



FORMULATION AND *IN VITRO* EVALUATION OF INDOMETHACIN MICROCAPSULES

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ABSTRACT

The objective of this research was to formulate and evaluate the Indomethacin microcapsules for controlled drug delivery by emulsification solvent evaporation technique, employing ethyl cellulose as coating material. Prepared microcapsules were evaluated for average particle size, Flow properties, Microencapsulation efficiency and *in vitro* drug release studies. The drug-polymer interaction evaluated by FT-IR spectroscopy. They were found to be discrete, free flowing high percentage of drug entrapment efficiency and also retard the release for 12 hrs. The *in vitro* dissolution study confirmed that the formulations followed zero order kinetics and peppas release mechanism.

Key words: *In vitro*, Indomethacin microcapsules, Drug delivery.

INTRODUCTION

Sustained/controlled release dosage forms are designed to achieve a prolonged therapeutic action by releasing the medication over an extended period of time by administration of single dose. Microencapsulation is one of the methods used to prepare these dosage forms.

Indomethacin, a non steroidal anti-inflammatory agent has a biological half life 2.6-11.2 hrs. Oral dose for adults was 25-50 mg, 2-3 times a day. To reduce the dosage frequency, controlled release formulations of Indomethacin were designed in the form of microcapsules for patient compliance and reduce adverse effects. The effect of polymer concentration on physical properties and drug release from the microcapsules were studied in the present investigation.

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EXPERIMENTAL

Materials and methods

Indomethacin was a gift sample from Hetro drugs pvt limited, Hyderabad, India, Ethylcellulose from central drug house private limited, Methanol, Sodium hydroxide, potassium dihydrogen phosphoate from qualigens fine chemicals, Mumbai.

Preparation of microcapsules²

Microcapsules of indomethacin were prepared by an emulsification-solvent evaporation method employing ethyl cellulose as coating material.

Ethylcellulose (1 gm) was dissolved in chloroform (20 mL) to form homogenous polymer solution, Indomethacin (1 gm) was dissolved in it and mixed thoroughly. The resulting mixture was then added drop by drop into a beaker containing 200 mL of an aqueous mixture of sodium CMC (0.5% w/v) stirring at 1000 rpm for 2 hrs to emulsify the added dispersion as fine droplets. A REMI medium duty stirrer with speedometer (model RQT 124) was used for stirring, Stirring was continued until the evaporation of chloroform at room temperature to produce spherical microcapsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water and the product was then dried to obtain discrete microcapsules. In each case different proportions of core:coat ratio 5 : 1(MC₁), 3 : 1(MC₂), 1 : 1 (MC₃), 1 : 3 (MC₄) and 1 : 5 (MC₅) were used to prepare microcapsules.

Preformulation studies

Drug-polymer compatability studies; FT-IR spectrophotometer used to study the interactions between rug and polymer and the spectrum was recorded in the wavelength region of 400-4000 cm.

Evaluation of microspheres³

The prepared microcapsules were evaluated for the following parameters:

Sizeanalysis, Angle of Repose, Bulk Density, Tapped Density, Carr's Index, Hausner'sratio, Drug Content, Drug Entrapment Efficiency and *In vitro* dissolution studies.

Size analysis

For size distribution analysis, different sizes from each formulation were separated

by sieving using a standard sieves. The amounts retained on different sieves were weighed and mean particle size of the samples were calculated by the following formula.

$$D_{avg} = \frac{\sum nd}{\sum n}$$

Where n = Frequency weight

d = mean size

Angle of repose

The flow characteristics of microcapsules were studied by measuring the angle of repose employing fixed funnel method. The angle of repose was calculated by using the following formula.

$$\tan \theta = \frac{h}{r}$$

$$\theta = \tan^{-1} \frac{h}{r}$$

h = height of pile,

r = radius of the base of the pile,

θ = angle of repose.

Bulk density and tapped density⁴

Bulk density and tapped density were measured by using bulk density apparatus. The samples were placed in a 100 mL graduated cylinder. The cylinder was fixed on the bulk density apparatus and timer knob was set for 100 tappings. Bulk density and tapped density were calculated from the following formulae.

$$\text{Bulk density} = \frac{\text{Weight of microcapsules}}{\text{Bulk volume of microcapsules}}$$

Carr's Index and Hausner's ratio

Carr's index and Hausner ratio were determined from the tapped and bulk densities of a known weight of samples using a bulk density apparatus. The following formulas were used for calculating Carr's index and Hausner's ratio:

$$\text{Carr's index} = \frac{\text{Tapped density-bulk density}}{\text{Tapped density}}$$

$$\text{Hausner' ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Microencapsulation efficiency⁵

