ORIGINAL RESEARCH PAPER

Volume-7 | Issue-9 | September-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

FORMULATION OF LORNOXICAM FLOATING TABLETS EMPLOYING OLIBANUM GUM AND HPMC K 15 M

Pharmaceutical

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ABSTRACT

The objective of the study is to formulate and evaluate floating tablets of lornoxicam employing olibanum gum, a natural gum resin in comparison to HPMC K15 M, a synthetic cellulose derivative. Floating tablets of Lornoxicam were prepared employing olibanum gum and HPMC K15 M as matrix formers, sodium bicarbonate as gas generating agent and bees wax and ethyl cellulose as floating enhancers and the tablets were evaluated for *In vitro* buoyancy and drug release characteristics.

The floating characteristics of the formulations which contained sodium bicarbonate (15%) alone were not satisfactory with both the two polymers and need to be improved. Increasing the strength of sodium bicarbonate from 15% to 20% has not much improved the floating characteristics. Addition of beeswax (15%) and ethyl cellulose (5%) has significantly enhanced the buoyancy of the tablets formulated with both the two polymers. Lornoxicam release from the floating tablets prepared was slow and spread over 12 h and depended on the polymer used and composition of the tablets.

Drug release was diffusion controlled and followed zero order kinetics. Non-Fickian diffusion was the drug release mechanism from all the tablets formulated. Lornoxicam release from the tablets containing beeswax and ethyl cellulose along with the matrix forming polymers was slow and spread over more than 12 h. The T90 values were in the range 9 h to over 12 h with these tablets. These tablets exhibited a floating time of 33 h after a floating lag time in the range 2-9 min. Olibanum is found suitable as matrix former for floating tablets and is comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release. Since olibanum gum is of natural origin it is non-toxic biocompatible and cheaper.

KEYWORDS

Floating tablets, Olibanum gum, HPMC K15 M, Lornoxicam, Sustained Release

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 gastric 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 sustained release drug delivery systems is to prolong the residence time of the dosage form in the stomach or upper gastro intestinal 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 sustained release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer. Several polymers such as various viscosity grades of HPMC, Carbopol 934P, Eudragit RL, calcium alginate, chitosan, xanthan gum, guargum, ethyl cellulose etc., have been used [10] in the design of floating tablets of various APIs.

Lornoxicam is an non-steroidal anti-inflammatory drug, which is selective cyclooxygenase-1 and 2 (COX 1 and 2) inhibitors. Used in the treatment of Osteoarthritis, acute pain rheumatoid arthritis, post operative dental pain and primary dysmenorrhoea [11]. Dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Lornoxicam has a short biological half-life of 3-4 hours and is eliminated rapidly [12]. Therefore sustained release floating tablet formulations are needed for lornoxicam to prolong its duration of action and to increase its oral bioavailability and to improve patient compliance. In the present study olibanum gum, a natural gum-resin was evaluated as matrix former in the design of floating tablets of lornoxicam. Floating tablets of lornoxicam were designed employing olibanum gum and hydroxyl propyl methyl cellulose, HPMC K15 M (for comparison) as matrix formers, sodium bicarbonate as gas generating agent, bees wax and ethyl cellulose as floating enhancers and the tablets were evaluated for floating and drug release characteristics.

EXPERIMENTAL

MATERIALS

Lornoxicam was a gift sample from M/s. Glenmark limited, PVP K 30 and HPMC K15M was gift samples from M/s Natco Pharma Pvt. Ltd., Hyderabad, Olibanum gum (Procured from Girijan Cooperative Corporation, Govt. of AP, Visakhapatnam.), Lactose (Qualigens), Sodium Bicarbonate (Loba Chemie), Talc I.P. (Loba Chemie), Magnesium stearate I.P. (Loba Chemie) were procured from commercial sources.

