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FORMULATION AND EVALUATION OF SITAGLIPTIN PHOSPHATE GASTRO RETENTIVE TABLETS

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Key words:

Sitagliptin phosphate, Anti-diabetic drug, Floating Drug Delivery System, Gastro intestinal tract (GRT), Gastro retentive Drug Delivery System, Novel Delivery System

ISSN 0799-3757

http://caribjscitech.com/

ABSTRACT

The purpose of the present investigation is to formulate a novel gastro retentive system, floating tablets of Sitagliptin Phosphate, an anti diabetic agent by direct compression technique using lactose as diluent. The drug-excipients interaction was ruled out through FTIR studies. Nine formulations of Sitagliptin Phosphate tablets were prepared using HPMC K100 and HPMC K4M as release retarding agents in different concentrations of 10, 15 and 20% w/w. The prepared batches were evaluated for organoleptic properties, hardness, friability, weight variation and *in vitro* drug release. All the formulations showed low weight variation with rapid dispersion time and rapid *in vitro* dissolution. One amongst nine promising formulations, the formulation prepared by using 15% of HPMC K100 emerged as overall the best formulation. This optimized formulation showed good release profile with complete drug release with in 24 hours. It was concluded that floating tablets of Sitagliptin Phosphate can be successfully formulated by using release retarding polymers.

INTRODUCTION

Oral drug delivery is by far, the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility of formulations. Patients being treated with conventional oral formulations containing drugs with shorter half-lives require frequent dose administrations, which effect the patient compliance.[1,2] This can be overcome by sustaining the drug release. The real issue in the development of orally controlled release forms is not just to prolong the delivery of drug but prolong the presence of dosage form in the stomach or upper gastrointestinal tract (GIT) until all the drug is released for the desired period of time. [3,4] So gastro retentive systems were developed. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GIT is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e. gastroretentive dosage forms (GRDFs), will provide us with new and important therapeutic options. The most novel systems are Floating Drug Delivery Systems (as first described by Davis in 1968) have bulk density lower than that of the gastric fluid (1.004 g/cm^3) and thus remain buoyant in the stomach for the prolonged period causing improved bioavailability, less wastage of drug, improved solubility of poorly soluble drugs and localized action.[5]

Diabetes mellitus is a condition in which a person has a high blood sugar level, either because the body doesn't produce enough insulin, or because body cells don't properly respond to the insulin that is produced. To treat this diabetes medications or insulin therapy were used.[6,7] Under this, diabetes mellitus type II was most commonly occurred and only anti-diabetic drugs are used. Among those anti-diabetic medications Sitagliptin was more acceptable.

Sitagliptin Phosphate is a Dipeptidyl Peptidase-4 (DPP-4) Inhibitor. Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretins GLP-1 and GIP, gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal.[8] The objective of the present study was to design and optimize the floating tablets of Sitagliptin Phosphate by direct compression method and by using different ratios of HPMC K 4M, HPMC K100 and combination. Poly ethylene glycol was used as plasticizer. Magnesium stearate and talc were also added. The optimized formulation was compressed into tablets by using directly compressible lactose. The dose of Sitagliptin Phosphate was 100mg. Hence, to maintain the bioavailability and to reduce the frequency of drug administration Sitagliptin Phosphate floating tablets were prepared.

MATERIALS AND METHODS

Materials

Sitagliptin Phosphate was obtained as a gift sample from Richer pharmaceuticals-Hyderabad. HPMC K4M, HPMC K 100, Carbomer, Lactose were procured from Narmada chemicals –Hyderabad. Poly ethylene glycol & Aerosil were procured from Drsugs India-Hyderabad. Magnesium Stearate and Talc were procured from Scot pharma Hyderabad. All the reagents and materials were of analytical or pharmacopoeia grade.

Drug polymer compatibility studies

Compatibility of drug with excipients was determined by carrying out IR studies. Infrared spectrum of Sitagliptin Phosphate and physical mixture of drug and polymer was determined on Fourier Transform Infrared spectrophotometer (8400 S Shimadzu) using KBr pellet method. The results were shown in figure I&II.

