ORIGINAL ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Design, Development, Formulation, and Evaluation of Gastro retentive Floating Tablet for Anti-diabetic Agent

Vasim Pathan[1]*, Vishal Gulecha[1], Amar Zalte[1], Anil Jadhav[2]

Abstract

The main aim of the research was to persist the gastric residence time of vildagliptin by designing its gastro-retentive tablet as well as to study the effect of different polymers on its release rate using 2^3 randomized full factorial designs. Tablets are manufactured by direct compression method. Hydroxypropyl methylcellulose was used as matrixing agent, M.C.C., and Na_2Co_3 were used. The manufactured tablets assessed for physicochemical parameters such as weight variety, hardness, friability, floating properties (total floating time and floating lag time), *in vitro* drug release, and drug content, and stability study. The drug- polymer interaction was studied by differential scanning calorimetry and Fourier transform infrared (FTIR). On the basis of preliminary batches, the PF3 batch giving more drug release so that the PF3 batch is used for DoE process. Formulation F7 had been selected as an optimum formulation as it displayed more comparison in dissolution profile with theoretical profile which is 99.89 ± 0.49%. The dissolution of batch F7 can be described by zero order kinetics ($R^2 = 0.954$), First order- $R^2 = 0.87$, Higuchi $R^2 = 0.989$, and Peppa's $R^2 = 0.99$. Also studied X-ray Photographic Studies in Rabbits and showed tablet was float more than 8 h in gastric region of the Albino rabbits. It could be concluded from this study that the prepared Gastro-retentive tablet could reduce the frequency of dosage, dose related side effects, and increase the bioavailability.

Keywords: Design expert, Direct compression, Floating tablets, Gastro-retentive drug delivery system, Hydroxypropyl methylcellulose, Vildagliptin

*Asian Pac. J. Health Sci., (*2021); DOI: 10.21276/apjhs.2021.8.4.1

Introduction

Among the different routes of drug delivery, oral administration has the most routes of drug administration to the patient and the clinician. Nonetheless, the peroral route of medications has disadvantages such as hepatic first-pass metabolism and enzymatic degradation inside the gastrointestinal (GI) tract, which preclude the oral route of specific classes of medications particularly proteins and peptides. Subsequently, other absorptive mucosa is considered as potential sites for delivery of drug.[1,2]. In the present time, focusing of the medication at a specific site has turned into a significant piece of pharmaceutical research.[3] Type 2 diabetes mellitus (T2DM) is a well-established disease that causes disability (blindness, limb amputation, kidney failure, or cardiovascular [CV] events) in affected patients.[4] Since 1980, the age-adjusted predominance of diabetes in adults has improved, which has brought about quadrupling of the quantity of influenced adults with diabetes in nations around the world.[5,6] Vildagliptin is a new anti-diabetic drug. It has a place with the dipeptidyl peptidase IV (DPP-4) inhibitors and takes action on the incretin system.[7] An incretin hormone Glucagon-like peptide 1 (GLP-1) is released inside the gut wall after food ingestion from the L-cells. This hormone stimulates insulin secretion and prevents glucagon secretion and quickly eliminated by DPP-4.[8] Vildagliptin prevents DPP-4 consequently results in improved concentrations of GLP-1 and reduced concentrations[9] of glucose. Chemical name of vildagliptin is (S)-{[(3-hydroxyadamantan-1-yl) amino] acetyl} pyrrolidine-2- carbonitril and chemical structure has presented in below (Figure 1).

This drug is a selective inhibitor of DPP-4 and potent. The drug has an orally active as well as increases control of glycemic in patients of T2DM by improving pancreatic (β as well as α) islet function. Thus drug suppress the inappropriate glucagon excretion in patients of T2DM as well as increases insulin secretion in patient. It also reduces glycated hemoglobin when given as a single drug, with a little hypoglycemia, without weight gain and, in combination with the different commonly prescribed classes of oral hypoglycemic drugs: A sulfonylurea or insulin, a thiazolidinedione.[10] When administered by oral route vildagliptin is quickly absorbed. 85% of drug is eliminate through renal excretion, around 70% of drug is metabolized through hydrolysis and 23% of drug is oral dose excreted unchanged in the urine. Food digestion is not modify the pharmacokinetics of the drug.[11] Vildagliptin, earlier launched DPP-4 inhibitors, is marketed in over 125 countries, as well as over 17 million patients are exposed to drug as its launch in 2007.[12] Being the first molecules under development, extensive in vitro and pre-clinical investigation had conducted with vildagliptin with its precursor, DPP-728, to map their off-target pharmacology. The in vitro and pre-clinical safety profiles had boosting, with only a few species-specific safety signals affecting to the CV, immune systems, and GI at concentrations that had approximately 5–7 times the anticipated human exposure.[12,13] The key objective of the current

