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FORMULATION AND *IN-VITRO* CHARACTERIZATION OF SUSTAINED RELEASE INDOMETHACIN MICROCAPSULES

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ABSTRACT

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 by using polymer with PVP, MCC and PECTIN in different concentrations and ethyl cellulose was used as coating material by emulsion solvent evaporation technique and characterized by using scanning electron microscope. Indomethacin meets all ideal characteristics, content uniformity and micromeritics properties. The compatibility studies done by FT IR spectroscopy and DSC shown no interaction between drug and polymers and they are compatible with each other. The in vitro release profiles of microcapsules in phosphate buffer pH 6.8 at 37±0.5°C .The concentration of drug release at different time intervals were determined by measuring the absorbance using UV spectrophotometer at 318nm with the help of standard graph.

Keywords: *Indomethacin, Pectin, Povidone, Microcrystalline cellulose, Ethylcellulose, Microcapsules.*

INTRODUCTION

Micro-encapsulation [3] 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 [1]. Generally spherical particles ranging in size from 1-1000µm. The material inside the capsule is referred to as the core, where as the wall is some times called a shell or membrane. Major advances in therapeutic sciences and substantial developments in field of biotechnology have taken place over past few years which have allowed synthesis of peptides and proteins on industrial scales. Their high sensitivities and fragilities together with very short biological half-lives seriously limit their therapeutic purpose thus represents major challenge to pharmaceutical scientist. In case of medicine, from the formulation point of view different drug delivery system involving e.g. liposome's, mixed micelles and nanoparticles, have shown, much promise, as have

controlled release implants. The excess of later technique has contributed to the renaissance of micro encapsulation. Micro encapsulation is process or technology by which thin coating can be applied reproducibly to small particles of solids, droplets of liquids dispersion thus forming micro particles (microcapsules, micro spheres).Uniqueness of micro encapsulation is the smallness of coated particles and their subsequent use and adaptation to a wide variety of dosage form and product application, due to smallness of particles drug moieties can be widely distributed throughout improving drug sorption

MATERIAL&METHODS

Indomethacin was obtained from Micro labs, Pondicherry, povidone & Ethyl cellulose from loba chemie Ltd, Mumbai, Microcrystalline cellulose, Pectin, Liquid paraffin(Light),Petroleum ether, Phosphoric acid from s.d fine chem. Ltd, Mumbai.

Preparation of Indomethacin Microcapsules [4]

The microcapsules were prepared by emulsion solvent evaporation technique[2]. In first stage prepared solid dispersion of indomethacin with different polymers ratio of povidone, microcrystalline cellulose (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 following table-1. Wight accurately all ingredients and transferred to a china dish. Then added 6ml of methanol and 12ml of dichloromethane in a ratio of (1:2) to the china dish containing drug and different polymer ratio. The china dish was heated on a water bath to evaporate the solvent. Now 1.5gm of ethyl cellulose was accurately weighted and dissolved in 25ml of acetone to from a homogenous polymer solution. To this solid dispersion containing in indomethacin was added dispersed throughly.The resulting mixture was added drop wise by glass syringe to light liquid paraffin (100ml) contained in a250ml 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 dessicator for 24 hrs.The ethyl cellulose was used as coating polymer and took 1.5gm constant in each formulation.

Table 1: Formulation of Indomethacin Microcapsules

S.No	Formulation	Drug: Polymer ratio(in mg)	Indomethacin	povidone	MCC	Pectin
1	F1	1:1:2.5:0.5	500	500	1250	250
2	F2	1:1:2:1	500	500	1000	500
3	F3	1:1:1.5:1.5	500	500	750	750
4	F4	1:1:1:2	500	500	500	1000
5	F5	1:1:0.5:2.5	500	500	250	1250

In-Vitro Dissolution Study [5]

In-vitro release profiles of indomethacin microcapsules were determined by USP dissolution apparatus1 and followed test 3 which containing 750ml of pH 6.8 phosphate buffer. The microcapsules were equivalent to 75mg of drug were filled in hard gelatin capsule and placed in dissolution medium at 37°±0.5C.the experiment was conducted up to 24 hrs at 75rpm.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 318nm with the help of standard graph.

