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Research Article

A COMPARATIVE EVALUATION OF ETHYL CELLULOSE AND ETHYLENE VINYL ACETATE MICROCAPSULES OF PIOGLITAZONE FOR CONTROLLED RELEASE

K. P. R. CHOWDARY*, VEERAIAH ENTURI AND K.R.JAGADISH

University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam 530003. A.P., India.
Email: prof.kprchowdary@rediffmail.com.

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ABSTRACT

The objective of the study is to prepare and compare the ethyl cellulose (EC) and ethylene vinyl acetate copolymer (EVA) 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 hypoglycaemia, to enhance clinical efficacy and patient compliance. EC and EVA microcapsules of pioglitazone were prepared by an industrially feasible emulsification – solvent evaporation method and the microcapsules were evaluated for permeability and drug release characteristics. The microcapsules prepared are spherical, discrete, free flowing and multi nucleate monolithic type. Microencapsulation efficiency was in the range of 96.34-104.30% in the case of EC and 95.0-101.25% in the case of EVA. Pioglitazone release from the microcapsules was slow over 24 hours and depends on core: coat ratio, wall thickness and size of the microcapsules in both the cases. 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 in both the cases. EC microcapsules were more permeable than EVA microcapsules and gave relatively rapid release of pioglitazone. With very low permeability EVA microcapsules were found to be more suitable for the design of controlled release of pioglitazone.

Keywords: Ethyl Cellulose, Ethylene Vinyl Acetate Copolymer, Microcapsules, Controlled Release, Pioglitazone

INTRODUCTION

Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of the action 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 are used as a coat plays vital role in controlling the drug release from the microcapsules. Microencapsulation by using various polymers and their applications were described in standard text books[1,2]. A wide range of polymers and other release retarding materials are available for microencapsulation to obtain controlled release. Though polymers such as ethyl cellulose (EC) and ethylene vinyl acetate copolymer (EVA) are extensively studied[3-6] for microencapsulation, no reports are available on comparison of their rate controlling efficiency and permeability of the microcapsules prepared by using them as coat polymers.

Pioglitazone is an effective oral anti–diabetic agent that belongs to the thiazolidinediones drug class. Pharmacological studies indicate that pioglitazone improves glycaemic control while reducing circulating insulin level[7]. Pioglitazone has short biological half-life of 3-5 hours and is eliminated rapidly[8]. Therefore control release (CR) products are needed for pioglitazone to prolong its duration of action and to improve patient compliance. There are few reports[9,10] 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 large 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 objectives of the present investigation are (i) to prepare and evaluate ethyl cellulose and EVA microcapsules of pioglitazone for controlled release and (ii) to make a comparative evaluation of the permeability and drug release characteristics of EC and EVA microcapsules for controlled release of pioglitazone.

MATERIALS AND METHODS

Materials

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°C), Ethylene vinyl acetate copolymer (Grade1408) were procured from M/s Polyolefins industries Ltd., Mumbai. 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.

Methods

Preparation of microcapsules

The EC and EVA microcapsules containing pioglitazone were prepared by an emulsification-solvent evaporation method employing chloroform as the solvent for the polymer.

Polymer (2g) was dissolved in chloroform (100 ml) to form a homogenous polymer solution. Core material, pioglitazone (0.8 g) was added to the polymer solution (10ml) 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°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 to coat materials namely 9:1, 8:2 and 7:3 were used in each case 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 of 1- 10 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 %, respectively. No interference was observed with the excipients used in the study.

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 percent drug content in microcapsules / theoretical percent 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 are uniform and spherical, wall thickness of the microcapsules was determined by the method described by Luu *et al.*[11] 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° C).

Drug release study

Drug release from the microcapsules was studied by 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 and EVA microcapsules of pioglitazone could be prepared by an emulsification–solvent evaporation method employing chloroform as solvent for the polymer. The method involves emulsification of the polymer 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 EC and EVA.

