International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2014; 4(1):94-99

Research Article

DESIGN AND EVALUATION OF FLOATING TABLETS OF PIOGLITAZONE EMPLOYING SELECTED NATURAL AND SYNTHETIC POLYMERS

K.P.R.Chowdary and D. Udaya Chandra*
Vishwa Bharathi College of Pharmaceutical Sciences, Guntur-09, A.P, India.

*Corresponding Author: D. Udaya Chandra; Email: udayachandradoppalapudi@yahoo.com

Abstract: Floating tablets of pioglitazone were formulated employing (i) olibanum (a natural gum resin) (ii) PGS-Cellulose co-processed polymer (a new modified starch) and (iii) HPMCK15M (a synthetic polymer) with an objective of evaluating them as matrix formers in the design of floating tablets of pioglitazone. Floating tablets of pioglitazone were designed employing the above mentioned three polymers as matrix formers, sodium bicarbonate as gas generating agent and bees wax and ethyl cellulose as floating enhancers and the tablets were evaluated for floating and drug release characteristics. Floating tablets formulated employing (i) olibanum (a natural gum resin), (ii) PGS-Cellulose co-processed polymer (a new modified starch) and (iii) HPMCK15M (a synthetic polymer) as matrix formers and sodium bicarbonate as gas generating agent, beeswax and ethyl cellulose as floating enhancers (PF7, PF8, PF9) exhibited a floating time of more than 22 hours after a floating lag time in the range 1– 4 min. These floating tablets also provided slow and complete release of pioglitazone over 12 hours. Release was diffusion controlled and followed zero order kinetics. Non – Fickian diffusion was the release mechanism from all the floating tablets formulated. As such these tablets (PF7, PF8, PF9) are considered as good floating tablets for controlled release of pioglitazone. Olibanum and PGS-Cellulose co-processed polymer are suitable as matrix formers for floating tablets and are comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release.
Key words: Floating tablets, Pioglitazone, Olibanum, PGS-Cellulose, HPMCK15M

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 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 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 three polymers namely (i) olibanum (a natural gum resin) (ii) PGS-Cellulose co-processed polymer (a new modified starch) and (iii) HPMCK15M (a synthetic polymer) were evaluated as matrix formers in the design of floating tablets of pioglitazone. Floating tablets of pioglitazone were designed employing the above mentioned three polymers as matrix formers, sodium bicarbonate as gas generating agent and bees wax and ethyl cellulose as floating enhancers and the tablets were evaluated for floating and drug release characteristics. Pioglitazone is an effective oral anti diabetic agent that belongs to the thiazolidonediones drug class. Pioglitazone belongs to BCS class II and exhibits low and variable oral bioavailability. It majorly absorbs from stomach[10]. Pioglitazone has a short biological half life of 3-5 hours and is eliminated rapidly[11]. Hence controlled release floating formulations are needed for pioglitazone to improve its oral bioavailability and also to prolong its duration of action and to improve patient compliance.

EXPERIMENTAL

Materials: Pioglitazone was a gift sample from M/s Dr. Reddys Labs Ltd., Hyderabad. PGS-Cellulose co-processed polymer (prepared in the laboratory), Olibanum (procured from Girijan Cooperative Corporation, Govt. of AP, Visakhapatnam), Hydroxy propyl methyl cellulose (K15M, Colorcon) Bees wax, I.P and ethyl cellulose were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods:

Preparation of Pregelatinized Starch – Cellulose: (A New Co-Processed Polymer):

Potato starch 5 parts and cellulose 5 parts were dispersed in 30 ml of water to form slurry. 35 ml of water was boiled in a 150 ml beaker on a water bath. The prepared slurry was added to the boiling water on water bath and mixed thoroughly. The mixing was continued for about 25-30 min until gelatinization was occurring. The formed gelatinized mass was transferred on to watch glass and dried

completely at 85-90^0 c for 2h. The dries product was powdered and passed through mesh no 120.

