

# EVALUATION OF OLIBANUM RESIN AS MICROENCAPSULATING AGENT FOR CONTROLLED DRUG DELIVERY

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## ABSTRACT

*Olibanum resin was evaluated as microencapsulating agent and to prepare resin coated microcapsules. Olibanum resin coated microcapsules of indomethacin were prepared by an industrially feasible emulsification-solvent evaporation method and the microcapsules were investigated. The resin-coated microcapsules are spherical, discrete, free-flowing and multinucleate monolithic type. Microencapsulation efficiency was in the range 99-112 %. Indomethacin release from the resin-coated microcapsules was slow over 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release was by fickian diffusion mechanism. Good linear relationships were observed between wall thickness of microcapsules and release rate ( $K_1$ ) and  $T_{50}$  values. Resin coated microcapsules exhibited good controlled release characteristic and were found suitable for once a day oral controlled release products.*

**Key words:** *Olibanum, Resin, Microencapsulation, Controlled Release, Indomethacin.*

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## INTRODUCTION

Controlled release drug delivery systems (CRDDS) are aimed at controlling the rate of drug delivery, sustaining the duration of the activity and targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible. Among various techniques, microencapsulation and microcapsules are widely accepted for controlled release. Polymers and release retarding materials used as a coat play a vital role in controlling the drug release from the microcapsules. Microencapsulation by various polymers and their applications are described in standard text books<sup>1,2</sup>. Though a variety of polymeric materials are available to serve as a release retarding coat materials, there is a continued need to develop new, safe and effective release retarding coat materials for microencapsulation.

Olibanum is a gum resin obtained from *Boswellia serrata*, Roxburgh and other species of *Boswellia*. Olibanum consists<sup>3</sup> of chiefly of an acid resin (56-60 percent), gum (30-36 percent) and volatile oil (3-8 percent). The resin contains<sup>4</sup> mainly a resin acid (boswellic acid) and a resene (olibanoresene) in equal proportions. Ether soluble resin extracted from olibanum exhibited<sup>5</sup> excellent release retarding properties in matrix tablets for controlled release due to its hydrophobic water repellent properties. Preliminary studies indicated that the resin has good film forming property when dried from chloroform solution. In the present work the resin extracted from the olibanum was evaluated as coat in microencapsulation. Studies were carried out on microencapsulation of indomethacin by the resin and evaluation of the resin coated microcapsules of indomethacin for controlled drug release. Indomethacin is a widely used non-steroidal anti inflammatory, analgesic and antipyretic drug. The oral dose is 25 mg, 3 to 4 times a

day. It is associated with G.I side effects majorly peptic ulceration with bleeding. Earlier studies<sup>6</sup> indicated that the incidence of these side effects was significantly lower with sustained release and microencapsulated formulations. Hence it requires controlled release formulation to slow down its release in the G.I system not only to prolong its therapeutic action but also to minimize its side effects. Indomethacin Extended Release Capsules are official in USP XXIV<sup>7</sup>.

## EXPERIMENTAL

### Materials :

Indomethacin was a gift sample from M/s. Micro Labs Ltd., Pondicherry. Chloroform GR (Merck), Diethyl ether (Qualigens), methanol (Qualigens), sodium carboxy methyl cellulose (sodium CMC having a viscosity of 1500-3000 cps of a 1% w/v solution at 25<sup>0</sup>C) were used. The resin used as coat material was extracted from olibanum in the laboratory as follows:

Powdered olibanum (10 g) was extracted repeatedly with 4 x 50 ml quantities of solvent ether. The ether extracts were collected in a porcelain dish and concentrated to dryness at 40<sup>0</sup>C. The dry mass was powdered and the size was reduced to 200 mesh.

