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Original Research Article

Formulation, Development and Evaluation of Gastroretentive Floating Tablets of Saxagliptin for Effective Treatment of Type II Diabetes

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ABSTRACT

The objective of this study was to develop a floating tablet of Saxagliptin. Saxagliptin is an orally active hypoglycemic (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Nine formulations of Saxagliptin tablets are prepared by direct compression method using HPMC, lactose, talc, citric acid and sodium bicarbonate as polymers and excipients. PVP K 30 used as granulating agent. The formulations were evaluated for physical parameters like thickness, hardness, friability, uniformity of weight, drug content, buoyancy time, and drug release mechanism. The formulations were optimized on the basis of buoyancy time and *in vitro* drug release. The prepared tablets were evaluated for physicochemical parameters and found to be within range. The optimized formulation was found to be F7 which released 99.78 % of drug in 12 hrs. and follow first order kinetics.

Key words: Gastro retentive, Saxagliptin, Floating tablets, Hydroxyl propyl methyl cellulose (HPMC), PVP K30.

INTRODUCTION

Floating drug delivery system (FDDS) shows buoyancy in stomach for extended time period thus offers extended gastric residence time for the dosage form ensuring optimal bioavailability (BA) (Jimenez-Martínez *et al*., 2008). The residence time of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states (hepatic failure, diabetes,

chrons disease). Other techniques for gastro retentive dosage forms involve swelling, mucoadhesion, sedimentation, microballoons (Arora *et al*., 2011; Nagaich *et al*., 2010) and low density systems. Out of all systems available, the floating beads, floating tablets and floating microspheres have gained major importance. FDDS possess lower bulk density than the gastric fluid exerting buoyancy in the stomach leading to slow drug release in an extended manner before it reaches absorption window (Sathiyaraj *et al*., 2011). In this present formulation, dual benefits of buoyancy as well as sustained action are achieved with an intention to maintain the steady state of drug release (Negi e*t al*. 2011). Hydrophilic matrix system is one of the easiest approaches for developing modified and sustained release dosage forms. A polymer like hydroxyl propyl methyl cellulose (HPMC) function as a pH independent gelling agent and drug release is shown by swelling and erosion mechanism occurring simultaneously contributing to overall drug release (Samyuktha Rani *et al.,* 2010). Matrix system is the commonly used method for modulating the drug release (Yadav and Jain, 2010). The manufacture of matrix tablets by direct compression is cheaper, simpler process, broad regulatory acceptance, and allows flexibility in obtaining desirable release profiles (Yadav and Jain, 2011). Saxagliptin is chemically called as (1S, 3S, 5S)-2-[(2S)-2-Amino-2-(3 hydroxytricyclo[3.3.1.13, 7] dec-1-yl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile. It is theoral hypoglycemic (antidiabetic) agent, class of dipeptidyl peptidase (DPP-4) inhibitor (Deacon and Holst, 2009). Saxagliptin was inhibiting the activity of dipeptidyl peptidase-4(DPP-4) enzyme by increasing the insulin production in response to meal and decreasing the gluconeogensis rate in the liver, in blood glucose regulation is thought to be through degradation of GIP (Mentlein *et al.,* 1993) and the degradation of GLP-1 (Ahren *et al.,* 2004). Saxagliptin was used for the treatment of type-2 diabetics in the form of mono or combination of with other drugs. Hence, it was selected in the present investigation as a suitable candidate for the design of gastric floating drug delivery system for improved retention time and bioavailability. The present study is to develop a floatable drug delivery system of Saxagliptin using hydroxy propyl methyl cellulose for sustained drug delivery and gastric retentive property. Thus the study aims to improve the oral bioavailability of the drug and to achieve extended retention in the

stomach which may result in prolonged absorption.

Materials and methods

Materials

Hydroxy Propyl Methylcellulose, Magnesium stearate, Sodium bicarbonate, Talc, Carbopol, were procured from S. D. Fine Chem. Ltd, Mumbai, India. All other solvents and reagents were purchased from Merck (Germany) and were of analytical grade.

