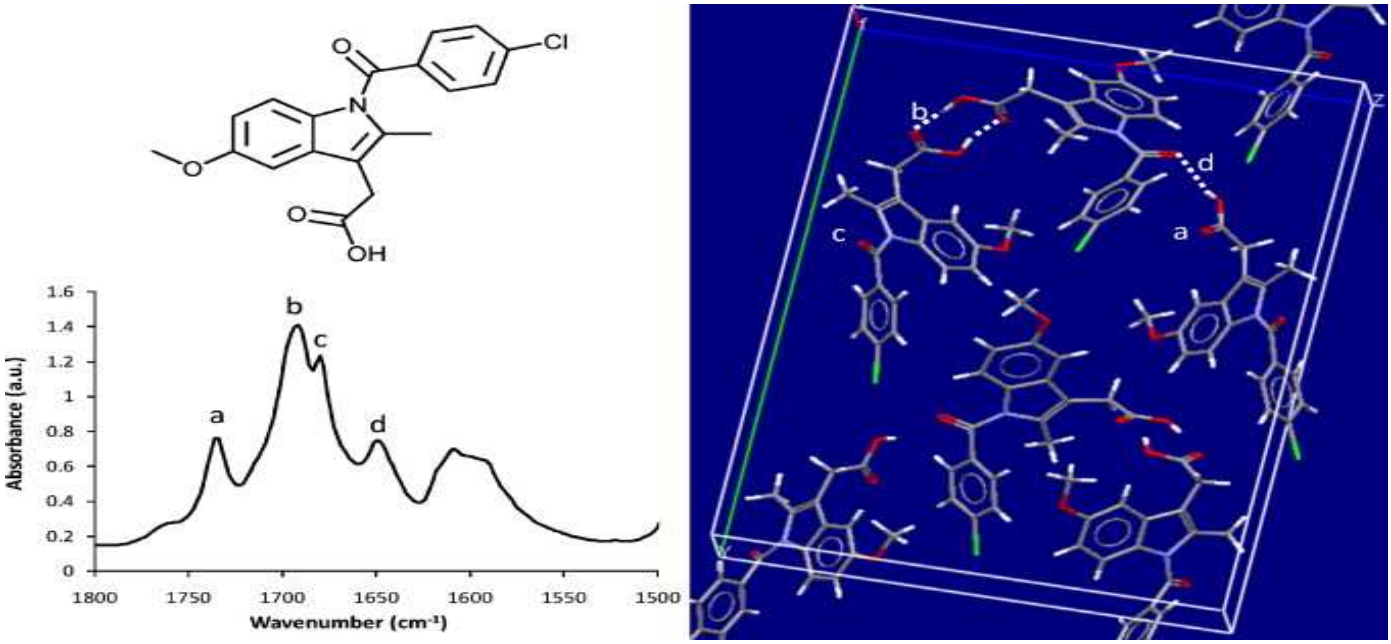


Fig-2: IR Spectrum of Ethyl cellulose.

