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Preparation and Evaluation of Mucoadhesive Microcapsules Employing Olibanum Resin for Controlled Release of Aceclofenac

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The objective of the study is to evaluate olibanum resin, a natural resin polymer as coat for mucoadhesive microcapsules and to design mucoadhesive microcapsules of aceclofenac for controlled release. Olibanum resin coated microcapsules of aceclofenac were prepared by an emulsification-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 characters by SEM, drug release kinetics and mechanism and mucoadhesiveness. The olibanum resin coated microcapsules prepared were found to be discrete, spherical, free flowing and multinucleate monolithic type. Drug content was uniform (c.v. < 1.2 %) in each batch of microcapsules and the microencapsulation efficiency was in the range 99-102.5 %. 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 Fickian diffusion. Good linear relationships were observed between wall thickness of the microcapsules and release rate (K_0) and (K_1) values. In the *in vitro* wash-off test olibanum resin coated microcapsules exhibited good mucoadhesive property. Olibanum resin was found to be a new and an efficient microencapsulating agent for mucoadhesive microcapsules and the olibanum resin coated microcapsules were found suitable for oral controlled release of aceclofenac over 24 h.

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

INTRODUCTION

Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to tissue. Drug release from these systems should be at a desired rate predictable and reproducible. Among various oral controlled release systems, microencapsulation and microcapsules are widely accepted[1,2]. A new novel promising technology for obtaining controlled release and enhancing the bioavailability is a combination of mucoadhesion principle and microencapsulation to result in mucoadhesive microcapsules. Mucoadhesive microcapsules consist of either entirely of a mucoadhesive polymer or having an outer coating enclosing the drug particles.

They facilitate an intimate and prolonged contact with the absorption surface to provide controlled release and enhanced bioavailability of the contained drug over longer period of time to prolong its therapeutic action. The polymer used in mucoadhesive microcapsules plays a vital role in either controlling the drug delivery or enhancing bioavailability of the contained drug. Though a wide range of polymers are reported for preparing mucoadhesive microcapsules, there is a continued need to develop new, safe and effective polymers for mucoadhesive microcapsules. The objective of the present study is to evaluate olibanum resin as coat for mucoadhesive microcapsules for controlled release.

Olibanum is a gum resin obtained from *Boswellia serrata*, Roxburgh and other species of Boswellia. Olibanum consists[3] of chiefly of an acid resin (50-60 %), gum (30-36 %) and volatile oil (3-8 %). The resin consists[4] mainly a resin acid (boswellic acid) and a resin (olibanoresene) in equal proportions. Ether soluble resin extracted from olibanum exhibited excellent release retarding and rate controlling properties in matrix tablets and microcapsules for controlled release[5-7]. Preliminary studies indicated that the resin also has good mucoadhesive property. In the present work, aceclofenac was microencapsulated by olibanum resin and the microcapsules were evaluated for mucoadhesiveness and controlled release of aceclofenac. Aceclofenac has a short biological half-life of 2-4 h and is 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 gastrointestinal tract. Hence controlled release or sustained release formulations are needed for aceclofenac to prolong its duration of action, reduce frequency of administration with better patient compliance and to reduce undesired gastric disturbances. A few sustained release products of aceclofenac are available commercially.

EXPERIMENTAL

Aceclofenac was a gift sample from M/s Aristo Pharmaceuticals Ltd., Mumbai. Olibanum gum was procured from M/s Grijan Co-operative Corporation Ltd., Government of Andhra Pradesh, Visakhapatnam. Sodium carboxy methyl cellulose (high viscosity grade 1500-3000 cps of a 1 % w/v solution at 25 °C) (Loba-chemie) and chloroform AR (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 in a porcelain dish and concentrated to dryness at 40 °C. The dried mass obtained was powdered and passed through mesh No. 120.

Preparation of microcapsules: An emulsification-solvent evaporation method was tried to prepare olibanum resin coated microcapsules. Olibanum resin (2 g) was dissolved in chloroform (100 mL) to form a homogeneous solution. Core material

i.e. medicament (aceclofenac) (0.8 g) was added to 10 mL polymer (resin) solution which provides 0.2 g of polymer 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 °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 *viz.*, 19:1 (MC1), 9:1 (MC2), 8:2 (MC3) and 7:3 (MC4) were used to prepare microcapsules with varying coat thickness.

Estimation of aceclofenac: A UV-spectrophotometric method based on the measurement of absorbance at 275 nm in phosphate buffer of pH 6.8 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 0-10 µg/mL. When a standard drug solution was assayed repeatedly (n = 6) low RSD (< 0.33 %) 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 range of standard sieves. The amounts retained on different sieves were weighed.

Microencapsulation efficiency: Microencapsulation efficiency was calculated using the equation:

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated per cent drug content in microcapsules}}{\text{Theoretical per cent drug content in microcapsules}} \times 100$$

Scanning electron microscopy: The microcapsules prepared were observed under a scanning electron microscope (Jeol JXA 8100 LTD, Tokyo, Japan). The samples were fixed on a brass stub using double sided sticking tape and then gold coated in vacuum by a sputter coater. The pictures were the taken at an excitation voltage of 15 Kv.

