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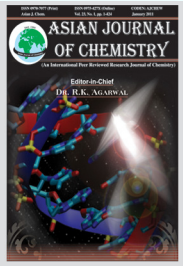

Design and Evaluation of Floating Tablets of Glipizide Employing Olibanum Gum and Hydroxy Propyl Methyl Cellulose

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The objective of the study is to evaluate olibanum gum (a new natural gum resin) and hydroxy propyl methyl cellulose K15M as matrix formers for floating tablets on gas generating principle and to design floating tablets of glipizide. Floating tablets of glipizide were prepared employing olibanum gum and hydroxy propyl methyl cellulose as matrix formers and sodium bicarbonate as gas generating agent and the tablets were evaluated for *in vitro* buoyancy and drug release characteristics. Tablets formulated with hydroxy propyl methyl cellulose exhibited a floating time of more than 48 h with a floating lag time in the range of 18-54 s. Tablets formulated with olibanum gum also exhibited a floating time of more than 48 h but after a floating lag time of 1.0-1.5 h. Glipizide release from all the floating tablets formulated was slow, spread over more than 24 h and depended on the polymer used and its strength and concentration of the sodium bicarbonate in the tablet. Drug release was diffusion controlled and followed first order kinetics in the case of hydroxy propyl methyl cellulose tablets and zero order kinetics in the case of tablets prepared with olibanum gum. Fickain diffusion was the drug release mechanism from all the tablets formulated. Based on the *in vitro* buoyancy and drug release characteristics floating tablet formulation F6 (prepared using 50 % hydroxy propyl methyl cellulose and sodium bicarbonate 20 %) and F9 (prepared using 50 % olibanum gum and sodium bicarbonate 20 %) are considered as best floating tablets formulated and these formulations were found suitable for 24 h *i.e.*, once-a-day administration.

Key Words: Floating tablets, Olibanum gum, Hydroxy propyl methyl cellulose, Glipizide.

INTRODUCTION

The oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has certain problems such as unpredicatble gastric emptying rate, short gastro-intenstinal time (8-12 h) and existence of an adsorption window in the gastric and upper small intenstine for several drugs[1,2] leading to low and variable oral adsorption over short period of time. The real issue in the development of oral drug delivery systems is to prolong the residence time of the dosage form in the stomach or upper GI tract until the drug is completely released and absorbed. Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems[3], swelling and expandable systems[4,5], floating systems[6,7] and other delayed emptying devices[8,9]. The principle of floating tablets offer a simple and practical approach to achieve increased gastric residence time to enhance the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer. In the present study olibanum gum (a new natural gum resin) and HPMC K15M (a known synthetic polymer) were evaluated as matrix formers in the design of floating tablets of glipizide. Glipizide, an oral antidiabetic agent is poorly soluble in water and majorly absorbed from stomach and upper GI tract. Formulation of floating tablets of glipizide enhances its oral bioavailability by prolonging its stay in the stomach. Glipizide also requires controlled release formulation because of its short biological half life and also for better control of hypo-glycemia, for enhancing its therapeutic efficacy and patient compliance. Floating tablets of glipizide are designed with an objective of enhancing the oral bioavailability and to achieve controlled release of glipizide.

EXPERIMENTAL

Glipizide was a gift sample from M/s Micro Labs., Ltd., Pondicherry, India. Olibanum gum was procured from M/s Girijan Cooperative Corporation, Govt. of Andhra Pradesh, Vishakhapatnam. Hydroxy propyl methyl cellulose (K15M, Colorcon) and sodium biocarbonate (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Preparation of tablets: Matrix tablets each containing 10 mg of glipizide were formulated employing (i) olibanum

gum at 50 % concentration and (ii) HPMC K15M at 25 and 50 % concentration in the formulae. Sodium bicarbonate was used as gas generating agent at 10, 15 and 20 % strength in each case. The required quantities of glipizide, olibanum gum (size 120 mesh), HPMC K15M, lactose, sodium bicarbonate were thoroughly mixed in a mortar by following geometric dilution technique. The granulating fluid (a mixture of water and alcohol in 1:1 ratio) was added and mixed thoroughly to form a dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60 ºC for 2 h. The dried granules were passed through mesh No. 16 to break aggregates. The lubricants, talc (2 %) and magnesium stereate (2 %) were passed through mesh No. 60 on to dry granules and blanded in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16 station rotary multi-station tablet punching machine (M/s Cadmach Machineries Pvt. Ltd., Mumbai) to a hardness of 8-10 kg/cm^{-1}.