Methods

Method for preparation of saxagliptin floating tablet

Direct compression was followed to manufacture the gas generating floating tablets of Saxagliptin. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression (Desai and Bolton, 1993). All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation.

Various formulations of Saxagliptin Gastro Retentive floating tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Saxagliptin	5	5	5	5	5	5	5	5	5
HPMC K 5	100	110	120	-	-	-	50	55	60
HPMC K 16	-	-	-	100	110	120	50	55	60
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	10	10	10	10	10	10	10	10	10
$NaHCO_3$	15	15	15	15	15	15	15	15	15
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10
Lactose	40	30	20	40	30	20	40	30	20
Total Weight	200	200	200	200	200	200	200	200	200

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic

properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated (Ajay *et al.*,2010).

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined (Prakash *et al.,* 2009). The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 210 nm using of 0.1 N HCl as blank (Table 1).

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) (Table 1).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated (Table 1).

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated (Table 1).

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method (Rosa *et al.,* 1994). The tablets were placed separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time (Table 1).

Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type) (Wagner, 1969; Gibaldi and Feldman, 1967; Higuchi, 1963). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.5ºC and rpm of 75. One Saxagliptin tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The

fresh dissolution medium (37°C) was replaced every time with the same quantity of the sample and take the absorbance at 210.0 nm using spectroscopy.

Results

Different formulation F1-F9 were prepared using different of excipient (HPMC K 4, HPMC K 15 and PVP K30) and evaluate for thickness, hardness, weight variation, friability, drug content, total floating and floating lag time. The Thickness was found in the range of 3.2±0.2mm to 3.5±0.2mm and hardness 4.5±0.2 to 4.6±0.2. Drug Content was found in the range of 98.74±0.85 to 99.98±0.23 and the total floating time was found more than 12 hrs.

Table 1: Results of post compression properties of Saxagliptin FGR tablets

Formulation code	Thickness* (mm)	Hardness* (kg/cm2)	Weight variation* (mg)	Friability* (%)	Drug content* (%)	Total floating duration* (h)	Floating lag times* (sec)
F1	3.2±0.2	4.5±0.2	205±4	0.895±0.12	99.89±0.25	MT 12	45±5
F2	3.5±0.1	4.6±0.1	204±3	0.698±0.14	98.85±0.33	MT 12	46±6
F3	3.4±0.2	4.3±0.3	204±4	0.785±0.15	98.78±0.41	MT 12	52±3
F4	3.4±0.1	4.5±0.2	198±5	0.658±0.14	98.75±0.52	MT 12	53±4
F5	3.5±0.2	4.6±0.1	205±2	0.652±0.12	99.85±0.74	MT 12	60±5
F6	3.4±0.3	4.5±0.2	201±4	0.478±0.12	98.74±0.85	MT 12	48±6
F7	3.4±0.2	4.5±0.3	204±5	0.658±0.14	99.12±0.65	MT 12	56±3
F8	3.3±0.2	4.6±0.2	203±6	0.789±0.20	99.65±0.41	MT 12	59±5
F9	3.4±0.2	4.5±0.4	204±4	0.741±0.21	99.98±0.23	MT 12	63±3

***Average of three determinations (n=3)**

Table 2: *In-vitro* drug release study of GRF tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	55.65	50.45	45.58	40.56	38.98	35.85	25.65	22.45	19.56
1	88.98	72.12	55.69	51.15	48.85	42.58	39.98	28.98	25.65
1.5	92.32	88.95	69.45	63.47	59.65	55.65	45.58	36.69	32.45
2	98.82	92.23	76.69	72.25	68.89	63.36	55.62	45.65	40.85
3	-	98.25	89.98	85.65	75.45	78.98	63.12	55.52	49.98
4	-	-	98.45	92.45	88.98	89.98	76.65	69.98	55.74
6	-	-	-	99.85	94.65	95.65	88.98	75.12	64.87
8	-	-	-	-	98.85	99.45	93.45	88.65	78.89
12	-	-	-	-	-	-	99.78	91.45	82.12

