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Research Article

Formulation Development and Evaluation of Gastroretentive Floating Tablet of Vildagliptin

Suraj Kothule[*1], Smita Aher[2], Rishikesh Bachhav[3]

[1]*Department of Pharmaceutical Quality Assurance, R. G, Sapkal College of Pharmacy, Anjaneri - 422212*
[2]*Department of Pharmaceutical Chemistry, R. G, Sapkal College of Pharmacy, Anjaneri, - 422212*
[3]*Department of Pharmacology, R. G, Sapkal College of Pharmacy, Anjaneri - 422212*

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ABSTRACT

The present study was an attempt to formulate and evaluate a floating tablet of vildagliptin using polymers such as HPMC K4M, Carbopol 934, NaHCO3, and citric acid as gas producers. vildagliptin, an antidiabetic drug with 85% oral bioavailability, short half-life (1.5 hours) and largely associated with an acidic pH, is believed to increase gastric survival and therapeutic efficacy. This can be achieved by making floating pills that stay in the stomach for a long time to release the drug. The tablets are formulated using the direct compression method. The effects of sodium bicarbonate and citric acid on pharmacokinetic and potentiating properties were studied. The tablets were evaluated for pressure parameters before and after compression such as fragility, hardness, thickness, drug content, weight change, in vitro buoyancy studies, and in vitro drug release studies, and the results were in range. In vitro drug release studies were performed in USP Type II with 0.1 N HCl. Of all the prepared formulas (F1 to F9), Trust F3 was the best with a lift delay of 82 seconds. This tablet is fresh for more than 12 hours. The drug release data were fitted into various kinetic models in vitro and the best fit was obtained with zero order models. The improved F3 formula follows zero diffusion kinetics through non-viscous diffusion.

INTRODUCTION

The most appropriate oral route is a wide range of drug delivery between all the methods examined for the supply of ordinary drugs [1, 2]. In the development of a sustainable drug delivery system and other main challenge is to change the time of GI shipping. Stomach maintenance is more than expanding the delivery of the drug and improves biodiversity and local useful work [3].

***Corresponding Author**: Suraj kothule
Address: [1]*Department of Pharmaceutical Quality Assurance, R. G, Sapkal College of Pharmacy, Anjaneri - 422212*
Email ✉ : surajkothule91@gmail.com

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Gastric release systems are designed to maintain long-term stomach and earn their active components and thus allows continuous and drug entries for the upper part of the git [4]. A modified drug delivery system is very important for long-term residence time, especially for drugs for working locally in the stomach. The presence of a gastric absorption window or at the top of the good intestine; Which is unsteady in the intestinal or thick environment; Or those with high values of pH [5]. For the formulation of the drug delivery system in a successful mineral stomach, many methods are currently used as FDDs, low density systems and rapid systems that contain an angel, high intensity or mucosal and super hydro-hydrogen cutting systems are. All this, the floating dosage forms were used [6]. Floating drug delivery systems contain high density than the stomach and therefore remain in the stomach without affecting the effect of gastric implant for a long time [7]. While the system floats on the contents of the stomach, the drug slowly launches the optimum level. The remaining system is discharged after the drug version. This is the result of increasing time and fluctuations controlled in plasma drug concentration [8].

Drugs easily absorbed from the gastrointestinal tract and drugs with short half-lives are rapidly eliminated from the systemic circulation due to the repeated administration required. To reduce this problem, intestinal drug delivery systems are being developed that provide effective plasma concentrations of the drug over long periods of time and thus reduce the frequency of doses [16, 17]. It also has the advantage of reducing the fluctuations in the drug concentration in the plasma in a controlled and reproducible manner as a result of the drug release [18, 19]. Therefore, in the present study, vildagliptin supernatants were prepared using HPMC K4M and Carbopol 934 as the copolymer, NaHCO3 as the gas producer and citric acid as the enhancer. The aim of this study was to investigate the effect of polymers on drug release and the effect of sodium bicarbonate on buoyancy.

EXPERIMENTAL SECTION

Materials:

Vildagliptin was used as the active ingredient and was purchased from Invochem Laboratory. HPMC K4M and Carbopol 934 were used as polymers. Sodium bicarbonate was used as the gas generating agent. The other ingredients used were citric acid, magnesium stearate, and lactose. All the material used in the experimental work, except the drug, was obtained from CDH distributors. All reagents used were analytical grade.