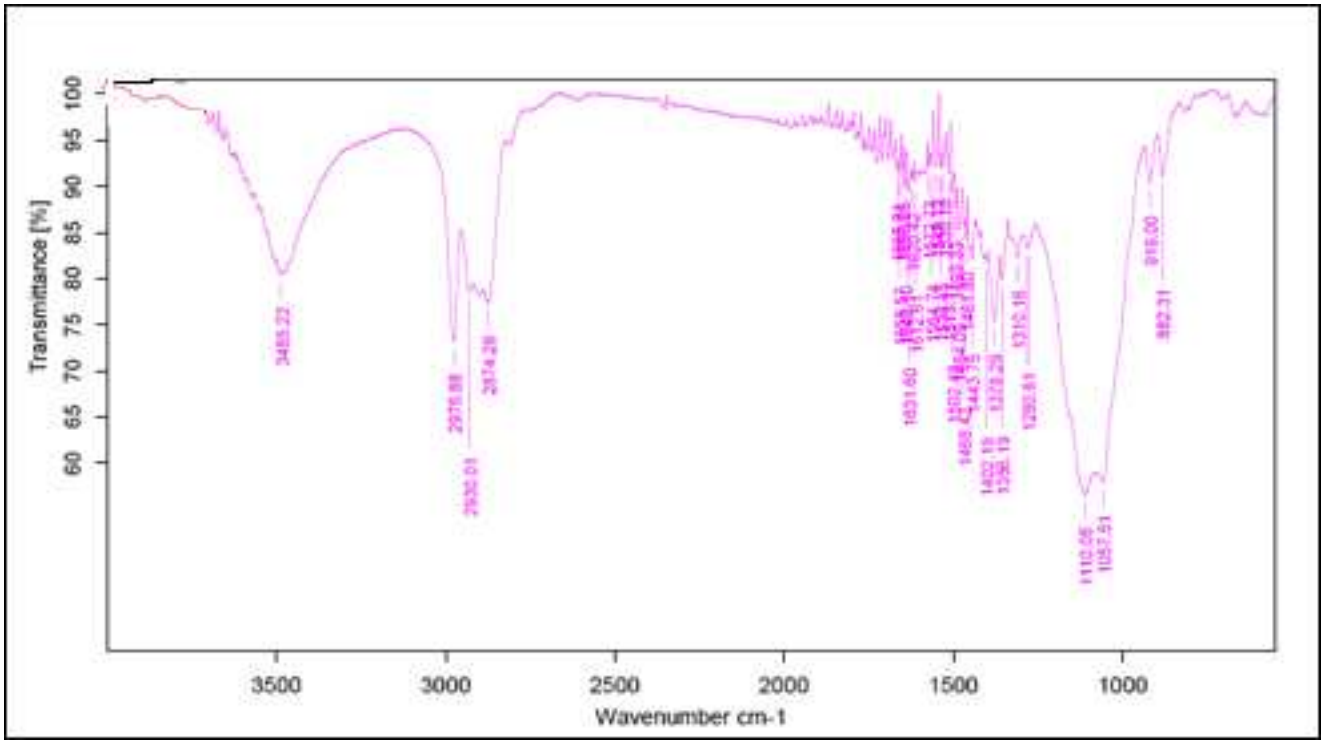


Fig: 3 IR Spectrum of Pectin.

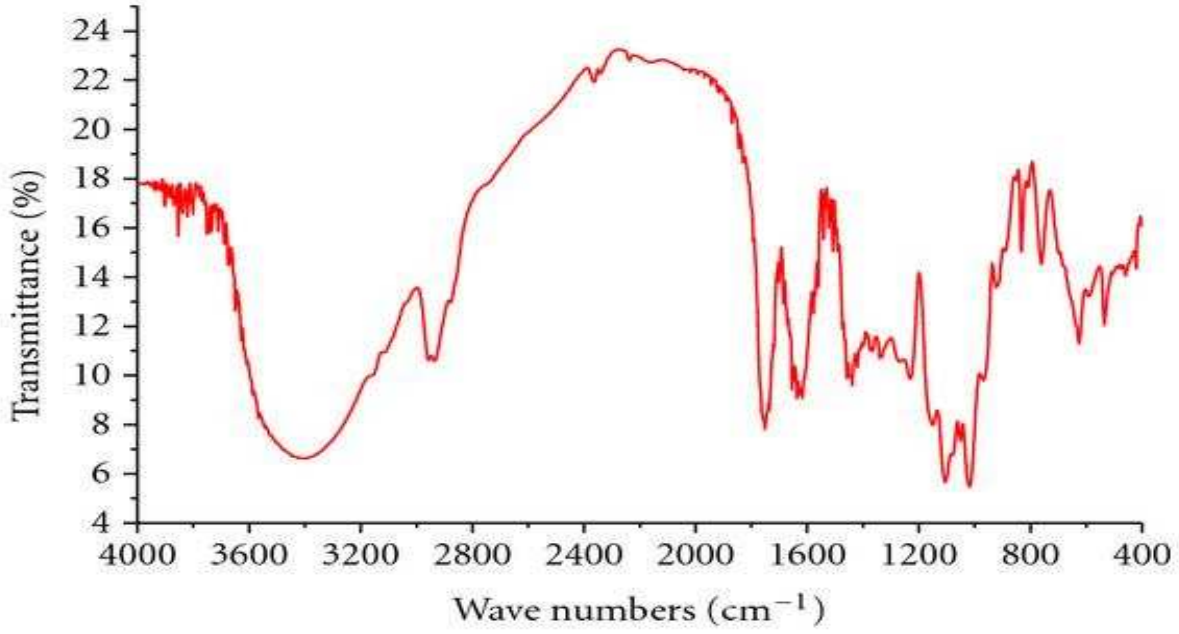


Fig-4: IR Spectrum of PVP.

