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Preparation and Evaluation of Olibanum Resin Coated Microcapsules for Controlled Release of Aceclofenac

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The objective of the study is to evaluate olibanum resin, a natural resin as a coat for controlled release microcapsules of aceclofenac. Olibanum resin coated microcapsules were prepared by an emulsion-solvent evaporation method employing different proportions of core and coat and the microcapsules were evaluated for size, drug content and microencapsulation efficiency, wall thickness, surface character by SEM and drug release kinetics. The olibanum resin coated microcapsules prepared were found to be discrete, spherical and free flowing. Drug content was uniform (c.v. = 0.13 %) in each batch of microcapsules and the microencapsulation efficiency was in the range 95.74-99.03 %. Aceclofenac release from the olibanum resin coated microcapsules was slow and spread over a period of 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was majorly by non-fickian diffusion. Good linear relationships were observed between wall thickness of the microcapsules and release rate (K_0) and (K_1). Microcapsules prepared employing chloroform as solvent for olibanum exhibited higher release rates when compared to those prepared employing dichloromethane as solvent. Olibanum resin was found to be a new and efficient microencapsulating agent for controlled release microcapsules and the olibanum resin coated microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release of aceclofenac over 24 h.

Key Words: Olibanum resin, Aceclofenac, Controlled release, Microcapsules.

INTRODUCTION

Controlled release drug delivery systems 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. Microencapsulation and microcapsules are widely accepted for controlled release. Polymers and release retarding materials used as 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[1,2]. Though a variety of polymer materials are available to serve as release retarding coat materials, there is a continued need to develop new, safe and effective release retarding coat materials for microencapsulation. The objective of the present study is to evaluate olibanum resin as coat for controlled release microcapsules and to prepare olibanum resin coated microcapsules for controlled release. Olibanum resin coated microcapsules containing aceclofenac were prepared by an industrially feasible method of microencapsulation and the microcapsules were evaluated for controlled release of aceclofenac.

EXPERIMENTAL

Aceclofenac was a gift sample from M/s Medlay Phrama., Jammu. Olibanum gum was procured from M/s Girijan Co-operative Coporation, Ltd., Visakhapatnam. Sodium carboxy methyl cellulose (high viscosity grade 1500-3000 cps of a 1% w/v solution at 250 C), Chloroform (Merck), Dichloromethane (Merck) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Preparation of olibanum resin: Olibanum resin used as coat material was extracted from olibanum gum in the laboratory as follows: Powdered olibanum (10 g) was extracted repeatedly with 4 × 50 mL quantities of solvent ether. The ether extracts were collected into a porcelain dish and concentrated to dryness at 40 ºC. The dried mass obtained was powdered and passed through mesh No.120.

Preparation of microcapsules: An emulsification-solvent evaporation method was tried to prepare resin-coated microcapsules. Olibanum resin (2 g) was dissolved in chloroform or dichloromethane (100 mL) to form a homogenous polymer solution. Core material, aceclofenac (0.8 g) was added to the polymer solution (10 mL) and mixed thoroughly. The

resulting mixture was then added in a thin stream to 300 mL of aqueous mucilage of sodium CMC (0.5 % w/v) contained in a 500 mL beaker while stirring at 1600 rpm to emulsify the added dispersion as fine droplets. A Remi medium duty stirrer with speed meter (model RQT124) was used for stirring. The solvent chloroform or dichloromethane was then removed by continuous stirring at room temperature (30 ºC) for 3 h to produce spherical micro capsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules.

Olibanum coated microcapsules of aceclofenac were prepared employing chloroform and dichloromethane as solvent for the polymer (olibanum resin). Different proportions of core: coat such as 7:3, 8:2, 9:1 and 19:1 were used in each case to prepare microcapsules with varying coat thickness. The microcapsules prepared are listed in Table-1.

Estimation of aceclofenac: An UV spectrophotometric method based on the measurement of absorbance at 275 nm in phosphate buffer of pH 7.4 was used to estimate the aceclofenac content of the microcapsules. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range of 0-50 mcg/mL. When a standard drug solution was assayed repeatedly, (n = 6) low RSD (≤ 0.43 %) values ensured reproducibility of the method. No interference from the excipients was observed.