CHARACTERIZATION OF PREPARED TABLETS

Fourier transform infrared analysis

Infrared spectroscopy was conducted using FT-IR spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing the sample (drug alone, mixture of drug and excipients and the optimized formulation) in KBr and compressed into discs by applying a pressure of 5 tons for 5 minutes in a hydraulic press. The pellet was placed in the light path and the

spectrum was recorded.

Analytical method: The standard graph of Sitagliptin Phosphate in 0.1N HCl showed good linearity with R^2 value of 0.999

***In Vitro* Release Studies**

The tablets equivalent to 50mg of drug were subjected to invitro release studies. The *in-vitro* release of sitagliptin phosphate floating tablets were studied using USP basket apparatus with a stirring rate of 50 rpm. The temperature was maintained at 37 ± 0.5°C. Drug release was carried out in 900ml of 0.1N HCL . An aliquot of 5ml sample was collected over a period of 12 h and was assayed spectrophotometrically for the drug at λ_{max} = 265 nm. Each time sample was withdrawn, and 0.1N HCL was added to keep the dissolution medium volume constant. A kinetic treatment of the data was performed to determine the mechanism of the release of the drug. The cumulative release profiles of the formulations were represented in figure III.

Stability Studies

Stability study has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

Stability testing of pharmaceutical products is done for the following purposes

1. To ensure the efficacy, safety and quality of active drug substance and dosage forms.

2. To establish shelf-life or expiration period and to support tablet claims.

Haynes divided the countries of world into 4 zones namely

Zone = I (Moderate)

Zone = II (Mediterranean)

Zone = III (Hot, Dry)

Zone = IV (Very hot, moist)

India falls under Zone-III & IV

As per ICH guidelines following storage conditions are specified for solid oral dosage form to conduct stability study under accelerated condition for zone III and IV countries.

Accelerated study: 40^{O}C/ 75%RH sampling were done after 3 months.

Procedure: In the present study, stability studies were carried out at 40^{O}C/ 75%RH

Formulation was analyzed for following parameter.

- Physical properties
- Drug content
- Invitro dissolution study of Sitagliptin Phosphate formulation.

FORMULATION & EVALUATION OF SITAGLIPTIN PHOSPHATE FLOATING TABLETS

Table 1. Composition of different formulations of Sitagliptin phosphate

S.NO	Ingredients	Purpose	F1	F2	F3	F4	F5	F6	F7	F8 (1:1)	F9 (1:2)
1.	**Sitagliptin phosphate**	Model drug	50	50	**50**	50	50	50	50	50	50
2.	**Lactose monohydrate**	Diluents	86	66	**76**	61	51	41	31	76	86
3	**Poly ethylene glycol**	Plasticizer	8	8	**8**	8	8	8	8	8	8
4.	**HPMC (K4M)**	Release controlling polymer	-	-	**-**	30	40	50	60	10	10
5.	**HPMC(K100)**	Release controlling polymer	20	40	**30**	-	-	-	-	10	20
6.	**Sodium bicarbonate**	Gas generating agent	20	20	**20**	20	20	20	20	20	20
7.	**Carbomer**	Binder	-	-	**-**	16	16	16	16	-	-
8.	**Aerosil**	Glidant	6	6	**6**	10	10	10	10	6	6
9.	**Magnesium stearate**	lubricant	6	6	**6**	5	5	5	5	6	6
10.	**Talc**	Glidant	4	4	**4**	-	-	-	-	4	4
11.	**Tablet weight**	-	200	200	**200**	200	200	200	200	200	200

Preparation of sitagliptin phosphate floating tablets

Tablets containing 50mg of Sitagliptin were prepared according to the design depicted in table I by direct compression method**.** The weighed quantities of respective powders, namely the active ingredient Sitagliptin, release modifying polymers HPMC K100M or HPM K4M, gas generating agents sodium bicarbonate, carbomer binder; lactose diluent were passed through sieve #16 separately. Mixing of powders was carried out using a pestle in a mortar for 10min. Magnesium stearate and talc were then added to the mixed powders. Mixing was continued for another 5min. Finally 200mg of the powdered mixture was weighed approximately and was fed manually into the die of a multistation rotary tablet press (Rimek Mini Press II compression machine) to produce the desired tablets. The hardness of the tablets was adjusted at 5kg/cm^2 using Monsanto hardness tester.

