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Formulation Development and Evaluation of Sitagliptin Floating Tablets Containing Natural Polymer

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ABSTRACT

The purpose of this investigation was to prepare a gastroretentive drug delivery system of Sitagliptin. Floating tablets of Sitagliptin were prepared employing different polymers like guar gum, carbopol 940, and HPMC and magnesium stearate by effervescent technique. Sodium bicarbonate and citric acid were incorporated as gas generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, swelling studies, dissolution studies, disintegration studies and stability studies. The drug release studies and floating studies were investigated. The prepared tablets exhibited satisfactory physicochemical characteristics. All the prepared batches showed good results of *in vitro* studies of tablets. It was aimed to prepare for prolong residence in the stomach over conventional gastroretantive approaches. The tablets were produced by direct compression method.

INTRODUCTION

Oral route of administration is the most convenient and easily acceptable route for drug delivery. The benefit for long term delivery system or technology has not been fully realized for dosage form design for oral administration. This is mainly due to the fact that the extent of drug absorption from gastrointestinal tract is determined by gastrointestinal physiology irrespective of the controlled release properties of the device, prolonged gastric retention improves bioavailability. Gastroretentive dosage forms are designed to be retained in the stomach and prolong the gastric residence time of the drug. Prolonged gastric retention improves solubility of drugs that are less soluble in high pH environment. When floating tablets are reached to stomach; carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the jellified hydrocolloid. This is prepared by swellable polymer like HPMC, guar gum, carbolpol 940 and effervescent components like sodium bicarbonate; citric acid etc. Sitagliptin is an antidiabetic drug that works by increasing level of natural substances called incretins. Incretins helps to control blood sugar by increasing insulin release, especially after meal, also decrease sugar formed by liver. Sitagliptin used in patients, having type II diabetes mellitus. Sitagliptin inhibits dipeptide peptidase -4(DPP-4) thus called DPP-4 inhibitor[2]. It is soluble in pH range 4-6. However its absorption is erratic in diabetic patients due to improved gastric motility or gastric emptying, the present study was designed to formulate gastroretentive controlled release Sitagliptin tablet by using different polymers. The objective of the study is to prepare floating tablets in controlled fashion. The gas generating agents were added for retardation and investigation of release profile by using Electrolab TDT8L dissolution apparatus.

MATERIALS

The drug Sitagliptin was a generous gift sample from Concept Pharma Pvt. Ltd., Aurangabad. Guar gum, HPMC, Carbopol 490, Magnesium stearate, Citric acid, $NaHCO_3$, Talc were supplied by S. D. Fine Chemicals (Mumbai). Other reagents and organic solvents used were of analytical grade.

METHODS

Floating tablet of Sitagliptin was prepared by direct compression method by using gas generating agent like $NaHCO_3$, Citric acid together with binding agent like HPMC. Magnesium stearate and talc were used as lubricants.

PREPARATION OF MOUTH DISSOLVING TABLET

Tablets are prepared by direct compression technique using varying concentration of different grades of polymers with sodium bicarbonate and citric acid. Accurately weighed quantities of polymers were taken in a mortor and mixed geometrically. To the mixture quantity of required Sitagliptin was added and mixed slightly with pestle. The mixture was passed through 40# sieve and later collected in a plastic bag and blended for 5 minutes. Required amount of sodium bicarbonate, Mg stearate and talc were added and final blend was again passed through 40# sieve. The powder was then compressed into tablets by using 8 mm flat punches and corresponding dies at a hardness of 6 kg/cm^2 8 station tablet punching machine[5].

Table No.01 Batches to prepare mouth dissolving tablet

Sr. No.	Ingredients	F 1 (mg)	F 2 (mg)	F 3 (mg)
1	Sitagliptin	100	100	100
2	Guar gum	50	55	55
3	HPMC	40	40	40
4	Carbopol 490	44	44	44
5	$NaHCO_3$	35	30	35
6	Citric acid	25	25	20
7	Mg. Stearate	3	3	3
8	Talc	3	3	3

DRUG EXCIPIENT INTERACTION STUDY

FOURIER TRANSFORMS INFRARED SPECTROSCOPY (FT-IR)

FT-IR spectroscopy was found to be the most reliable technique for predicting the possible interaction between the drug and polymers. Physical mixtures comprising of drug and polymers in a ratio of 1:1 were prepared by triturating in mortar and pestle. Samples were subjected to FT-IR studies using Brucker alpha instrument and the IR spectrum of pure drug and drug-excipient mixtures were compared to find any interaction between drug and excipients used for the formulation of floating tablets of Sitagliptin.

