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Evaluation of Ethyl Cellulose as Microencapsulating Agent for Controlled Release of Glimepiride

K.P.R. CHOWDARY* and SRINIVAS PANGULURI
University College of Pharmaceutical Sciences
Andhra University, Visakhapatnam-530 003, India
Fax: (91)(891)2525611; Tel: (91)(891)2844925
E-mail: profkprc@rediffmail.com

The objective of the study is to evaluate ethyl cellulose, a plastic insoluble polymer for its application as microencapsulating agent for controlled release of glimepiride. Ethyl cellulose coated microcapsules of glimepiride were prepared by an industrially feasible emulsification-solvent evaporation method and were evaluated for controlled release. These microcapsules were spherical, discrete, free flowing and multinucleate monolithic type. Microencapsulation efficiency was in the range 68-89 %. Glimepiride 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 (anamolous) diffusion mechanism. Good linear relationship was observed between wall thickness of the microcapsules and release rate.

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

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. Glimepiride is an effective oral antidiabetic agent that belongs to the sulphonylurea drug class. The recommended[5] dosage of glimepiride is 1-8 mg/d; 2 mg q.i.d or 4 mg b.i.d. The biological half-life ($t_{½}$) of glimepiride is reported[6] as 2.3 ± 0.8 h after a single dose of 3 mg and increasing to 5.3 ± 3.0 h after multiple dosing. The pharmacokinetics and

dosage schedules support once-daily controlled release formulation for glimepiride for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance[7]. The objective of the present work is to evaluate ethyl cellulose as coating material in microencapsulation for obtaining controlled release of glimepiride.

EXPERIMENTAL

Glimepiride was a gift sample from M/s Orchid Health Care, Chennai. 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: An emulsification-solvent evaporation method was tried to prepare ethyl cellulose coated microcapsules containing glimepiride.

Ethyl cellulose (2 g) was dissolved in chloroform (100 mL) to form a homogenous polymer solution. Core material, glimepiride (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 200 mL of an aqueous mucilage of sodium CMC (0.5 %) contained in a 500 mL beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A medium duty stirrer with speed meter (Remi, model RQT 124) was used for stirring. The solvent was then removed by continuous stirring at room temperature (28 ºC) 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 (MC1), 7:3 (MC2) and 5:5 (MC3) were used to prepare microcapsules with varying coat thickness.

Estimation of glimepiride: An ultraviolet spectrophotometric method based on the measurement of absorbance at 230 nm in phosphate buffer of pH 7.4 was used for estimation of glimepiride. The method obeyed Beer-Lambert's law in the concentration range of 1-20 μg/mL. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.7 and 1.4 % respectively. No interference from the excipients used 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 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 of Luu *et al.*[8] using the equation

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

where h = wall thickness, $\bar{r}$ = arithmetic mean radius of the microcapsules, d_1 = density of the core material, d_2 = density of the coat material and 'p' = proportion of the medicament in the micro-capsules. 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. Water containing 1 % sodium lauryl sulphate (900 mL) was used as dissolution fluid to maintain sink condition. A sample of microcapsules equivalent to 8 mg of glimepiride were used in each test. A 5 mL aliquot of dissolution medium was withdrawn through a filter (0.45 μm) at different time intervals and assayed spectrophotometrically by measuring absorbance at 230 nm. All drug release experiments were conducted in triplicate.

RESULTS AND DISCUSSION

An emulsification-solvent evaporation method was developed for microencapsulation of glimepiride by the ethyl cellulose. The method involves emulsification of the polymer (ethyl cellulose) solution in chloroform containing the dispersed drug particles in an immiscible liquid medium (0.5 % w/v solution of sodium CMC) as microdroplets, followed by removal of solvent chloroform by continuous stirring to form rigid microcapsules. Ethyl cellulose-coated microcapsules of glimepiride could be prepared by emulsification-solvent evaporation method. The microcapsules were found to be discrete, spherical and free flowing. The nature of the method of preparation

indicated that the microcapsules were of multinucleate and monolithic type. SEM (Fig. 1) indicated that the microcapsules were spherical with smooth surface and completely covered with the polymer coat.

