Asian Journal of Chemistry Vol. 20, No. 7 (2008), 5391-5398

Evaluation of Olibanum Resin 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 olibanum resin, a natural lipophilic polymer for its application as microencapsulating agent for controlled release of glimepiride. Controlled release formulations are needed for glimepiride for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance. Olibanum resin coated microcapsules of glimepiride were prepared by industrially feasible emulsification-solvent evaporation method and the microcapsules were evaluated for controlled release. The resin coated microcapsules prepared are spherical, discrete, free flowing and multinucleate monolithic type. Microencapsulation efficiency was in the range 84-108 %. 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 diffusion mechanism. Good linear relationship was observed between wall thickness of the microcapsule and release rate. Olibanum resin was found suitable as a new microencapsulating agent and the resin coated microcapsules exhibited good controlled release characteristics. Glimepiride release from the olibanum resin coated microcapsules, MC 2 (size 20/30) fulfilled the theoretical controlled release needed for glimepiride based on its pharmacokinetics.

Key Words: Olibanum resin, Glimepiride, Controlled release, Microencapsulation.

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 various standard text books[1,2]. Though a variety of polymeric materials are available to serve as release retarding coat materials, there is a continued need to develop new, safe and effective release retarding coat materials for microencapsulation.

Glimepiride is an effective oral antidiabetic agent that belongs to the sulphonylurea drug class. The recommended[3] 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[4] 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[5]. Olibanum is a gum resin obtained from *Boswellia serrata*, Roxburgh and other species of *Boswellia*. Olibanum consists[6] chiefly an acid resin (50-60 %), gum (30-36 %) and volatile oil (3-8 %). The resin consists[7] mainly a resin acid (boswellic acid) and a resene (olibanoresene) in equal proportions. Ether soluble resin extracted from olibanum exhibited[8] excellent release retarding properties in matrix tablets for controlled release due to its hydrophobic water repellent properties. Preliminary studies indicated that the resin has good film forming property when dried from chloroform solution. The objective of the present work is to evaluate the resin extracted from the olibanum as coating material in microencapsulation for obtaining controlled release of glimepiride. Studies were carried out on microencapsulation of glimepiride by the resin and evaluation of the resin-coated microcapsules of glimepiride for controlled drug release.

EXPERIMENTAL

Glimepiride was a gift sample from M/s Orchid Health Care, Chennai. Sodium carboxy methyl cellulose (high viscosity grade 1500-3000 cps) and chloroform AR (Merck) were procured from commercial sources. Olibanum gum (*Boswellia serrata*, Roxburgh) was procured from M/s Girijan Co-operative Corporation, Visakhapatnam, India. All other materials used were of pharmacopoeial grade.

Preparation of olibanum resin: Olibanum resin used as coat material was extracted from olibanum gum in the laboratory as follows:

Powdered olibanum (10 g) was extracted repeatedly with 4 × 50 mL quantities of solvent ether. The ether extracts were collected in a porcelain dish and concentrated to dryness at 40 ºC. The dried mass obtained was powdered and passed through mesh no. 120.

Preparation of microcapsules: An emulsification-solvent evaporation method was tried to prepare resin-coated microcapsules containing glimepiride.

Olibanum resin 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 (UV) spectrophotometric method based on the measurement of absorbance at 230 nm in phosphate buffer of pH 7.4 was used for the 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.*[9] 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 µ) 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 olibanum resin. The method involves emulsification of the polymer (resin) 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. Resin-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 (resin) coat.

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 (30-40 %) and 30/50 (35-40 %) mesh.

Low coefficient of variation in percent drug content (< 1.0 %) indicated uniformity of drug content in each batch of microcapsules (Table-1). The microencapsulation efficiency was in the range 84-108 %. 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 as described by Luu *et al.*[9]. Microcapsules prepared with various ratios of core:coat was found to have different wall thickness. Smaller microcapsules have thinner walls.

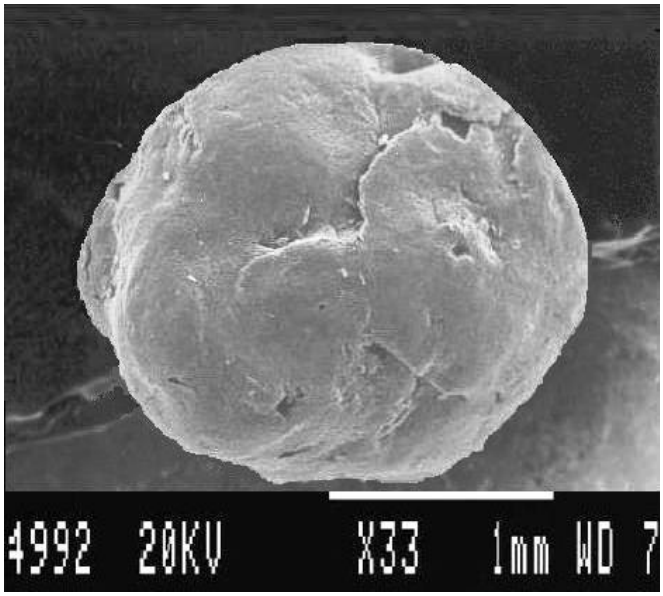

Fig. 1. SEM of olibanum microcapsules, MC2 (size 20/30)

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_0 (mg/h)	'n' value in Peppas equation
Size 20/30							
MC1(9:1)	79.72 (0.59)*	25.64	87.78	3.5	11.0	0.527	0.777
MC2(7:3)	73.33 (0.41)	32.90	104.29	8.0	17.5	0.347	0.741
MC3(5:5)	54.18 (0.38)	55.72	108.00	10.5	19.0	0.296	0.836
Size 30/50							
MC1(9:1)	76.65 (0.26)	18.16	84.44	1.0	2.5	2.266	0.933
MC2(7:3)	73.78 (0.55)	20.41	104.29	6.2	14.5	0.377	0.756
MC3(5:5)	49.54 (0.43)	38.26	98.00	9.5	21.5	0.343	0.977

*Figures in parentheses are coefficient of variation values.

