

Olibanum Resin Coated Microcapsules of Gliclazide: Preparation and Evaluation for Controlled Release

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The objective of the study is to evaluate olibanum resin, a natural lipophilic polymer for its application as microencapsulating agent and to prepare and evaluate olibanum resin-coated microcapsules of gliclazide for controlled release. Controlled release formulations are needed for gliclazide for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance. Olibanum resin coated microcapsules of gliclazide were prepared by an 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 98-104 %. Gliclazide 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 microcapsules and release rate. Olibanum resin was found suitable as a new microencapsulating agent and the resin coated microcapsules exhibited good controlled release characteristics. Gliclazide release from the olibanum resin coated microcapsules, MC2 (size 20/30) was similar to that from Diamicon MR tablets, a commercial controlled release formulation of gliclazide.

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

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.

Gliclazide is an effective oral anti-diabetic agent that belongs to the sulfonylureas drug class. The recommended daily dosage of gliclazide is 30-120 mg in divided doses 2 to 3 times a day. The drug 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 needed³ for gliclazide for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficacy, to reduce g.i disturbances and to enhance patient compliance. A few controlled release formulations of gliclazide are available commercially.

Olibanum is a gum resin obtained from *Boswellia serrata*, Roxburgh and other species of *Boswellia*. Olibanum consists⁴ chiefly an acid resin (50-60 %), gum (30-36 %) and volatile oil (3-8 %). The resin consists⁵ mainly a resin acid (boswellic acid) and a resene (olibanoresene) in equal proportions. Ether soluble resin extracted from olibanum exhibited³ 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 gliclazide. Studies were carried out on microencapsulation of gliclazide by the olibanum resin and evaluation of the resin-coated microcapsules of gliclazide for controlled drug release.

EXPERIMENTAL

Gliclazide was a gift sample from M/s Ranbaxy Research Labs, Gurgaon, India. 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 of ether. The ether extracts were collected in a porcelain dish and concentrated to dryness at 40 °C. The dried mass obtained was powdered and passed through mesh no. 120.

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

Olibanum resin (2 g) was dissolved in chloroform (100 mL) to form a homogenous polymer solution. Core material, gliclazide (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 °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 (MC1), 8:2 (MC2) and 7:3 (MC3) were used to prepare microcapsules with varying coat thickness.

Estimation of gliclazide: Gliclazide content of the microcapsules was estimated by UV spectrophotometric method based on the measurement of absorbance at 229 nm in phosphate buffer of pH 7.4. 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.

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.*⁶ 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 °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 ± 1 °C. Phosphate buffer of pH 7.4 (900 mL) was used as dissolution fluid. A sample of microcapsules equivalent to 30 mg of gliclazide 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 229 nm. All drug release experiments were conducted in triplicate.

RESULTS AND DISCUSSION

An emulsification-solvent evaporation method was developed for micro-encapsulation of gliclazide 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 gliclazide 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 (44-46 %) and 30/50 (27-30 %) mesh.

Low coefficient of variation in per cent drug content (< 0.5 %) indicated uniformity of drug content in each batch of microcapsules (Table-1). The microencapsulation efficiency was in the range 98-104 %. 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.*⁶. Microcapsules prepared with various ratios of core:coat were found to have different wall thickness. Smaller microcapsules have thinner walls.

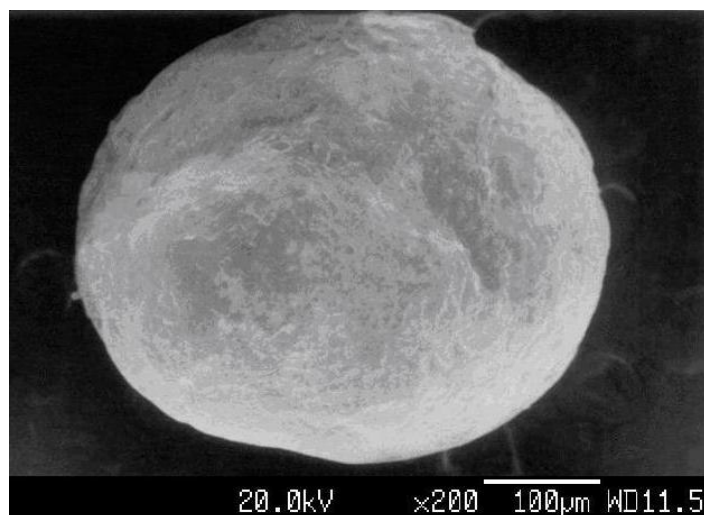


Fig. 1. SEM of olibanum microcapsules, MC2 (size 20/30) of gliclazide

TABLE-1
DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL
THICKNESS AND RELEASE RATE OF OLIBANUM RESIN
COATED MICROCAPSULES OF GLICLAZIDE