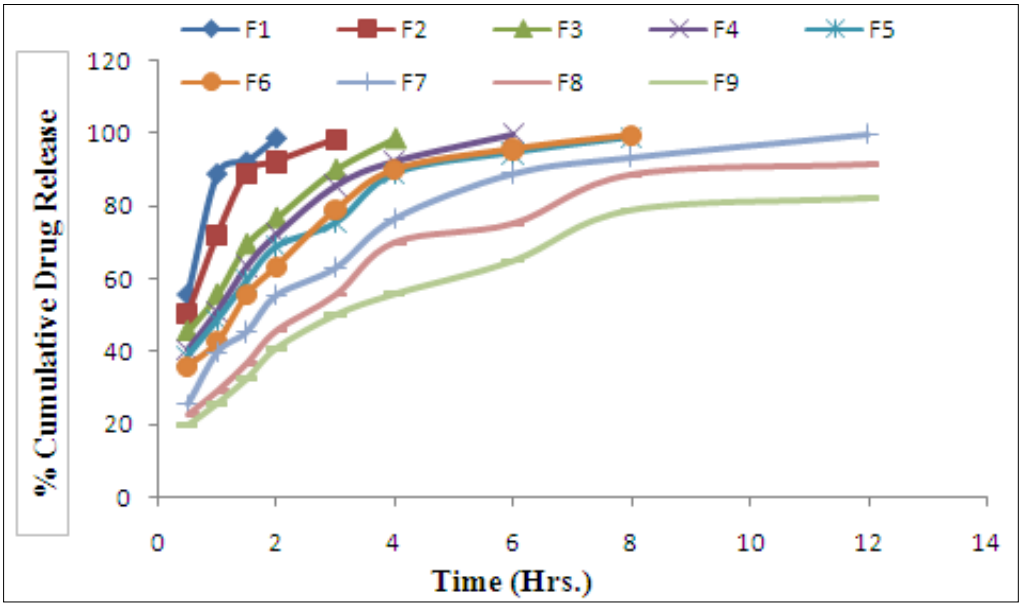

Figure 1: *In-vitro* drug release study of GRF tablets

Discussion

Different formulation F1-F9 were prepared using different of excipient (HPMC K 4, HPMC K 15 and PVP K30) and evaluate for Thickness, Hardness, Weight variation, Friability, Drug content, Total floating duration, and floating lag time. The Thickness was found in the range of 3.2±0.2mm to 3.5±0.2mm and hardness 4.5±0.2 to 4.6±0.2. Drug Content was found in the range of 98.74±0.85 to 99.98±0.23 and the total floating time was found more than 12 hrs. The Drug release Was found for formulation F1, F2, F3, F4, F5, F6, F7, F8 and F9 (98.82, 98.25, 98.45, 99.85, 98.85, 99.45, 99.78, 91.45 and 82.12). The Maximum Drug release in comparison to all formulation was found to maximum in F7 that is 99.78. It was observed that when the Concentration of polymers like HPMC-K4 and HPMC K-15 was increased the release of drug controlled. The optimized formulation F7 Showed controlled release 99.78% after 12 hrs. selected as optimized formulation. When the regression coefficient values of were compared, it was observed that 'r^2' values of first order was maximum i.e. 0.941 hence indicating drug release from formulations was found to follow first order kinetics.

Conclusions

Hydrodynamically balanced systems of saxagliptin with shorter lag time can be prepared by direct compression method using HPMC and $NaHCO_3$ as gas generating agent. All the prepared tablet formulations were found to be good without capping and chipping. As the amount of polymer in the tablet formulation increases, the drug release rate decreases. Most of the designed formulations of saxagliptin displayed first order release kinetics, and drug release follows first order kinetic model.

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