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Preparation and evaluation of ethylcellulose coated microcapsules for controlled release of Diclofenac

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ABSTRACT

The objective of the study is to evaluate ethylcellulose as a coat for controlled release microcapsules of diclofenac. Ethylcellulose 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 ethylcellulose coated microcapsules prepared were found to be discrete, spherical, and free flowing. Drug content was uniform (c.v.≤ 0.11%) in each batch of microcapsules and the microencapsulation efficiency was in the range 98.85-101.81%. Diclofenac release from the ethylcellulose coated microcapsules was slow and spread over a period of 12- 16 h and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was 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 exhibited higher release rates when compared to those prepared employing dichloromethane as solvent. Ethylcellulose was found to be an efficient microencapsulating agent and the ethylcellulose microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release of diclofenac over 12-16 h

Keywords: Ethylcellulose, Diclofenac, Controlled Release, Microcapsules

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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 [1-3]. The objective of the present study is to evaluate ethylcellulose as microencapsulating agent and to prepare ethylcellulose coated microcapsules of diclofenac for controlled release. Ethylcellulose coated microcapsules containing diclofenac were prepared by an industrially feasible method of microencapsulation and the microcapsules were evaluated for controlled release of diclofenac.

EXPERIMENTAL

Materials

Diclofenac was a gift sample from M/s Medlay Phrama., Jammu. Ethllcellulose was procured from SD Fine chemicals Mumbai.Sodium carboxy methyl cellulose (high viscosity grade 1500-3000 cps of a 1% w/v solution at 25^0 C), Chloroform (Merck), Dichloromethane (Merck) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Preparation of microcapsules

An emulsification- solvent evaporation method was tried to prepare resin-coated microcapsules. Ethylcellulose (2 g) was dissolved in chloroform or dichloromethane (100 ml) to form a homogenous polymer solution. Core material, diclofenac (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 (30^0C) for 3 hours 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.

Ethylcellulose coated microcapsules of diclofenac were prepared employing chloroform and dichloromethane as solvent for the polymer (ethylcellulose). Different proportions of coat: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 Diclofenac

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 diclofenac 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 (≤0.193%) 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 percent drug content in the microcapsules/ Theoretical percent drug content in the microcapsules) x 100

Wall thickness

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

$$H = r(1-p)\,d_1/3[pd_2 + (1-p)\,d_1]$$

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 10KV 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 ± 0.5^0c were maintained throughout the experiment. A sample of microcapsules equivalent to 100 mg diclofenac was used in each test.

Aliquot equal to 5ml of dissolution medium was withdrawn at different time intervals through a filter (0.45µ) and assayed at 275 nm. All drug release studies were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

Ethylcellulose is a non-biodegradable, biocompatible, non-toxic, cellulose polymer having good film forming properties [4] and it has been extensively used in coating [5,6] and microencapsulation [7,8]. In the present work ethylcellulose was evaluated as coat in microencapsulation of diclofenac for controlled release. Studies were carried out on microencapsulation of diclofenac by ethylcellulose employing (i) chloroform and (ii) dichloromethane as solvents for the polymer and the resulting microcapsules were evaluated.

Diclofenac has a short biological half life of 1-2 h and required to be administered repeatedly 3or 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 diclofenac to prolong its duration of action, reduce frequency of administration with increased patient compliance and to reduce undesired gastric disturbance.

Ethylcellulose coated microcapsules of diclofenac could be prepared by the emulsification-solvent evaporation method developed. The ethylcellulose 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 -30 +50 (398µm) mesh. Overall about 71.962 percent (average of all products) were in size range of -30+50 (398µm). The method used to prepare the microcapsules employing ethylcellulose is reproducible with regard to size and size distribution of the microcapsules. Low c.v (≤ 0.11%) in percent drug content indicated uniformity of drug content in each batch of microcapsules. The microencapsulation efficiency was in the range 98.85 -101.81. Microcapsules prepared with various ratios of coat:coat were found to have different wall thickness.

Diclofenac release from all the ethylcellulose coated microcapsules was slow and spread over more than 12- 16 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 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 firsr order model in all the cases when compared to those in the zeroorder model. Plots of percent released vs square root of time were found to be linear with R^2> 0.990 indicating that drug release from these

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microcapsules was diffusion controlled. When the release data were analysed as per Peppas equation, the release exponent (n) was in the range 0.4740-0.867 in all the cases indicating non fickian diffusion as the release mechanism from all the microcapsules. Good linear relationships (Fig 2, 3) 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 ethylcellulose exhibited higher release rates when compared to those prepared employing dichloromethane as solvent.