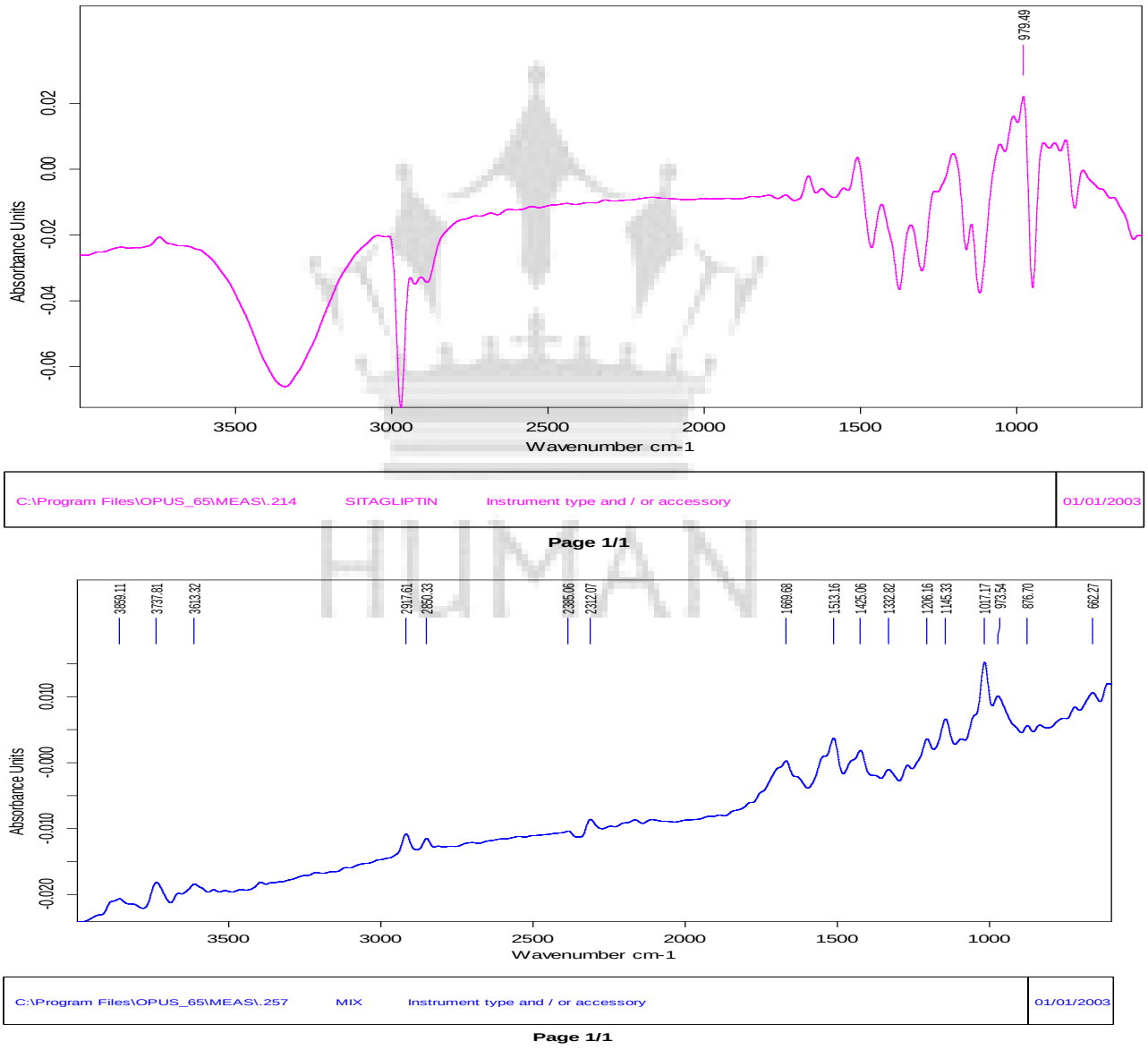

Fig No.1: FTIR Data of Pure Drug and excipient

MICROMERITICS STUDIES OF BLEND

The microspheres were characterized by their Micromeritics properties, such as, bulk density, tapped density, Carr's compressibility index, Hausner ratio and flow property.

