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Preparation and Evaluation of Ethyl Cellulose Coated Microcapsules of Pioglitazone for Controlled Release

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The objective of the study is to prepare and evaluate ethyl cellulose coated microcapsules of pioglitazone for controlled release. Controlled release formulations are needed for pioglitazone because of its short biological half life and for better control of blood glucose levels to prevent hypoglycemia, to enhance clinical efficacy and patient compliance. Ethyl cellulose microcapsules of pioglitazone were prepared by an industrially feasible emulsification-solvent evaporation method and the microcapsules were evaluated for controlled release. The ethyl cellulose microcapsules prepared are spherical, discrete, free flowing and multi nucleate monolithic type. Microencapsulation efficiency was in the range 96.34-104.30 %. Pioglitazone release from the microcapsules was slow over 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release from the microcapsules was by non-fickian diffusion mechanism. Good linear relationships were observed between wall thickness of the microcapsules and release rate. Ethyl cellulose was found suitable as a microencapsulating agent for pioglitazone and the ethyl cellulose microcapsules exhibited good controlled release characteristics and were found suitable for once-a-day administration of pioglitazone.

Key Words: Ethyl cellulose, Microencapsulation, Controlled release, Pioglitazone.

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 the 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 plays vital role in controlling the drug release from the microcapsules. Microencapsulation by various polymers and their applications are described in standard text books[1,2]. Ethyl cellulose is reported[3,4] as an effective microencapsulating agent for controlled release.

Pioglitazone is an effective oral antidiabetic agent that belongs to the thiazolidonediones drug class. Pharmacological studies indicate that pioglitazone improves glycaemic control while reducing circulating insulin level[5]. Pioglitazone has short biological half-life of 3-5 h and is eliminated rapidly[6]. Therefore control release products are needed for pioglitazone to prolong its duration of action and to improve patient compliance. There are few reports[7,8] on controlled release formulations of pioglitazone employing coated granules and matrix tablets. The drug also causes gastro intestinal disturbances such as gastric pain, constipation, nausea and vomiting if present in larger concentration in g.i. tract. Controlled release formulation is also needed for pioglitazone for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficacy, to reduce g.i. disturbances and to enhance patient compliance.

The objective of the present investigation is to prepare and evaluate ethyl cellulose coated microcapsules of pioglitazone for controlled release. Ethyl cellulose microcapsules containing pioglitazone were prepared by an industrially feasible method of microencapsulation and the microcapsules were evaluated for controlled release of pioglitazone.

EXPERIMENTAL

Pioglitazone was a gift sample from M/s Matrix Laboratories, Hyderabad. Ethyl cellulose (having an ethoxyl content of 47.5 % by weight and a viscosity of 22 cps in a 5 % concentration by weight in a 80:20 toluene-ethanol solution at 25 ºC), Chloroform (Merck), sodium carboxy methyl cellulose (sodium CMC with a viscosity of 1500 - 3000 cps of a 1% w/v solution at 25°C, Loba-Chemie) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Preparation of microcapsules: Ethyl cellulose microcapsules containing pioglitazone were prepared by an emulsification-solvent evaporation method employing chloroform as the solvent for the polymer.

Ethyl cellulose (2 g) was dissolved in chloroform (100 mL) to form a homogenous polymer solution. Core material, pioglitazone (0.8 g) was added to the polymer (ethyl cellulose) 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 500 mL beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A medium duty stirrer (Remi Model RQT 124) was used for stirring. The solvent, chloroform was then removed by continuous stirring at room temperature (28 ºC) for 3 h to produce spherical microcapsules. The micro-capsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules. Different proportions of core to coat materials namely 9:1 (ECMC 1), 8:2 (ECMC 2) and 7:3 (ECMC 3) were used to prepare microcapsules with varying coat thickness.

Characterization of microcapsules

Estimation of pioglitazone: Pioglitazone content of the microcapsules was estimated by UV spectrophotometric method based on the measurement of absorbance at 269 nm in hydrochloric acid (0.1N). The method was validated for linearity, precision and accuracy. The method obeyed Beer's law in the concentration range 1-10 mg/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 %, respectively. No interference from the excipients used was observed.

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:

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

Scanning electron microscopy: The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S340, UK). Microcapsules were mounted directly on to the SEM sample stub, using double sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

Wall thickness: Assuming the microcapsules to be uniform and spherical, wall thickness of the microcapsules was determined by the method described by Luu *et al.*[9] 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 core material, d_2 is the density of the coat material and 'p' is the proportion of the medicament in the microcapsules. Mean radius of the microcapsules was determined by sieving. Densities were measured using petroleum ether as a displacement fluid at room temperature (28 ºC).