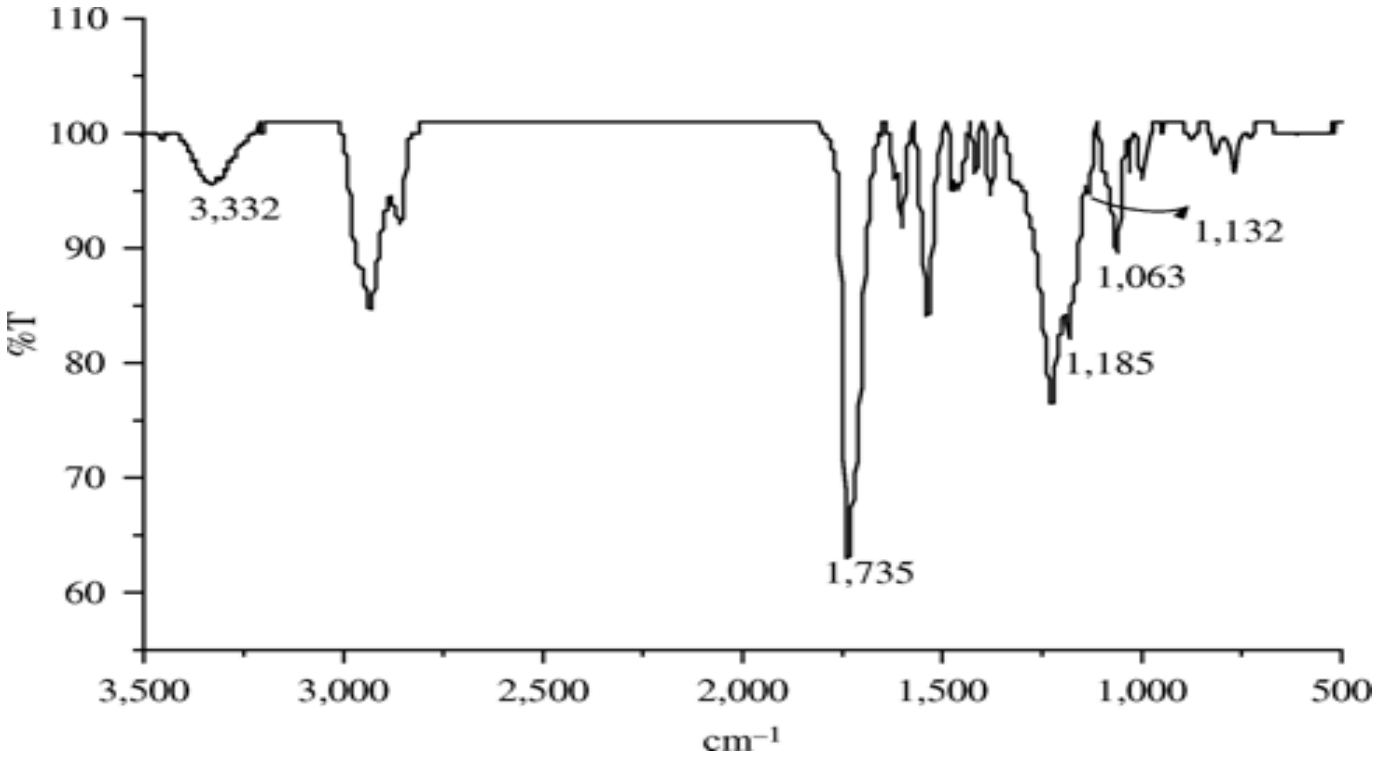
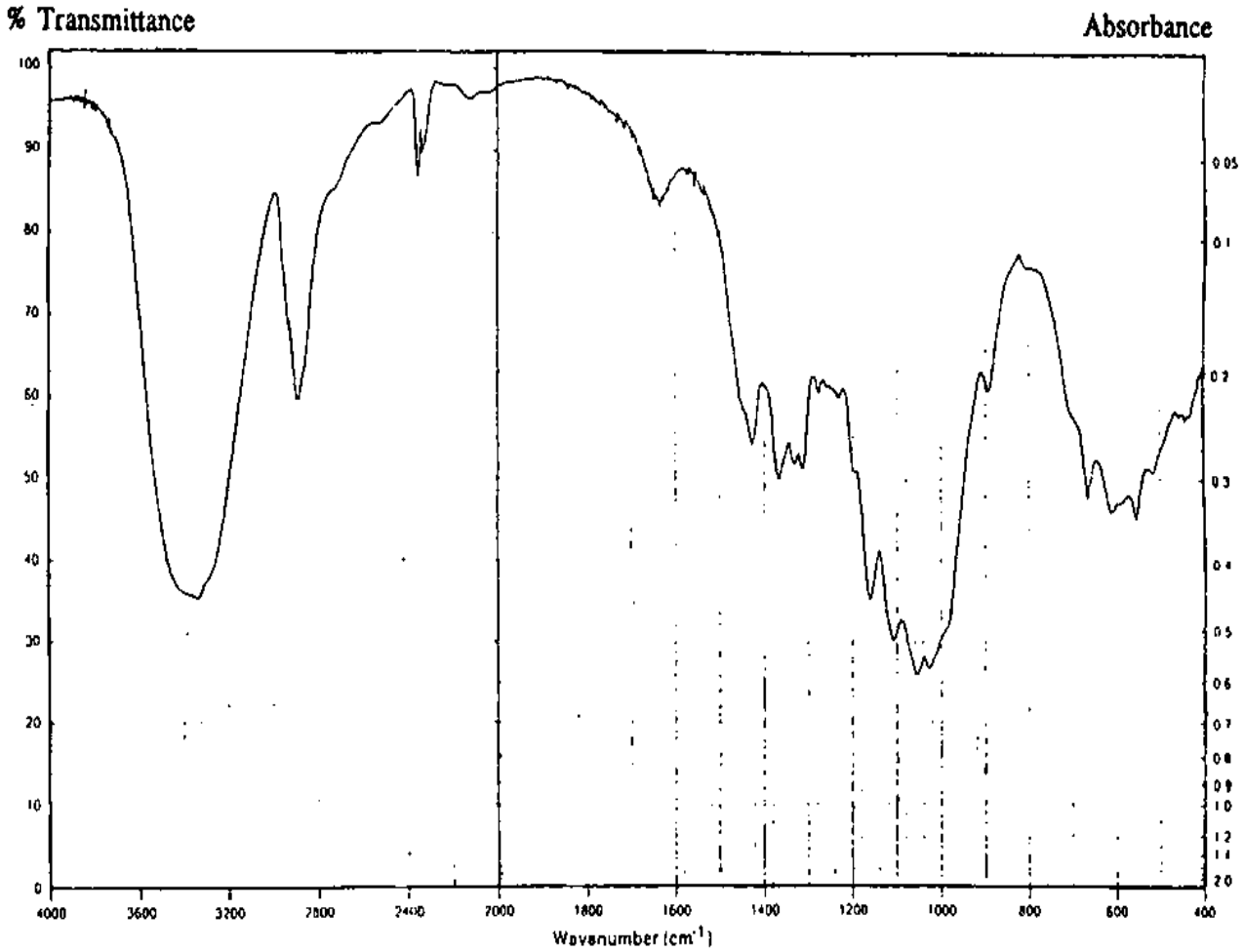