Preparation of floating tablets: Matrix tablets each containing 30 mg of pioglitazone were formulated employing (i) olibanum (a natural gum resin) (ii) PGS-Cellulose co-processed polymer (a new modified starch) and (iii) HPMCK15M (a synthetic polymer) as per the formulae given in Table 1. Sodium bicarbonate was used as gas generating agent at 15% strength in each case. Bees wax (15%) and ethyl cellulose (5%) were used as floating enhancers in all the formulations.

The required quantities of pioglitazone, olibanum, PGS-Cellulose co-processed polymer, HPMC K15M, bees wax, ethyl cellulose and lactose as per the formulae 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 dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60^0 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 polyethylene bag. The tablet granules were compressed into tablets on a 16- station tablet punching machine (M/s Cadmach Machineries Pvt. Ltd., Ahmedabad) to a hardness of 8 – 10 kg/sq.cm.

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 thermionic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the test fluids.

Estimation of pioglitazone: An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 269 nm in 0.1N hydrochloric acid was used for the estimation of pioglitazone. The method obeyed Beer-Lambert's law in the concentration range of 5-25 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 0.41% and 1.2% 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^o ± 1^{0}C. 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 269 nm. All drug release experiments were conducted in triplicate (n=3).

Data analysis: Drug release data were analyzed as per zero order, first order, Higuichi[12] and peppas[13] equation models to assess drug release kinetics and mechanism from the tablets.

RESULTS AND DISCUSSION

Floating tablets of pioglitazone were prepared employing (i) olibanum (a natural gum resin) (ii) PGS-Cellulose co-processed polymer (a new modified starch) and (iii) HPMCK15M (a synthetic polymer) with an objective of evaluating them as matrix formers in the design of floating tablets of pioglitazone. Floating tablets of pioglitazone were designed employing the above mentioned three polymers as matrix formers, sodium bicarbonate as gas generating agent and bees wax and ethyl cellulose as floating enhancers and the tablets were evaluated for floating and drug release characteristics. Floating tablets of pioglitazone were designed in the present study to enhance its oral bioavailability and to achieve controlled release over 12 h for twice-a- day administration.

Olibanum is a natural gum resin obtained from *Boswellia serrata*, Roxburgh and other species of Boswellia. Olibanum consists[14] chiefly an acid resin (50-60%), gum (30-36%) and volatile oil (3-8%). The resin contains[15] mainly a resin acid (boswellic acid) and a resene (olibanoresene) in equal proportions. Chowdary, et al.[16-23] reported first time olibanum gum and resin as efficient matrix formers and microencapsulating agents for controlled release.

Modified starches are promising and having good potential as release retardants and rate controlling polymers for controlled release. PGS-Cellulose co-processed polymer is a modified starch prepared by gelatinization of starch in the presence of cellulose. The co-processed polymers generally swell in water and aqueous fluids to form gelatinized matrices suitable for controlled release. PGS-Cellulose co-processed polymer is a new efficient rate controlling matrix former for controlled release.

The matrix formers were used at strength of 50% in the matrix tablets. The matrix tablets were prepared by wet granulation method employing water - alcohol (1:1) as granulating fluid. A total of 9 floating tablet formulations of pioglitazone were prepared employing sodium bicarbonate as gas generating agent at 15% strength in the tablets, beeswax (15%) and ethyl cellulose (5%) as floating enhancers. The formulae of these matrix tablets are given in Table 1. All the matrix tablets prepared were evaluated for hardness, friability, floating characteristics, disintegration and drug release characteristics.