Drug release study: Drug release from the microcapsules was studied using 8-Station Dissolution Rate Test Apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at a temperature of 37 ± 1 °C. 0.1N Hydrochloric acid (900 mL) was used as dissolution fluid. A sample of microcapsules equivalent to 30 mg of pioglitazone were used in each test. A 5 mL aliquot of dissolution medium was withdrawn through a filter (0.45 µ) at different time intervals and assayed spectrophotometrically by measuring absorbance at 269 nm. All drug release experiments were conducted in triplicate (n = 3).

RESULTS AND DISCUSSION

Ethyl cellulose (EC) microcapsules of pioglitazone could be prepared by an emulsification-solvent evaporation method employing chloroform as solvent for ethyl cellulose. The method involves emulsification of the polymer (ethyl cellulose) solution in chloroform containing the drug (pioglitazone) in an immiscible liquid medium as micro droplets and removal of solvent by continuous stirring to form rigid microcapsules of ethyl cellulose. The micro-capsules were found to be discrete, spherical and free flowing. SEM (Fig. 1) indicated that the microcapsules are spherical with smooth surface. The nature of the method of preparation indicates that the microcapsules were multi-nucleated and monolithic type. The sizes could be separated and a more uniform size range of microcapsules could readily be obtained. Size analysis of the microcapsules showed that generally about 19.4, 38.57 and 27.45 % (average of all products) were in the size range of -10/+20 (1267 µ), -20/+30 (715 µ) and -30/+50 (443 µ) mesh, respectively.

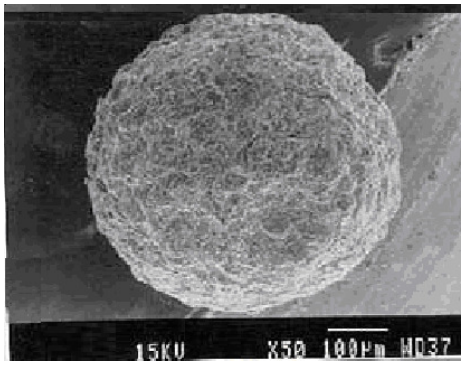


Fig. 1. SEM of ethyl cellulose microcapsules, ECMC 2, (size 20/30) of pioglitazone

Low c.v. (< 1.0 %) in per cent drug content indicates uniformity of drug content in each batch of microcapsules (Table-1). The microencapsulation efficiency was in the range of 96.34-104.30 %. Drug content of the microcapsules was found to be nearly the same in different sieve fractions. As the microcapsules are spherical, the theoretical mean thickness of the wall that surrounds the core particles in the microcapsule was calculated as described by Luu *et al.*[9]. Microcapsules prepared by employing various ratios of core: coat were found to have different wall thickness. Smaller microcapsules have thinner walls.

TABLE-1
DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE RATE OF ETHYL CELLULOSE COATED MICROCAPSULES OF PIOGLITAZONE

Microcapsules (core: coat ratio)	Drug content (%)	Wall thickness (μm)	Micro-encapsulation efficiency (%)	T_{50} (h)	T_{90} (h)	K_0 (mg/h)	Release rate K_1 (h^{-1})	'n' value in Peppas equation
Size 10/20								
ECMC1 (9:1)	88.70 (0.9)	90.88	97.76	6.0	14.0	1.331	0.198	0.779
ECMC2 (8:2)	78.90 (0.6)	158.71	97.12	8.0	20.0	1.136	0.121	0.785
ECMC3 (7:3)	69.30 (0.4)	210.97	104.0	12.0	24.0	1.016	0.078	0.805
Size 20/30								
ECMC1 (9:1)	88.78 (0.7)	55.36	96.34	5.0	11.0	1.812	0.239	0.786
ECMC2 (8:2)	79.70 (0.8)	95.43	99.04	6.0	14.0	1.308	0.191	0.728
ECMC3 (7:3)	69.30 (0.4)	124.83	103.3	7.0	17.0	1.227	0.172	0.777
Size 30/50								
ECMC1 (9:1)	89.10 (0.5)	31.88	98.46	3.0	8.0	3.121	0.451	0.809
ECMC2 (8:2)	79.50 (0.7)	54.22	98.14	4.0	9.0	2.570	0.276	0.812
ECMC3 (7:3)	69.30 (0.4)	73.73	103.8	5.0	10.0	2.486	0.345	0.880

*Figures in parentheses are coefficient of variation (c.v) values.