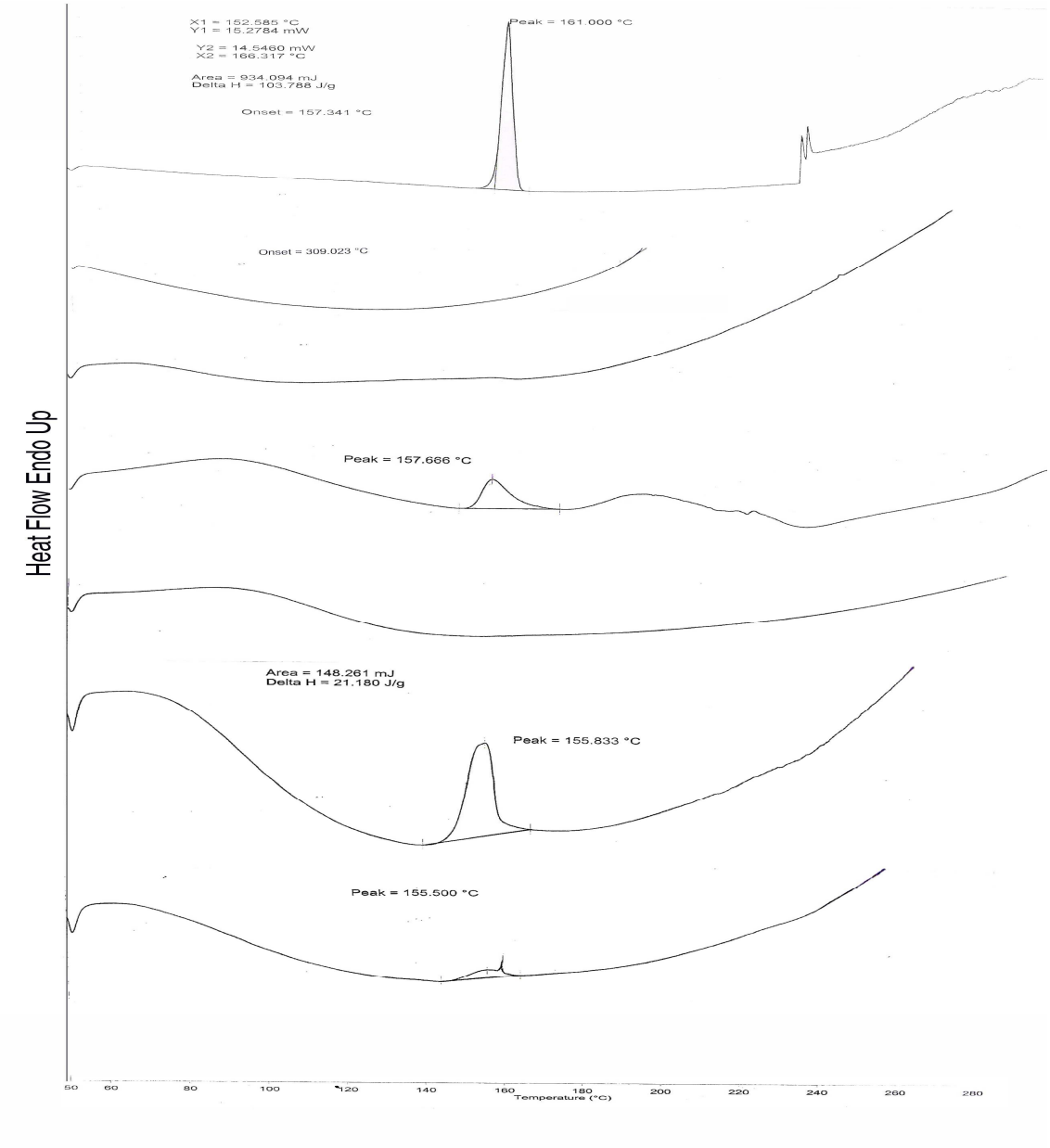
Fig: 5 IR Spectrum of MCC.