TIME (Hrs)	F1	F2	F3	F4	F5
1	54.87	57.83	51.78	38.46	58.78
2	73.17	67.46	66.07	53.84	62.83
4	82.37	77.09	76.78	67.30	75.,10
6	85.98	83.13	80.35	71.15	79.05
12	93.29	92.16	92.85	80.76	89.18
24	----	99.39	98.21	96.15	----

TABLE NO-2: In vitro Cumulative % release Profile of Indomethacin Microcapsules

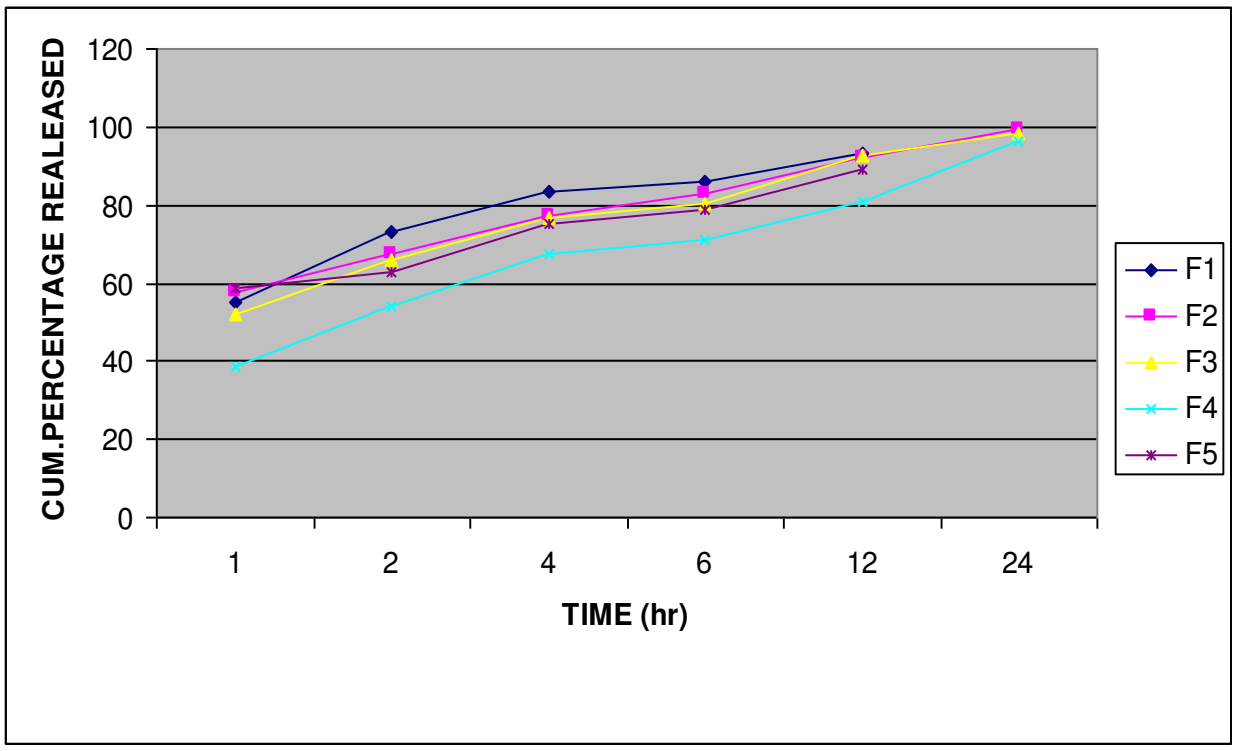


Fig.1 In-Vitro Dissolution Test of Indomethacin Microcapsules

CHARACTERIZATION OF INDOMETHACIN MICROCAPSULES

a) Fourier transforms infrared spectroscopic analysis
b) Differential scanning calorimeter (DSC) Analysis
c) %yield determination
d) Determination of shape&size of microcapsules
e) Micromeritics properties of indomethacin microcapsules
1) Bulk density 2) True density 3) Porosity 4) Angle of repose
f) Drug content analysis
g) In-vitro dissolution studies

EVALUATION OF MICROCAPSULES

Size and shape of microcapsules:

The microcapsules were found to be discrete, spherical and free flowing. The mean size of the microcapsules were found to be 318.8µm, 497.75µm, 510.50µm, 521.25µm, and 336.33 µm, respectively in the batches of microcapsules prepared employing indomethacin with different polymers ratio of povidone, microcrystalline cellulose (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 following Table No-3.The particle size range increased as the combination ratio of pectin and Microcrystalline cellulose was increased and particle size range decrease, either of pectin and MCC ratio was increased.