[1]Department of Pharmacy, Sandip University, School of Pharmaceutical Sciences, Nashik, Maharashtra, India

[2]Department of Pharmacy, Sandip Foundation's Sandip Institute of Pharmaceutical Sciences, Nashik, Maharashtra, India

Corresponding Author: Vasim Pathan, Department of Pharmacy, Sandip University, School of Pharmaceutical Sciences, Nashik, Maharashtra, India. E-mail: vasimpathan.256@gmail.com

How to cite this article: Pathan V, Gulecha V, Zalte A, Jadhav A. Design, Development, Formulation, and Evaluation of Gastro retentive Floating Tablet for Anti-diabetic Agent. Asian Pac. J. Health Sci., 2021;8(4):1-12.

Source of support: Nil

Conflicts of interest: None.

Received: 22/05/21 **Revised:** 11/06/21 **Accepted:** 29/06/21

research had to make a gastro-retentive drug delivery system comprising vildagliptin using 2^3 factorial design as an optimization method. The current studies displayed the design of vildagliptin gastric floating tablets using polymers: HPMK15M, hydroxypropyl methylcellulose (HPMC) K100M, HPMC K4M and study of the effect of polymers on *in vitro* drug release and the floating behavior.[14]

Materials and Methods

The drug (Vildagliptin) was received Pharma International Pvt. Ltd. is a Mumbai based company as a gift sample. Sodium bicarbonate was gotten from Loba Chem. Pvt. Ltd., HPMC K15M, HPMC K100M, HPMC K4M, Microcrystalline cellulose (MCC), Mg. Stearate was got from Signet chemical corporation, Mumbai. All other reagents are of pharmaceutical or analytical grade and deionized water taken by reverse osmosis. Other chemicals used in the studies had of analytical grade. All the chemicals had used as received.

Preliminary Screening

Preliminary screening had performed using three various grades of HPMC, that is, HPMC K15M, HPMC K100M, and HPMC K4M, two different concentrations of MCC to select proper floating lag time, total floating time, and sustain the release up to 12 h. PF1-PF6 batches as shown in Table 1 Tablets prepared using different polymers were tested for floating lag time, total floating time, % drug content, hardness, weight variation, friability, *in vitro* drug release, etc.

Preliminary Study

FTIR spectroscopy

FTIR spectroscopy had found to be the most reliable technique for predicting the possible interaction between the polymers and drug. Physical mixtures including polymers and drug in a ratio of 1:1 had manufactured by triturating in mortar and pestle. Samples were subjected to Fourier transform infrared (FTIR) studies using Brucker alpha instrument and the IR spectrum of API and drug-excipient mixtures had compared to see any interaction in drug and excipients that are used for the formulation of floating tablets of Vildagliptin.

Organoleptic Characteristics

The sample had investigated for organoleptic characters such as odor, color, and appearance.[15]

Melting point (MP)

The MP of Vildagliptin had done by a capillary method and an M.P. apparatus (KUMAR, VMP-D). The Vildagliptin was kept inside glass capillary and using a flame its one end sealed. Capillary containing Vildagliptin immersed in liquid paraffin inside the Thiele's tube and heated using a flame. The temperature where it starts to melt was observed as a MP, mechanical assembly records temperature beginning with underlying stage varies in temperature and finishing with done changed temperature phase. Finally, the study had done in triplicate.[16]