Methods:

Preparation of floating tablets of Vildagliptin

Floating tablets containing vildagliptin (50 mg) were prepared by direct compression method using the formula given in Table No. 1. HPMC K4M and carbopol 934 were used as swellable polymers. Baking soda has been used as a gas generating agent and citric acid as a floating enhancer. Lactose was added as a diluent in different proportions to the floating tablets to achieve a uniform weight. The tablets were prepared by mixing the required amounts of the drug, HPMC K4M, carbopol 934, sodium bicarbonate, citric acid and lactose. All excipients were passed through no. 45, mixed with mortar and pestle for 10 min. and it is lubricated with 0.5% magnesium stearate and the mixture is mixed again before compression. The drug mixtures were compressed directly using a rotary compression machine with constant compression force. The excipients were taken based on the weight of the drug.

Table No. 1: Composition of floating tablet of Vildagliptin

Ingredients	Formulation code								
Quantity (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Vildagliptin	50	50	50	50	50	50	50	50	50
HPMC K4M	50	50	50	60	60	60	70	70	70
Carbopol 934	10	15	20	10	15	20	10	15	20
Sodium Bicarbonate	40	40	40	40	40	40	40	40	40
Citric acid	30	30	30	30	30	30	30	30	30
Mg Stearate	3	3	3	3	3	3	3	3	3
MCC	25	25	25	25	25	25	25	25	25
Lactose	47	42	37	37	32	27	27	22	17
Total Weight	255	255	255	255	255	255	255	255	255

EVALUATION PARAMETERS OF DRUG AND EXCIPIENTS

Fourier transforms infrared spectroscopy (FTIR):

The primary objective of this investigation was to identify the drug using FTIR spectrophotometer [20, 21]. For FTIR the sample was send into the laboratory and the results given below in fig. 1.

Differential scanning calorimetry (DSC):

DSC is a temperature analysis system that measures the difference in temperature required to raise the temperature of the reference and the sample as a function of temperature. A sample was sent to the laboratory for DSC testing. [22, 23].

Preliminary study

On the basis of buoyancy study the preliminary study of formulation was done. After that few formulations were selected and given in table no. 1 for further evaluation.

Pre Compression Parameters

Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hauser ratio were calculated. While the flow properties of the powder blend were accessed from the angle of repose [24].

Post Compression Parameters

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The Monsanto hardness tester was used to determine the tablet hardness. It is expressed in kg/cm2 . Five tablets were randomly picked and hardness of tablets was determined [25, 26].

Friability

Tablet strength was tested by using Roche friabilator. 20 tablets were weighed and placed in the friabilator and operated for 100 revolutions, taken out and were dedusted. The percentage weight loss was calculated by reweighing the tablets. The % friability was calculated by:

$$F= [(W_{initial}- W_{final}) \times 100]/ W_{initial}$$

Thickness

Control of physical dimension of the tablet such as thickness is essential for tablet uniformity and consumer acceptance. The diameter and thickness

of the tablet was measured using vernier calipers and expressed in mm.

Weight variation

20 tablets were selected randomly from each batch were weighed individually and together in a single electronic balance. The average weight was noted.

$$PD= [(W_H-W_L) \times 100]/ W_H$$

Where, PD= percentage deviation

W_H= highest weight (mg)

W_L= lowest weight (mg)

Uniformity of drug content

10 tablets were weighed and powdered. Then powder equivalent to 10 mg of drug was taken and dissolved in 0.1N HCL, made up the volume up to 10 ml. after that 10 ppm solution was prepared and absorbance was measured at 242 nm by using SHIMADZU UV-1800 spectrophotometer.

In-vitro Buoyancy studies

The in vitro flotation behavior of the tablets was determined by the float delay time. The tablets were placed in a 100 ml beaker containing 0.1 N HCL. The float delay time (time taken for the tablet to reach the surface) was determined [27]. The time between introduction of the dosage form and its buoyancy in 0.1N HCl and the time during which the dosage form remains buoyant. The total length of time that the dosage form remains buoyant is called the total float time. (TFT).

In-vitro drug release study

Drug release from the floating tablets was evaluated by dissolution testing with a USP type II dissolution apparatus equipped with paddles at 37 ° C ± 0.5 ° C at 50 rpm. The test was carried out using 900 ml of 0.1N HCl as the dissolution medium. A 5 ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium. The samples were filtered and diluted if necessary. The absorbances of these solutions were determined at 242 nm using a UV-visible spectrophotometer.

