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FORMULATION OF PIOGLITAZONE FLOATING TABLETS: A COMPARATIVE EVALUATION OF OLIBANUM, STARCH ACETATE AND HPMC K15M

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ABSTRACT

Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems, floating systems and other delayed gastric emptying devices. 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 former. Though several polymers are available for floating tablets, there is a continued need to develop new, effective and efficient polymers for controlled release floating tablets. The objective of the present study is to evaluate (i) olibanum (a natural gum resin), (ii) Starch acetate (a modified starch) as matrix former in the design of controlled release floating tablets of pioglitazone in comparison to a widely studied polymer, HPMC KI5M.

Floating tablets of pioglitazone were prepared employing (i) Olibanum (ii) starch acetate and (iii) HPMC K15M as rate controlling matrix formers at 50% strength, sodium bicarbonate (20%) as gas generating agent, bees wax (15%) and ethyl cellulose (5%) as floating enhancers and the tablets were evaluated.

All the floating tablets prepared employing olibanum, starch acetate and HPMC K15M were of good quality with regard to drug content, hardness and friability. The floating characteristics of the formulations, which contain sodium bicarbonate (20%) alone were not satisfactory with all the three polymers and need to be improved. Formulations containing sodium bicarbonate (20%), beeswax (15%) and ethyl cellulose (5%) exhibited excellent floating characteristics. Floating time was in the range 44-48 h and floating lag time was 1-3 min with HPMC; 4-7 min with starch acetate and 5-6 min with olibanum. Pioglitazone release from all the floating tablets prepared was slow and spread over 24 h and depended on the polymer used and composition of the tablets. Pioglitazone release from all floating tablets was diffusion controlled and followed zero order kinetics. Non-fickian (anomalous) diffusion was the release mechanism from all the floating tablets prepared with various polymers. Pioglitazone release from the tablets containing sodium bicarbonate, beeswax and ethyl cellulose along with the matrix forming polymers was slow and spread over 24 h. Based on the release characteristics of tablets PF7, PF8 and PF9 which contain sodium bicarbonate (20%), beeswax (15%) and ethyl cellulose (5%), the order of release retarding efficiency of various polymers was olibanum > starch acetate = HPMC (based on K_0).Floating and drug release characteristics of matrix tablets formulated with olibanum and starch acetate are comparable with those of tablets formulated with HPMC K15M.

Keywords: Floating Tablets, Pioglitazone, HPMC K15 M, Olibanum, Starch Acetate.

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 (8-12h) 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

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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 former. 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 in the design of floating tablets of various APIs. Though these polymers are available for floating tablets, there is a continued need to develop new, effective and efficient polymers for controlled release floating tablets.

The objective of the present study is to evaluate (i) olibanum (a natural gum resin), (ii) Starch acetate (a modified starch) as matrix former in the design of controlled release floating tablets of pioglitazone in comparison to a widely studied polymer, HPMC KI5M. Olibanum is a natural gum resin obtained from *Boswellia serrata,* Roxburgh and other species of Boswellia. Olibanum consists[10] chiefly an acid resin (50-60%), gum (30-36%) and volatile oil (3-8%). The resin contains[11] mainly a resin acid (boswellic acid) and a resine (olibanoresene) in equal proportions. Chowdary, et al.[12-19] reported first time olibanum gum and resin as efficient matrix formers and microencapsulating agents for controlled release. Starch acetate (SA) is a novel modified starch that is produced by acetylating raw starch. It is reported[20] to have direct compressible matrix forming properties. Starch acetate is also reported[21] to have good potential for application in coating because of its film forming properties. In a few studies[22-26] it is reported as an efficient coat material in microencapsulation and also as a matrix former for controlled release tablets.