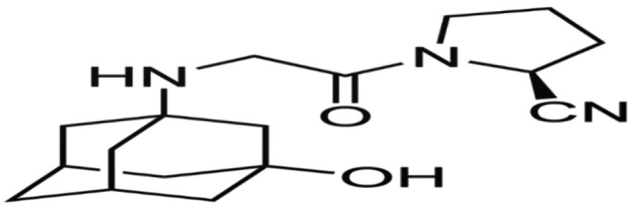

Figure 1: Structure of vildagliptin

Solubility

Study of solubility was completed by taking some specified drug (about 5–10 mg) in clean and dry 10 mL flasks and adding 10 mL of each solvent at 37°C and put for 3 days for equilibrium in shaking incubator. Solubility balance was resolved: Taking supernatant and investigating it on ultraviolet (UV) spectrophotometer.[17]

Loss on drying

It is a broadly utilized technique to decide moisture content; infrequently it might be unstable material from the example. Limit of detection (LOD) is directly measured by IR moisture balance (Mettler Toledo HB43-S). First, the instrument calibrated by pressing the button and then distributed 5.00 g of powder into the sample pan uniformly and closes the unit. Set the temperature: IR moisture balance at 60°C - 10 min (Note: LOD determined at 60°C due to the drug has MP at 102–105°C) and took the reading by start bottom and check LOD.

Drug-Polymer Compatibility Study using Differential Scanning Calorimetry (DSC)

The DSC study had done by DSC-60 (SHIMADZU) differential scanning calorimeter with thermal analyzer (TA-60WS). Pure Vildagliptin sample of 7.8 mg had kept in aluminum pan as well as sealed before heating below nitrogen flow (300 mL/min) at a scanning rate of 10°C min^{-1} from 30°C to 550°C. An empty aluminum pan had used as reference. Composition of tablets of Preliminary batches is given in Table 1.

Experimental Design (Optimization by 2^3 Full Factorial Design)

A 2^3 randomized full factorial design had used in the present study. In this design, three independent factors had evaluated, each at two levels, and trials of experiments had done for all eight possible combinations. The concentrations of M.C.C. (X_1), HPMC K15M (X_2), and $NaHCO_3$ (X_3) had selected as independent variables in 2^3 full factorial design and Floating lag time, duration of floating, *in vitro* Drug Release Studies had chosen as

Table 1: Composition of tablets of preliminary batches

Ingredient name (mg)	*PF1*	*PF2*	*PF3*	*PF4*	*PF5*	*PF6*
Vildagliptin	30	30	30	30	30	30
HPMC K4M	30	45	-	-	-	-
HPMC K15 M	-	-	30	45	-	-
HPMC K100M	-		-	-	30	45
M.C.C	101.1	86.1	101.1	86.1	101.1	86.1
$NaHCO_3$	16.2	16.2	16.2	16.2	16.2	16.2
Mg. Stearate	0.9	0.9	0.9	0.9	0.9	0.9
Talc	1.8	1.8	1.8	1.8	1.8	1.8
Total. Wt.	180	180	180	180	180	180

HPMC: Hydroxypropyl methylcellulose

dependent variables**.** Coded values have displayed in Table 2. The layout of formulation for the factorial design formulations (F1–F8) is presented in Table 3. Prepared tablets had assessed for hardness, thickness, duration of floating and floating lag time, and *in vitro* drug release.

Formulation of Vildagliptin Floating Bio-adhesive Tablets as Per CCD

Tablets are manufactured by direct compression technique. Exactly weighed quantities of M.C.C. and polymer had taken in a mortar and mixed methodically, in that mixture required amount of vildagliptin added and slightly mixed using pestle. Sodium bicarbonate weighed accurately and separately taken in a mortar which was crushed with pestle. The mixture had passed through 40# sieve and later taken in a plastic bag and blended for 5 min. Required amount of Mg stearate and talc added and final blend had again passed through 40# sieve. Then, the powder was compressed into tablets with the help of 8 mm flat punches and equivalent dies at a hardness of 6 kg/cm^2 8 station tablet punching machine.[18]

Selection of Suitable Design of Experiment

A 2^3 randomized full factorial design had selected in the present study. In this design, three independent factors had assessed, each at two levels, and experimental trials had done for all eight possible combinations. The concentrations of M.C.C. (X_1), HPMC K15M (X_2), and $NaHCO_3$ (X_3) had chosen as independent and % drug release was selected response variables in 2^3 full factorial design. From the above preliminary batches, PF5 batch had optimized results than other batches so that PF5 batch is selected for factorial design and Design expert software actual design in Table 4.