Drug release kinetics

To study the drug release kinetics, the data from in-vitro drug release studies were subjected to various kinetic models: zero order (eq. 1) as cumulative amount of drug release Vs time, first order (eq. 2) as log % drug remaining Vs time, higuchi model (eq. 3) as % CDR Vs square root of time and Korsmeyer – Peppas model (eq. 4) as log T Vs log % CDR [28, 29].

$$C= K_o t \ldots\ldots (1)$$

Where K_o= zero order constant (concentration/time) t= time (hrs)

$$\text{Log } C= \text{Log } C_o - Kt/2.3 \ldots.. (2)$$

Where C_o= initial concentration of drug (first order constant) t= time

$$Q= kt1/2 \ldots.. (3)$$

Where K= constant t= time (hr)

$$Mt/M\infty = Ktn$$

Where $Mt/M\infty$= fractional solute release t= release time, K= kinetic constant

RESULTS AND DISSCUSSION

FTIR spectroscopy:

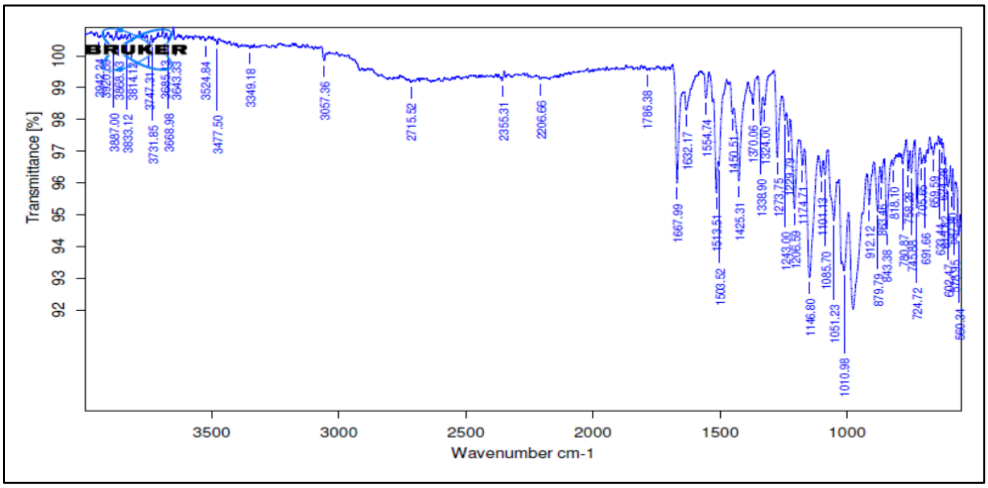

Fig. No. 1: IR spectra of Vildagliptin

Table No. 2: Interpretation of drug (Vildagliptin)

Sr. No.	Functional Groups	Observed Ranges (cm-1)	Standard Ranges (cm-1)
1.	CH stretching alkane	3057.36	3000-3200
2.	C=N Stretching	1632.17	1600-1650
3.	CH bending(alkane)	1370.06	1300-1450
4.	CN Vibrations	1146.80	1100-1250
5.	C-H stretching(aromatic)	3057.36	3000-3100
6.	C=O stretching	1667.99	1600-1750

Interpretation of FTIR spectra is given in table no. 2. According to this interpretation the observed peak of drug was found to be in the range.

Differential Scanning Calorimetry studies:

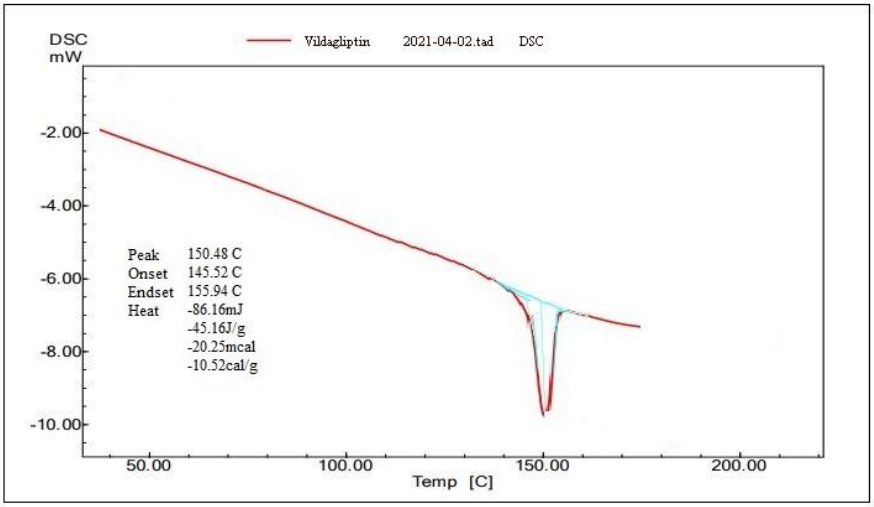

Fig. No. 2: DSC study of Vildagliptin

The DSC analysis of Vildagliptin is given in fig. 2. On the basis of DSC analysis the melting point of Vildagliptin was found to be 150.48^{0}C.

