



PREPARATION AND EVALUATION OF ETHYLENE VINYL ACETATE COPOLYMER COATED MICROCAPSULES OF PIOGLITAZONE FOR CONTROLLED RELEASE

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ABSTRACT

The objective of the study is to prepare and evaluate ethylene vinyl acetate copolymer (EVA) 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. Ethylene vinyl acetate copolymer (EVA) microcapsules of pioglitazone were prepared by an industrially feasible emulsification – solvent evaporation method and the microcapsules were evaluated for controlled release. The ethylene vinyl acetate copolymer (EVA) microcapsules prepared are spherical, discrete, free flowing and multi nucleate monolithic type. Microencapsulation efficiency was in the range 95.0-101.25%. Pioglitazone release from the microcapsules was slow over 24 hours 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. Ethylene vinyl acetate copolymer (EVA) was found suitable as a microencapsulating agent for pioglitazone and the ethylene vinyl acetate copolymer (EVA) microcapsules exhibited good controlled release characteristics and were found suitable for once-a-day administration of pioglitazone.

Key words: Ethylene vinyl acetate copolymer (EVA), 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

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the drug release from the microcapsules. Microencapsulation by various polymers and their applications are described in standard text books^{1,2}. Ethylene vinyl acetate copolymer (EVA) is reported³⁻⁵ as an effective microencapsulating agent for controlled release.

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 level⁶. Pioglitazone has short biological half-life of 3-5 hours and is eliminated rapidly⁷. Therefore, control release (CR) products are needed for pioglitazone to prolong its duration of action and to improve patient compliance. There are few reports^{8,9} on the formulation of pioglitazone employing coated granules and matrix tablets. The drug also causes gastrointestinal 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 ethylene vinyl acetate copolymer (EVA) coated microcapsules of pioglitazone for controlled release. Ethylene vinyl acetate copolymer (EVA) microcapsules containing pioglitazone were prepared by an industrially feasible method of microencapsulation and the microcapsules were evaluated for controlled release of pioglitazone.

EXPERIMENTAL

Materials and methods

Pioglitazone was a gift sample from M/s Matrix Laboratories, Hyderabad. Ethylene vinyl acetate copolymer (EVA), 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

Ethylene vinyl acetate copolymer (EVA) microcapsules containing pioglitazone were prepared by an emulsification-solvent evaporation method employing chloroform as the solvent for the polymer.

Ethylene vinyl acetate copolymer (EVA) (2 g) was dissolved in chloroform (100 mL) to form a homogeneous polymer solution. Core material, pioglitazone (0.8 g) was added to

the polymer (EVA) 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°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 (EVAMC 1), 8 : 2 (EVAMC 2) and 7 : 3 (EVAMC 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 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 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 -

$$\text{Microencapsulation efficiency} = \left(\frac{\text{Estimated percent drug content in microcapsules}}{\text{theoretical percent drug content in microcapsules}} \right) \times 100 \quad \dots(1)$$

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.*¹⁰ using the equation -

$$h = \frac{\bar{r} (1 - p)d_1}{3 [pd_2 + (1 - p)d_1]} \quad \dots(2)$$

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 using 8-Station Dissolution Rate Test Apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at a temperature of $37^\circ \pm 1^\circ\text{C}$. 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

Ethylene vinyl acetate copolymer (EVA) microcapsules of pioglitazone could be prepared by an emulsification-solvent evaporation method employing chloroform as solvent for EVA. The method involves emulsification of the polymer (EVA) 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 EVA. The microcapsules 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 22.7, 40.6 and 23.46 percent (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.

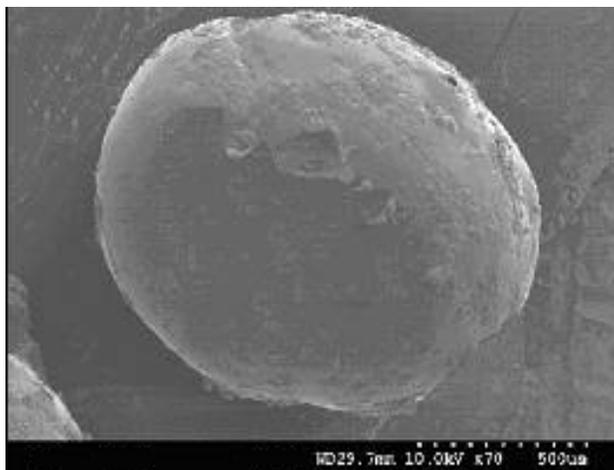


Fig. 1: SEM of ethylene vinyl acetate copolymer (EVA) microcapsules, EVAMC1, (size 10/20) of pioglitazone

Low c.v. ($< 2.0\%$) in percent drug content indicates uniformity of drug content in each batch of microcapsules (Table 1). The microencapsulation efficiency was in the range of 95.0-101.25%. 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.¹⁰ Microcapsules prepared by employing various ratios of core : coat were found to have different wall thickness. Smaller microcapsules have thinner walls.