Table 2: Coded values for final formulation

Polymers	*−1*	*+1*
HPMC K15M	30	45
M.C.C.	101.1	86.1
$NaHCO_3$	18.2	16.2

HPMC: Hydroxypropyl methylcellulose

Table 3: Compositions of formulations of factorial design

Ingredient name (mg)	*Quantity in (mg/tablet)*							
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*
Vildagliptin	30	30	30	30	30	30	30	30
HPMC K15M	30	30	45	45	30	30	45	45
M.C.C	101.1	86.1	101.1	86.1	101.1	86.1	101.1	86.1
$NaHCO_3$	18.2	18.2	18.2	18.2	16.2	16.2	16.2	16.2
Mg. Stearate	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Talc	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8

HPMC: Hydroxypropyl methylcellulose

Evaluation of Tablets

The formulated tablets had examined for friability, weight variation, hardness, content uniformity, *in vitro* dissolution study, total floating time, floating lag time, etc.

Appearance

The bio-adhesive tablet was identified visually by checking the difference in the color, shape, and texture.[19]

Hardness

Hardness of bio-adhesive floating tablet was measured in the hardness test. It had measured by Hardness tester model EH-01 (Electro lab). It was measured in kg/cm^2.

Thickness

Thickness of the tablets had measured using digital Vernier caliper. The test had completed in triplicate. Its average was determined.[20]

Friability

Friability of tablet determined with the help of Rolex tablet friabilator (Roche friabilator). It was performed by accurately weighing ten tablets before dusting, keeping them in the friabilator and rotating the plastic cylinder vertically for 4 min at 25 rpm. The tablet had dedusted by soft muslin cloth and reweighed. The % friability had calculated according to formula.[21]

$$\text{Friability} = 100 \times \frac{\text{Tablet weight (before weight)} - \text{Tablet weight (after test)}}{\text{Tablet weight (before the test)}}$$

Where, W0 is the tablet weight before the test and W is the tablet weight after the test.

Weight variation

The weight variation test was determined to what extent the weight of an individual tablets deviates with respect to the average tablet tested. To calculate the weight variation, 20 tablets at random had weighed as well as then the average weight had noted. Then, the weight deviation and percentage deviation were calculated.[22]

Table 4: Design expert software actual design

Std Run	*A: HPMC K15M (mg)*	*B: M.C.C. (mg)*	*C: $NaHCO_3$*	*Response 1: % Drug Release*	*Response 2: Floating lag time (sec)*
1	30	101.1	18.2	86.12	68
2	30	86.1	18.2	90.519	57
3	45	101.1	18.2	94.374	55
4	45	86.1	18.2	87.485	69
5	30	101.1	16.2	80.192	67
6	30	86.1	16.2	80.174	70
7	45	101.1	16.2	99.664	72
8	45	86.1	16.2	81.45	68

HPMC: Hydroxypropyl methylcellulose

$$\text{Deviation}\ (\%) = \frac{\text{Weight}\ (\text{individual})\ - \text{Weight}\ (\text{average})}{\text{Weight}\ (\text{average})} \times 100$$

Weight (average)

In Vitro Buoyancy Study

Floating lag time and total of floating time

Floating characteristics of the manufactured formulations had determined using USP XXII paddle apparatus under sink conditions. 900 mL of HCL buffer pH 1.2 had taken as medium and the temperature had kept at 37 ± 0.5°C thought the study. The time between the introduction of tablet as well as its buoyancy on the gastric fluid requisite for the tablet to float on the gastric fluid (floating lag time) and the time during which dosages for measurement buoyant (duration of floating) had measured. The integrity of the test tablets had saw visually throughout study.[23]