Table 1: Drug content, microencapsulation efficiency, wall thickness and release rate of ethyl cellulose 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								
ECMC4 (9:1)	88.78 (0.7)	55.36	96.34	5.0	11.0	1.812	0.239	0.786
ECMC5 (8:2)	79.70 (0.8)	95.43	99.04	6.0	14.0	1.308	0.191	0.728
ECMC6 (7:3)	69.30 (0.4)	124.83	103.3	7.0	17.0	1.227	0.172	0.777
Size 30/50								
ECMC7 (9:1)	89.10 (0.5)	31.88	98.46	3.0	8.0	3.121	0.451	0.809
ECMC8 (8:2)	79.50 (0.7)	54.22	98.14	4.0	9.0	2.570	0.276	0.812
ECMC9 (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

The microcapsules were found to be discrete, spherical and free flowing with both the polymers. 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 in each batch. Size analysis of the microcapsules showed that generally about 19.4, 38.57 and 27.45 percent (average of all products) were in the size range of -10/+20 (1267µ), -20/+30 (715µ) and -30/+50 (443µ) mesh respectively with both EC and EVA.

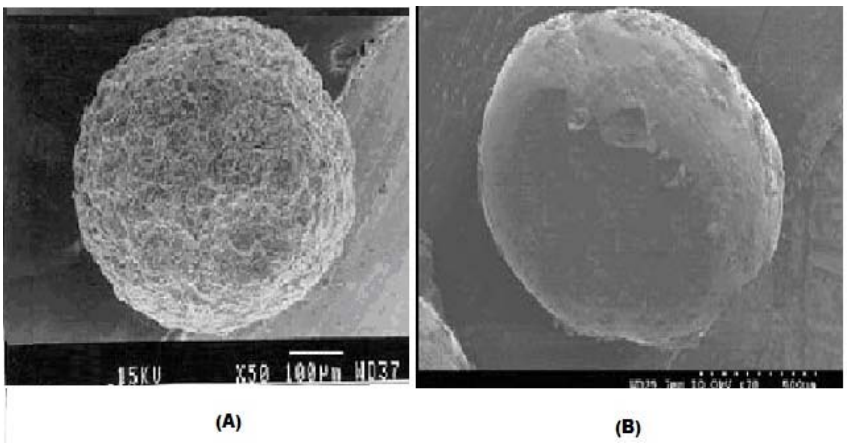

Fig. 1: SEM of (A) ethyl cellulose microcapsules ECMC 2 and (B) EVA microcapsules EVAMC1 of pioglitazone

Low c.v. (< 2.0 %) in percent drug content indicated uniformity of drug content in each batch of microcapsules (Tables.1,2). The microencapsulation efficiency was in the range 96.34-104.30% in the case of EC microcapsules and 95.0-101.25% in the case of EVA microcapsules. 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[11]. Microcapsules prepared by employing various ratios of core:coat were found to have different wall thicknesses. Smaller microcapsules have thinner walls in both the cases.

Table 2: Drug content, microencapsulation efficiency, wall thickness and release rate of ethylene vinyl acetate 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								
EVAMC1 (9:1)	90.60 (0.5)	47.98	96.67	6.0	16.0	1.1742	0.164	0.762
EVAMC2 (8:2)	82.0 (1.0)	90.10	101.25	8.0	> 24	0.9465	0.069	0.780
EVAMC3 (7:3)	69.30 (0.4)	149.42	100.00	16.0	> 24	0.8313	0.047	0.860
Size 20/30								
EVAMC4 (9:1)	89.60 (0.5)	28.41	100.56	5.0	13.0	1.5825	0.202	0.797
EVAMC5 (8:2)	81.80 (1.0)	53.33	95.00	6.0	18.0	1.1658	0.150	0.790
EVAMC6 (7:3)	68.30 (0.9)	88.45	99.29	12.0	24.0	1.0623	0.081	0.780
Size 30/50								
EVAMC7 (9:1)	90.40 (0.5)	16.78	96.67	4.0	9.0	2.2449	0.281	0.819
EVAMC8 (8:2)	82.0 (1.0)	31.50	101.25	5.0	11.0	1.8144	0.232	0.806
EVAMC9 (7:3)	69.60 (0.6)	52.24	100.00	6.0	15.0	1.4262	0.170	0.769