Drug content, hardness, friability and disintegration time of various tablet formulations are given in Table 2. Hardness of the matrix tablets was in the range 7.5-8.5 kg/sq.cm. Weight loss in the friability test was less than 0.45% in all the cases. All the tablets prepared contained

pioglitazone 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 HPMC K15M, olibanum and PGS-Cellulose co-processed polymer were 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 7.5-9 h with all the three polymers. Floating lag time was relatively longer, 17.5±0.48 min with olibanum and 11.2±1.43 min with PGS-Cellulose co-processed polymer and HPMC K15M tablets exhibited a short floating lag time in the range 7-9 min. The floating characteristics of the formulations PF1, PF2 and PF3 which contain sodium bicarbonate (15%) were not satisfactory with all the three polymers and need to be improved. Beeswax and ethyl cellulose, which are lipophillic 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 PF4, PF5 and PF6 retaining sodium bicarbonate (15%) in these formulations. Floating time was in the range 11-20 h and floating lag time was in the range 5-12 min. Among the three polymers, HPMC K15M exhibited better floating characteristics than the other two. Based on the floating characteristics, the order of performance of various polymers tested was HPMC K15M > PGS-Cellulose co-processed polymer > Olibanum.

Formulations PF7, PF8 andPF9 contain ethyl cellulose (5%) in addition to beeswax (15%). These formulations exhibited excellent floating characteristics. Floating time was in the range 21-26 h and floating lag time 1-2 min with HPMC; 2-3 min with PGS-Cellulose co-processed polymer and 3-4.5 min with olibanum. Thus the floating characteristics of matrix tablets formulated with olibanum (PF7) and PGS-Cellulose co-processed polymer (PF8) are comparable with those of tablets formulated with HPMC K15M (PF9) when floating enhancers (beeswax, ethyl cellulose) are included in the tablet formulations.

Pioglitazone release from the floating tablets was studied in 0.1 N hydrochloric acid. The release characteristics are shown in Tables 3. Pioglitazone 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[12] and Peppas[13] equation models. The coefficient of determination (R^2) values in various models are given in Table 4. When the release data were analyzed as per zero and first order models, the 'R^2' values were relatively higher in zero order model with all the floating tablets formulated indicating that the drug release from all these tablets followed zero order kinetics. Pioglitazone release data also obeyed Higuchi[12] and Peppas[13] equation models with 'R^2' values greater than 0.919. When percent release was plotted against √time, linear regressions with 'R^2' > 0.919 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[13] equation, the release exponent 'n' (Table.4) was found in the range 0.630 to 0.878 indicating non-fickian (anomalous) diffusion as the release mechanism from all the floating tablets prepared with various polymers.

Pioglitazone release from the floating tablets prepared with the three polymers alone (i.e. PF1, PF2, PF3) was relatively rapid. T_{90} (time for 90% release) was 6.25, 6.55 and 6.8 respectively with floating tablets prepared employing olibanum, PGS-Cellulose co-processed polymer and HPMCK15M alone. As such these tablets (i.e. PF1, PF2, and PF3) are considered not suitable for controlled release over 12 h. When beeswax (15%) was included in the tablets (PF4, PF5, PF6), the drug release rate was decreased when compared to the corresponding tablet formulations containing the matrix forming polymers alone. The T_{90} values were in the range 7.6 – 8.7 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. Pioglitazone release from the tablets containing beeswax and ethyl cellulose along with the matrix forming polymers (PF7, PF8, PF9) was slow and spread over more than 12 h. The T_{90} values were in the range 10.5– 12 h with these tablets. These tablets also exhibited good floating characteristics apart from controlled release over 12h. Based on the release characteristics of tablets PF7, PF8 and PF9, which contain sodium bicarbonate (15%), beeswax (15%), ethyl cellulose (5%), the order of release retarding efficiency of various polymers was HPMCK15M> PGS-Cellulose co-processed polymer > olibanum (based on K_0). The results, thus, indicated that both olibanum and PGS-Cellulose co-processed polymer are suitable as matrix formers for floating tablets and are comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release.

CONCLUSIONS

Floating tablets formulated employing (i) olibanum (a natural gum resin) (ii) PGS-Cellulose co-processed polymer (a new modified starch) and (iii) HPMCK15M (a synthetic polymer) as matrix formers and sodium bicarbonate as gas generating agent, beeswax and ethyl cellulose as floating enhancers (PF7, PF8, PF9) exhibited a floating time of more than 22 hours after a floating lag time in the range 1–4 min. These floating tablets also provided slow and complete release of pioglitazone over 12 hours. Release was diffusion controlled and followed zero order kinetics. Non – Fickian diffusion was the release mechanism from all the floating tablets formulated. As such these tablets (PF7, PF8, PF9) are considered as good floating tablets for controlled release of pioglitazone. Olibanum and PGS-Cellulose co-processed polymer are suitable as matrix formers for floating tablets and are comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release.