Pioglitazone is an effective oral anti–diabetic agent that belongs to the thiazolidone diones drug class and is widely prescribed in the management of non-insulin dependent (Type II) diabetes mellitus. It is poorly soluble in aqueous fluids and is majorly absorbed from stomach[27]. Dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Pharmacological studies indicate that pioglitazone improves glycemic control while reducing circulating insulin level[28]. Pioglitazone has short biological half-life of 3-6 hours and is eliminated rapidly.[27] Therefore control release (CR) products are needed for pioglitazone to prolong its duration of action and to improve patient compliance. Controlled release formulation is needed for pioglitazone for better control of blood glucose levels to prevent hypoglycemia and to enhance their clinical efficacy and patient compliance.

EXPERIMENTAL

Materials:

Pioglitazone was a gift sample from M/s Micro labs Ltd., Pondicherry. Olibanum (Procured from Girijan Cooperative Corporation, Govt. of AP, Visakhapatnam.) Hydroxypropyl Methyl Cellulose (HPMC K 15M), Bees wax, Ethyl Cellulose (250 cps) and Sodium Bicarbonate were procured from commercial sources. Starch acetate was prepared in the laboratory as per a known method. All other materials used were of pharmacoepial grade.

Methods:

Preparation of Starch Acetate:

Potato starch (20 parts), acetic anhydride (80 parts) and sodium hydroxide 50% solution (4.4 parts) were mixed and refluxed for 5 h at 150^{o}C. The reaction mixture was added to cold water to precipitate the starch acetate formed. The product was collected by vacuum filtration, washed repeatedly with water and dried at 80^{o}C for 2 h.

Starch acetate prepared was found to be a white crystalline powder. The percent acetylation was 42.38 % and the degree of substitution was 2.72.

Preparation of Floating Tablets

Matrix tablets each containing 30mg of pioglitazone was formulated employing (i) olibanum (ii) starch acetate and (iii) HPMC K15M as per the Formula given in the Table 1. Sodium bicarbonate was used as gas generating

agent at 20% strength in each case. The required quantities of pioglitazone, olibanum, starch acetate, HPMC K15M, lactose, sodium bicarbonate, ethyl cellulose and bees wax were thoroughly mixed in a mortar by following geometric dilution technique. The granulating fluid (a mixture of water and alcohol in 1:1ratio) 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^{o}C for 2 h. The dried granules were passed through mesh No. 16 to break aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No.100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16 station rotary multi- station tablet punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8-10 kg/sq.cm. using 9 mm round and flat punches.

Estimation of Pioglitazone in Tablets

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 25 mg of Pioglitazone was taken into 100 ml conical flask and extracted with 3×10 ml quantities of methanol. The methanolic extracts were filtered and collected in a 50 ml volumetric flask. The solution was then made up to the volume with methanol. The methanolic solution was subsequently diluted suitably with 0.1 N hydrochloric acid and assayed for pioglitazone at 269 nm. Four samples of tablet powder were analyzed in each case.

Hardness

Hardness of the matrix tablets prepared was tested using a Monsanto Hardness Tester.

Friability

Friability of the matrix tablets prepared was determined in a Roche Friabilator.

Disintegration time

Disintegration times were determined in Thermonic Tablet Disintegration Test Machine using 0.1 N HCl, distilled water and phosphate buffer of Ph 7.4 as the test fluids.

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 during which the tablet remains floating was determined as floating time.

Drug release study

Drug release from floating tablets prepared was studied using 8 station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37± 0.5^{0}C. 0.1 N HCL (900 ml) was used as dissolution fluid. Samples of 5 ml of each were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 269 nm for Pioglitazone using an Elico SL 164 double beam UV-spectrophotometer. The drug release experiments were conducted in triplicate.

Data analysis:

Release data were analyzed as per zero order, first order, Higuchi[29] and Peppas[30] equation models to assess the drug release kinetics and mechanism from the matrix tablets prepared.

RESULTS AND DISCUSSION

Floating tablets of pioglitazone were formulated employing (i) Olibanum (ii starch acetate and (iii) HPMC K15M as rate controlling matrix formers and sodium bicarbonate (20%) as gas generating agent with an objective of developing floating tablets of pioglitazone and to make a comparative evaluation of the three matrix formers for floating tablets. 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 20% 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 7.0-8.5 kg/sq.cm. Weight loss in the friability test was less than 0.3% 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 starch acetate were of good quality with regard to drug content, hardness and friability.