Micromeritic properties of tablet formulation powder blends [9]

Determination of bulk density and tapped density:

About 5 gms of formulation powder blend was weighed and transferred to a 25 ml measuring cylinder. The bulk volume was noted. The bulk density was calculated by the formula:

$$\text{Bulk density} = \frac{\text{WEIGHT OF POWDER}}{\text{BULK VOLUME OF POWDER}}$$

$$\text{Tapped density} = \frac{\text{WEIGHT OF POWDER}}{\text{TAPPED VOLUME OF POWDER}}$$

Angle of Repose:

Angle of repose was measured by using open cylinder method. Two side open cylinder was taken and cleaned thoroughly, accurately weighed 5 gms of formulation powder blend was transferred to the open cylinder. Then the cylinder was lifted up. Height of pile and radius of the base of the pile was measured with ruler. Then the angle of repose was measured with the following formula.

The angle of repose (θ) was calculated by using the formula,

$\theta = \text{Tan}^{-1}\frac{h}{r}$ Where h= height of pile

r= radius of pile

θ = angle of repose

Compressibility index:

Accurately weighed, 5 gms of formulation powder blend was transferred to a 25 ml measuring cylinder and bulk volume was measured. Then it was subjected to 100 tapings. The tapped volume was measured. Carr's index was calculated by the following formula:

$$\text{Compressibility index (\%)} = \frac{\text{TAPPED DENSITY} - \text{BULK DENSITY}}{\text{TAPPED DENSITY}} \times 100$$

Hausner ratio

Accurately weighed formulation powder blend was transferred to a 25ml measuring cylinder. The bulk volume was measured and then subjected to 100 tappings. The tapped volume was measured. Hausner ratio was calculated by the following formula:

$$\text{Hausner ratio} = \frac{\text{TAPPED DENSITY}}{\text{BULK DENSITY}}$$

The results of micromeritic properties of microsponge formulation powder blends were represented in table II.

EVALUATION OF PREPARED MATRIX TABLETS

The following evaluation tests were conducted for the prepared matrix tablets

Physical characteristics evaluation of prepared matrix tablets

Thickness:

The thickness of the tablets was determined using a vernier calliper. Five tablets from each formulation were used, and average values were calculated.

Tablet thickness=V.S.R+ (M.S.RXL.C)

V.S.R= vernier scale reading

M.S.R= main scale reading

L.C= least count

Weight variation test:

Twenty tablets were collected and were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated using the formula

$$\% \text{ weight variation} = \frac{Average\ weight - individual\ weight}{Average\ weight} \text{ X } 100$$

Hardness test:

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The lower plunger was then forced against a spring by tuning threaded bolts until the tablet fractured.

Then the final reading was recorded. The hardness was calculated by deducting the initial pressure from the final pressure. The results were expressed as an average of 5 readings in terms of $kg/cm^{2.}$

Friability:

This test was performed to know the effect of friction and shock on tablets. Twelve tablets from each formulation were collected and accurately weighed. Then the tablets were collected and placed in Roche friabilator and operated for 100rpm (25 rpm speed).Tablets were dusted and reweighed. The test complies if tablets not lose more than 1% of their weight. Friability Percentages of the tablets were calculated using the formula

$$\%\text{Friability} = \frac{W_1 - W_2}{W_1}$$

W1=initial weight of tablets

W2=weight of tablets after friabilation

Drug content determination

Twenty tablets from each formulation were selected for the estimation of drug content. The tablet was weighed,triturated and transferred the powder to a 100 ml flask containing 50 ml of 0.1N HCL . The content of the flask was filtered through a filter, kept in a 100 ml volumetric flask. The residue was washed with another 40 ml of 0.1N HCL and the volume was made up to the mark . The sample was suitably diluted and analysed spectrophotometrically against blank (0.1N HCL) at 265 nm using double beam uv visible spectro photometer.

Invitro buoyancy test

The *invitro* buoyancy was determined by observing floating lag time, as per the method described by Rosa. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was considered as the floating lag time.