Characterization of microcapsules

Size analysis: For size distribution analysis, different sizes in a batch were separated by sieving using a set of standard sieves (IP). The amounts retained on different sieves were weighed.

Microencapsulation efficiency: Microencapsulation efficiency was calculated using the formula:

Microencapsulation efficiency = (Estimated per cent drug content in the microcapsules/ Theoretical per cent drug content in the microcapsules) × 100

Wall thickness: Wall thickness of the microcapsules was determined by the method of Luu *et al.*[3] using the equation:

$$H = \frac{r(1-p)d_1}{3[pd_2 + (1-p)d_1]}$$

where H is wall of thickness of microcapsules, r is arithmetic mean radius, d_1 is density of core material, d_2 is density of coat material and p is proportion of medicament in microcapsules.

Scanning electron microscopy: The SEM analysis was carried out using a scanning electron microscope (instruments-300 version-1) prior to examination. For scanning electron microscopic study the microcapsules were coated with gold (24 carate) in ion scaterring unit and moulded as to the SEM sample tube and the instrument energy of 10 KV and then microcapsules were scanned.

Drug release study: Drug release from the microcapsules was studied using an eight station dissolution rate test apparatus (Lab India, Disso 2000) in phosphate solution of pH 7.4 (900 mL). The paddle speed at 50 rpm and bath temperature at 37 ± 0.5 ºC were maintained throughout the experiment. A sample of microcapsules equivalent to 100 mg aceclofenac was used in each test. Aliquot equal to 5 mL of dissolution medium was withdrawn at different time intervals through a filter (0.45 µ) and assayed at 275 nm. All drug release studies were conducted in triplicate (n = 3).

RESULTS AND DISCUSSION

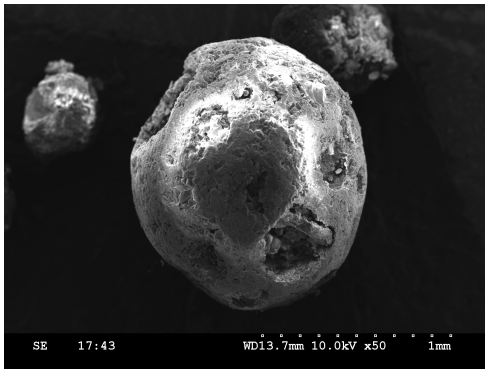
Olibanum is a gum resin obtained from *Boswellia serrata*, Roxburgh and other species of *Boswellia*. Olibanum consists[4] of mainly of an acid resin (56-60 %), gum (30-36 %) and volatile oil (3-8 %).The resin contains[5] mainly a resin acid (boswellic acid) and a resene (olibanoresence) in equal proportions. Ether soluble resin extracted from olibanum exhibited[6] excellent release retarding properties in matrix tablets for controlled release due to its hydrophobic water repellent properties[7,8]. 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 aceclofenac by olibanum resin employing (i) chloroform and (ii) dichloromethane as solvents for the resin and the resulting microcapsules were evaluated.

Aceclofenac has a short biological half life of 2-4 h and required to be administered repeatedly 3 or 4 times a day. It causes gastric disturbances such as nausea, ulceration with bleeding, vomiting, abdominal pain and constipation if present in large concentration in the gastro intestinal tract (GIT). Hence controlled release formulations are needed for aceclofenac to prolong its duration of action, reduce frequency of administration with increased patient compliance and to reduce undesired gastric disturbance.

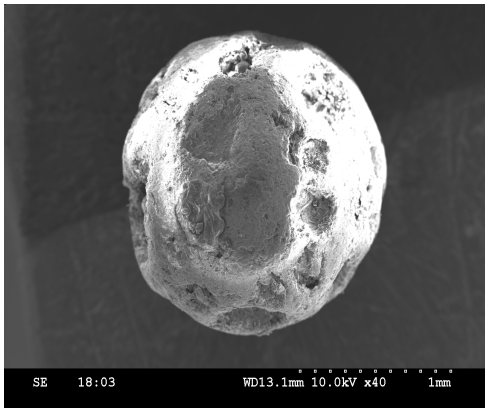
TABLE-1
DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE CHARACTERISTICS OF OLIBANUM RESEIN COATED MICROCAPSULES OF ACECLOFENAC