### Methods

**Microcapsule preparation:** An emulsification-solvent evaporation method<sup>8</sup> was tried to prepare resin-coated microcapsules. Resin (4 g) was dissolved in chloroform (100 ml) to form a homogenous solution. Core material, indomethacin (1.6 g) was added to the polymer (resin) solution (10 ml) and mixed thoroughly. The resulting mixture was then added in a thin stream to 200 ml of an aqueous mucilage of sodium CMC (0.5% w/v) contained in a 450 ml beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A Remi Medium Duty stirrer with Speed Meter (Model RQT 124) was used for stirring. The solvent, chloroform was then removed by continuous stirring at room temperature (28<sup>0</sup>C) for 3 h to produce spherical microcapsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules. Different proportions of core: coat namely 9:1 (MC1), 8:2 (MC2) and 7: 3 (MC3) were used to prepare microcapsules with varying coat thickness.

**Estimation of indomethacin:** Indomethacin content of the microcapsules was estimated by UV spectrophotometric method based on the measurement of absorbance at 318 nm in phosphate buffer of pH 6.2. The method was validated for linearity, accuracy, and precision. The method obeyed Beer's law in the concentration range 0-25 µg/ml. When a standard drug solution was assayed repeatedly (n= 6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6 and 0.8 per cent respectively.

**Characterization of microcapsules:** For the size distribution analysis, different sizes in a batch were separated by sieving using a range of standard sieves. The amounts retained on different sieves were weighed.

Encapsulation efficiency was calculated using the equation, encapsulation efficiency = (estimated percent drug content/ theoretical percent drug content) x100. Theoretical mean wall thickness of the microcapsules was determined by the method of Luu et al.<sup>9</sup> using the equation,  $h = \bar{r} (1-p) d_1 / 3[p d_2 + (1-p) d_1]$  where h is the wall thickness,  $\bar{r}$  is the mean of the microcapsules,  $d_1$  is the density of the core material,  $d_2$  is the density of the coat material and p is the proportion of the medicament in the microcapsules.

The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S430, UK). For SEM the microcapsules were mounted directly onto the SEM sample stub, using

double side sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

### Drug Release Study

Release of indomethacin from the resin coated microcapsules of size 20/30, 30/50 and 50/80 was studied in phosphate buffer of pH 6.2 (900 ml) using an eight station dissolution rate test apparatus (model Disso-2000, M/s LABINDIA) with a paddle stirrer at 50 rpm and  $37 \pm 0.5^{\circ}\text{C}$  as prescribed for Indomethacin Extended Release Capsules in USP XXIV. A sample of microcapsules equivalent to 75 mg of indomethacin were used in each test. Samples were withdrawn through a filter ( $0.45\mu$ ) at different time intervals and were assayed at 318 nm for indomethacin using a Shimadzu UV-150 double-beam spectrophotometer. The drug release experiments were conducted in triplicate.

### Data analysis

Release data were analyzed as per zero order, first order, Higuchi<sup>10</sup> and Ritger and Peppas<sup>11</sup> models to assess the drug release kinetics and mechanism from microcapsules.

## RESULTS AND DISCUSSION

An emulsification-solvent evaporation method was developed for microencapsulation of indomethacin by the resin. The method involves emulsification of the polymer (resin) solution in chloroform containing the dispersed drug particles in an immiscible liquid medium (0.5% w/v solution of sodium CMC) as microdroplets, followed by removal of the solvent chloroform by continuous stirring to form rigid microcapsules. Resin coated microcapsules of indomethacin could be prepared by the emulsification-solvent evaporation method developed. The microcapsules were found to be discrete, spherical and free flowing. The nature of the method of preparation indicated that the microcapsules were of multinucleate and monolithic type. SEM (Fig.1) indicated that the microcapsules were spherical with smooth surface and completely covered with the polymer (resin) coat.

The sizes could be separated by sieving and a more uniform size range of microcapsules could readily be obtained. The sieve analysis of different microcapsules showed that a large proportion of microcapsules (60-70%) in a batch were in the size range of  $-20 +30$  ( $715\mu\text{m}$ ) mesh. A log-normal size distribution of the microcapsules was observed in all the batches prepared. Indomethacin release from the microcapsules was studied in phosphate buffer of pH 6.2 as prescribed for Indomethacin Extended Released Capsules in USP XXIV. Indomethacin release from the microcapsules was slow and spread over a period of more than 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. As the proportion of the coat was increased, indomethacin release rate was decreased. Smaller microcapsules gave higher release rates due to increased surface area.

Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from the microcapsules followed first order kinetics. When the release data was analyzed as per Peppas equation<sup>11</sup>, the release exponent 'n' was  $< 0.5$  with all the microcapsules indicating fickian diffusion as the release mechanism. Plots of percent released Vs square root of time were found to be linear ( $r > 0.9820$ ) indicating that the drug release from the microcapsules was diffusion controlled. Linear relationships were observed between wall thickness of the microcapsules and release rate ( $K_1$ ) and  $T_{50}$  (time for 50% release) values (Fig. 2).

**Table-1: Indomethacin Content, Microencapsulation Efficiency, Wall Thickness and Release Characteristic of Olibanum Resin Coated Microcapsules**

$T_{50}$  is the time for 50% release and  $K_1$  is first order release rate constant.

\* Figures in parentheses are Coefficient of Variation (CV) values

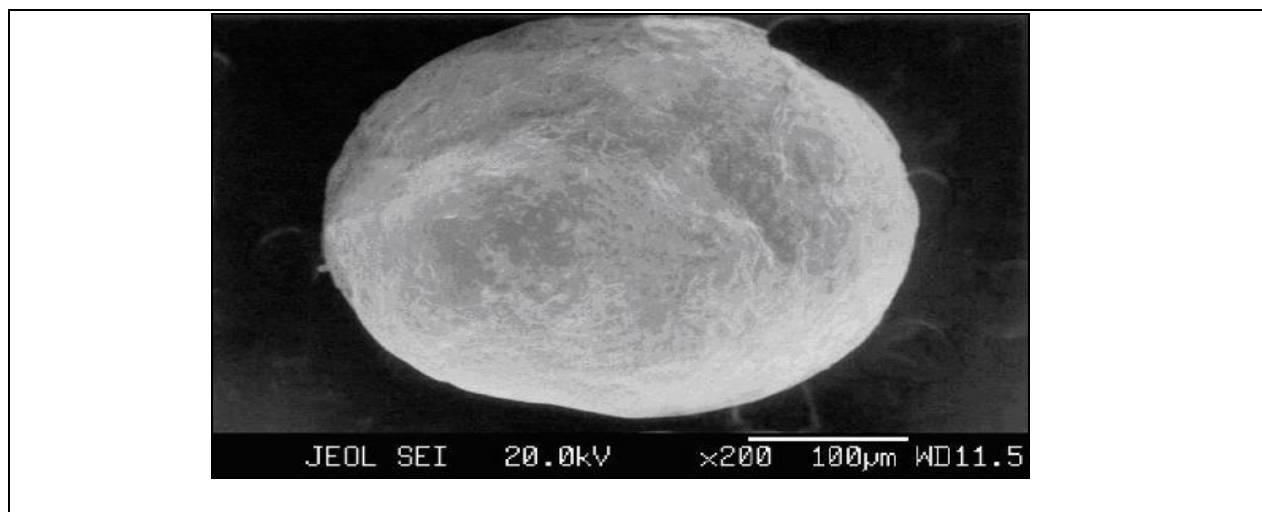
Microcapsules (Size)	Indomethacin content (%)	Microencapsulation efficiency (%)	Wall thickness ( $\mu$ )	$T_{50}$ (h)	$K_1$ ( $h^{-1}$ )
MC1(20/30)	89.55 (0.17)*	99.5	68.65	1.4	0.097
MC1 (30/50)	94.14 (0.14)	104.6	30.55	1.0	0.102
MC1 (50/80)	94.09 (0.19)	104.5	16.28	0.8	0.130
MC2 (20/30)	88.88 (0.41)	111.1	71.71	3.0	0.092
MC2 (30/50)	90.05 (0.37)	112.6	40.68	2.4	0.099
MC2 (50/80)	89.64 (0.79)	112.05	29.95	1.8	0.123
MC3 (20/30)	69.91 (0.11)	99.87	98.40	3.1	0.089
MC3 (30/50)	70.19 (0.12)	100.27	60.93	3.0	0.095
MC3 (50/80)	71.18 (0.13)	101.68	32.28	2.2	0.109