Floating characteristics of various matrix tablets formulated are given in Table 3. Formulations PF1, PF2 and PF3 were formulated respectively with olibanum, starch acetate and HPMC K15M and sodium bicarbonate at 20% strength. The floating characteristics of these tablets were not satisfactory. When beeswax (15%) and ethyl cellulose (5%) were incorporated in the tablets the floating characteristics of the tablets were much improved. In the case of formulations PF7, PF8 and PF9, which contain respectively olibanum, starch acetate and HPMC as matrix formers and sodium bicarbonate (20%), beeswax (15%) and ethyl cellulose (5%), the floating time was increased to 46-48 h with a floating lag time in the range 2 - 5 min. As such, these formulations exhibited excellent floating characteristics. Addition of beeswax (15%) and ethyl cellulose (5%) has significantly enhanced the buoyancy of the tablets formulated with all the three polymers.

Pioglitazone release from the floating tablets was studied in 0.1 N hydrochloric acid. The drug release parameters are given in Tables 4-5. Pioglitazone release from all the floating tablets prepared was slow and spread over 24 h and depended on the polymer used and composition of the tablets. Release data were analyzed by zero order, first order, Higuchi[1] and Peppas[2] equation models. The correlation coefficient (r) values in various models are given in Table 4. 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 (PF1 to PF9) followed zero order kinetics. Pioglitazone release data also obeyed Higuchi[29] and Peppas[30] equation models with 'r' values greater than 0.913. When percent release was plotted against √time, linear regressions with 'r' > 0.943 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[2] equation, the release exponent 'n' was found in the range 0.481 to 0.955 indicating non-fickian (anamalous) diffusion as the release mechanism from all the floating tablets prepared with various polymers.

As the floating and drug release characteristics of the tablets prepared employing the polymers (olibanum, starch acetate, HPMC) alone are not satisfactory, floating enhancers (beeswax and ethylcellulose) were incorporated in the tablets with a view to prolong both floating time and drug release over longer periods of time. The release rate was much reduced when beeswax and ethylcellulose were incorporated into the floating tablets as floating enhancers. Pioglitazone release from the tablets containing beeswax and ethylcellulose along with the matrix forming polymers (PF7, PF8, PF9) was slow and spread over more than 24 h. The T_{90} values were in the range 19 – 24 h with these tablets. These tablets also exhibited good floating characteristics apart from controlled release over 24h.

Based on the order of release characteristics of tablets PF7, PF9 and PF9 which contain sodium bicarbonate (20%), beeswax (15%) and ethyl cellulose (5%), the order of release retarding efficiency of various polymers was olibanum > starch acetate = HPMC (based on K_0).

The results, thus, indicated that both olibanum and starch acetate 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. Floating tablets formulated employing these three polymers as matrix formers and sodium bicarbonate as gas generating agent, beeswax and ethyl cellulose as floating enhancers (formulations PF7, PF8, PF9) exhibited a floating time of more than 44 hours after a floating lag time in the range 2 – 6 min. These floating tablets also provided slow and complete release of pioglitazone over 24 hours. As such these tablets (PF7, PF8 and PF9) are considered as good floating tablets for controlled release of pioglitazone.

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	35	35	35	8	8	8	--	--	--
Olibanum	125	--	--	160	--	--	200	--	--
Starch acetate	--	125	--	--	160	--	--	200	--
HPMC	--	--	125	--	--	160	--	--	200
Sodium Bicarbonate (20%)	50	50	50	64	64	64	80	80	80
Beeswax (15%)	--	--	--	48	48	48	60	60	60
Ethyl Cellulose (5%)	--	--	--	--	--	--	20	20	20
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	320	320	320	400	400	4