Micromeritics

Micromeritic[6] investigations such as bulk density, true density, porosity, angle of repose and consolidation index were carried out on indomethacin microcapsules to standardize the product and to optimize the pilot production of dosage forms. The properties are studied to determine compressibility and flow properties. The values for true density, bulk density and porosity are shown in Table-3. The angle of repose of microcapsules was found to be 22.80, 21.85, 18.50, 21.79, and 23.14 for the formulation F1, F2, F3, F4, and F5. The result showed that angle of repose is less than 25^{o} which indicate good flow properties.

Table No- 3 Evaluation of microcapsules

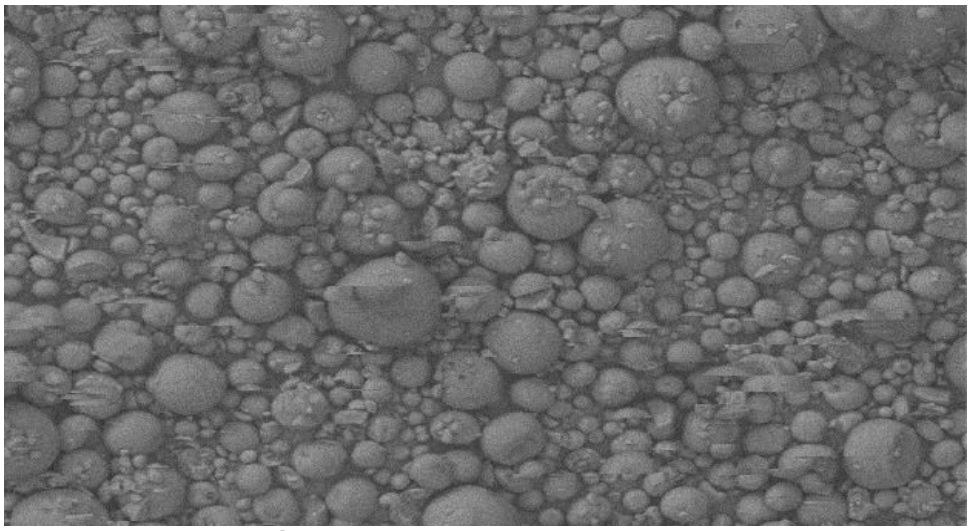
FORMULATION	Bulk density(gm/ml)	True density	Porosity %	Angle of repose	Particle size ±sem µm	Percentage yield	Drug content (%)
F-1	0.492	0.910	45.93	22.80°	318.8±5.2	90.02	54.66
F-2	0.500	0.783	42.72	21.85°	497.7±4.5	87.00	55.33
F-3	0.614	0.990	37.97	18.50°	510.5±8.1	81.25	56.00
F-4	0.508	0.950	46.52	21.79°	521.2±7.3	85.30	52.00
F-5	0.504	0.980	48.57	23.14°	336.3±6.8	89.10	49.33

Evaluation studies:

Scanning Electron Microscope Study: The microcapsules were observed under a scanning electron microscope. The instrument used for this study was Hitachi S-450 scanning electron microscope. The microcapsules were mounted directly on to the SEM sample stub, using double-sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

FT -IR Analysis: The drug was identified and confirmed by an IR spectrum. Fig.3 Shows the IR spectrum of indomethacin, Fig.4 Shows the IR spectrum of physical mixture Fig.5 Shows the IR spectrum of the microcapsules formulation of indomethacin. From the spectrum it was concluded the incorporation of the drug in to the polymer didn't change the characteristics of the drug.

DSC Analysis: DSC thermo grams of indomethacin, Povidone, Microcrystallines cellulose, pectin and ethyl cellulose. In (Fig. 6) the DSC thermo gram of intact indomethacin demonstrates the melting peak at 161.00^{0}C, pectin shown melting peaks at 157.66^{0}C while thermo gram of microcapsules shown melting peaks at 155.50^{0}C and 160^{0}C The lower melting point in formulation was probably due to the change in melting behavior of indomethacin in polymer environment. The thermo grams of formulation does not shows any characteristic change in melting peak which indication the no interaction occur between the drug and polymer and they are compatible with each other.



