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Formulation and Evaluation of Floating Tablets of Diltiazem Employing Olibanum Gum

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The objective of the study is to formulate and evaluate floating tablets of diltiazem employing olibanum gum, a natural gum resin in comparison to HPMC K15M, a synthetic cellulose derivative. Floating tablets of diltiazem were prepared employing olibanum gum and HPMC, K15M as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer and the tablets were evaluated for *in vitro* buoyancy and drug release characteristics. Tablets formulated employing olibanum gum (50 %), sodium bicarbonate (10 %) and bees wax (10 %) exhibited floating over 48 h with a floating lag time of 5-10 min. Diltiazem release from the floating tablets formulated was slow, spread over more than 24 h and depended on the polymer used and its strength and concentration of sodium bicarbonate in the tablets. Drug release was diffusion controlled and followed first order kinetics. Fickian diffusion was the drug release mechanism from all the tablets formulated. Olibanum gum gave slow, controlled and complete drug release in 24 h, whereas HPMC, K15M gave slow but incomplete drug release. Olibanum was found to be a better matrix former than HPMC for floating tablets. Since olibanum gum is of natural origin, it is non-toxic, biocompatible and cheaper.

Key Words: Floating tablets, Olibanum gum, Diltiazem hydrochloride.

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 unpredictable gastric emptying rate, short gastro-intestinal transit time (8-12 h) and existence of an absorption window in the gasric and upper small intestine for several drugs[1,2] leading to low and variable oral absorption over shorter 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 g.i. 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 expanding systems[4,5], floating systems[6,7] and other delayed gastric emptying devices[8,9]. The principle of floating tablets offers 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 natural gum-resin was evaluated as matrix former in the design of floating tablets of diltiazem. Floating tablets of diltiazem were designed employing olibanum gum and hydroxy propyl methyl cellulose (HPMC) (for comparison) as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer and the tablets were evaluated for floating and drug release characteristics.

EXPERIMENTAL

Diltiazem hydrochloride was a gift sample from M/s. Micro Labs. Ltd., Pondicherry. Olibanum gum was procured from M/s. Girijan Cooperative Corporation, Government of Andhra Pradesh, Visakhapatnam. Hydroxy propyl methyl cellulose (K15M, Colorcon) and Bees wax, I.P were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Preparation of floating tablets: Matrix tablets each containing 90 mg of diltiazem were formulated employing (i) olibanum gum and (ii) HPMC, K15M, each at 25 and 50 % concentration in the formula. Sodium bicarbonate was used as gas generating agent at 10 and 20 % strength in each case. Bees wax was used as floating enhancer at 10 % concentration in all the formulations.

The required quantities of diltiazem, olibanum gum (size No. 100 mesh), HPMC K15M, bees wax, lactose 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 the aggregates. The lubricants, talc (2 %) and magnesium stearate (2 %) were passed through mesh No. 60 on to the dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16-station tablet punching machine (M/s Cadmach Machinaries Pvt. Ltd., Ahmedabad) to a hardness of 8-10 kg/cm^2.

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

Estimation of diltiazem: An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 240 nm in 0.1 N hydrochloric acid was used for the estimation of diltiazem. The method obeyed Beer-Lambert's law in the concentration range of 1-10 µm/mL. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.60 and 1.20 %, respectively. No interference from the excipients used was observed.

Floating lag time and floating 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 during which the tablet remains floating was determined as floating time.

Drug release study: Drug release from the matrix tablets was studied using 8- station dissolution rate test apparatus (Labindia, Disso 2000) employing a paddle stirrer at 50 rpm and at temperature of 37 ± 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 240 nm. All drug release experiments were conducted in triplicate.

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

RESULTS AND DISCUSSION

Matrix tablets of diltiazem hydrochloride were prepared employing (i) olibanum gum and (ii) HPMC, K15M as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer with an objective of evaluating olibanum gum as matrix material for floating tablets. Olibanum is a gum resin obtained from *Boswellia serrata* Roxburgh and other species of Boswellia. Olibanum consists[12] of mainly an acid resin (50-60 %), gum (30-36 %) and volatile oil (3-8 %). The resin contains[13] mainly a resin acid (boswellic acid) and a resin (olibanoresene) in equal proportions. The olibanum gum and the resin extracted from olibanum exhibited[14] excellent release retarding properties in matrix tablets for controlled release. Diltiazem is a calcium channel bloker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension. It has short biological half life of about 3.5 h and is rapidly eliminated. It is favourably absorbed from stomach and the oral bioavailability is 40 % in humans[15]. Floating tablets of diltiazem were designed in the present study to enhance its bioavailability and to achieve controlled release over 24 h for once a day administration.

Hardness of the tablets was in the range 7-9 kg/cm^2. Weight loss in the friability test was less than 0.6 % in all the cases. All the tablets prepared contained diltiazem hydrochloride within 100 ± 3 % of the labeled claim. All the tablets prepared were found to be non-disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such, the prepared tablets were of good quality with regard to drug content, hardness and friability. In the *in vitro* buoyancy study, the floating lag time of various tablets was in the range 5-12 min and all the tablets exhibited a floating time more than 24 h (Table-1). As such the tablets formulated employing olibanum gum and HPMC exhibited good floating characteristics.