TABLE -1: DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE CHARACTERISTICS OF ETHYLCELLUOSE COATED MICROCAPSULES OF DICLOFENAC

Microcapsules Core: coat ratio	Drug Content (%)	Microcapsules 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)	69.20	98.85	9.24	4.00	8.38	7.26	0.29	0.527
F2(8:2)	81.45	101.81	8.21	3.00	9.36	8.36	0.35	0.533
F3(9:1)	89.60	99.55	7.12	2.36	8.36	9.10	0.39	0.474
F4(19:1)	94.70	99.68	5.88	2.24	7	9.91	0.42	0.490
Dichloromethane								
F5(7:3)	69.80	99.71	8.43	3.00	9.48	6.11	0.11	0.821
F6(8:2)	79.80	99.75	7.48	2.48	8.36	8.87	0.25	0.830
F7((9:1)	89.21	99.11	7.11	2.36	8.24	8.91	0.28	0.826
F8(19:1)	96.20	102.26	6.16	2.12	7.10	9.68	0.44	0.867

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

Microcapsules (core: coat ratio)	Correlation Coefficient (R^2) value			
	Zero order	First order	Higuchi	Peppas
Chloroform				
F1(7:3)	0.880	0.910	0.981	0.973
F2 (8:2)	0.920	0.928	0.989	0.970
F3(9:1)	0.933	0.972	0.975	0.968
F4(19:1)	0.910	0.983	0.984	0.963
Dichloromethane				
F5(7:3)	0.873	0.923	0.981	0.936
F6(8:2)	0.918	0.928	0.990	0.998
F7(9:1)	0.920	0.942	0.976	0.968
F8(19:1)	0.915	0.926	0.988	0.913

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CONCLUSIONS

1. Spherical ethylcellulose coated microcapsules of diclofenac 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 98.85-101.85
2. Diclofenac release from the ethylcellulose coated microcapsules was slow and spread over more than 12-16 h and depended on core: coat ratio, wall thickness and size of the microcapsules.
3. Drug release from these microcapsules was by non -fickian diffusion and followed first Order kinetics.
4. Good linear relationships were observed between wall thickness of the microcapsules and release rates.
5. Microcapsules prepared employing chloroform as solvent for etylcellulose exhibited higher release rates when compared to those prepared employing dichloromethane as solvent.
6. Ethylcellulose was found to be an efficient microencapsulating agent and the ethylcellulose coated microcapsules exhibited good controlled releasecharacteristics and were found suitable for oral controlled release of diclofenac over 12- 16 h.

(A) (B)

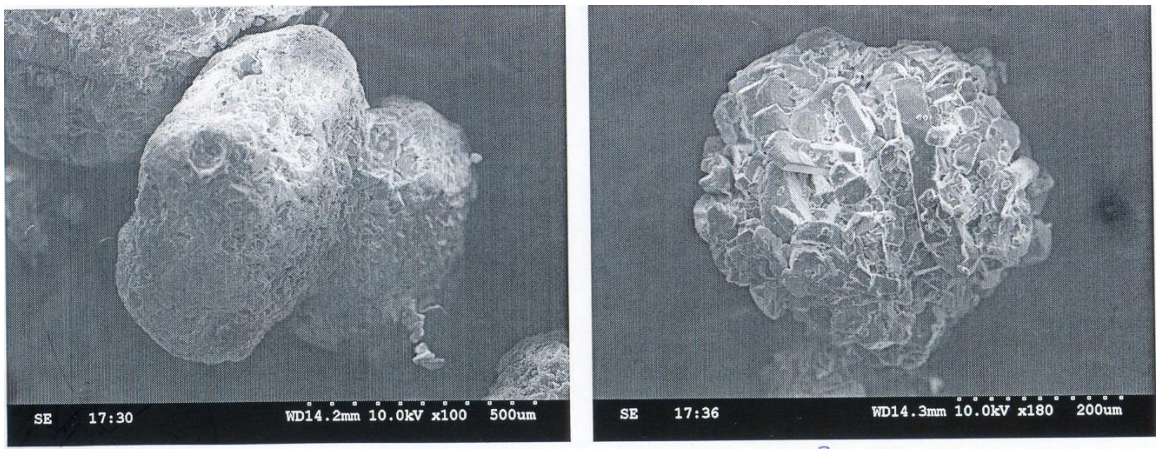

Fig.1. SEM of ethylcellulose coated Microcapsules of Diclofenac F2 Prepared Employing Chloroform (A) and Microcapsules F6 Prepared Employing Dichloromethane (B) as Solvents for the Polymer