Preparation of floating tablets

Matrix tablets each containing 12 mg of lornoxicam were formulated employing (i) olibanum gum and (ii) HPMC K15M each at 50 % concentration in the formula. Sodium bicarbonate was used as gas generating agent at 15 % and 20 % strength in each case. Bees wax and ethyl cellulose were used as floating enhancers at 15 % and 5% concentration respectively in some of the formulations.

The required quantities of lornoxicam, olibanum gum (sieve # 120), PVP K 30, HPMC K15 M, 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°C 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 polythene bag. The tablet granules were compressed into tablets on a 16 station rotary multi-station tablet punching machine (M/s Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8-10 kg/sq.cm using 9 mm round and flat punches.

EVALUATION OF TABLETS

Hardness of the tablets was tested using 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 lornoxicam

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 380 nm in 0.1Nhydrochloric acid was used for the estimation of lornoxicam. 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 0.80 and 1.10 %, 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 (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at temperature 37 ± 0.5^{0}C. Hydrochloric acid, 0.1 N (900 ml) was used as dissolution fluid. A 5 ml sample of dissolution fluid was withdrawn at different time intervals through a filter (0.45 µm) over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. The samples withdrawn were assayed spectrophotometrically by measuring the absorbance at 380 nm. All drug release experiments were conducted in triplicate.

Data analysis

Drug release data were analyzed as per zero order, first order, Higuchi [13] and Peppas equation [14] models to assess drug release kinetics and mechanism from the tablets.

RESULTS AND DISCUSSION

Floating tablets of lornoxicam were formulated employing (i) Olibanum gum and (ii) HPMC K15M as rate controlling matrix formers and sodium bicarbonate (15 %) as gas generating agent with an objective of developing floating tablets of Lornoxicam and to make a comparative evaluation of the two matrix formers for floating tablets. The matrix formers were used at strength of 50 % in the matrix tablets. Olibanum is a gum resin obtained from *Boswellia serrata* Roxburg and other species of boswellia. Olibanum consist [15] of mainly an acid resin (50-60 %), gum (30-36 %) and volatile oil (3-8 %), the resin contain [16] mainly a resin acid (boswellic acid) and a resin (olibanoresene) in equal proportion. The olibanum gum and the resin extracted from olibanum exhibited [17] excellent release retarding properties in matrix tablets for controlled release. Floating tablets of lornoxicam were designed in the present study to enhance its oral bioavailability and to achieve sustained release over 12 h for twice-a-day administration.

The matrix tablets were prepared by wet granulation method employing water - alcohol (1:1) as granulating fluid as per the formulae given in Table 1. A total of 12 floating tablet formulations of lornoxicam were prepared employing sodium bicarbonate as gas generating agent at 15 % and 20 % strength in the tablets; beeswax (15 %) and ethyl cellulose (5 %) as floating enhancers. All the matrix tablets prepared were evaluated for hardness, friability, floating characteristics, disintegration and drug release characteristics.

TABLE - 1: COMPOSITION OF FLOATING TABLETS FORMULATED EMPLOYINGOLIBANUM GUM HPMC

Ingredient (mg/tablet)	Formulation											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lornoxicam	12	12	12	12	12	12	12	12	12	12	12	12
PVP K 30	12	12	12	12	12	12	12	12	12	12	12	12
Lactose	53.5	53.5	26	26	11	11	41	41	14	14	6	6
Olibanum	125	--	150	--	150	--	125	--	160	--	200	--
HPMCK15M	--	125	--	150	--	150	--	125	--	160	--	200
Sod.bicarb	37.5	37.5	45	45	45	45	50	50	64	64	80	80
Bees wax	--	--	45	45	45	45	--	--	48	48	60	60
Ethylcellulose	--	--	--	--	15	15	--	--	--	--	20	20
Mg.st.	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Weight of the tablet	250	250	300	300	300	300	250	250	320	320	400	400

***Note: PVP: Poly vinyl pyrolidine, HPMC: Hydroxy propyl methyl cellulose, Sod. Bicarb: Sodium bicarbonate, Mg. St: Magnesium stearate.**