Pre compression characterization: The bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose of floating tablet are given in table no. 3.

Table No. 3: Pre compression characterization

Formulation code	Bulk density (gm/ml)	Tapped density (gm/m)	Angle of Repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.359±0.0078	0.478±0.0036	29.35±0.56	8.15±0.64	1.51±0.025
F2	0.389±0.0004	0.415±0.0078	22.68±0.06	12.35±0.18	1.15±0.029
F3	0.315±0.0065	0.416±0.0044	28.36±0.74	10.39±0.89	1.18±0.030
F4	0.329±0.0048	0.448±0.0055	18.30±0.41	21.26±0.28	1.36±0.018
F5	0.378±0.0048	0.497±0.0015	21.36±0.74	9.15±0.94	1.08±0.026
F6	0.315±0.0036	0.415±0.0076	19.38±0.21	13.48±0.89	1.38±0.048
F7	0.325±0.0045	0.448±0.0036	21.66±0.15	8.29±0.97	1.84±0.018
F8	0.335±0.0079	0.486±0.0074	19.54±0.28	22.36±0.94	1.38±0.029
F9	0.345±0.0024	0.436±0.0034	20.36±0.81	18.29±0.59	1.15±0.023

Mixture of all formulation has good to excellent flow property range. The angle of repose of all formulations shows excellent to passable flow.

Post compression characterization: All batches of formulation were evaluated for various physical parameters and results tabulated in table no. 4.

Table No. 4: Post compression characterization

Formulation code	Hardness (kg/cm^2) ± S.D.	Drug content (%) ± S.D.	(%) Friability ± S.D.	Swelling index %	Thickness (mm)	Weight Variation (mg)
F1	3.62±0.087	96.35±0.062	0.365±0.027	41.29±0.290	3.48±0.96	223.62±0.926
F2	3.89±0.067	99.15±0.064	0.311±0.065	39.29±0.99	3.87±0.97	223.6 ± 0.062
F3	3.92±0.015	99.36±0.064	0.365±0.015	42.29±0.14	3.59±0.99	223.66±0.25
F4	3.25±0.084	99.31±0.048	0.398±0.054	40.29±0.49	3.35±0.29	223.62±0.62
F5	3.24±0.026	100.84±0.024	0.411±0.048	41.29±0.54	3.79±0.55	223.65±0.25
F6	3.18±0.015	100.64±0.087	0.398±0.084	46.59±0.48	3.28±0.99	223.42±0.251
F7	3.29±0.094	98.35±0.017	0.518±0.084	46.59±0.45	3.38±0.57	225.67±0.063
F8	3.19±0.739	96.35±0.028	0.494±0.054	49.59±0.48	3.79±0.57	223.62±0.926
F9	3.29±0.843	101.43±0.058	0.295±0.054	45.48±0.24	3.48±0.76	225.36±0.036

The weight variation of each formulation was within the range. According to the thickness of the entire formulation, it was found to be uniform in size. The hardness of the tablet was within the standard range and the friability was found to be less than 1%. All these parameters were satisfactory as specified in the pharmacopoeia.

In-vitro Buoyancy studies: Buoyancy studies were performed using 0.1N HCL solution at 37ºC; the tablets floated and remained buoyant are shown in table no. 5.

In-vitro drug release study: The % CDR and drug content are given in table no. 5 and the in-vitro drug release profiles of F1 To F9 are shown in fig. 3.

Table No. 5: Drug release, drug content and in-vitro buoyancy data

Formulation	% cumulative drug release	Floating lag Time	Floating Duration
F1	79.53	52	12
F2	84.48	69	12
F3	97.64	82	12
F4	81.72	122	12
F5	89.63	134	12
F6	88.82	152	12
F7	87.43	178	12
F8	77.87	224	12
F9	69.97	239	12

The concentration of HPMC K4M, carbopol 934, NaHCO3 and citric acid optimized on the basis of floating lag time and floating time. The optimized concentration of HPMC K4M, carbopol 934, NaHCO3 and citric acid was 20-30%, 20-30%, 5% and 15% respectively. To find in-vitro drug release, F1 to F9 formulations were prepared.