3.2. Differential Scanning Calorimetry (DSC) Analysis:

The DSC thermograms of indomethacin, pectin, PVP, EC, MCC, and physical mixture of indomethacin, pectin, PVP, EC, MCC and microcapsules shown in (Fig.6). The DSC thermogram of intact indomethacin demonstrates the melting peak at 161.00^0C (Peak-I) and pectin shows melting peak at 157.666^0C (Peak-II). The thermogram of physical mixture shows melting peak at 155.83^0C (Peak-III), while thermogram of microcapsules formulation shows melting peaks at 155.50^0C (Peak-IV) and 160^0C (Peak-V). The lower melting point in formulation was probably due to the change in melting behavior of indomethacin in polymers environment. The thermograms of formulation does not shows any characteristic change in melting peak which indicates the no interaction occur between the drug and polymers and they are compatible with each other.

Fig-6:



3.3. Shape and Size of Microcapsules:

The mean particle size of the obtained microcapsules containing indomethacin was determined by the optical microscopy under 45X magnification. The arithmetic mean size of microcapsules of formulation F_1 is 318.8 µm F_2 is 497.75 µm, F_3 is 510.5 µm, F_4 is 521.25 µm and F_5 is 336.33 µm which is shown in table from table 2 and graph shown in Fig.7 The particle size range increased as the combination ratio of pectin and MCC was increased and particle size range decrease, either MCC or pectin ratio was increased. The particles size distributions of microcapsules were also done by sieve analysis and resulting data are tabulated in table 3.

Table-2: Microcapsules Size Distribution by Microscopic Method.

S.No	Size range (μ)	1	F 2	F 3	F 4	F 5
1.	0 – 100	500	300	300	350	500
2.	100 – 200	3300	2700	1800	2250	3150
3.	200 – 300	11250	6500	4000	5750	9250
4.	300 – 400	29750	11550	9800	10500	32550
5.	400 – 500	9000	43650	40950	46350	8550
6.	500 – 600	6050	7700	19250	8800	8250
7.	600 – 700	4550	3900	7800	3900	3250
		Σnd = 64400	Σnd = 79000	Σnd = 86600	Σnd = 73130	Σnd = 65500

Fig: 7

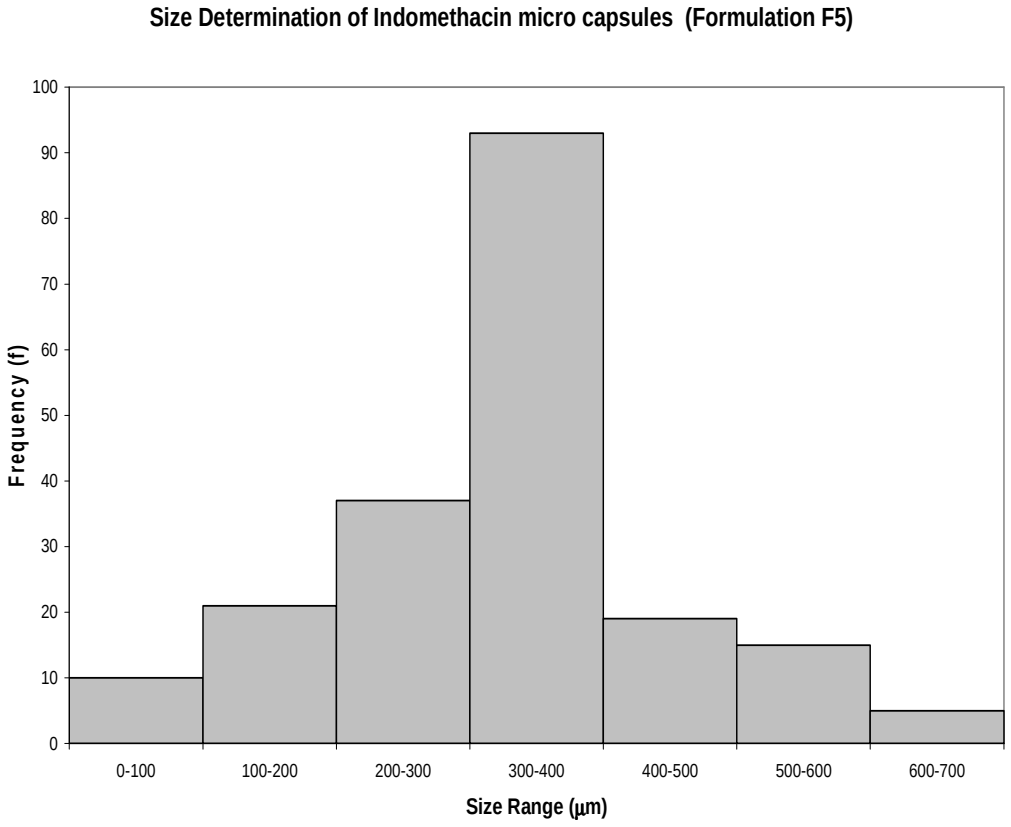


Table:-: Microcapsules Size Distribution By Sieve Analysis (Formulation F_5).