X180-----→500µm 0000

Fig. 2 The Scanning Electron Microscope of Microcapsules of Indomethacin

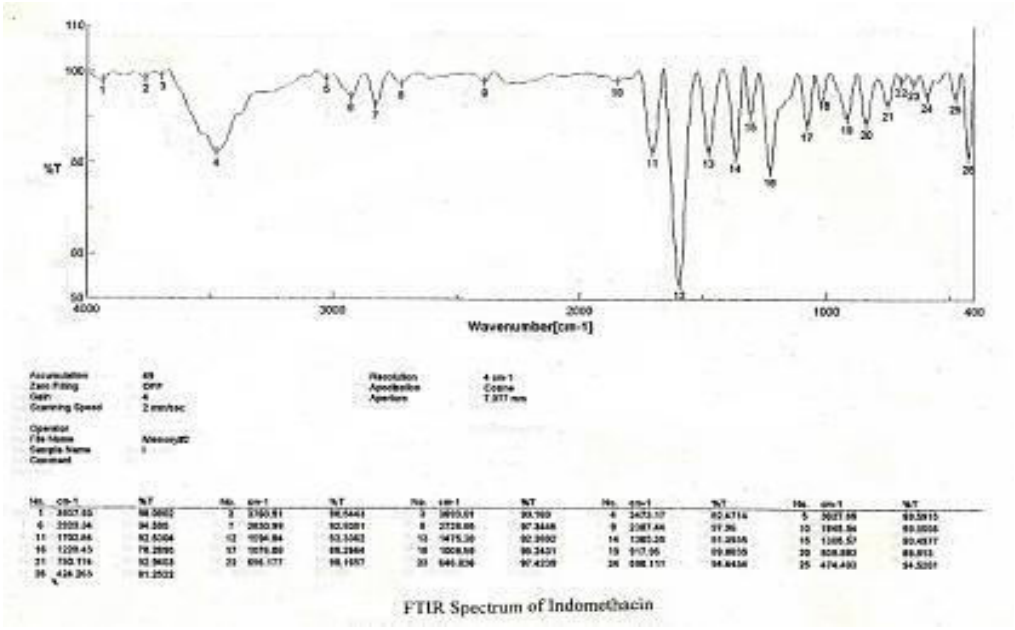
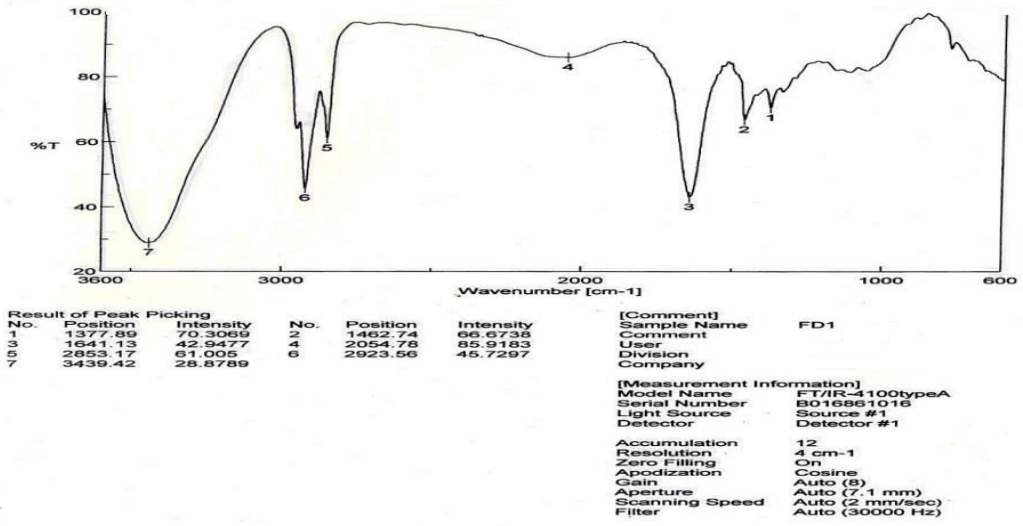
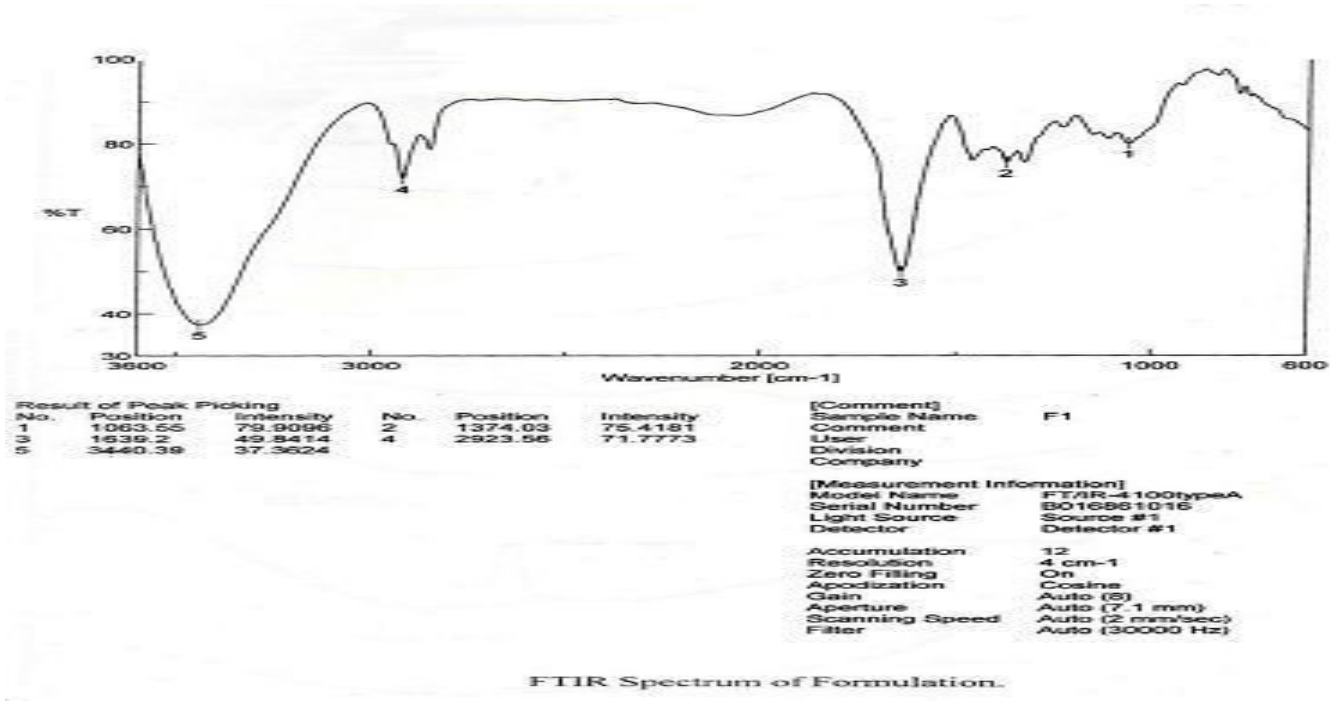