Swelling Study:

The swelling studies were carried out by determining % swelling index. The individual tablets were weighed accurately and kept in a beaker containing 0.1N HCl. Tablets were taken out carefully after designated time, blotted with filter paper to remove the liquid present on the surface and weighed accurately. Percentage swelling was calculated by using formula

$$\text{Swelling index} = \frac{wet\ weight - dry\ weight}{dry\ weight} \times 100$$

***In vitro* drug release studies** [10,11]

The in vitro dissolution studies were carried out using USP dissolution apparatus-II which was set at 50 rpm. Dissolution test was carried out in 900 ml of HCl at 37±0.5^{o}c. Sampling was done for every one hour. Then at each interval of time, 5 ml of samples were collected and replaced with the same amount of dissolution medium. The samples withdrawn were analyzed spectro photo metrically at 265 nm using *UV* visible double beam spectro photometer. Five tablets from each formulation were used for the *in-vitro* dissolution study. The drug

release profile was fitted into several mathematical models to get an insight of the release mechanism of the drug from the dosage form. The zero order and peppas plots of optimized formulations were represented in figures IV & V. Model fitting release profiles of optimized formulations were shown in the table VII.

RESULTS

Figure I: IR spectra of pure Sitagliptin Phosphate

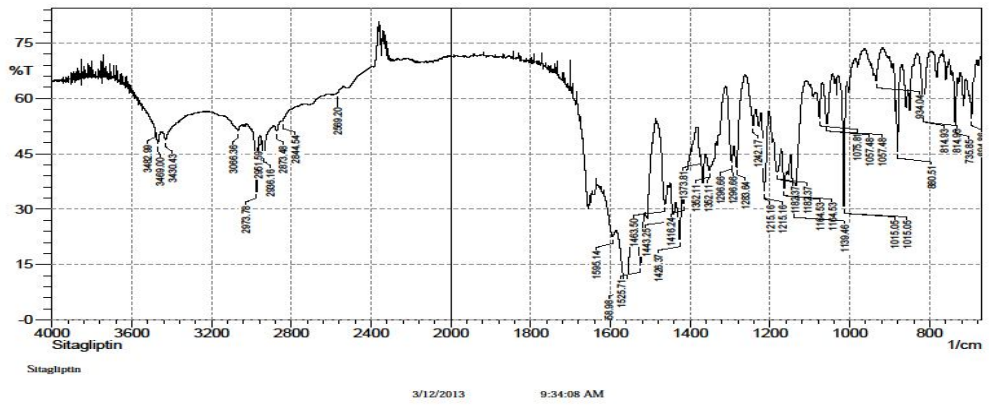

Figure II: IR spectra of Sitagliptin Phosphate and HPMC K 100 (optimized formulation F3)