Sl No	Sieve no	Particle size rang (mm)	Arith matic mean size of opening(mm)	Amount of sphere retained (g)	% weight of sphere retained	Weight size	% w/w under size
1.	14 / 20	1.41 - 0.84	1.125	0.02	1	1.125	1
2.	20 / 30	0.84 - 0.59	0.715	0.08	4	2.86	5
3.	30 / 60	0.59 - 0.25	0.420	1.55	77.5	32.55	82.5
4.	60 / 80	0.25 - 0.177	0.213	0.26	13	2.769	95.5
5.	80 / 120	0.177 - 0.125	0.151	0.09	4.5	0.679	100

Mean diameter = 0.399mm = 399.83µm

3.4. Digital Photographs:

The shape and surface morphology of indomethacin microcapsules were observed by digital photographs shows in Fig.8 and 9. Normal size of microcapsules and zoomed size indomethacin microcapsules. The obtained microcapsules are round to oval in shape. The microcapsules are pale yellow in colour.

Fig:8 Normal size of indomethacin microcapsules by digital photography	**Fig:9 Zoom size of indomethacin microcapsules by digital photography**
	

3.5. Micromeritics Properties:

The micromeritics properties such as angle of repose, bulk density, true density and porosity were studied. The bulk density of microcapsules were increased as the combination ratio of pectin and MCC was increased i.e. $F_1<F_2<F_3$

$>F_4>F_5$. The results of micromeritics properties are tabulated in table 4. The obtained value of angle of repose (θ) ranges from 18.50^o to 23.14^o which indicates that all formulations are free flowing and order of angle of repose was followed $F_1>F_2>F_3>F_4>F_5$. Porosity of F_3 is less than other formulation. The above micromeritic studies show that the formulation F_3 has more bulk density, less porosity and less angle of repose than other formulations.

3.6. **Drug Content Determination:**

The drug contents of formulation F_1, F_2, F_3, F_4, F_5 and F_6 are 54.66%, 55.33%, 56%, 52%, 49.33% and 85.33% respectively (Table 4). The formulation F_3 contains pectin: MCC ratio is 1:1 having highest drug content than other formulations.

Table-4: Drug Content and Other Micromeritics Properties.

Formulations	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**
Percentage yield	90	87	81.25	85.30	89.10
Drug content (%)	54.66	55.33	56	52	49.33
Bulk density (gm/ml)	0.492	0.500	0.614	0.508	0.504
True density	0.910	0.873	0.990	0.950	0.980
% Porosity	45.93	42.72	37.97	46.52	48.57
Angle of repose (θ)	22.80^0	21.85^0	18.50^0	21.79^0	23.14^0
Sieve analysis (μm)	396.08	609.76	601.02	609.29	399.83
Microscopic analysis (μm)	318.8	497.75	510.5	521.25	336.33

3.7. In Vitro Release Studies:

The in vitro studies profile of indomethacin microcapsules were determined by USP dissolution apparatus I (75rpm) containing 750 ml dissolution medium such as phosphate buffer 6.8pH . Microcapsules equivalent to 75 mg drugs was taken in dissolution medium and temperature was maintain at $37^o\pm0.5^oC$. 5 ml of sample was withdrawn periodically, at intervals of 1 hr and same volume of fresh medium was replace in the dissolution medium. The concentration of drug released at different time intervals were determined using UV spectrophotometer at 318 mm with the help of the standard graph.

The data of cumulative percentage release of indomethacin microcapsules are tabulated in (Table 5). Among the six formulations, formulation F_4 complies with USP 23 (Test 3). The drug released from microcapsules by

dissolution followed by diffusion. Because of solid dispersion the enhancement of dissolution rate may be due to reduction of particle size, thus increases the effective surfaces are made available for the dissolution medium. Further the use of water-soluble carries (PVP) improved the wettability of drug particles and hence high dissolution rates. As ratio of pectin (natural polymer) increase from formulation F_1 to F5 release rate was sustained. When pectin absorbed dissolution medium, it form a swollen viscous layer that retains considerable order structure with respect to the polymer, and thus is expected to influence greatly the dissolution . Later Swelling will increase progressively in water, controlling the penetration in the complex and hence opposing the rapid release of the drug. Pores in microcapsules are created due to dissolution of membrane, which permit the entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug from the system. Formulation F_1, F_2, F_3 contain low amount of pectin, which released drug up to 98.78% within 18 - 20 hours. And formulation F_4 was best fitted as per USP 23 (test 3). Means F_4 has been complies with USP23 (test 3), and 99.50% drug release within 24 hours. Formulation F_5 was able to release 99.32% within 20 hours due to low ratio of MCC to pectin. The release patterns of formulations are shown in table No. 5.

The formulation F_6 and F_7 was prepared by simple solid dispersion, without microencapsulation technique. It was released the 98.60 of drug within 6 hours which indicates the microencapsulation of indomethacin by emulsion solvent evaporation is a suitable for a sustained release formulation.

Table: 5.In vitro release profiles of indomethacin microcapsules.