Microcapsules (core: coat ratio)	Drug content (%)	Micro encapsulation efficiency (%)	Wall thickness (µm)	T_{50} (h)	T_{90} (h)	K_0 (mg/h)	K_1 (h^{-1})	'n' in Peppas equation
Chloroform								
F1 (7:3)	68.76	98.23	20.18	4.3	13.00	4.041	0.176	0.545
F2 (8:2)	77.87	97.34	14.17	4.1	9.48	5.146	0.229	0.548
F3 (9:1)	89.13	99.03	6.88	3.4	9.12	7.716	0.313	0.536
F4 (19:1)	91.65	96.47	5.27	1.3	8.12	7.587	0.338	0.318
Dichloromethane								
F5 (7:3)	69.14	98.77	19.93	4.6	16.36	3.835	0.123	0.561
F6 (8:2)	78.85	98.56	24.04	5.5	11.24	4.096	0.174	0.534
F7 ((9:1)	88.14	97.93	7.51	1.5	10.24	6.347	0.269	0.542
F8 (19:1)	90.95	95.74	5.72	1.5	9.00	6.979	0.295	0.334

Olibanum resin coated microcapsules of aceclofenac could be prepared by the emulsification-solvent evaporation method developed. The olibanum resin microcapsules prepared were found to be discrete and free flowing. The nature of the method of preparation indicated that the microcapsules were of monolithic type. SEM (Fig. 1) indicated that the microcapsules were spherical with smooth surface and completely covered with resin polymer coat. Size analysis showed that a large proportion of microcapsules in a batch were in the size range of -20 +30 (670µm) and -30 +50 (398µm) mesh. Overall about 38.2 and 27.4 % (average of all products) were in the size range of -20 +30 (670 µm) and -30 +50 (398 µm) mesh. The method used to prepare the microcapsules employing olibanum resin is reproducible with regard to size and size distribution of the microcapsules. Low c.v (≤ 0.13 %) in percent drug content indicated uniformity of drug content in each batch of microcapsules. The microencapsulation efficiency was in the range 95.74-99.03 %. Microcapsules prepared with various ratios of core : coat were found to have different wall thickness.



(A)



(B)

Fig. 1. SEM of olibanum resin coated microcapsules of aceclofenac F2 prepared employing chloroform (A) and microcapsules F6 prepared employing dichloromethane (B) as solvents for the polymer

Aceclofenac release from all the olibanum resin coated microcapsules was slow and spread over more than 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. The release data were analyzed as per zero order, first order, Higuchi[9] and Ritger and Peppas[10] equation models. The drug release parameters of various microcapsules are summarized in Table-1. The correlation coefficient (R^2) values observed in fitting the release data into various kinetic models are given in Table-2. Analysis of release data as per zero order and first order kinetic models indicated that the drug release followed first order kinetics in all the cases. The correlation coefficient (R^2) values were higher in the first order model in all the cases when compared to those in the zero order model. Plots of per cent released *versus* square root of time were found to be linear with $R^2 > 0.9304$ indicating that drug release from these microcapsules was diffusion controlled. When the release data were analyzed as per Ritger and Peppas[10] equation, the release exponent (n) was in the range 0.534-0.548 in all the cases except microcapsules prepared with a core : coat ratio of 19:1 indicating non-fickian diffusion as the drug release mechanism from these microcapsules. In the case of microcapsules prepared with a core:coat ratio of 19:1 which exhibited relatively fast release, the release was by fickian diffusion mechanism. Good linear relationships (Fig. 2) were observed between wall thickness of the microcapsules and release rate (K_0) and (K_1) values in each case. Microcapsules prepared employing chloroform as solvent for olibanum exhibited higher release rates when compared to those prepared employing dichloromethane as solvent.