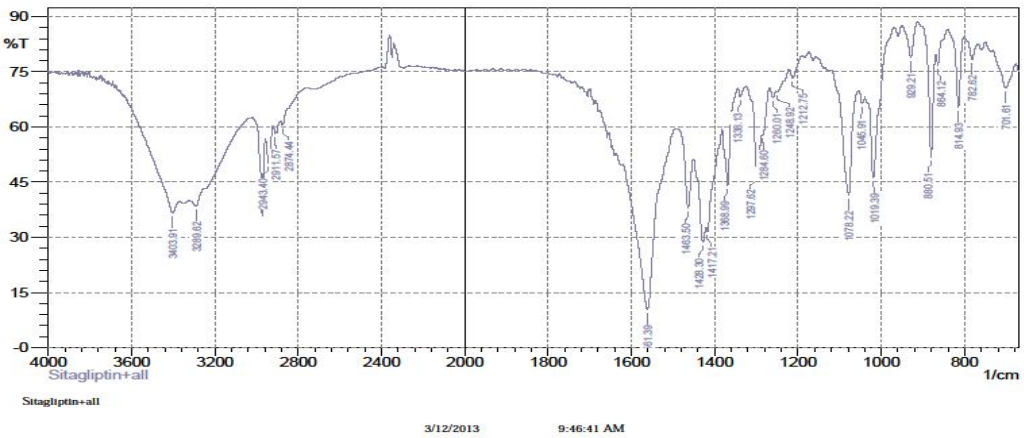

Table II. Micromeritic properties of tablet formulation

Formulation Grades	**Bulk Density**	**Tapped Density**	**Compressibility Index**	**Hausner's Ratio**	**Angle of repose**
F1	0.4	0.476	19	1.19	36.7
F2	0.408	0.50	22.5	1.22	42
F3	0.4	0.487	21.7	1.21	41.7
F4	0.416	0.512	23.2	1.23	42.5
F5	0.4	0.512	28	1.28	46
F6	0.416	0.512	23.27	1.23	43.2
F7	0.411	0.552	25.5	1.34	43
F8	0.41	0.495	24.3	1.20	36
F9	0.413	0.503	22.5	1.21	41

Table III. Physical characteristics of Sitagliptin phosphate floating tablets prepared by employing direct compression techniques

Formulation	Avg.Wt Mean ± SD (mg)	Thickness (mm) Mean ± SD	Diameter(mm) Mean ± SD	Hardness (Kg\cm^2) Mean ± SD	Friability Mean ± SD	Mean % Drug Content	Buoyancy lag Time (sec)	Total floating Time (hrs)
F1	201±0.901	2.8±0.17	8.7±0.07	5.5±0.208	0.14±0.02	99.89	177	>12
F2	201±0.905	2.6±0.18	8.7±0.07	5.4±0.22	0.09±0.05	102.06	82	8
F3	204±1.77	2.7±0.13	8.7±0.07	5.1±0.05	0.2±0.04	98.62	142	>12
F4	200.5±1.15	2.8±0.15	8.7±0.07	6±0.3	0.07±0.06	100.69	25	>12
F5	200±1.41	2.5±0.14	8.7±0.07	5.6±0.1	0.12±0.01	99.4	18	>12
F6	202±1.16	2.6±0.125	8.7±0.07	5.4±0.12	0.07±0.02	100.78	10	5
F7	201±1.5	2.6±0.18	8.7±0.07	5.5±0.13	0.12±0.007	100.69	364	4
F8	203±1.25	2.6±0.175	8.7±0.07	5.5±0.21	0.14±0.001	102.06	235	>12
F9	201±1.10	2.65±0.152	8.7±0.07	5.4±0.19	0.09±0.09	99.01	112	>12

Table IV. Swelling studies of Sitagliptin phosphate drug formulations

Formula	1hr	2hr	3hr	4hr	5hr	6hr
F1	14.5	32	60.5	82.5	94	-
F2	11.5	22	35.5	59.5	70.5	94.5
F3	15.6	28.4	44.87	60.64	88	98.02
F4	7	27	30	49.5	64.5	79.5
F5	8.6	19.4	37	55.01	63.8	81.5
F6	5.6	15.41	24.6	50.1	59.9	76.58
F7	12.86	26.47	47.8	66.12	86	97.1
F8	12.9	22.41	34	59.4	70.25	89.7
F9	8.9	18.7	30.14	49.4	68.95	76.77

Table V. Dissolution studies of Sitagliptin phosphate drug formulations

F code	**0.5hrs**	**1hrs**	**1.5hrs**	**2hrs**	**3hrs**	**4hrs**	**5hrs**	**6hrs**	**7hrs**	**8hrs**	**9hrs**	**10hrs**	**12hrs**
F1	14.99	22.19	27.58	36	38.38	53.38	56.39	65.98	71.38	79.79	88.79	92.98	95.4%
F2	21.6	28.8	32.99	38.8	54	57.6	66.6	70.78	83.98	90.58	91.8	93.6	93.6%
F3	*10.78*	*21.98*	*26.38*	*35.38*	*38.98*	*52.78*	*55.8*	*64.8*	*67.78*	*71.38*	*81.58*	*88.2*	*98.38%*
F4	16.2	21.6	32	35	39.6	54	60.4	64.8	72.4	83.2	87.4	92.98	92.98%
F5	15.58	19.8	25.6	36.4	38.3	50.98	58.68	65.98	69.58	81	90.58	94.78	94.78%
F6	18.58	22.78	42.58	54	59.4	63.58	70.78	84.6	90	94.18	94.18	94.18	94.18%
F7	18	20.38	27	34.78	41.94	52.2	56.34	61.79	68.98	72	80.38	88.79	95.99%
F8	15.5	23.4	30.6	40.19	46.8	56.38	65.9	84.6	87.4	91.8	91.8	91.8	91.8%
F9	23.4	25.78	34.78	38.38	46.18	51.58	58.18	64.8	72.58	83.98	89.38	89.38	89.38%