Time (Hrs)	**Dissolution as per USP specification**	**Dissolution test of formulation (Released in percentage)**					
		F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
1	Between 15% to 40%	54.87	57.83	51.78	38.46	58.78	53.90
2	Between 35% to 55%	73.17	67.46	66.07	53.84	62.83	64.06
4	Between 55% to 75%	82.31	77.09	76.78	67.30	75.00	91.40
6	Between 65% to 85%	85.97	83.13	80.35	71.15	79.05	99.60
12	Not less than 75%	98.29	97.16	97.85	83.76	97.18	98.25
24	Not less than 85%	-	-	98.21	98.60	-	-

Fig: 10

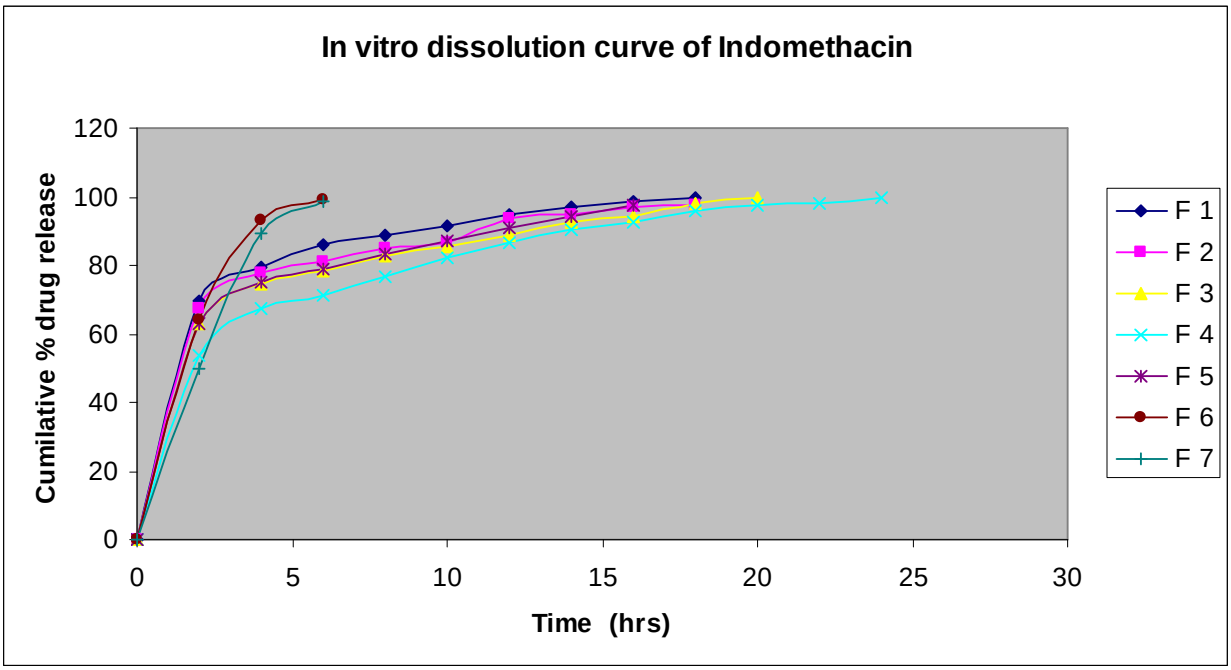
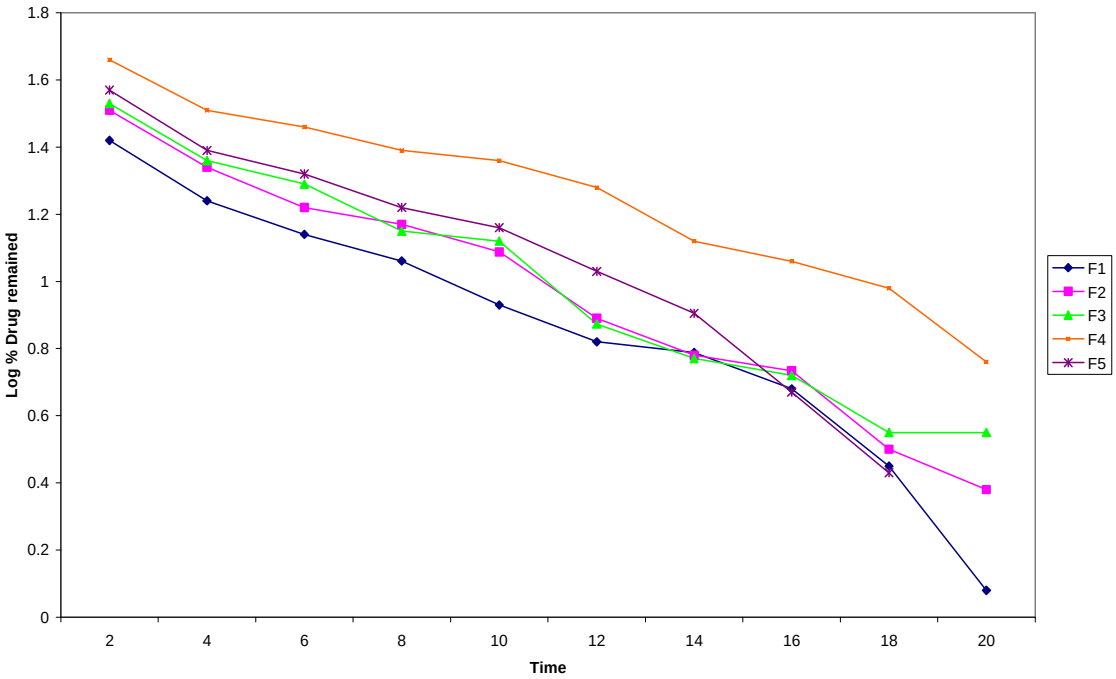


Fig-11: Log % drug remained in different formulations.