Fig. 3 FT - IR (KBr) SPECTRUM OF INDOMETHACIN



FTIR Spectrum of physical mixture of indomethacin, PVP, MCC, Pectin and EC.

Fig. 4 FT-IR (KBr) SPECTRUM OF PHYSICAL MIXTURE



FTIR Spectrum of Formulation.

Fig.5 FT – IR (KBr) SPECTRUM OF FORMULATION

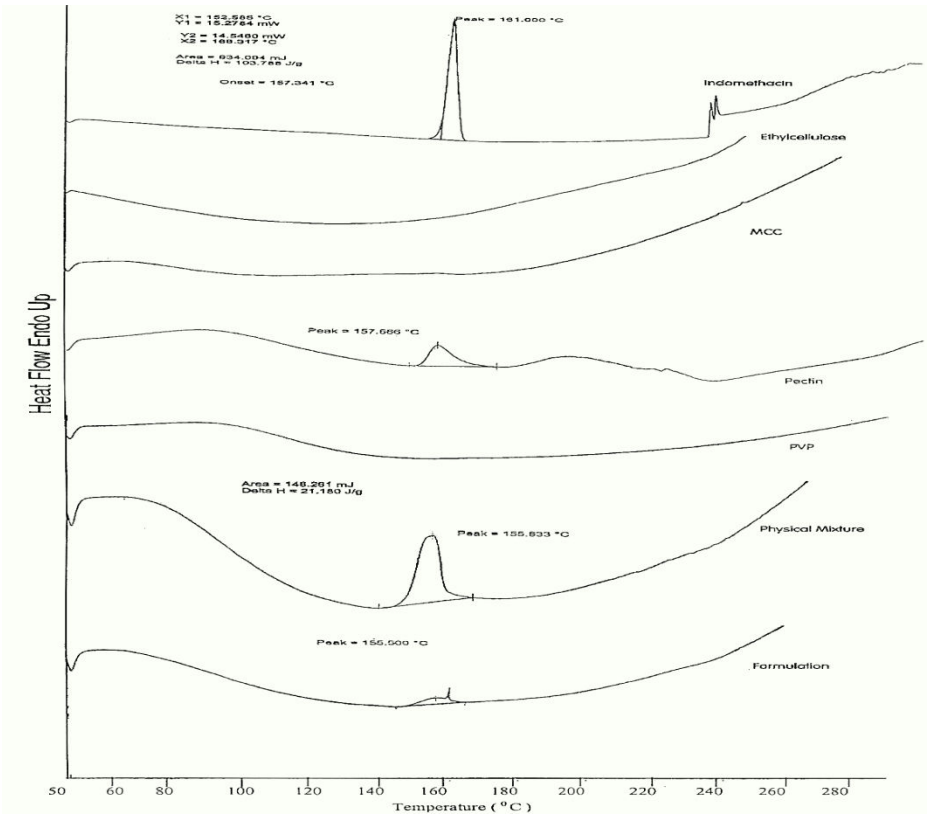


Fig. 6 DSC Thermo gram

Stability Studies

Physical stability and effect of aging on the drug release were studied in the control as well as microcapsules. All microcapsules formulations were kept in a small air tight glass containers and stored at different temperatures of 4±1°C in a refrigerator, 25±5°C and 40±5°C in the oven and in a dessicator containing saturated solution of conc.H_2SO_4 (13.1 ml to100 ml with Distilled .water to obtain75±5 % RH, effect of aging on their release characteristics was studied after 12th week using dissolution method. Table No.4 shows the stability of microcapsules formulation at various temperatures like 4±1°C, 25±5° C and 40±5°C/75±5% RH. There was no significant change in the release pattern when it was stored at 4±1°C and 25±5° C. The release rate was little bit affected when it was stored at 40±5°C and 75±5% RH.

Table -4 The Stability Of Microcapsules Formulations Various Temperatures

Formulation	4±1°C	25±5°C,60±5%RH	40±5 ° C,75±5%RH
FC 1	88.62%	88.51%	87.75%
FC 2	87.91%	87.32%	86.53%
FC 3	87.25%	87.11%	86.22%
FC 4	85.98%	85.62%	85.14%
FC 5	84.83%	84.23%	83.19%

RESULTS AND DISCUSSION:

The sustained release microcapsules of indomethacin were prepared by using polymers like Povidone, Micro crystalline cellulose (MCC), Pectin and evaluated with an aim to prevent side effects and increase bioavailability. It also leads to reduction in frequency of dosing which in turn improve patient compliance and reduce fluctuation in drug levels.

IR spectrum and DSC of the microcapsules formulation of indomethacin, it was concluded the incorporation of the drug in to the polymer didn't change the characteristics of the drug. The microcapsules formulation of Indomethacin using povidone, MCC, pectin retards the release of indomethacin from the microcapsules and produces the sustained action. The microcapsules prepared with the core: coat ratio of indomethacin with different polymers ratio of povidone, microcrystalline cellulose (MCC) and pectin, the microcapsules size distribution was found between 318.8µm to521.2µm by microscopic method. The microcapsules of formulation F3 showed maximum bulk density, true density and minimum porosity as compare to other formulations. While F2, F4, F5 showed intermediate and F1 showed less bulk density and true density. Three formulations F2, F3, F4 were able to release drug up to 24 hrs, F1 and F5 were able to release drug up to 20 hrs. such as 1:1:2.5:05(F1) releases 93.29%; 1:1:2:1(F2) releases 99.39%; 1:1:1.5:1.5(F3) releases 98.21%; 1:1:1:2(F4) releases 96.15%; 1:1:0.5:2.5(F5) releases 89.18%;indomethacin at 24 hrs .The results shows F4 formulation release pattern as per USP 23 (test 3)was suitable for sustained release preparation.

CONCLUSION

Future work is required to stabilize the product, in vivo studies, estimate the amount of drug present in the various organs with disposition kinetics and establish appropriate dosage regimens to gauge the significance changes in the metabolism of the drug before studies in the clinic.

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