Drug content, hardness, friability and disintegration time and floating characteristics of various tablet formulations are given in Table 2. Hardness of the matrix tablets was in the range 6.5 – 8.0 kg/sq.cm. Weight loss in the friability test was less than 0.75 % in all the cases. All the tablets prepared contained lornoxicam within 100 ± 5 % of the labeled claim. All the matrix tablets prepared were found to be non-disintegrating in water and aqueous fluids of acidic pH (1.2) and alkaline pH (7.4). As such all the matrix tablets prepared employing olibanum gum and HPMC K15M was of good quality with regard to drug content, hardness and friability. Floating characteristics of various matrix tablets formulated are given in Table 2. Tablets formulated with sodium bicarbonate (15 %) alone exhibited floating time in the range 5-8 h with both the two polymers. Floating lag time was relatively longer, 27.33±4.2 min with olibanum and HPMC K15 M tablets exhibited a short floating lag time in the range 7-15 min. The floating characteristics of the formulations F1 and F2 which contain sodium bicarbonate (15 %) were not satisfactory with both the two polymers and need to be improved. Beeswax and ethyl cellulose, which are lipophilic materials having density less than one, are tried to decrease the hydrophilic property of the formulation to increase the buoyancy. Beeswax (15%) was incorporated in formulations F3 and F4 retaining sodium bicarbonate (15 %) in these formulations. Floating time was in the range 18-21 h and floating lag time was in the range 9-12 min. HPMC K15 M exhibited better floating characteristics than the olibanum.

TABLE 2: PHYSICAL PROPERTIES OF FLOATING TABLETS FORMULATED EMPLOYING OLIBANUM GUM AND HPMC

Formulation	Lornoxicam content (mg/tablet)	Hardness (kg/cm^2)	Friability(% weight loss)	Floating lag time (min)	Floating time (h)
F1	12.6	8.0	0.65	27.33±4.2	8±1.63
F2	12.5	6.5	0.70	15.0±2.4	6±0.88
F3	12.4	7.0	0.25	11.6±0.4	19.6±1.24
F4	11.9	7.5	0.45	10.66±0.9	22.3±2.05
F5	11.4	8.0	0.75	8±2.38	36±0.0
F6	11.2	6.5	0.35	7.0±2.16	32.6±2.49
F7	12.5	8.0	0.50	8.66±1.88	6.3±1.24
F8	11.2	6.5	0.55	9.33±0.9	11.3±4.98
F9	11.3	7.0	0.34	8±1.6	27.33±2..49
F10	12.2	7.5	0.44	9.66±1.69	26.6±2.49
F11	12.6	7.5	0.66	9.33±2.49	30.6±3.39
F12	11.8	8.0	0.52	11.33±3.39	33.3±4.89

Formulations F5 and F6 contain ethyl cellulose (5%) in addition to beeswax (15%). These formulations exhibited excellent floating characteristics. Floating time was in the range 32-36 h and floating lag time was 5-8 min with HPMC and 6-8 min with olibanum. Thus the floating characteristics of matrix tablets formulated with olibanum (F5) are comparable with those of tablets formulated with HPMC

K15M (F6) when floating enhancers (beeswax and ethyl cellulose) are included in the tablet formulations. The sodium bicarbonate strength in the matrix tablets was increased to 20% in formulations F7 to F12 to evaluate the effect of strength of sodium bicarbonate on the floating and drug release characteristics of the floating tablets formulated employing olibanum and HPMC K15 M. In the case of formulations which contained olibanum and HPMC as matrix formers and sodium bicarbonate (20 %), beeswax (15 %) and ethyl cellulose (5 %), the floating time was increased to 27-33 h with a floating lag time in the range 8-12 min. Overall, increasing the strength of sodium bicarbonate from 15 % to 20% has not much improved the floating characteristics. Addition of beeswax (15 %) and ethyl cellulose (5 %) has significantly enhanced the buoyancy of the tablets formulated with both the two polymers.