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)	90.41 (0.2)*	12.05	100.44	6.3	18.0	1.226	0.621
MC2(8:2)	82.40 (0.2)	21.66	102.54	6.5	22.0	1.197	0.691
MC3(7:3)	69.21 (0.5)	37.25	98.57	8.0	> 24	1.067	0.685
Size 30/50							
MC1(9:1)	89.14 (0.2)	8.22	98.89	2.5	5.5	4.428	0.632
MC2(8:2)	83.27 (0.2)	12.69	103.75	2.5	6.0	3.753	0.623
MC3(7:3)	71.01 (0.5)	21.62	101.43	3.0	9.5	2.698	0.602
Diamicron MR	—	—	—	7.6	22.2	1.234	0.879

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

Gliclazide release from the microcapsules was studied in phosphate buffer of pH 7.4 (900 mL). Gliclazide 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, Higuchi⁷ and Peppas equation⁸ models. The correlation coefficient (R^2) values observed in fitting the release data to 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)	0.864	0.989	0.972	0.873
MC2 (8:2)	0.860	0.981	0.965	0.855
MC3 (7:3)	0.915	0.996	0.986	0.882
Size 30/50				
MC1 (9:1)	0.965	0.948	0.981	0.967
MC2 (8:2)	0.958	0.955	0.986	0.961
MC3 (7:3)	0.916	0.976	0.973	0.920
Diamicron MR	0.955	0.956	0.963	0.850

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 equation⁸, the release exponent 'n' was in the range of 0.602-0.691 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 ($R^2 > 0.965$) indicating that the drug release from the microcapsules was diffusion controlled. As the proportion of the coat was increased, gliclazide 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).

For comparison, gliclazide release from Diamicron MR tablets, a commercial controlled release formulation of gliclazide was also studied. Olibanum resin-coated microcapsules, MC2 (size 20/30) gave a release profile similar to that of the commercial controlled release product tested. Drug release profiles of microcapsules MC2 (size 20/30) and Diamicron MR tablets 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 11.2 and 142.5, respectively for the comparison of release profiles of microcapsules MC2 (size 20/30)

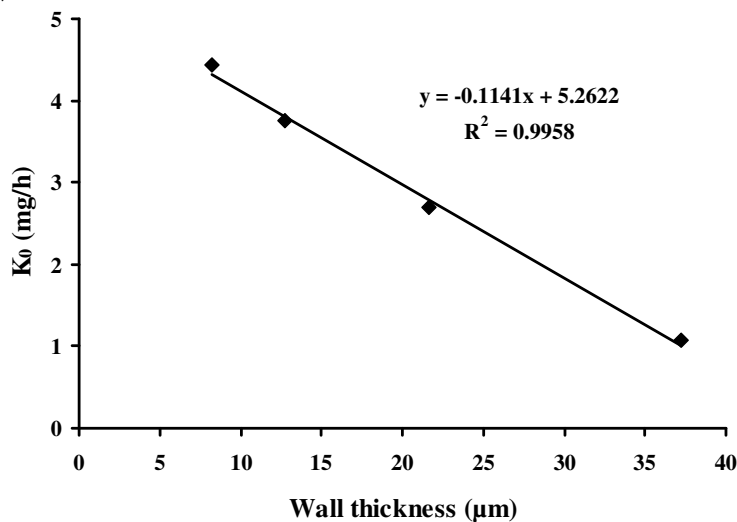


Fig. 2. Relationship between wall thickness and release rate (K_0) of olibanum resin coated microcapsules of gliclazide

and Diamicon MR tablets indicating that the release profiles of these two products are similar. Hence, olibanum resin coated microcapsules, MC2 (size 20/30) are considered suitable for controlled release of gliclazide over 24 h.

Conclusion

(i) Spherical olibanum resin coated microcapsules of gliclazide 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 98-104 %. (iii) Gliclazide 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) Gliclazide release from olibanum resin coated microcapsules (size 20/30) was similar to that from Diamicon MR tablets, a commercial controlled release formulation of gliclazide. (vi) 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 gliclazide. (vii) Olibanum is reported as non-toxic⁹ 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. C. Kilo, J. Dudley and B. Kalb, *Diabetes Res. Clin. Pract.*, **14**, S79 (1991).
4. S.K. Nigam and C.R. Mitra, *Indian Drugs*, **16**, 80 (1979).
5. R.S. Srinivas and B. Madhu, *Indian J. Chem.*, **176**, 168 (1976).
6. S.N. Luu, P.F. Carlier, P. Delort, K. Gazzola and D. Lanfont, *J. Pharm. Sci.*, **62**, 452 (1973).
7. T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).
8. P.L. Ritger and L.N.A. Peppas, *J. Control. Release*, **5**, 37 (1987).
9. G. Joerg, B. Thomas and J. Christof, *PDR for Herbal Medicines*, Medical Economics Company, Montvale, New Jersey, edn. 2, p. 319 (2000).

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