* 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 both EC and EVA microcapsules was slow and spread over more than 24 hours. The drug release parameters of various microcapsules are summarized in Tables 1,2. The release data were analyzed as per zero order, first order, Higuchi[12] and Peppas[13] equation models. 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 percent released Vs square root of time were found to be linear with R^2 >0.945 indicating that the drug release from these 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 both EC and EVA microcapsules prepared. The release rate (K_0) depended on core:coat ratio, wall thickness and size of the microcapsules in both the cases. As the proportion of coat was increased, wall thickness of the microcapsules was increased and pioglitazone release rate was decreased. 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) (Figs.2, 3).

Table 3: Permeability (P_m) of EC and EVA microcapsules of pioglitazone

Microcapsules	Permeability P_m (mg.cm/ h) x 10^4	
	Ethyl Cellulose Microcapsules	EVA Microcapsules
MC1	120.96	56.33
MC2	180.29	85.27
MC3	214.34	124.21
MC4	100.31	44.95
MC5	124.82	62.17
MC6	153.16	93.96
MC7	99.49	37.66
MC8	139.34	57.15
MC9	183.29	74.50

Permeability constant (P_m) is a better parameter to compare the release characteristics of the microcapsules as it includes the influence of all variables involved in the release process. The permeability constant (P_m) ($cm^2.hr^{-1}$) of the microcapsules was calculated as described by Koida *et al*[14]. Using the equation:

$$P_m = \frac{Ko.V.H}{A.C_S}$$

Where,

P_m is the permeability coefficient (cm^2/min)

K_0 is the release rate constant (mg/h) calculated from the slope of the early linear portion of the dissolution curves,

V is the volume of dissolution medium (cm^3),

H is the wall thickness of microcapsules (cm),

A is the surface area of the microcapsules (cm^2) and

C_s is the solubility of the core in the dissolution medium (mg).

Under standard conditions of drug release study of the microcapsules of a particular size and drug, the V, A, C_s remain constant and the above equation of P_m reduces to,

$$P_m = K_o.H.$$

Where K_o is the release rate and H is wall thickness.

The permeability (P_m) values of EC and EVA microcapsules are given in Table. 3. The pioglitazone microcapsules prepared employing EC as coat material have shown higher permeability constants. The

microcapsules prepared employing EVA as coat materials were found to be less permeable. The order of increasing permeability of the microcapsules prepared employing EC and EVA was EC>EVA. Thus, the results indicated that the polymer employed has significant influence on the permeability of the microcapsules. The coat wall of the microcapsules normally acts as a barrier for drug release, the resistance of which is influenced by the nature of the film former and its degree of crystallinity, its thickness, the occurrence of pores i.e. porosity and tortuosity. Thus, there is every possibility that the observed differences in the permeability of EC and EVA microcapsules to be dependent on the polymer employed. With very low permeability EVA microcapsules were found to be more suitable for the design of controlled release drug delivery systems of pioglitazone.