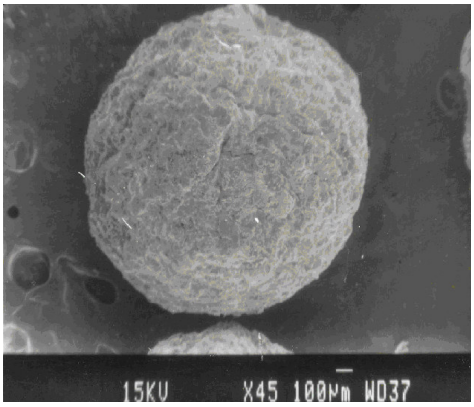

Fig. 1. SEM of ethyl cellulose microcapsule, MC2 (size 30/50) of glimepiride

The sizes could be separated by sieving and a more uniform size range of microcapsules could readily be obtained. The sieve analysis of different microcapsules showed that a large proportion of microcapsules were in the size range 20/30 (55-65 %) and 30/50 (20-30%) mesh.

Low coefficient of variation in percent drug content (< 1.0 %) indicated uniformity of drug content in each batch of microcapsules (Table-1). The

TABLE-1
DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE RATE OF GLIMEPIRIDE MICROCAPSULES PREPARED

Micro-capsules (core:coat ratio	Drug content (%)	Wall thickness (µm)	Micro-encapsulation efficiency (%)	T_{50} (h)	T_{90} (h)	Release rate K_1 (h^{-1})	'n' value in Peppas equation
Size 20/30							
MC1 (9:1)	73.31 (0.65)*	30.66	81.11	2.0	14.5	0.162	0.692
MC2 (7:3)	62.67 (0.49)	43.46	88.57	11.5	>24	0.068	0.831
MC3 (5:5)	38.22 (0.43)	72.03	76.00	13.5	>24	0.046	0.984
Size 30/50							
MC1 (9:1)	78.23 (0.51)	15.45	86.67	1.5	21	0.107	0.675
MC2 (7:3)	61.13 (0.62)	27.69	87.14	7.5	22	0.087	0.707
MC3 (5:5)	34.19 (0.58)	47.69	68.00	11.5	>24	0.057	0.901

*Figures in parentheses are coefficient of variation values.

microencapsulation efficiency was in the range 68-89 %. Drug content of the microcapsules was found to be 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 microcapsules was calculated[8]. Microcapsules prepared with various ratios of core:coat were found to have different wall thickness. Smaller microcapsules had thinner walls.

Glimepiride release from the microcapsules was studied in water containing 1 % sodium lauryl sulphate. Sodium lauryl sulphate was included in the dissolution medium to maintain sink condition. Glimepiride release from the microcapsules was slow and spread over a period of more than 24 h and depended on core:coat ratio, wall thickness and size of the microcapsules. Drug release parameters of various microcapsules are summarized in Table-1. The release data were analyzed as per zero order, first order, Higuchi[9] and Peppas equation[10] models. The correlation coefficient (R^2) values observed in fitting the release data into various kinetic models are given in Table-2. Analysis of the release data as per zero and first order kinetic models indicated that the drug release from the microcapsules more obeyed first order kinetics. Correlation coefficient (R^2) values in the first order model are higher than those in the zero order model. When the release data was analyzed as per Peppas equation[10], the release exponent 'n' was in the range of 0.675-0.984 with various microcapsules indicating non-fickian (anomalous) diffusion as the release mechanism. Plots of percent released *vs.* square root of time were found to be linear ($R^2 > 0.879$) indicating that the drug release from the microcapsules was diffusion controlled. As the proportion of the coat was increased, glimepiride release rate was decreased. Smaller microcapsules gave higher release rates due to increased surface area. A good linear relationship was observed between wall thickness of the microcapsules and release rate (K_o) (Fig. 2).