The dissolution of indomethacin microcapsules from various formulation followed first order kinetics. The dissolution rate constants were calculated from the slopes of Log percentage drug remained Vs time plots. From the graph, slope was calculated between two points and the rate constant K was calculated by following equation.

$$K = - \text{Slope} \times 2.303$$

Table-6: The release pattern followed first order kinetics in pH 6.8 phosphate buffer.

Formulation	K (hr^{-1}) at pH 6.8 (phosphate buffer)
F_1	0.1535
F_2	0.1458
F_3	0.1381
F_4	0.1151
F_5	0.1074
F_6	0.5834

Summary

In present work an attempt has been made to formulate sustained release microcapsules of indomethacin by using natural polymer, which is preferably used as an anti-inflammatory and analgesic. Microcapsules were prepared using polymer with PVP, MCC and Pectin in different concentration and ethyl cellulose was used as coating material, by emulsion solvent evaporation technique. Indomethacin meets all the ideal characteristics to formulate in the form of microcapsule sustained drug delivery system.

The compatibility evaluations were performed by FT-IR spectroscopy and DSC analysis. Both studies imply that the drug and polymers are compatible with each other. There was no interaction found between polymers and drug.

All the formulations were characterized on the basis of their micromeritics properties. Shape and surface was observed by digital photography, drug content determination and in-vitro dissolution studies.

Shapes of microcapsules were observed round to oval and pale yellow in colour. The microcapsules size distribution was found between 318.8µm to 521.25µm by microscopic method.

The microcapsules of formulation F_3 showed maximum bulk density, true density and minimum porosity as compare to other formulations while F_2, F_4, F_5 showed intermediate and formulation F_1 showed less bulk density and true density. The result of angle of repose showed all formulations were free flowing and F_3 having less angle of repose than other formulations.

The drug content was found maximum 56% in formulation F_3 and order of drug content followed by formulations $F_3 > F_2 > F_1 > F_4 > F_5$.

The mechanism of drug release from microcapsules was dissolution followed by diffusion. Three formulations F_1, F_2, F_3, were able to release drug up to 20 hrs and F_4 released maximum 99.50% drug during 24 hrs. Formulation F_1 and F_2 were able to release drug up to 20 hrs. Among five formulations, F_4 only complies with the USP, which maintained the release pattern as per mention USP 23 (test 3). Rest of the formulations (F_1, F_2, F_3, F_5) ware unable to maintain release rate as per given USP 23 (test 3).

Formulation F_6 was prepared by simple solid dispersion released the drug up to 99.60% within 6 hours, which indicates that microencapsulation by emulsion solvent evaporation technique was superior to simple solid dispersion method.

The release rate of indomethacin from microcapsules followed first order kinetics, which was obtained by plotting, a graph of log percentage cumulative drug remained Vs time, and rate constant K of different formulations were obtain

Conclusion

In the present study an attempt was made to develop a new sustained drug delivery for indomethacin microcapsules by using natural polymer to improve bioavailability and efficacy**.**

Sustained release formulations of indomethacin microcapsules was developed by using different concentrations of drug, polymers and were evaluated to a satisfactory level in term of drug release, content uniformity and micromeritics properties. The compatibility studies were done by FT IR spectroscopy and DSC analysis. Both a studies imply that there was no interaction between drug and polymers and they are compatible with each other. The micromeritics data showed that there was not much significant difference in term of angle of repose, bulk density and porosity. Size distribution by sieve analysis and microscopic method showed not much significant difference in formulations F_1, F_2, F_3 and F_4, while formulations F_5 having small particle size than remaining formulation. In vitro studies showed that F_1, F_2, F_3 and F_5 were able to release the drug up to 20 hrs, but only formulation F_4 followed the release pattern as per USP 23 (test 3). Results showed that drug, polymers ratio of indomethacin: PVP: MCC: pectin (1:1:1:2) was suitable for sustained release preparation.

Formulation F_4 was a satisfactory attempt to develop sustained release formulation, which will overcome the inherent drawbacks associated with conventional drug delivery of indomethacin and will have an improved bioavailability, therapeutic efficacy and patient compliance.

Furthermore the result of formulation $F_{6,}$ F_7 shows that the microencapsulation by Emulsion solvent evaporation technique was superior to simple solid dispersion method. The drug release from all formulations by dissolution, followed by diffusion and follows first order release kinetic

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