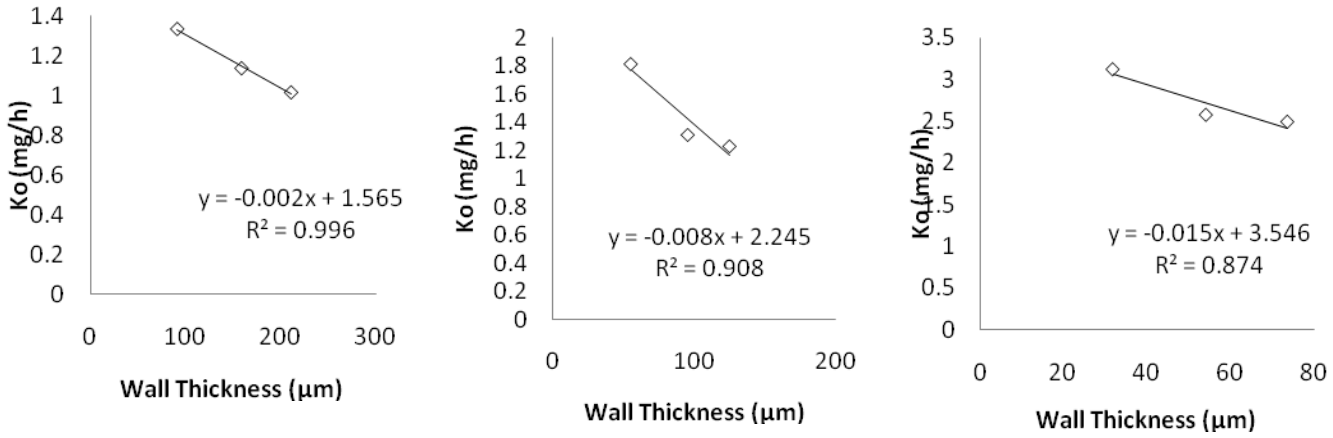

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Fig. 2: Relationship between wall thickness and release rate (K_0) of ethyl cellulose microcapsules of pioglitazone

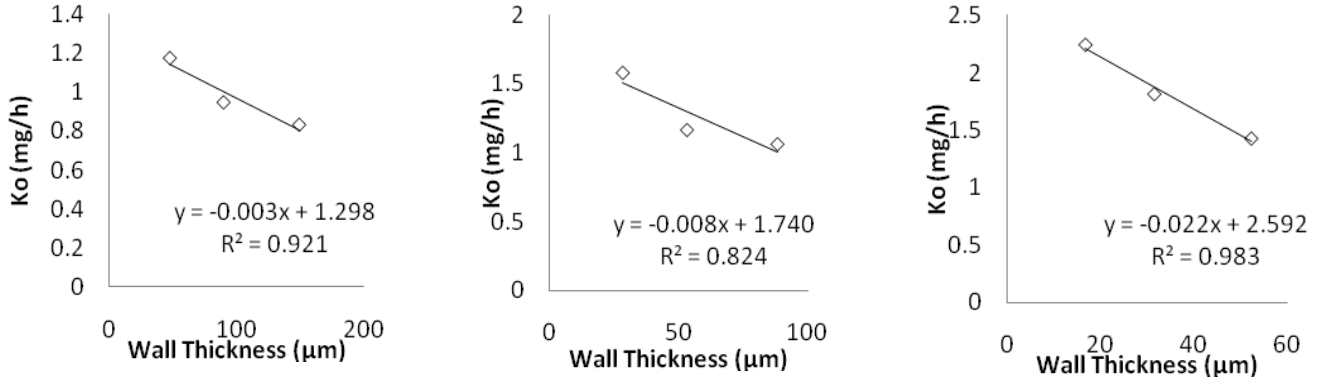

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Fig. 3: Relationship between wall thickness and release rate (K_0) of EVA microcapsules of pioglitazone

CONCLUSION

Ethyl cellulose and EVA microcapsules of pioglitazone could be prepared by an industrially feasible emulsification – solvent evaporation method. The microcapsules prepared are spherical, discrete, free flowing and multi nucleate monolithic type. Microencapsulation efficiency was in the range 96.34-104.30% in the case of EC and 95.0-101.25% in the case of EVA. Pioglitazone release from the microcapsules was slow over 24 hours and depended on core: coat ratio, wall thickness and size of the microcapsules in both the cases. 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 (Ko) in both the cases. EC microcapsules were more permeable than EVA microcapsules and gave relatively rapid release of pioglitazone. With very low permeability EVA microcapsules were found to be more suitable for the design of controlled release of pioglitazone.

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