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

Microcapsules (core:coat ratio)	Correlation coefficient (R^2 value)			
	Zero order	First order	Higuchi model	Peppas model
Size 20/30				
MC1 (9:1)	0.709	0.929	0.908	0.484
MC2 (7:3)	0.935	0.980	0.987	0.727
MC3 (5:5)	0.917	0.974	0.979	0.980
Size 30/50				
MC1 (9:1)	0.680	0.936	0.879	0.471
MC2 (7:3)	0.893	0.979	0.983	0.569
MC3 (5:5)	0.917	0.974	0.979	0.980

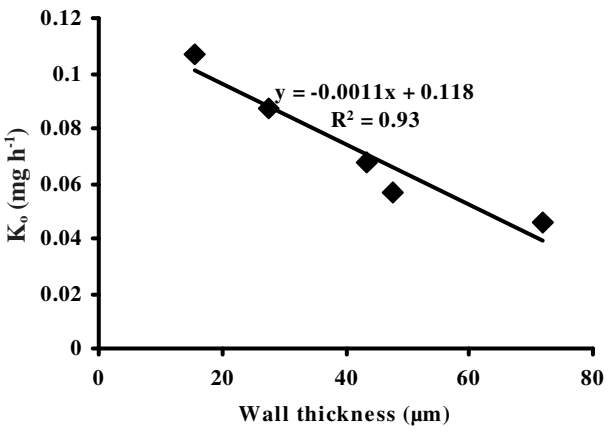

Fig. 2. Relationship between wall thickness and release rate (K_o) of ethyl cellulose microcapsules of glimepiride

As there are no sustained release dosage forms of glimepiride available in Indian market, theoretical sustained release needed for glimepiride for once-a-day (24 h) administration was calculated based on its pharmacokinetics as suggested by Wagner[11] and the release profiles of formulated micro-capsules were compared with the theoretical sustained release needed to select the optimized formulation. A once-a-day controlled release product of glimepiride should contain a total dose of 8 mg (initial 1.74 mg; maintenance dose 6.28 mg) and the drug should be released at a rate (K_0) of 0.2614 mg/h. Based on these doses and release rate (K_0), an oral controlled release dosage form of glimepiride should provide a release of 25 % in 1 h, 28.3 % in 2 h, 34.8 % in 4 h, 47.9 % in 8 h, 60.9 % in 12 h and 100 % in 24 h. Overall ethyl cellulose microcapsules, MC2 (30/50)gave a release profile similar to the theoretical sustained release needed for once-a-day (24 h) administration of glimepiride. These microcapsules provided a release of 23.57 % in 1 h; 29.76 in 2 h; 38.24 % in 4 h; 55.48 % in 8 h; 69.54 % in 12 h and 100 % in 24 h. Drug release profile of ethyl cellulose microcapsules MC2 (size 30/50) and theoretical release profile were compared by calculating difference factor f_1 and similarity factor f_2. A value of $f_1 < 15$ and $f_2 > 50$ indicates similarity of the two drug release profiles. The values of f_1 and f_2 were found to be 7.6 and 135.3, respectively for the comparison of release profile of microcapsules MC2 (size 30/50) and theoretical release profile indicating that these two release profiles are similar. Hence, ethyl cellulose microcapsules, MC2 (size 30/50) are considered suitable for once-a-day controlled release of glimepiride.

Conclusion

(i) Spherical ethyl cellulose coated microcapsules of glimepiride 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 of 68-89 %. (iii) Glimepiride release from the ethyl cellulose coated microcapsules was slow and extended over 24 h and depended on core:coat ratio, wall thickness and size of the micro-capsules. Drug release from these microcapsules was by non-fickian (anamalous) diffusion mechanism. (iv) A good linear relationship was observed between wall thickness of the microcapsules and release rate. (v) Ethyl cellulose was found suitable as a microencapsulating agent for glimepiride and the ethyl cellulose coated microcapsules of glimepiride exhibited good controlled release characteristics and were found suitable for oral controlled release of glimepiride.

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