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

Formulation	Matrix composition	Diltiazem content (mg/tablet)	Hardness (kg/cm^2)	Friability (loss %)	Floating lag time (min)	Floating time (h)
F1	OG (25 %) Bicarb (10 %) BW (10 %)	89.6	8.0	0.4	12	24
F2	OG (25 %) Bicarb (20 %) BW (10 %)	89.8	7.5	0.6	10	35
F3	OG (50 %) Bicarb (10 %) BW (10 %)	90.2	8.5	0.2	5	40
F4	OG (50 %) Bicarb (20 %) BW (10 %)	90.5	7.0	0.1	5	48
F5	HPMC (25 %) Bicarb (10 %) BW (10 %)	90.1	8.0	0.2	8	48
F6	HPMC (25 %) Bicarb (20 %) BW (10 %)	89.8	8.5	0.1	5	48
F7	HPMC (50 %) Bicarb (10 %) BW (10 %)	88.6	9.0	0.2	10	48
F8	HPMC (50 %) Bicarb (20 %) BW (10 %)	91.2	7.0	0.3	9	48

OG: Olibanum gum, Bicarb: Sodium bicarbonate, BW: Bees wax.

Diltiazem release parameters of the floating tablets formulated are summarized in Table-2. Drug release from the prepared tablets was slow and spread over more than 24 h and depended on the polymer used and its strength and the concentration of sodium bicarbonate in the tablets. Diltiazem release followed first order kinetics. First order release rate constants (K_1) are given in Table-2. When the release data was analyzed as per Peppas equation, the release exponent 'n' was found to be in the range 0.296-0.462 indicating 'Fickian diffusion' as the release mechanism from all the floating tablets prepared.

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

Formulation	T_{50} (h)	T_{90} (h)	K_1 (h^{-1})	'n' in Peppas equation
F1	1.38	10.2	0.235	0.345
F2	1.15	4.2	0.540	0.384
F3	3.50	17.6	0.135	0.462
F4	2.25	14.4	0.165	0.372
F5	4.20	13.6	0.155	0.428
F6	3.20	12.5	0.195	0.430
F7	13.50	> 24.0	0.018	0.296
F8	12.00	> 24.0	0.032	0.345

With both olibanum gum and HPMC, as the polymer concentration was increased from 25-50 %, the release rate (K_1) was decreased. When the sodium bicarbonate concentration was increased, the floating time was increased and the release rate was decreased. Overall floating tablets formulated with HPMC gave slow and incomplete drug release when compared to those formulated employing olibanum gum. Tablets formulated employing olibanum gum gave slowand complete release of diltiazem over 24 h. Floating tablets (F_3) formulated employing olibanum gum (50 %), bees wax (10 %) and sodium bicarbonate (10 %) were found to be the best floating formulation developed based on *in vitro* buoyancy and drug release characteristics and these tablets were found suitable for 24 h *i.e.*, once-a-day administration.

Conclusion

Olibanum gum is an efficient matrix former for floating tablets based on gas generation principle. Floating tablets, formulated employing olibanum gum as matrix material and sodium bicarbonate as gas generating agent, gave slow and controlled release of diltiazem over 24 h apart from exhibiting good floating characteristics. Olibanum gum exhibited better controlled release characteristics and was found to be a better matrix former than HPMC, K15M for floating tablets. Since olibanum gum is of natural origin, it is non-toxic, biocompatible and cheaper.

REFERENCES

1. G.A. Agyilirah, M. Green and R. Ducret, *Int. J. Pharm*., **75**, 241 (1991).
2. A.F. Hoffman, J.H. Pressman and C.F. Code, *Drug Dev. Ind. Pharm*., **9**, 1077 (1983).
3. G. Santus, G. Lazzarini and G. Bottoni, *Eur. J. Pharm. Biopharm*., **44**, 39 (1997).
4. A.A. Deshpande, C.T. Rhodes, N.H. Shah and A.W. Malick, *Drug Dev. Ind. Pharm*., **22**, 531 (1996).
5. A.A. Deshpande, N.H. Shah, C.T. Rhodes and W. Malick, *Pharm. Res*., **14**, 815 (1997).
6. A. Menon, W.A. Ritschel and A. Sakr, *J. Pharm. Sci*., **83**, 239 (1994).
7. L. Whitehead, J.T. Fell, J.H. Collett, H.L. Sharma and A.M. Smith, *J. Control. Rel.*, **55**, 3 (1998).
8. B. Singh and K. Kim, *J. Control. Rel*., **63**, 235 (2000).
9. G. Chawla and A. Bansal, *Pharm. Tech*., **27**, 50 (2003).
10. T. Higuichi, *J. Pharm. Sci*., **52**, 1145 (1963).
11. R.W. Korsmeyer, R. Gurny, E. Doelkar, P. Buri and N.A. Peppas, *Int. J. Pharm*., **15**, 25 (1983).
12. S.K. Nigam and C.R. Mitra, *Indian Drugs*, **16**, 80 (1979).
13. R.S. Srinivas and B. Madhu, *Ind. J. Chem*., 176 (1976).
14. K.P.R. Chowdary, P. Mohapatra and M.N. Murali Krishna, *Indian. J. Pharm. Sci*., **68**, 497 (2006).
15. E. Kinney, R.M. Moskovitz and R.F. Zelis, *J. Clin. Pharmacol*., **21**, 337 (1981).

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