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

Formulation	Hardness (Kg/sq.cm)	Friability (%)	Disintegration Time (min)	Pioglitazone content (mg/tab)
PF1	8.5	0.25	Non- disintegrating	28.8
PF2	7.0	0.15	Non- disintegrating	29.4
PF3	8.0	0.30	Non- disintegrating	30.3
PF4	8.5	0.15	Non- disintegrating	29.4
PF5	7.5	0.15	Non- disintegrating	29.1
PF6	8.0	0.05	Non- disintegrating	29.4
PF7	8.0	0.20	Non- disintegrating	28.8
PF8	8.0	0.25	Non- disintegrating	30.3
PF9	7.0	0.12	Non- disintegrating	29.4

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

Formulation	Floating Lag Time (min)				Floating Time (h)			
	1	2	3	$\bar{x}$ ± s.d	1	2	3	$\bar{x}$ ± s.d
PF1	Broken	Broken	Broken	-	Broken	Broken	Broken	-
PF2	12	14	10	12±2	10	10	8	9.3±1.15
PF3	8	8	7	7.6±0.57	10	10	10	10±0
PF4	5	6	5	5.3±0.57	30	28	28	28.6±1.15
PF5	5	6	7	6±1	38	38	39	38.3±0.57
PF6	3	1	3	2.3±1.15	45	48	46	46.3±1.52
PF7	6	5	5	5.3±0.57	45	46	46	45.6±0.57
PF8	6	4	5	5±1	46	48	49	47.6±1.52
PF9	4	1	2	2.3±1.52	46	48	44	46±2

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

Formulation	Correlation coefficient (r)			
	Zero order model	First order model	Higuchi model	Peppas equation
PF1	0.948	0.925	0.986	0.913
PF2	0.951	0.909	0.984	0.944
PF3	0.949	0.829	0.979	0.968
PF4	0.964	0.940	0.982	0.963
PF5	0.978	0.922	0.979	0.952
PF6	0.975	0.925	0.970	0.945
PF7	0.969	0.911	0.986	0.968
PF8	0.999	0.922	0.995	0.977
PF9	0.985	0.915	0.992	0.958

Table 5: 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	2.1	4.7	4.209	0.418	0.639
PF2	2.3	5.5	3.768	0.384	0.676
PF3	4.0	8.6	2.772	0.270	0.650
PF4	4.5	10.1	2.277	0.240	0.576
PF5	5.3	14.1	0.891	0.253	0.498
PF6	4.9	14.3	0.948	0.268	0.529
PF7	7.3	19.3	0.906	0.192	0.595
PF8	9.9	22.1	0.999	0.136	0.764
PF9	11.5	24.0	0.996	0.099	0.885

CONCLUSIONS

1. All the floating tablets prepared employing olibanum, starch acetate and HPMC K15M were of good quality with regard to drug content, hardness and friability.
2. The floating characteristics of the formulations, which contain sodium bicarbonate (20%) alone were not satisfactory with all the three polymers and need to be improved.
3. Formulations containing sodium bicarbonate (20%), beeswax (15%) and ethyl cellulose (5%) exhibited excellent floating characteristics. Floating time was in the range 44-48 h and floating lag time was 1-3 min with HPMC; 4-7 min with starch acetate and 5-6 min with olibanum.
4. Pioglitazone release from all the floating tablets prepared was slow and spread over 24 h and depended on the polymer used and composition of the tablets. Pioglitazone release from all floating tablets was diffusion controlled and followed zero order kinetics. Non-fickian (anomalous) diffusion was the release mechanism from all the floating tablets prepared with various polymers.
5. Pioglitazone release from the tablets containing sodium bicarbonate, beeswax and ethyl cellulose along with the matrix forming polymers was slow and spread over 24 h. Based on the release characteristics of tablets PF7, PF8 and PF9 which contain sodium bicarbonate (20%), beeswax (15%) and ethyl cellulose (5%),

the order of release retarding efficiency of various polymers was olibanum > starch acetate = HPMC (based on K_0).

6. Floating and drug release characteristics of matrix tablets formulated with olibanum and starch acetate are comparable with those of tablets formulated with HPMC K15M.

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