Wall thickness: Assuming the microcapsules to be uniform and spherical, wall thickness of the microcapsules in the present study was determined by the method described by Luu *et al.*[8] using the equation:

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

where 'h' is the wall thickness, '$\bar{r}$' is the arithmetic mean radius of the microcapsule, '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 microcapsule. Densities were determined using petroleum ether as displacement fluid for drug and water as displacement

fluid for resin at room temperature. Mean radius of the microcapsules was determined by sieving.

Drug release study: Drug release from the olibanum resin coated microcapsules of size 20/35 and 35/50 was studied using 8 station dissolution rate test apparatus (model Disso-2000, M/s LABINDIA) with a paddle stirrer at 50 rpm at 37 ± 0.5 °C. Phosphate buffer of pH 6.8 (900 mL) was used as dissolution fluid. A sample of microcapsules equivalent to 100 mg of drug was used in each test. Samples of dissolution fluid (5 mL) were withdrawn through a filter (0.45 μm) at different time intervals over a period of 24 h and were assayed for aceclofenac content at 275 nm. The sample (5 mL) taken at each sampling time was replaced with fresh dissolution medium (5 mL). The drug release experiments were conducted in triplicate.

Evaluation of mucoadhesiveness: The mucoadhesive property of the olibanum resin coated microcapsules was evaluated by an *in vitro* adhesion testing method known as wash-off method[9]. The mucoadhesiveness of the microcapsules prepared was compared to that of non-bioadhesive material, ethylene vinyl acetate (EVA) microcapsules. Pieces of goat intestinal mucosa (2 cm × 2 cm) were mounted onto glass slides (3 × 1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of a USP tablet disintegration test machine. By operating the disintegration test machine the tissue specimen was given a slow regular up and down movement in 900 mL test fluid at 37 ºC taken in a 1 L vessel of the disintegration test machine. At the end of 0.5 h, 1 h and later at hourly intervals up to 8 h, the machine was stopped and the number of microcapsules still adhering on to the tissue was counted. The test was performed in 0.1 N HCl and in phosphate buffer of pH 6.2.

RESULTS AND DISCUSSION

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, spherical, free flowing with an angle of repose in the range 15°-20°. The nature of the method of preparation indicated that the microcapsules were of multinucleate monolithic type. SEM (Fig. 1) indicated that the microcapsules were spherical with smooth surface and completely covered with polymer (resin) coat. Size analysis showed that a large proportion of microcapsules in a batch were in the size range of -20 +35 (670 μm) and -35 +50 (398 μm). The emulsification-solvent evaporation method used to prepare the mucoadhesive microcapsules employing olibanum resin is reproducible with regard to size and size distribution of the microcapsules. Drug content was uniform (C.V. < 1.2 %) in each batch of microcapsules. The microencapsulation efficiency was in the range 99-102.5 %. Microcapsules prepared with various ratios of core: coat were found to have different wall thickness with both the drugs. Smaller microcapsules have thinner walls in each case (Table-1).

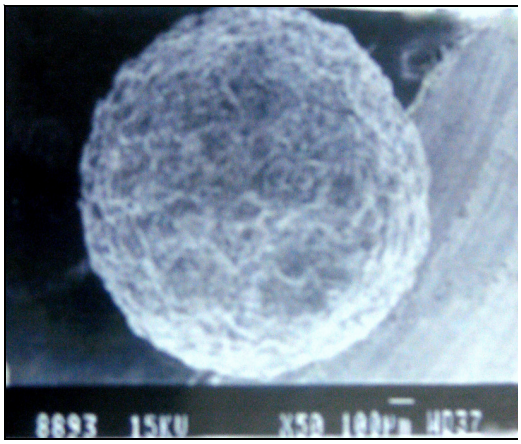

Fig. 1. SEM of olibanum resin coated microcapsule (size 20/35) of aceclofenac

TABLE-1
DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE CHARACTERISTICS OF OLIBANUM RESIN 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
Size 20/35								
MC1(19:1)	94.9(0.56)*	99.9	18.5	2.5	12.0	4.3451	0.239	0.4088
MC2(9:1)	90.6(0.57)	100.6	22.5	4.0	15.7	3.7083	0.1807	0.4301
MC3 (8:2)	82(1.00)	102.5	24.0	5.3	22.4	3.5166	0.0987	0.5033
MC4 (7:3)	69.3(0.42)	99.0	25.5	6.8	>24.0	3.3521	0.0762	0.5591
Size 35/50								
MC1(19:1)	95.2(0.82)	100.2	9.0	1.1	4.2	10.8595	0.5957	0.3503
MC2(9:1)	89.1(0.62)	99.0	13.5	1.4	9.2	6.3564	0.2252	0.3255
MC3 (8:2)	79.9(0.62)	99.9	16.0	2.4	12.0	4.1847	0.2084	0.3856
MC4 (7:3)	70.7(1.14)	101.0	17.5	2.9	17.0	3.5986	0.1545	0.4598

*Figures in parentheses are coefficient of variation values (C.V. %).