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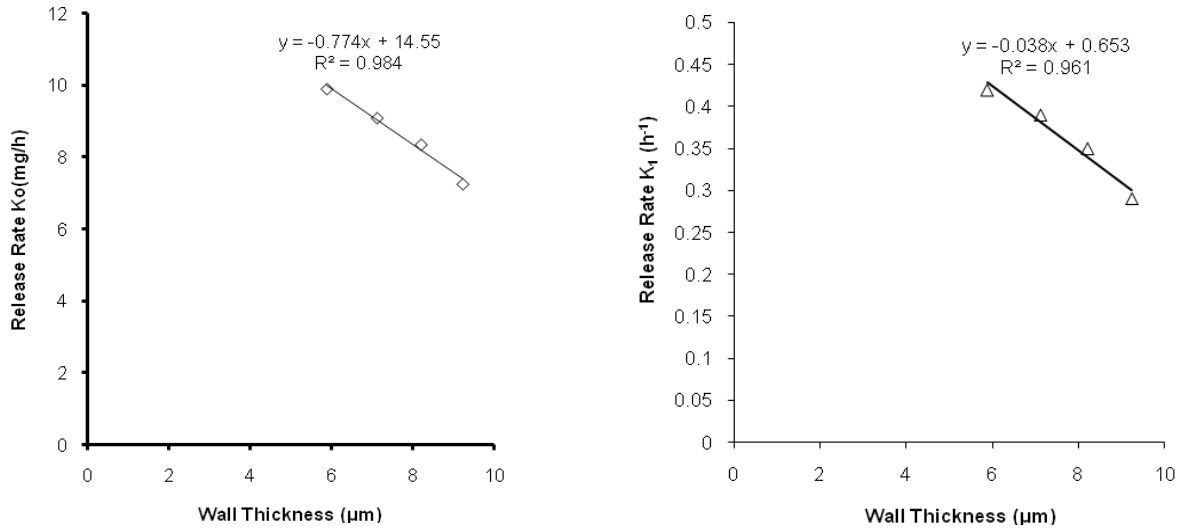

Fig.2. Relationship between Wall Thickness and Release Rates (K_o and K_1) ofEthylcellulose Coated Microcapsules of Diclofenac Prepared Employing Chloroform as Solvent

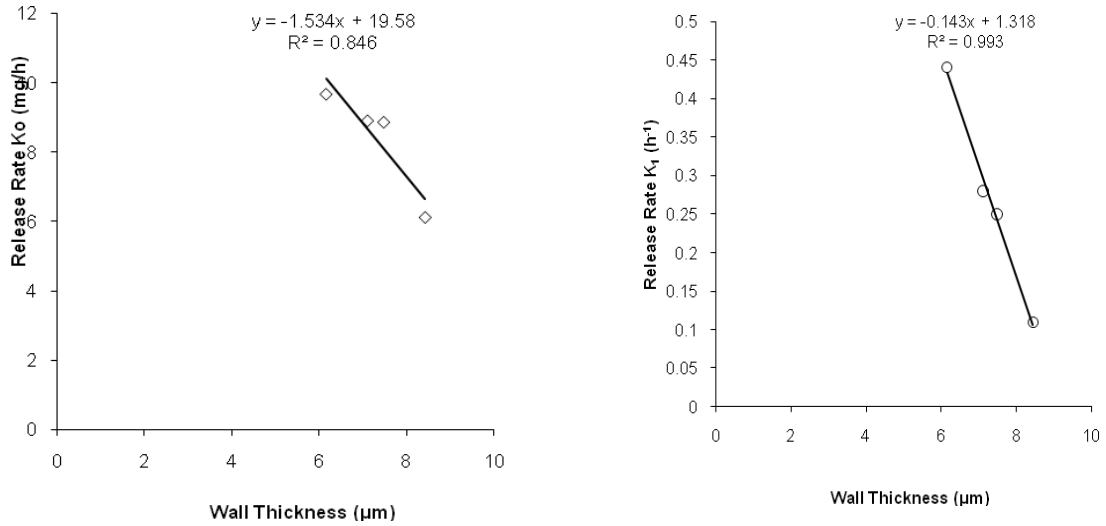

Fig..3. Relationship between Wall Thickness and Release Rates (K_o and K_1) ofEthylcellulose Coated Microcapsules of Diclofenac Prepared Employing Dichloromethane as Solvent

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