Low c.v. (< 1.0%) in percent drug content indicated uniformity of drug content in each batch of microcapsules (Table 1). The microencapsulation efficiency was in the range 99-112%. Drug content of the microcapsules was found to be the same in different sieve fractions. As the microcapsules are spherical, the theoretical average wall thickness of the microcapsules was calculated as per Luu *et al*<sup>9</sup>. Microcapsules prepared with various ratios of core: coat were found to have different wall thickness (Table 1).

### CONCLUSION

1. Spherical olibanum resin coated microcapsules of indomethacin could be prepared by the emulsification-solvent evaporation method developed. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely.
2. Microencapsulation efficiency was found to be in the range 99-112 %.

3. Indomethacin release from the olibanum resin-coated microcapsules was slow and extended over longer periods of time and depended on core: coat ratio, wall thickness and size of the microcapsules.
4. Drug release from the olibanum resin-coated microcapsules was by fickian diffusion mechanism.
5. Good linear relationships were observed between wall thickness of the microcapsules and release rate ( $K_1$ ) and  $T_{50}$  values.
6. Olibanum resin was found suitable as microencapsulating agent and the resin-coated microcapsules of indomethacin exhibited good controlled release characteristics and were found suitable for once a day oral controlled release of indomethacin.
7. Since the resin is of natural origin, it is non-toxic, biocompatible and cheaper.

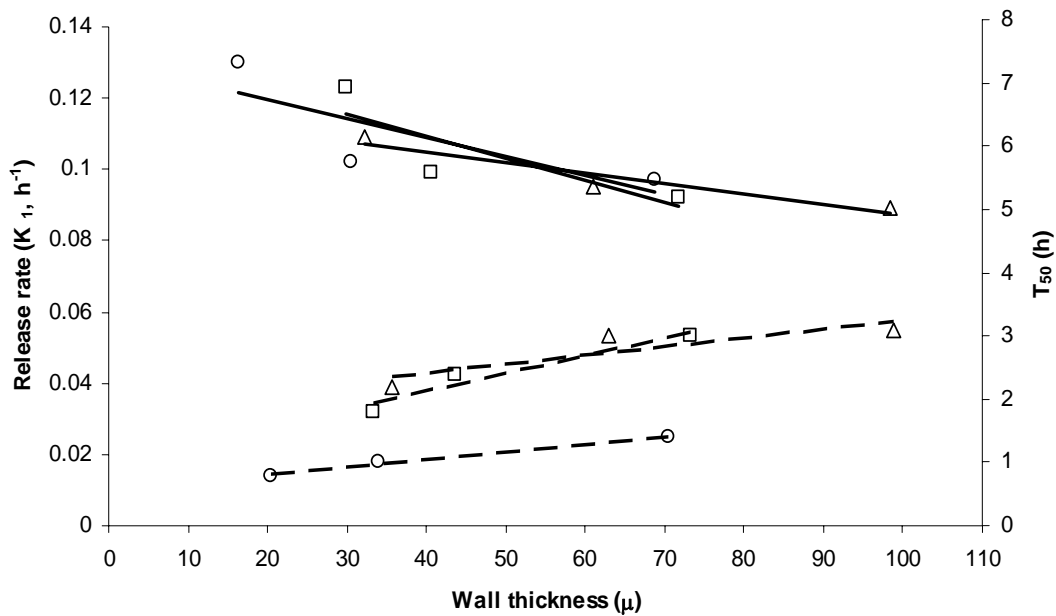


**Fig.1: SEM of Olibanum Resin-Coated Microcapsules of Indomethacin**

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**Fig. 2:** Relationships between wall thickness of Olibanum resin-coated microcapsules and the release rate (—) and T<sub>50</sub> values (— — —) for microcapsules, MC1 (○), MC2 (□) and MC 3 (Δ).

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