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. The release data were analyzed as per zero order, first order, Higuchi[10] and Peppas[11] equation models. Drug release from the olibanum resin coated microcapsules was diffusion controlled and followed first order kinetics indicated by the higher correlation coefficient values obtained (Table-2). Aceclofenac release mechanism from the olibanum resin coated microcapsules was majorly by Fickian diffusion as the release exponent 'n' was in the range 0.3255-0.5591. Good linear relationships were observed between wall thickness of the microcapsules and release rate (K_0) and (K_1) values. (Fig. 2).

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' values			
	Zero order	First order	Higuchi	Peppas
Size 20/35				
MC1(19:1)	0.767	0.9567	0.9518	0.9606
MC2(9:1)	0.8356	0.9474	0.9798	0.9898
MC3 (8:2)	0.8722	0.9918	0.9883	0.9839
MC4 (7:3)	0.8852	0.9896	0.9887	0.9843
Size 35/50				
MC1(19:1)	0.7548	0.9858	0.9460	0.9397
MC2(9:1)	0.6913	0.9495	0.9069	0.8973
MC3 (8:2)	0.7375	0.9678	0.9366	0.9848
MC4 (7:3)	0.7672	0.9695	0.9450	0.9115

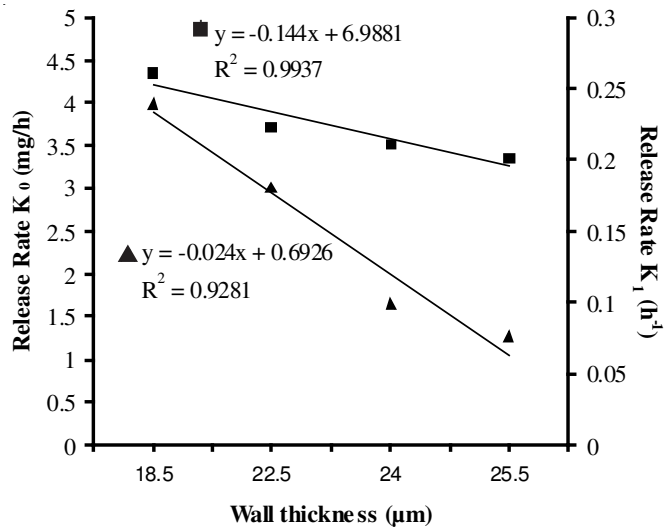

Fig. 2. Relationship between wall thickness and release rates (K_0 ■) and (K_1 ▲) for olibanum resin coated microcapsules of aceclofenac (size 20/35)

Olibanum resin coated microcapsules exhibited good mucoadhesive property when compared to non-mucoadhesive EVA microcapsules. The wash-off was slow in the case of olibanum resin coated microcapsules when compared to EVA microcapsules. In the case of olibanum resin coated microcapsules the wash-off was faster at intestinal pH (6.2) than at gastric pH (1.2). The rapid wash-off observed at intestinal pH (6.2) is due to ionization of carboxyl group in the acid resin of olibanum at this pH, which increases its solubility and reduces adhesive strength. Thus, the results indicated that olibanum resin coated microcapsules have good mucoadhesive property (Table-3).

TABLE-3
RESULTS OF *in vitro* WASH-OFF TEST TO ASSESS MUCOADHESIVE PROPERTY OF OLIBANUM RESIN COATED MICROCAPSULES

Microcapsules (Size 20/35)	Percent microcapsules adhering to tissue after time (h)									
	In 0.1 N HCl, pH 1.2					In phosphate buffer, pH 6.2				
	1	2	4	6	8	1	2	4	6	8
MC3	86 (1.2)*	68 (2.1)	54 (1.8)	42 (2.4)	31 (1.6)	63 (1.8)	45 (2.1)	31 (2.4)	9 (2.0)	6 (1.4)
EVA	56 (2.8)	40 (3.1)	10 (2.6)	–	–	51 (2.4)	39 (3.2)	9 (1.8)	–	–

*Figures in parentheses are coefficient of variation (C.V. %) values.

Conclusion

(i) 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. Microencapsulation efficiency was in the range 99-102.5 %. (ii) 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 Fickian diffusion. (iii) Good linear relationships were observed between wall thickness of the microcapsules and release rate (K_0) and (K_1) values. (iv) In the *in vitro* wash-off test olibanum resin coated microcapsules exhibited good mucoadhesive property (v) Olibanum resin was found to be a new and an efficient microencapsulating agent for mucoadhesive microcapsules for oral controlled release. Controlled release mucoadhesive microcapsules of aceclofenac could be designed employing olibanum resin. Olibanum resin coated microcapsules of aceclofenac exhibited good mucoadhesion and controlled release characteristics and were found suitable for oral controlled release for 24 h. Olibanum is reported as non-toxic[12] and since it is of natural origin it is biocompatible and cheaper.

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