Pioglitazone release from the microcapsules was studied in 0.1N hydrochloric acid (900 mL). Pioglitazone release from the ethyl cellulose microcapsules was slow and spread over more than 24 h. The drug release parameters of various microcapsules are summarized in Table-1. The release data were analyzed as per zero order, first order, Higuchi[10] and Ritger and Peppas[11] equation models. 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 both the zero order and first order kinetic models are equally applicable to describe the release data. The (R^2) values were nearly the same in both the zero order and first order models. Plots of per cent released *versus* square root of time were found to be linear with $R^2 > 0.962$ indicating that the drug release from the microcapsules was diffusion controlled. When the release data were analyzed as per Peppas equation, the release exponent (n) was in the range 0.728-0.880 indicating non-fickian diffusion as the drug release mechanism from the microcapsules prepared. The release rate (K_0) depended on core : coat ratio, wall thickness and size of the microcapsules. As the proportion of coat was increased, wall thickness of the microcapsules was increased and pioglitazone release rate was decreased.

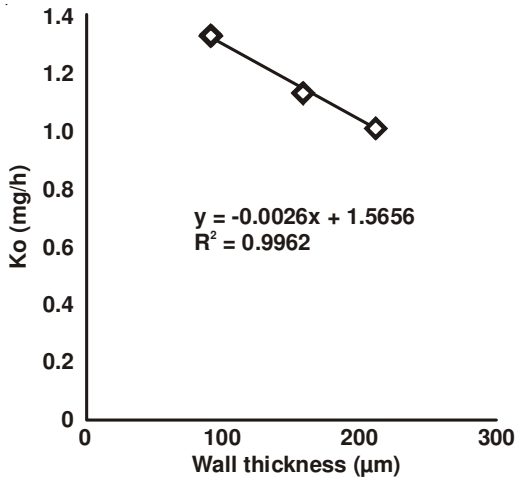
TABLE-2
CORRELATION COEFFICIENT (R^2) VALUES IN THE ANALYSIS OF RELEASE DATA OF ETHYL CELLULOSE MICROCAPSULES AS PER VARIOUS KINETIC MODELS

Microcapsules (core: coat ratio)	Regression coefficient (R^2 value)			
	Zero order	First order	Higuchi model	Peppas model
Size 10/20				
ECMC1 (9:1)	0.901	0.939	0.981	0.929
ECMC2 (8:2)	0.945	0.970	0.992	0.931
ECMC3 (7:3)	0.979	0.947	0.977	0.911
Size 20/30				
ECMC1 (9:1)	0.936	0.924	0.974	0.974
ECMC2 (8:2)	0.902	0.962	0.962	0.925
ECMC3 (7:3)	0.928	0.943	0.979	0.942
Size 30/50				
ECMC1 (9:1)	0.946	0.863	0.967	0.989
ECMC2 (8:2)	0.995	0.957	0.975	0.995
ECMC3 (7:3)	0.982	0.909	0.963	0.996

The release rate was increased as the size of the microcapsules was decreased. Good linear relationships were observed between wall thickness of the microcapsules and drug release rate (K_0) (Fig. 2). As pioglitazone release from microcapsules ECMC2 (size 20/30) was slow, controlled and complete in 24 h, these microcapsules are considered as the optimized formulation suitable for controlled release of pioglitazone over 24 h.

Conclusion

Spherical ethyl cellulose microcapsules of pioglitazone 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. Microencapsulation efficiency was in the range 96.34-104.30 %. Pioglitazone release from the ethyl cellulose microcapsules was slow and extended over 24 h and depended on core : coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was by non-fickian diffusion mechanism. Good linear relationships were observed between wall thickness of the microcapsules and release rate. Ethyl cellulose was found suitable as a microencapsulating agent for pioglitazone and the ethyl cellulose microcapsules of pioglitazone exhibited good controlled release characteristics and were found suitable for once-a-day (24 h) administration of pioglitazone.



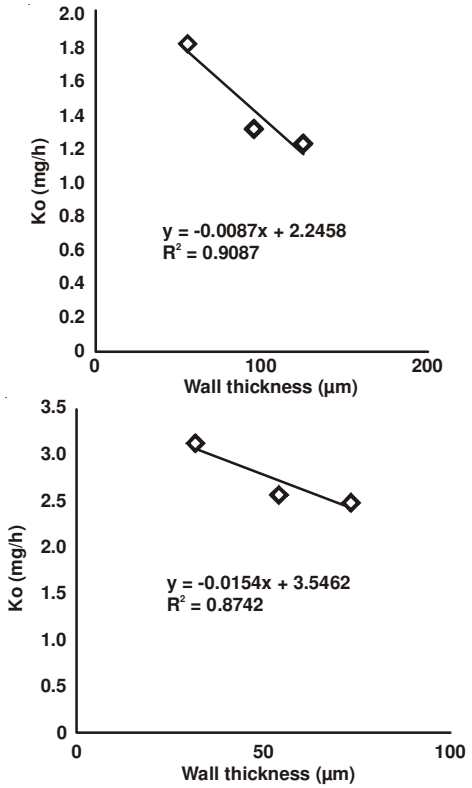


Fig. 2. Relationship between wall thickness and release rate (K_0) of ethyl cellulose microcapsules of pioglitazone

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