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.

The release data were analyzed as per zero order, first order, Higuchi[10] and Peppas equation[11] models. The correlation coefficient (R^2) values observed in fitting the release data into various kinetic models are given in Table-2.

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

Microcapsules (core:coat ratio)	Regression coefficient (R^2 value)			
	Zero order	First order	Higuchi model	Peppas model
		Size 20/30		
MC1 (9:1)	0.923	0.954	0.991	0.443
MC2 (7:3)	0.957	0.938	0.962	0.581
MC3 (5:5)	0.952	0.981	0.978	0.730
		Size 30/50		
MC1 (9:1)	0.824	0.879	0.888	0.787
MC2 (7:3)	0.978	0.818	0.883	0.572
MC3 (5:5)	0.969	0.830	0.945	0.842

Analysis of the release data as per zero and first order kinetic models indicated that both the models are equally applicable to describe the release data of the microcapsules. Correlation coefficient (R^2) values in the two models were nearly the same. When the release data was analyzed as per Peppas equation[11], the release exponent 'n' was in the range of 0741-0.977 with all the microcapsules indicating non-fickian diffusion as the release mechanism. Plots of percent released *vs.* square root of time were found to be linear ($R^2 > 0.883$) 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_0) (Fig. 2).

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 *et al.*[12] and the release profiles of formulated microcapsules 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

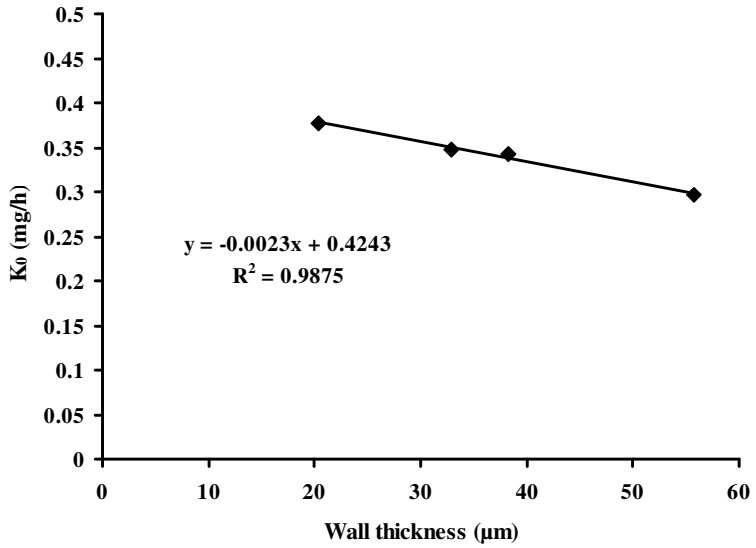

Fig. 2. Relationship between wall thickness and release rate (K_0) of olibanum resin coated microcapsules of glimepiride

olibanum microcapsules, MC2 of size 20/30 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 21.2 % in 1 h; 32.7 % in 4 h; 49.0 % in 8 h; 76.7 % in 12 h and 100 % in 24 h.

Conclusion

(i) Spherical olibanum resin 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 84-108 %. (iii) Glimepiride release from the olibanum resin-coated 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. (iv) A good linear relationship was observed between wall thickness of the microcapsules and release rate. (v) Olibanum resin was found suitable as a new microencapsulating agent and the olibanum resin coated microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release of glimepiride. (vi) Olibanum is reported as non-toxic[13] and since it is of natural origin, it is biocompatible and cheaper.

REFERENCES

1. A. Kondo, Microcapsule Processing and Technology, Marcel Dekker, Inc., New York, p. 18 (1979).
2. M.H. Gutcho, Microcapsules and Microencapsulation Techniques, Noyes Data Corporation, New Jersey, p. 236 (1976).
3. B. Rosenkranz, V. Profozic, Z. Metelko, V. Mrzljak, C. Lange and V. Malerczyk, *Diabetologia*, **39**, 1617 (1996).
4. R. Roβkamp, K. Wernicke-Panten and E. Draeger, *Diabetes Res. Clin. Practise*, **31**, S33 (1996).
5. B. Rosenkranz, *Horm. Metab. Res.*, **28**, 434 (1996).
6. S.K. Nigam and C.R. Mitra, *Indian Drugs*, **16**, 80 (1979).
7. R.S. Srinivas and B. Madhu, *Indian J. Chem.*, **176**, 168 (1976).
8. K.P.R. Chowdary, P. Mahopatra and M.N.M. Krishna, *Indian J. Pharm. Sci.*, **68**, 497 (2006).
9. S.N. Luu, P.F. Carlier, P. Delort, K. Gazzola and D. Lanfont, *J. Pharm. Sci.*, **62**, 452 (1973).
10. T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).
11. P.L. Ritger and L.N.A. Peppas, *J. Control. Rel.*, **5**, 37 (1987).
12. J.G. Wagner and E. Nelson, *J. Pharm. Sci.*, **52**, 610 (1963).
13. G. Joerg, B. Thomas and J. Christof, PDR for Herbal Medicines, Medical Economics Company, Montvale, New Jersy, edn. 2, p. 319 (2000).

(*Received*: 5 September 2007; *Accepted*: 2 May 2008) AJC-6551