Evaluation of tablets: Hardness of the matrix tablets was tested using a Monsanto hardness tester. Friability of the matrix tablets was determined in a Roche friabilator. Disintegration time of tablets was determined using a thermonic tablet disintegration test machine using distilled water, 0.1 N HCl and phosphate buffer on pH 7.4 as the test fluids.

Estimation of glipizide: An ultraviolet spectrophotometric method based on the measurement of absorbance at 276 nm in 0.1 N hydrochloric acid was used for the estimation of the glipizide. The method obeyed Beer-Lambert's law in the concentration range of 1-10 µm/mL. When the standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.80 and 1.2 %, respectively. No interference from excipients used was observed.

Floating time and floating lag time: *In vitro* buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a 250 mL glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration which the tablet remains floating was determined as floating time.

Drug release study: Drug release from floating tablets was studied using 8 station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37 ± 0.1 ºC. Hydrochloric acid 0.1 N (900 mL) was used as dissolution fluid. 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 276 nm. All the drug release experiments were conducted in triplicate.

Data analysis: Release data were analyzed as per zero order, first order, Higuchi[10] and Peppas[11] equation models to assess the drug release kinetics and mechanism from the matrix tablets prepared.

RESULTS AND DISCUSSION

Floating tablets of glipizide were prepared employing (i) olibanum gum and (ii) HPMC, K15M as matrix formers and sodium bicarbonate as gas generating agent with an objective of developing flating tablets of glipizide and to make a comparative evaluation of the two matrix formers for floating tablets. HPMC, K15M is a well known synthetic cellulose polymer widely used in tablet coating and in controlled release dosage forms. Olibanum is a gum resin obtained from *Boswellia serrata* Roxburgh and other species of Boswellia, Olibanum consists[12] of chiefly of an acid resin (50-60 %), gum (30-36 %) and volatile oil (3-8 %). The resin contains[13] mainly a resin acid (boswellic acid) a resin (libano resin) in equal proportions. The olibanum gum and the resin extracted from olibanum exhibited[14] excellent release retarding properties in matrix tablets for controlled release. Hardness of the tablets was in the range 7.0-8.5 kg/cm^2. Weight loss in the friability test was less than 0.30 % in all the cases. All the tablets prepared contained glipizide with in 100 ± 5 % of the labeled claim. All the tablets prepared were found to be non-disintegrating in water and aqeuous fluids of acidic pH (1.2) and alkaline pH (7.4). As such all the tablets prepared with HPMC, K15M and olibanum gum were of good quality with regard to drug content, hardness and friability.

In vitro buoyancy study, floating tablets formulated with HPMC, K15M exhibited a floating time of more than 48 h with floating lag time in the range of 18-54 s. In the case of olibanum gum, the tablets exhibited delayed floating after a lag period of 1.0-1.5 h. Floating time was more than 48 h (Table-1). Thus HPMC, K15M exhibited good floating characteristics. The floating characteristics of olibanum gum need to the improved, probably by adding floating enhancers such as bees wax and ethyl cellulose.