Pioglitazone release from the microcapsules was studied in 0.1N hydrochloric acid (900 mL). Pioglitazone release from the EC microcapsules was slow and spread over more than 24 hours. The drug release parameters of various microcapsules are summarized in Table 1. The release data were analysed as per zero order, first order, Higuchi¹¹ and Peppas¹² 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 percent released vs square root of time were found to be linear with $R^2 > 0.945$ indicating that the drug release from the microcapsules was diffusion controlled. When the release data were analysed as per Peppas equation, the release exponent (n) was in the range 0.762-0.860 indicating non-Fickian diffusion as the drug release mechanism from the microcapsules. 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. 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 EVAMC1 (size 10/20) was slow, controlled and complete in 24 hrs, these microcapsules are considered as the optimized formulation suitable for controlled release of pioglitazone over 24 hrs.

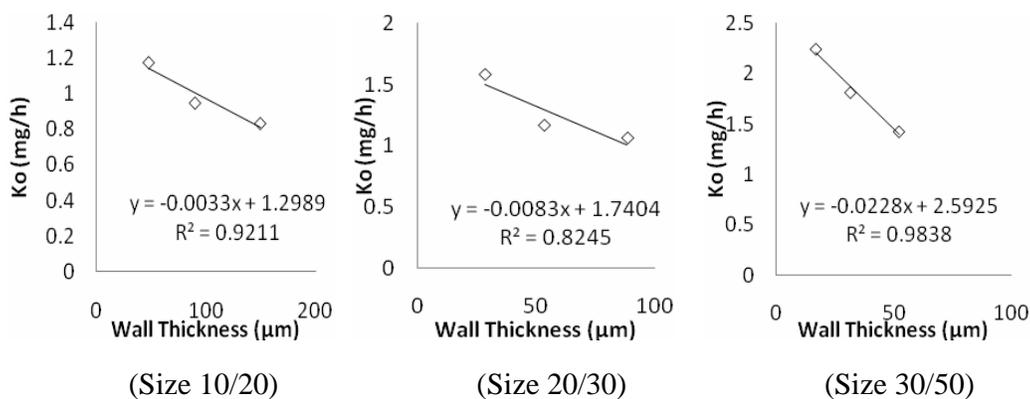
Table 1: Drug content, microencapsulation efficiency, wall thickness and release rate of ethylene vinyl acetate copolymer (EVA) coated microcapsules of pioglitazone

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								
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								
EVAMC1 (9 : 1)	89.60 (0.5)	28.41	100.56	5.0	13.0	1.5825	0.202	0.797
EVAMC2 (8 : 2)	81.80 (1.0)	53.33	95.00	6.0	18.0	1.1658	0.150	0.790
EVAMC3 (7 : 3)	68.30 (0.9)	88.45	99.29	12.0	24.0	1.0623	0.081	0.780
Size 30/50								
EVAMC1 (9 : 1)	90.40 (0.5)	16.78	96.67	4.0	9.0	2.2449	0.281	0.819
EVAMC2 (8 : 2)	82.0 (1.0)	31.50	101.25	5.0	11.0	1.8144	0.232	0.806
EVAMC3 (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

Table 2: Correlation coefficient (R^2) values in the analysis of release data of ethylene vinyl acetate copolymer (EVA) 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				
EVAMC1 (9 : 1)	0.902	0.939	0.991	0.911
EVAMC2 (8 : 2)	0.908	0.977	0.988	0.901
EVAMC3 (7 : 3)	0.974	0.991	0.983	0.896
Size 20/30				
EVAMC1 (9 : 1)	0.932	0.917	0.994	0.955
EVAMC2 (8 : 2)	0.901	0.962	0.959	0.906
EVAMC3 (7 : 3)	0.990	0.946	0.945	0.840
Size 30/50				
EVAMC1 (9 : 1)	0.957	0.902	0.984	0.990
EVAMC2 (8 : 2)	0.921	0.960	0.982	0.959
EVAMC3 (7 : 3)	0.959	0.906	0.983	0.890

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

CONCLUSIONS

- (i) Spherical ethylene vinyl acetate copolymer (EVA) 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.
- (ii) Microencapsulation efficiency was in the range 95.0-101.25%.
- (iii) Pioglitazone release from the ethylene vinyl acetate copolymer (EVA) microcapsules was slow and extended over 24 hours and depended on core : coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was by non-Fickian diffusion mechanism.
- (iv) Good linear relationships were observed between wall thickness of the microcapsules and release rate.
- (v) Ethylene vinyl acetate copolymer (EVA) was found suitable as a microencapsulating agent for pioglitazone and the EVA microcapsules of pioglitazone exhibited good controlled release characteristics and were found suitable for once-a-day (24 h) administration of pioglitazone.

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