Bulk Density

The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm^3. The sample of about 10 cm^3 of powder was carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$\mathbf{D_f = M / Vp}$$

Where, D_f = bulk density

M = weight of samples in grams

Vp = final volumes of granules in cm^3

Tapped Density

The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm^3. The sample of about 10 cm^3 of powder is carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface 100 times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$\mathbf{D_o = M / Vp}$$

Where, $_{Do}$ = bulk density

M = weight of samples in grams

Vp = final tapped volumes of granules in cm^3

Carr's Index

The percentage compressibility of microspheres was calculated according to equation given below:

$$\% \text{ Compressibility} = \frac{D_o - D_f}{D_o} \times 100$$

Where, D_f = bulk density; Do = Tapped density.

Table No. 02: Relationship between % compressibility and flowability

% Compressibility	Flowability
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
> 40	Extremely Poor

Hausner ratio

The hausner ratio of a microsphere was calculated according to equation given below:

$$\text{Hausner ratio} = D_o / D_f$$

D_o = Tapped density

D_f = bulk density

Angle of repose

The Angle of repose (θ) i.e. flow property of the microspheres, which measures the resistance to particle flow, was calculated as

$$\tan \theta = 2H / D$$

Where, 2H / D is the surface area of the freestanding height of the microspheres heap that is formed after making the microspheres flow from the glass funnel.

Table No. 03: Relationship between angle of repose (θ) and flow ability

Angle of Repose (θ)	Flowability
< 20	Excellent
20 – 30	Good
30 – 34	Passable
> 40	Very poor

The blends were characterized by mass-volume relationship (bulk density, tapped density, Hauser's ratio, compressibility index) and flow properties (static angle of repose)[6].

Table No.04: Evaluation of the Blends[1]

Parameter	F1	F2	F3
Bulk density (g/cm3)	0.3971 ±0.003	0.4018±0.003	0.4135±0.002
Tapped density (g/cm3)	0.5789±0.002	0.5912±0.003	0.5789±0.003
Compressibility Index	19.71±0.003	18.80±0.006	20.56±0.003
Angle of Repose	$27^0$60'±0.003	$27^0$64'±0.004	$28^0$10±0.005
Hausner ratio	1.457 ±0.004	1.471 ±0.003	1.400±0.002

*** Each sample was analyzed in triplicate (n = 3).**

EVALUATION OF PHYSICAL PROPERTIES OF FLOATING TABLET[6-7]

WEIGHT VARIATION

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated.

THICKNESS

Thicknesses of tablets were measured with Verniar caliper.

HARDNESS

Hardness of the tablet was tested using Monsanto hardness tester for each trial. The hardness range was determined for five tablets of each batch. The hardness of tablet was express in kg/cm^3.

FRIABILITY

Friability of the tablet of each tablet was determined by using Roche Friabilator. For this test, ten tablets were weighed and placed in friabilator which was operated for 100 revolutions at the speed of 25 revolutions per minute. The tablets were then dusted and reweighed.

IN VITRO BUOYANCY STUDY[5]

The *in vitro* buoyancy study was characterized by floating lag time and total floating time. The test was performed using Electrolab paddle apparatus, using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37^0C. The time required for tablets to rise to the surface of the dissolution medium were noted as floating lag time and total floating time.

Table 5: *In Vitro* Buoyancy Study

Batch	Floating lag time (sec)	Floating time (hr)
F1	900±1	15±2
F2	900±2	18±3
F3	902±1	17±2

Table No. 6: Post Compression Parameters

Sr. No.	Parameters	F 1	F 2	F3
1	Weight(mg)	300.02±0.02	300.80±0.02	300.13±0.02
2	Hardness(kgs)	5.4±0.3	5.1±0.2	5.4±0.1
3	Friability (%)	0.64±0.01	0.68±0.03	0.91±0.02
4	Thikness (mm)	2.08±0.05	2.14±0.03	2.07±0.2

*** Each sample was analyzed in triplicate (n = 3).**

IN VITRO DISSOLUTION STUDIES[1]

The *in vitro* dissolution study was performed by using an Electrolab paddle apparatus at a rational speed of 100 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at 37^0C. A sample (1 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 24 hours and the same volume was then replaced with pre-warmed dissolution media. The samples were diluted to suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 430 nm using a UV spectrophotometer (Labindia).