Microcapsules of indomethacin (50 mg) were powdered and extracted with 50 mL of methanol. It was filtered and 1 ml of filtrate was taken and suitably diluted with phosphate buffer pH 6.2 and the absorbance was measured at 318 nm. Microencapsulation efficiency was calculated using the following formula.

$$\text{Micro encapsulation efficiency} = \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \times 100$$

In vitro dissolution study⁶

Microcapsules [(22/44 mesh size , (535.5 μm)] containing equivalent to 75 mg of indomethacin were packed in hard gelatin capsule . the release of indomethacin from the capsules was studied in phosphate buffer of pH 6.2 (900 mL) using a United states pharmacopoeia (USP) type II dissolution apparatus with a rotating paddle stirrer at 50 rpm and $37 \pm 0.5^\circ\text{C}$. 5 mL samples were withdrawn through a filter (0.45 μm) at different time intervals and assayed at 318 nm using a UV-Visible spectrophotometer. The drug release experiment was conducted in triplicate.

RESULTS AND DISCUSSION

The present investigation was carried out on the formulation and evaluation of oral controlled release formulations of indomethacin microcapsules, which is having a short biological half-life, meant for treatment of Rheumatoid Arthritis, Osteo Arthritis, and Ankylosing Spongilitis.

Indomethacin microcapsules were developed by emulsification - solvent evaporation method employing Ethyl cellulose was coating material. The IR spectra for Indomethacin, ethylcellulose and its physical mixture were shown in Fig. 1.1. The results revealed that no interaction was found between drug and polymer. The microcapsules were found to be discrete, spherical, size range of different batches of microcapsules was in the range of 531 μm to 975 μm . the angle of repose values ranges from 16.11 to 26.5.

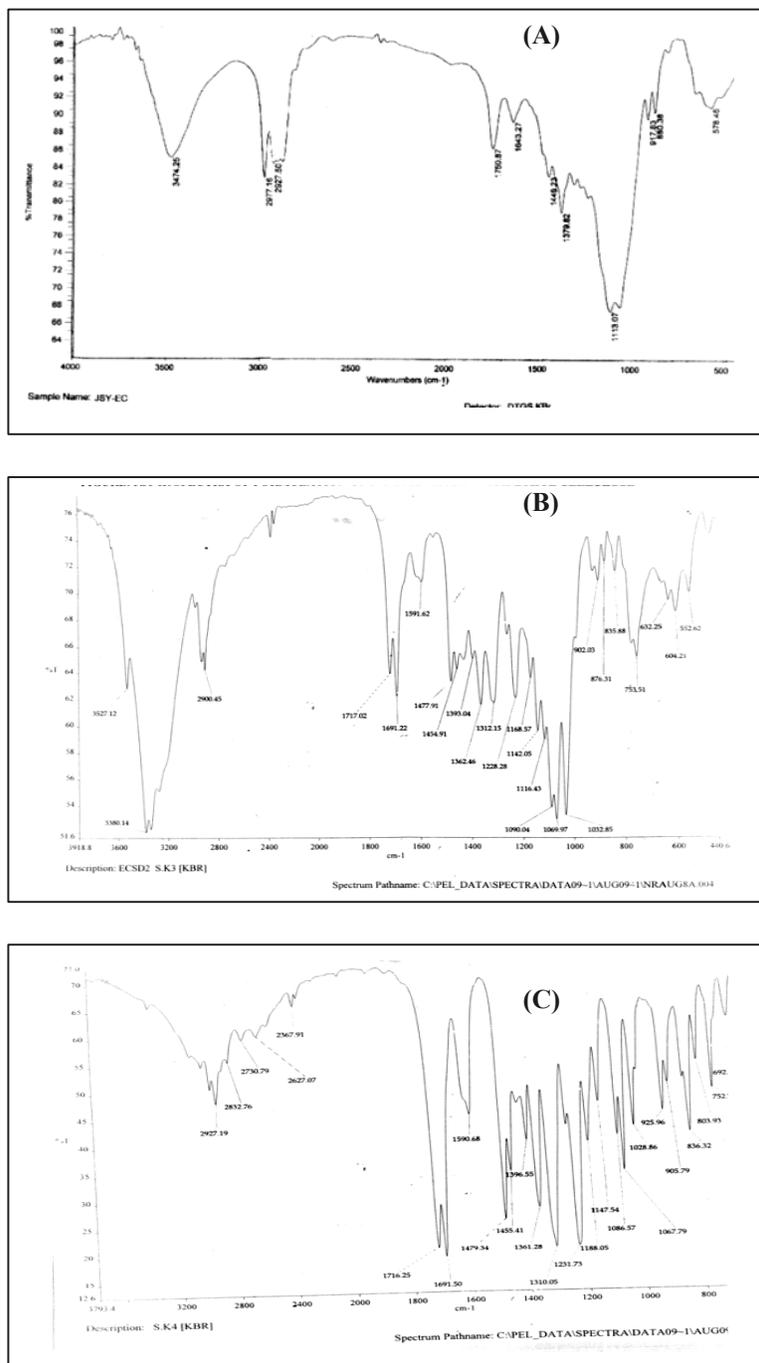


Fig 1.1: FT IR analysis for (a) Indomethacin (b) Ethylcellulose (c) physical mixture of indomethacin and ethylcellulose