Figure III. Invitro drug release comparison profiles of prepared floating tablets (F1 to F9)

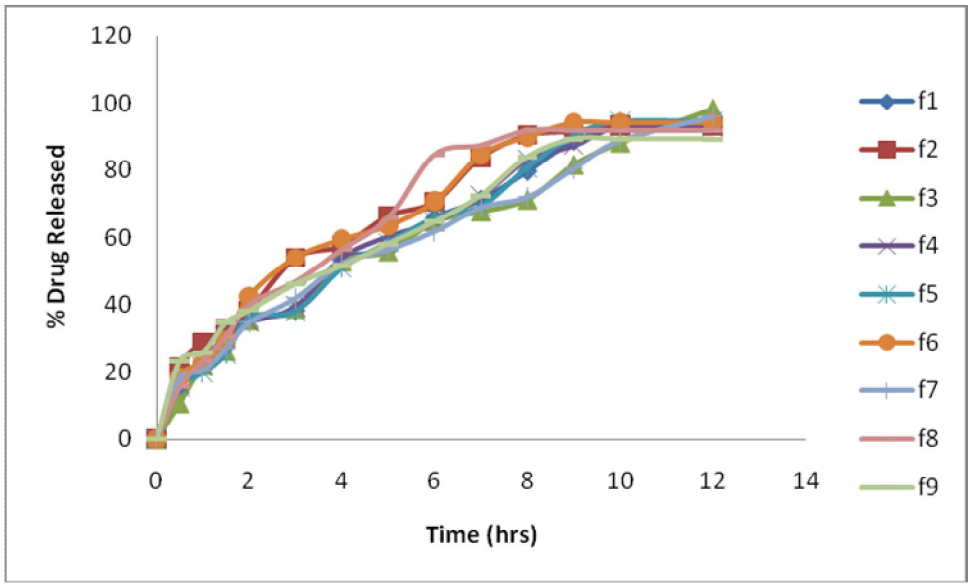

Figure IV. Zero order plot of optimized formulations F3

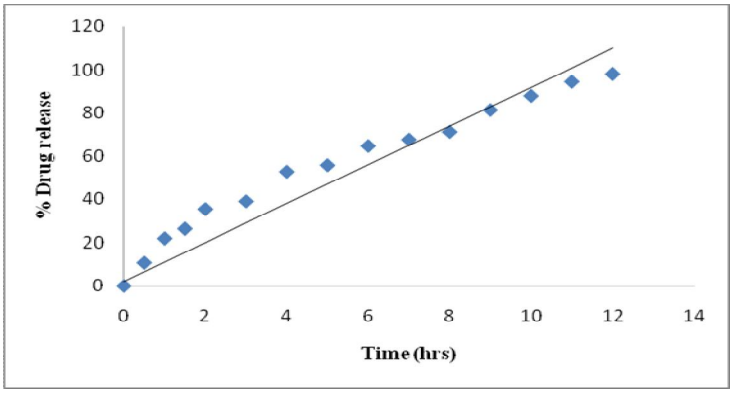

Figure V. Peppas plots of optimized formulation F3

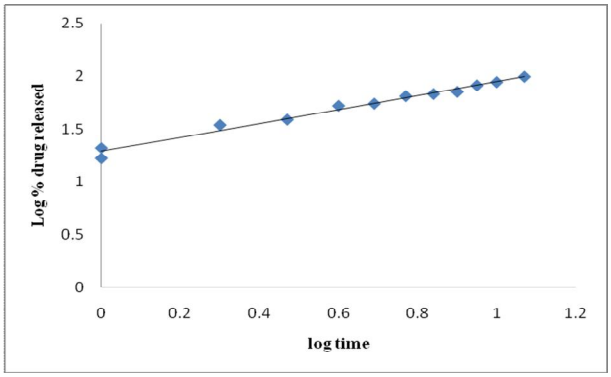

Table VI. Stability study data of optimized formulation (F3)