Table No 07: Cumulative % Drug Release

Time (hr)	F1	F2	F3
1	13.53±0.20	15.35±0.12	12.13±0.12
3	20.34±0.20	26.90±0.10	22.61±0.09
5	36.45±0.10	36.76±0.03	29.84±0.08
7	43.63±0.20	49.04±0.20	35.09±0.15
9	50.74±0.19	51.67±0.16	43.95±0.16
11	69.67±0.17	60.35±0.20	51.45±0.23
13	72.23±0.20	73.45±0.23	60.78±0.23
15	82.23±0.22	84.04±0.21	69.24±0.19
16	87.34±0.23	86.83±0.20	73.36±0.23
17	89.75±0.20	88.06±0.23	78.84±0.20
18	89.92±0.23	90.12±0.20	83.61±0.23

*** Each sample was analyzed in triplicate (n = 3).**

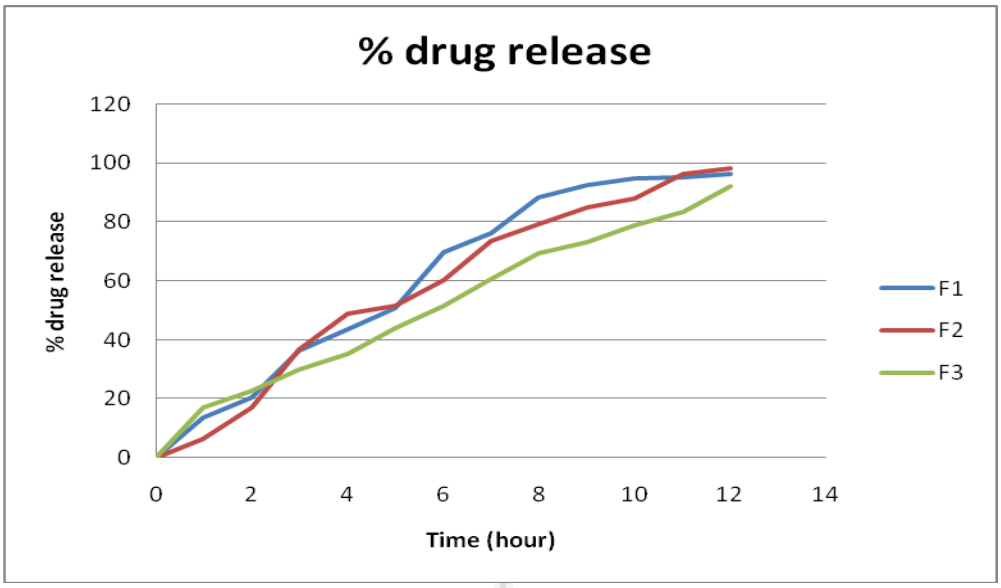

Fig No. 02. Cumulative % Drug Release

RESULTS AND DISCUSSION

The preparation of floating tablets with the use of natural excipient is highly effective and commercially feasible. This natural excipient accelerates floating time of tablets by virtue of their ability to absorb a large amount of stomach fluid when exposed to gastric environment. The absorption of stomach fluid results in swelling of tablets and therefore increase in floating time is reported to have an effect on release time of drug. In this research work, we have formulated total three batches which are coded as F1, F2, and F3. Out of these batches, batch F2 show the satisfactory result of hardness of 5.1±0.2, friability 0.68±0.03, average weight 300.80±0.02 floating lag time 900±2, floating time 18±3 and 90.12±0.20 drug release. A prepared floating tablet floats in the stomach and releases the drug as early as compared to its formulated conventional tablets. Two different gas generating agents namely sodium bicarbonate, citric acid and swelling agent guar gum were tried to achieve floating of tablets which has been satisfactorily proved by batch F2.

CONCLUSION

In summary, it is concluded that the formulation of the Sitagliptin gives satisfactory results and by the use of swelling agent and gas generating agents. We achieved the Sitagliptin floating tablets. Tablets containing guar gum along with HPMC and citric acid formulation F2 showed

more floating time, as shown in (Table 1). Characteristics of tablets are further tabulated in Table 2. The study shows that the floating time of Sitagliptin can be enhanced to a great extent by direct compression technique with the addition of mixture of swelling agent and gas generating agent.

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