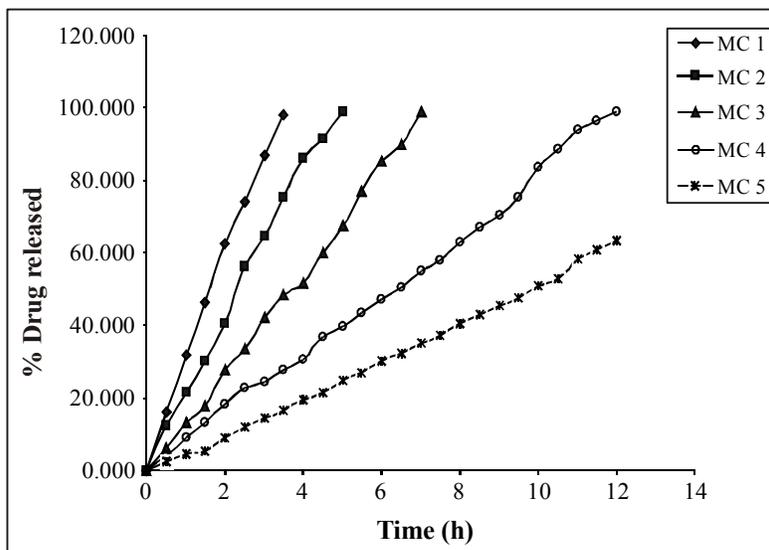


Fig. 1.2: Release profiles of indomethacin microcapsules formulated with ethyl cellulose by emulsion solvent evaporation method

It has been stated that, bulk density values less than 1.0 gm/mL, it was further supported by carr's index and hausners ratio. It indicates microcapsules found to be Good flow characteristics reported in Table 1.0.

Table 1: Physical properties of indomethacin microcapsules formulated with ethyl cellulose

Formulation code	Particle size (μm)	Angle of repose (θ)	Bulk density (gm/cm^3)	Compressibility index (%)	Hausner's ratio	Entrapment efficiency (%)
MC1	531.31	26.56	0.17	19.53	1.24	96.80
MC2	786.14	22.78	0.25	16.81	1.22	80.32
MC3	845.76	17.06	0.24	15.95	1.20	78.08
MC4	858.92	16.75	0.34	11.63	1.14	65.61
MC5	975.01	16.11	0.38	6.50	1.08	80.24

The drug entrapment efficiency analysis showed that, the entrapment of drug within each batch of microspheres ranges from 60.24 to 96.80.

Table 2: Release kinetics of indomethacin microcapsules formulated with ethylcellulose

Formulations	Correlation coefficient values	Release rate constant (K ₀) (mg/hr)	T ₅₀ % (hr)	T ₉₀ % (hr)	Correlation coefficient (n)			
	Zero order	First order	Matrix	Korsmeyer-Peppas				
MC1	0.9970	0.8797	0.9524	0.9993	20.98	1.60	2.88	0.9344
MC2	0.9963	0.8566	0.9377	0.9972	14.82	2.47	4.46	0.9437
MC3	0.9986	0.8818	0.9182	0.9988	10.50	3.86	6.60	0.9543
MC4	0.9975	0.8143	0.9135	0.9979	6.18	6.43	10.92	0.9759
MC5	0.9963	0.9748	0.9069	0.9979	3.96	9.91	16.93	1.0542

The in vitro drug release from the formulations was studied for 12 h and the data fitted into the zero order, first order, Higuchi and Peppas models. The formulation MC4 core:coat (1 : 3) retard the release for 12 h, further increment of the polymer concentration, i.e 1 : 5 (core:coat) retard the release more than 12 h. As the amount of polymer increased, drug release was retarded. This is because particle size, surface area available for drug release. The drug release from the formulations was found to be zero order kinetics and Peppas mechanism i.e n was found to be in the range of 0.9077 to 1.01, formulation exhibiting the non-fickian diffusion mechanism.

CONCLUSION

Ethyl cellulose coated microspheres of Aceclofenac could be successfully developed by Emulsion solvent evaporation technique, it involves emulsification and removal of solvent. Microcapsules exhibited good controlled release characteristics and were found to be suitable for oral controlled release for 12 hrs.

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