TABLE-2
CORRELATION COEFFICIENT (R^2) VALUES IN THE ANALYSIS OF RELEASE DATA OF OLIBANUM RESIN COATED MICROCAPSULES OF ACECLOFENAC AS PER VARIOUS KINETIC MODELS

Microcapsules (core: coat ratio)	Correlation Coefficient (R^2) value			
	Zero order	First order	Higuchi Model	Peppas Equation
Chloroform				
F1 (7:3)	0.7591	0.9889	0.9349	0.9415
F2 (8:2)	0.7979	0.9836	0.9465	0.9542
F3 (9:1)	0.935	0.9379	0.9941	0.9905
F4 (19:1)	0.8234	0.8447	0.9661	0.9961
Dichloromethane				
F5 (7:3)	0.7391	0.9348	0.9224	0.9304
F6 (8:2)	0.7333	0.9604	0.9168	0.9338
F7 ((9:1)	0.8773	0.9729	0.9806	0.9816
F8 (19:1)	0.8389	0.9010	0.9741	0.9965

Conclusion

Spherical olibanum resin coated microcapsules of aceclofenac could be prepared by the emulsification-solvent evaporation method developed. The method is industrially feasible as it involves emulsification and removal of solvent, which can be controlled precisely. The microencapsulation efficiency was in the range 95.74-99.03 %. Aceclofenac release from the olibanum resin coated microcapsules was slow and spread over more than 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was mainly by non-fickian diffusion and followed first order kinetics. Good linear relationships were observed between wall thickness of the microcapsules and release rates. Microcapsules prepared employing chloroform as solvent for olibanum exhibited higher release rates when compared to those prepared employing dichloromethane as solvent.

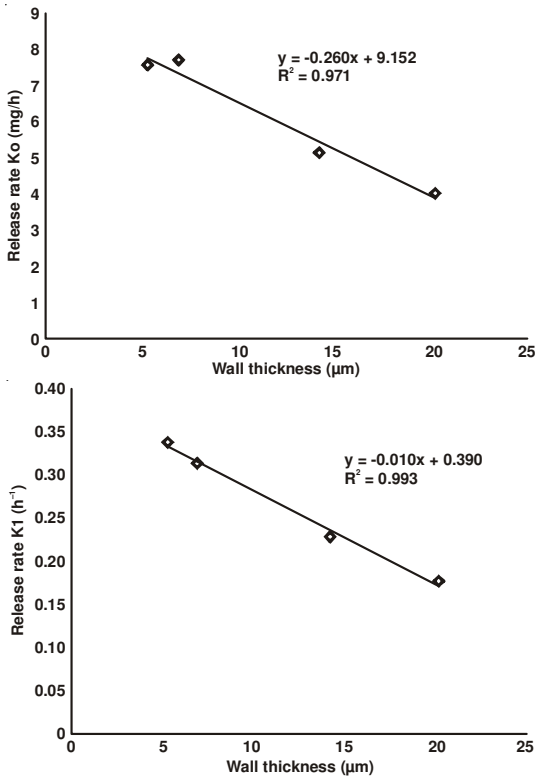
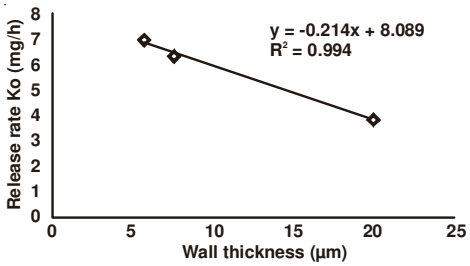


Fig. 2. Relationship between wall thickness and release rates (K_0 and K_1) of olibanum resin coated microcapsules of aceclofenac prepared employing chloroform as solvent



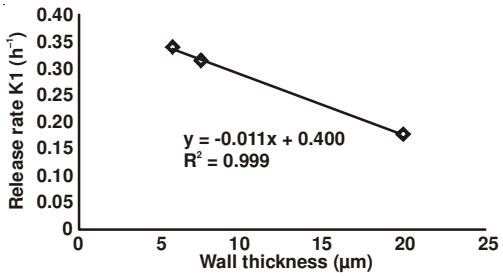


Fig. 3. Relationship between wall thickness and release rates (K_0 and K_1) of olibanum resin coated microcapsules of aceclofenac prepared employing dichloromethane as solvent

Olibanum resin was found to be a new and efficient micro-encapsulating agent for controlled release microcapsules and the olibanum resin coated microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release of aceclofenac over 24 h. Olibanum is reported[11] as non-toxic and since it is of natural origin it is biocompatible and cheaper.

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