Sl. No.	Time in days	Physical changes	Percentage of drug content* ±SD	Moisture content	Percentage of drug release * ±SD (99.5% of release label claim in 10 min).
1.	1st day (initial)	Round, white color uncoated tablets	99.51±0.48	0.82	99.5%
2.	30th day (1 month)	No changes	99.35±0.11	0.78	99.2%
3.	60th day (2 month)	No changes	98.12±0.13	0.80	99.3%
4.	90th day (3 month)	No changes	97.81±0.28	0.78	99.2%

Table VII. Model fitting release profile of optimized formulation Sitagliptin Phosphate

Formulation Code	Zero order	First order	Hixon-crowell	Higuchi	Korsemeyer – peppas	Best fit model
	R^2	R^2	R^2	R^2	R^2	
F3	0.91	0.90	0.95	0.97	0.98	Peppas

DISCUSSION

FTIR studies (figures I & II) of drug and excipients revealed that there was no interaction between the selected drug and polymers. The drug polymer ratio showed significant effect on the floating tablets of sitagliptin. All the powder blends (table II) exhibited the desired flow properties according to pharmacopoeial requirements. It was found that after 12hrs of dissolution study the formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9 (figure III) were showing 95.4%, 93.6%, 98.38%, 92.98%, 94.78%, 94.18%, 95.99% , 91.8% and 89.38% drug release respectively. Stability studies of optimized formulation (F3) (Table VI) of prepared sitagliptin tablets revealed that there was no significant change in the physical characteristics and invitro drug release profiles. Controlled release tablets were prepared from the optimized formulation F3. The formulated tablets were subjected to various quality control tests and the results were shown in (table II & III). All the tablets complied with the pharmacopoeial standards. The formulation F3 showed best release retardation up to 12 hrs where as the formulations F8 and F5 showed 8hrs and 10hrs respectively. The release profiles of optimised formulations followed zero order release kinetics. The data was fitted in the peppas plot (figure V) indicating Non-fickian diffusion mechanism of drug release (table VII).

CONCLUSION

Floating drug delivery based novel drug delivery system has been developed to provide a once daily controlled release tablets for per oral delivery of Sitagliptin Phosphate. The formulation F3 showed better release retardation of drug indicating better potential of delivery system.

REFERENCES:

1. Ravi P. Soni, Gastroretentive drug delivery systems: a review, *IJPWR* vol 2 issue 1 (Jan – Apr) – 2011.
2. S.H. Shaha, An overview of a gastro-retentive floating drug delivery system, *Asian Journal of Pharmaceutical Sciences* 2009, 4 (1): 65-80.
3. S.T.Prajapati, L.D. Patel and D.M.Patel. Gastric floating matrix tablets: Design and optimization using combination of polymers. *Acta Pharmaceutica* (2008); 58: 221-229.
4. Kagan L and Hoffman A. Systems for region selective drug delivery in the gastrointestinal tract: Biopharmaceutical considerations. *Expert Opinion on Drug Delivery,* 2008 June; 5(6): 681-92.
5. Desai S and Bolton S. A floating controlled release drug delivery systems: *in vitro – in vivo* evaluation. *Pharmaceutical Research,* 1993 Sept; 10(9): 1321-5.
6. http://en.wikipedia.org/wiki/Anti-diabetic_medication
7. http://ijod.uaeu.ac.ae/iss_1303/a.pdf
8. http://www.drugbank.ca/drugs/DB01261
9. Gilberts. Banker, Christopher T. Rhodes. Modern Pharmaceutics. 3 rd edition, New York: Marcel Dekker INC; 2005. P.23-7
10. The United States Pharmacopoeia.USP27/ NF22. The Official Compendia of Standards, Asian edition. Rockville: The United State Pharmacopoeial Convention, 2004. P. 1204.
11. Indian pharmacopoeia, Monographs on dosage forms, The Indian Pharmacopoeia Commission, Ghaziabad, 2007. P. 487.