Glipizide release parameters of the floating tablets are summarized in Table-2. Glipizide release from all the prepared floating tablets was slow and spread over more than 24 h and depended on the polymer used as matrix former and its strength and concentration of sodium bicarbonate used as gas generating agent. When the release data were analyzed as per zero order and first order models, the correlation coefficient (R^2) values were higher in the case of first order model with all the formulations prepared using HPMC as matrix former indicating that the drug release from these tablets followed first order kinetics. Whereas in the case of tablets formulated employing olibanum gum as matrix former, the release followed zero order kinetics. When the release data were analyzed as per the Peppas equation, the release exponent 'n' was found to be in the range 0.1623-0.5023 indicating Fickian diffusion as the release mechanism from all the floating tablets prepared. When the HPMC concentration in the matrix tablets was increased from 25-50 %, the release rate (K_0 and K_1) was decreased. There was no specific relationship between the concentration of sodium bicarbonate in the matrix tablets and the release rate with both the floating tablets formulated employing HPMC and olibanum gum. When the sodium bicarbonate concentration was increased the floating time was increased. For comparison glipizide release from glynase XL SR tablets was also studied. Glipizide release from glynase XL SR tablets was also slow and spread over 24 h. About 89.0 ± 1.40 % release was observed from these tablets in 24 h.

Conclusion

Tablets formulated with HPMC exhibited excellent floating characteristics, whereas those formulated with olibanum gum exhibited moderate floating characteristics. Glipizide release

TABLE-1
COMPOSITION AND PHYSICAL PROPERTIES OF FLOATING TABLETS FORMULATED EMPLOYING OLIBANUM GUM AND HPMC

Formulation	Matrix composition	Hardness (kg/cm^2)	Friability (%)	Glipizide content (mg/tab)	Floating lag time (s)	Floating time (h)
F1	HMPC (25 %) sodium bicarbonate (10 %)	8.5	0.20	9.2	36 sec	> 48
F2	HPMC (25 %) sodium bicarbonate (15 %)	7.0	0.15	10.1	40 sec	> 48
F3	HPMC (25 %) sodium bicarbonate (20 %)	8.0	0.30	9.5	20 sec	> 48
F4	HPMC (50 %) sodium bicarbonate (10 %)	8.5	0.15	9.6	54 sec	> 48
F5	HPMC (5 %) sodium bicarbonate (15 %)	7.5	0.10	9.2	44 sec	> 48
F6	HPMC (50 %) sodium bicarbonate (20 %)	8.0	0.10	10.0	18 sec	> 48
F7	Olibanum gum (50 %) sodium bicarbonate (10 %)	7.0	0.10	9.2	1 h 30 min	> 48
F8	Olibanum gum (50 %) sodium bicarbonate (15 %)	7.5	0.10	10.1	1 h 25 min	> 48
F9	Olibanum gum (50 %) sodium bicarbonate (20 %)	8.5	0.20	9.1	1 h 25 min	> 48

HPMC: Hydroxy propyl methyl cellulose.

TABLE-2
RELEASE CHARACTERISTICS OF GLIPIZIDE FLOATING TABLETS FORMULATED EMPLOYING OLIBANUM GUM AND HPMC K15M

Formulation	T_{50} (h)	T_{90} (h)	K_0 (mg/h)	K_1 (h^{-1})	'n' in Peppas equation
F1	3.25	9.51	0.6606	0.315	0.3521
F2	1.75	14.0	0.3432	0.231	0.2724
F3	3.52	16.1	0.3665	0.176	0.4253
F4	1.00	13.5	0.3522	0.241	0.2253
F5	3.50	17.7	0.3187	0.136	0.3512
F6	5.60	18.0	0.3382	0.171	0.4023
F7	12.60	> 24	0.2537	0.046	0.4621
F8	12.90	> 24	0.2822	0.054	0.5023
F9	16.50	17.7	0.3646	0.160	0.4752

from all the floating tablets formulated was slow, spread over 24 h and was diffusion controlled. Fickian diffusion was the drug release mechanism. Based on the *in vitro* buoyancy and drug release characteristics, floating tablet formulation F6 (prepared using 50 % HPMC and 20 % sodium bicarbonate) and F9 (prepared using 50 % olibanum gum and 20 % sodium bicarbonate) are considered as best floating tablets formulated and these formulations were found suitable for 24 h, *i.e.*, once-a-day administration. Glipizide release from these formulations was 99-100 % in 24 h was better than that from glynase XL SR tablets (a commercial SR tablets).

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