Table 1: Formulae of Floating Matrix Tablets of Pioglitazone Prepared Employing Various Polymers

Ingredient (mg/tablet)	Formulation								
	PF1	**PF2**	**PF3**	**PF4**	**PF5**	**PF6**	**PF7**	**PF8**	**PF9**
Pioglitazone	30	30	30	30	30	30	30	30	30
Lactose	47.5	47.5	47.5	20	20	20	5	5	5
Olibanum	125	--	--	150	--	--	150	--	--
PGS-Cellulose co-processed polymer	--	125	--	--	150	--	--	150	--
HPMC K15M	--	--	125	--	--	150	--	--	150
Sodium Bicarbonate (15%)	37.5	37.5	37.5	45	45	45	45	45	45
Beeswax (15%)	--	--	--	45	45	45	45	45	45
Ethyl Cellulose (5%)	--	--	--	--	--	--	15	15	15
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Weight of the Tablet (mg)	250	250	250	300	300	300	300	300	300

Table 2: Drug Content, Hardness, Friability and Floating Characteristics of the Pioglitazone Floating Tablets Prepared Employing Various Polymers

Formulation	Hardness (Kg/sq.cm)	Friability (%)	Pioglitazone Content (mg/tab)	Floating Lag Time (min) x ± s. d	Floating Time (h) x ± s. d
PF1	7.5	0.25	29.5	17.5±0.48	7.5±0.64
PF2	8.5	0.20	29.4	11.2±1.43	8.4±0.72
PF3	8.5	0.30	29.5	8.5±0.62	8.9±2.47
PF4	8.0	0.45	29.8	11.5±1.07	11.5±0.64
PF5	8.0	0.35	29.7	8.5±0.78	17.6±0.43
PF6	7.5	0.20	28.9	4.9±1.42	20.1±1.71
PF7	8.5	0.45	28.5	2.6±1.76	21±0.74
PF8	7.5	0.35	30.5	2.2±1.04	24.82±1.3
PF9	8.0	0.25	29.2	1.4±0.84	26.4±1.38

Table 3: Release Characteristics of Floating Matrix Tablets of Pioglitazone Formulated Employing Various Polymers

Formulation	T_{50}(h)	T_{90}(h)	K_0 (mg/h)	K_1 hr^{-1}	'n' in Peppas Equation
PF1	2.9	6.25	3.74	0.338	0.630
PF2	3.2	6.55	3.65	0.349	0.715
PF3	3.7	6.8	3.72	0.305	0.818
PF4	3.6	7.6	3.09	0.368	0.683
PF5	4.6	8.4	2.95	0.271	0.780
PF6	5.1	8.7	2.89	0.231	0.819
PF7	5.1	10.4	2.41	0.255	0.766
PF8	5.7	>12	2.17	0.166	0.850
PF9	6.6	>12	2.08	0.148	0.878

Table 4: Coefficient of Determination (R^2) Values in the Analysis of Release Data as per Zero Order, First Order, Higuchi and Peppas Equation Models

Formulation	Coefficient of Determination (R^2)			
	Zero order model	First order model	Higuchi model	Peppas equation
PF1	0.979	0.877	0.963	0.978
PF2	0.988	0.853	0.959	0.990
PF3	0.993	0.852	0.925	0.981
PF4	0.987	0.763	0.968	0.991
PF5	0.995	0.850	0.944	0.989
PF6	0.990	0.834	0.919	0.983
PF7	0.994	0.856	0.960	0.993
PF8	0.992	0.955	0.966	0.998
PF9	0.997	0.920	0.947	0.998

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