Lornoxicam release from the floating tablets was studied in 0.1N hydrochloric acid. Lornoxicam release from all the floating tablets prepared was slow and spread over 12 h and depended on the polymer used and composition of the tablets. Release data were analyzed by zero order, first order, Higuchi [13] and Peppas equation [14] models. When the release data were analyzed as per zero and first order models, the 'r' values were relatively higher in zero order models with all the floating tablets formulated indicating that the drug release from all these tablets followed zero order kinetics. Lornoxicam release data also obeyed Higuchi [13] and Peppas equation [14] models with 'r' values greater than 0.900. When percent release was plotted against √time, linear regressions with 'r' > 0.910 were observed with all the floating tablets prepared indicating that the drug release from all these tablets was diffusion controlled. When the release data were analyzed as per Peppas equation [14], the release exponent 'n' was found in the range 0.568 to 0.682 indicating Non-Fickian (anamalous) diffusion as the release mechanism from all the floating tablets prepared with various polymers.

TABLE 3: RELEASE CHARACTERISTICS OF FLOATING TABLETS FORMULATED EMPLOYING OLIBANUM GUM AND HPMC K15 M

Formulation	T_{50} (h)	T_{90} (h)	K1 $^{(hr\ -1)}$	'n' in Peppas equation
F1	4.5	9	0.162	0.682
F2	5	11	0.125	0.625
F3	4.8	>12	0.114	0.549
F4	6	>12	0.108	0.675
F5	6	>12	0.102	0.621
F6	6.5	>12	0.121	0.582
F7	2.8	7.8	0.250	0.568
F8	3.2	7.7	0.210	0.682
F9	3.9	9.9	0.210	0.625
F10	4.5	10.5	0.197	0.645
F11	8.8	>12	0.195	0.57
F12	9.7	>12	0.965	0.186

Comparison of release parameters of floating tablets prepared with the two polymers alone indicated that the drug release was relatively rapid with olibanum and slows with HPMC. T90 (time for 90 % release) was 9 and 11 respectively with floating tablets prepared employing olibanum and HPMC alone. As such these tablets are considered not suitable for controlled release over 12 h. When the strength of sodium bicarbonate was increased from 15 % to 20 %, drug release rate was increased with both the two polymers. When beeswax (15 %) was included in the tablets the drug release rate was decreased when compared to the corresponding tablet formulations containing the matrix forming polymers alone. The T90 values were more than 12 h in the case of tablets prepared incorporating beeswax (15 %) along with the polymers. These tablets also failed to provide controlled drug release over 12 h. The release rate was much reduced when beeswax and ethyl cellulose were incorporated into the floating tablets as floating enhancers. Lornoxicam release from the tablets containing beeswax and ethyl cellulose along with the matrix forming polymers was slow and spread over more than 24 h. The T90 values were over 12 h with these tablets. These tablets also exhibited good floating characteristics apart from controlled release over 12 h. The order of release retarding efficiency of olibanum and HPMC K15M was good and comparable.

CONCLUSIONS

Olibanum is suitable as matrix former for floating tablets and is comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release. Floating tablets formulated employing olibanum and HPMC K15 M as matrix formers and sodium bicarbonate as gas generating agent, beeswax and ethyl cellulose as floating enhancers exhibited a floating time of more than 9-12 hours after a floating lag time in the range 2 – 9 min. Lornoxicam release from the floating tablets prepared was slow and spread over 12 h and depended on the polymer used and composition of the tablets. Drug release was diffusion controlled and followed zero order kinetics. Non-Fickian diffusion was the drug release mechanism from all the tablets formulated. Olibanum is found suitable as matrix former for floating tablets and is comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release. Since olibanum gum is of natural origin it is non-toxic biocompatible and cheaper.

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