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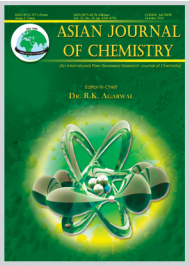

Formulation and Evaluation of Floating Tablets of Pioglitazone Employing Calcium Starch

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The objective of the study is to formulate and evaluate floating tablets of pioglitazone employing calcium starch, a new modified starch in comparison to hydroxy propyl methyl cellulose K15M, a synthetic cellulose derivative. Floating tablets of pioglitazone were prepared employing calcium starch and hydroxy propyl methyl cellulose, 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 calcium starch (50 %), sodium bicarbonate (10 %) and bees wax (10 %) exhibited floating over 36 h with a floating lag time of 5-10 min. Pioglitazone 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. Calcium starch gave slow, controlled and complete drug release in 24 h. Whereas hydroxy propyl methyl cellulose, K15M gave slow but incomplete drug release. Calcium starch was found to be a better matrix former than hydroxy propyl methyl cellulose for floating tablets.

Key Words: Floating tablets, Calcium starch, Pioglitazone.

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 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 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 calcium starch, a modified starch was evaluated as matrix former in the design of floating tablets of pioglitazone. Floating tablets of pioglitazone were designed employing calcium starch and hydroxy propyl methyl cellulose (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. 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 h 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

Pioglitazone was a gift sample from M/s Dr. Reddys Labs Ltd., Hyderabad. Calcium starch was prepared in the laboratory. Hydroxy propyl methyl cellulose (K15M, Colourcon) and Bees wax, I.P. were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Preparation of calcium starch: Potato starch (5 parts) was dispersed in purified water (50 parts) to form starch slurry. Sodium hydroxide (3 parts) was dissolved in water (30 parts) and the solution was added to starch slurry while mixing and mixing was continued for 0.5 min to form a thick gelatinized mass. The mass formed was added to 300 mL of calcium chloride (20 % w/v) solution contained in a vessel while stirring at 1000 rpm with a medium duty stirrer. The stirring was continued

TABLE-1
COMPOSITION AND PHYSICAL PROPERTIES OF FLOATING TABLETS FORMULATED EMPLOYING CALCIUM STARCH AND HPMC

Formulation	Matrix composition	Pioglitazone Content (mg/tablet)	Hardness (Kg/sq.cm)	Friability (% loss)	Floating Lag Time (min)	Floating Time (h)
F1	CS (25 %) Bicarb (10 %) BW (10 %)	59.6	8.0	0.4	12	24
F2	CS (25 %) Bicarb (20 %) BW (10 %)	59.8	7.5	0.6	10	35
F3	CS (50 %) Bicarb (10 %) BW (10 %)	60.2	8.5	0.2	5	40
F4	CS (50 %) Bicarb (20 %) BW (10 %)	60.5	7.0	0.1	5	36
F5	HPMC (25 %) Bicarb (10 %) BW (10 %)	60.1	8.0	0.2	8	36
F6	HPMC (25 %) Bicarb (20 %) BW (10 %)	59.8	8.5	0.1	5	36
F7	HPMC (50 %) Bicarb (10 %) BW (10 %)	58.6	9.0	0.2	10	36
F8	HPMC (50 %) Bicarb (20 %) BW (10 %)	61.2	7.0	0.3	9	36

CS – Calcium starch, Bicarb- Sodium bicarbonate, BW- Bees wax

for 1 h to precipitate calcium starch formed. The calcium starch formed was collected by vacuum filtration, washed repeatedly with water and dried at 80 ºC. The dried modified starch was powdered and passed through mesh no. 100.

Preparation of floating tablets: Matrix tablets each containing 60 mg of pioglitazone were formulated employing (i) calcium starch 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 pioglitazone, calcium starch, 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 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 thermonic 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 0.1 N hydrochloric acid was used for the estimation of pioglitazone. 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 1.2 % 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 ± 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 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

Matrix tablets of pioglitazone were prepared employing (i) calcium starch and (ii) HPMC, K15M as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer with an objective of evaluating calcium starch as matrix material for floating tablets. Calcium starch is a modified starch prepared by cross linking the alkali gelatinized starch with calcium chloride. Calcium starch is reported[14,15] as an efficient rate controlling matrix former for controlled release of gliclazide, diltiazem hydrochloride and diclofenac.

Floating tablets of pioglitazone were designed in the present study to enhance its oral bioavailability and to achieve controlled release over 24 h for once a day administration.

Hardness of the tablets was in the range 7.0-9.0 Kg/sq.cm. Weight loss in the friability test was less than 0.6 % in all the cases. All the tablets prepared contained pioglitazone 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 calcium starch and hydroxy propyl methyl cellulose exhibited good floating characteristics.

Pioglitazone 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. Pioglitazone 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 CALCIUM STARCH AND HYDROXY PROPYL METHYL CELLULOSE

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	13.5	> 24	0.018	0.296
F8	12.0	> 24	0.032	0.345

With both calcium starch and hydroxy propyl methyl cellulose, as the polymer concentration was increased from 25 % to 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 hydroxy propyl methyl cellulose gave slow and incomplete drug release when compared to those formulated employing calcium starch. Tablets formulated employing calcium starch gave slow and complete release of pioglitazone over 24 h. Floating tablets (F3) formulated employing calcium starch (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

Calcium starch is an efficient matrix former for floating tablets based on gas generation principle. Floating tablets, formulated employing calcium starch as matrix material and sodium bicarbonate as gas generating agent, gave slow, controlled and complete release of pioglitazone over 24 h apart from exhibiting good floating characteristics. Calcium starch exhibited better controlled release characteristics and was found to be a better matrix former than hydroxy propyl methyl cellulose, K15M for floating tablets.

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