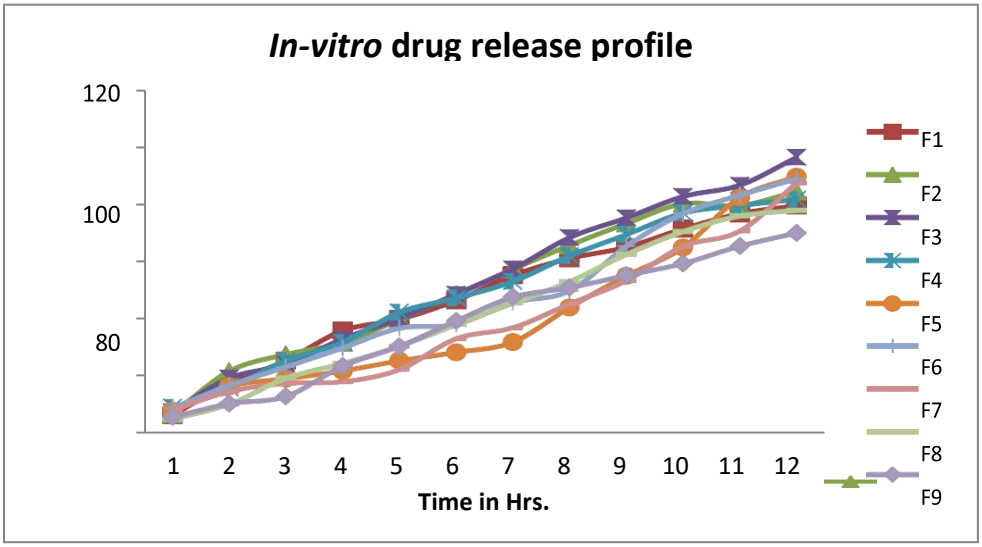

Fig. No. 3: Dissolution Profile of Formulation Batches (F1-F9) (Time Vs %CDR)

The drug content in each formulation was found in a uniform range. This range is uniform and meets the specifications of the Pharmacopoeia. Throughout the process, formulation F3 was considered the best based on drug release, drug content, and floating wait time. Drug release, drug content, and F3 floating delay time were 97.67%, 82 seconds respectively.

Drug release kinetics: Data of drug release kinetics is shown in table no.6.

Data were plotted according to the first and zero order higuchi model and the Korsmeyer-peppas pattern for drug release kinetics. The regression equation of the optimized formulation F3 was determined according to the zero order equation 0.9964, the first order equation 0.9938

and the Higuchi model 0.996 respectively. These values clearly indicate that the formulation is best expressed by zero order kinetics. It followed the zero order pattern.

Table No. 6: Data of release kinetics

Formulation	Zero order	First order	Higuchi order	Korsmeyer order
F1	0.9833	0.9894	0.9955	0.9806
F2	0.9807	0.9725	0.985	0.9724
F3	0.9964	0.9938	0.996	0.9963
F4	0.9885	0.9755	0.9462	0.9857
F5	0.9213	0.7646	0.8365	0.9293
F6	0.9774	0.8748	0.9321	0.9864
F7	0.9533	0.7994	0.8673	0.9404
F8	0.9940	0.9607	0.9691	0.9959
F9	0.9843	0.9882	0.9772	0.9835

Dissolution data was also plotted in the well-known exponential equation (Korsmeyer-peppas eq.), Which is often used to describe drug release behavior from the polymeric system. According to this model, the value indicates the type of super case II release. Case II generally refers to polymer chain erosion and abnormal (non-Fickian) transport refers to a combination of diffusion control drug release and erosion. Based on the n-value, the optimized formulation (F3) exhibits non-fickian-type drug release.

CONCLUSION

Vildagliptin floating tablets were successfully formulated using the mixture of carbopol 934 (9%), NaHCO3, (18%) and citric acid (13%). The floating drug delivery was a promising approach to achieve a prolongation of gastric residence time of drug. The gas generating agent NaHCO3 used to improve the floating capacity of tablet and citric acid used as a floating enhancer. Finally the optimized formulation shows desired drug release profile over 12 hrs.

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CONFLICT OF INTERESTS

Declare none

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