Tablet Swelling Ability

Studies of SI for batches were performed at R.T. It is completed with the dissolution apparatus of USP-II. 0.1N HCl medium of 900 ml was utilized pivoted to 100 RPM. Temperature of the medium was kept to 37°C ± 0.5°C all through the investigation. At times 4, 8, 16, and 24 h, withdrawn the tablets marked to expel water in excess then weighed. Properties of swelling were expressed as % swelling as following formulae.[24]

$$\%\ \text{swelling} = \frac{\text{Weight}\ (\text{swollen})\ - \text{Weight of tablet}\ (\text{initial})}{\text{Weight of tablet}\ (\text{initial})} \times 100$$

Drug Content

Drug content of all factorial batches is performed to select randomly 20 tablets whereas the successfully calculated average weights. Tablets squashed using a mortar whereas precisely normal gauged measure of tablets, selected triturate for examination. Tests replaced into various flasks whereas sufficiently diluted utilizing HCl of 0.1 N. The substance had shaken well and saved for 30 min for dissolving the total medication. Mixtures were separated and dilutions were done properly. In every tablet, the content of the drug was evaluated to 245 nm λ_{max} alongside considering reference as a blank.[25]

In Vitro Drug Release Studies of Batches

This investigation for fundamental bunches of the tablet was performed with disintegration mechanical assembly of USP – type II paddle (LAB INDIA-DISOTEST, 6 F 622). A 900 ml vehicle of disintegration reproduced fluid (0.1N HCL buffer) with no catalyst was put to cup 37 ± 0.5°C keeping up the temperature with 100 RPM. A tablet from each starter clump was set in each disintegration bin to get together. Run the get together for a time of 10 h. Withdraw of 5 ml test was every hour as long concerning 10 h by hand while separated all the examples. The withdrawn volume at each interval had replaced with exact amount of fresh dissolution medium kept at 37 ± 0.5°C. The samples were analyzed for drug releases by checking the absorbance at 244 nm using HPLC method.[26,27]

X-ray Photographic Studies in Rabbits

The selected tablet formula of *in vivo* investigation was reformulated with 15% BaS04 as opaqueing agent and prepared by wet granulation by single-punch tablet compression machine, fitted with 11 mm flat-faced punches.

This X-ray study was performed in 6 healthy Albino rabbits of either sex, weight 2 kg–2.5 kg. The animal had housed separately under environmental condition (25 0, 12 h dark, and light cycle). The rabbit had administrated with selected formulation (F7). A radiograph had prepared just before the administration of the $BaSo_4$ loaded tablet to check the lack of radio-opaque substance in the stomach. Then, the tablet had given orally by insertion them in hollow polyethylene tube. The tube had inserted inside the mouth of rabbit and blown using rubber bulb. Rabbit was placed upright posture for checking the position of tablet in gastric region by using X-ray machine. X-rays were taken at various time intervals such as 30 min, 1 h, 2 h, 4 h, and 8 h. X-ray imaging studies results showed that tablet was float more than 8 h in gastric region of the Albino rabbits.[28-30]

Data Analysis

To investigate release rate kinetics and the mechanism of release of the dosage form, the obtained data had fitted into first-order, zero-order, Higuchi matrix, and Korsemeyer-peppas model, depend on the r value and the best fit model had chosen.[31]

$$\frac{Mt}{M\infty} = K_1 t^n + k_2 t^{2n}$$

Comparison with Marketed Formulation

The *in vitro* dissolution profile of optimized bath had compared with the marketed formulation in 0.1 N HCl of pH 1.2. The *in vitro* dissolution profile (optimized formulation) had compared with the marketed formulation in 0.1 N HCl of pH 1.2. The *in vitro* dissolution profile of optimized formulation had compared with the marketed formulation in 0.1 N HCl of pH 1.2. The *in vitro* dissolution profile of optimized batch had compared with the marketed formulation in 0.1 N HCl of pH 1.2.[32]

Accelerated Stability Studies

The formulation optimized was enveloped by the foil of aluminum and exposed to 40 ± 0.5°C temperature inside the dependability chamber (Thermo lab, TH 200S). The preparation was broke down for organoleptic qualities, hardness, the content of the drug, and dissolution. In any rotational structure and evaluation of doses for drugs, the dependability of API is the noteworthy criterion in deciding their acknowledgment or dismissal. Soundness contemplates were finished by ICH Q1A rules. During the security examination, the item is presented to ordinary conditions, for example, temperature and dampness. The upgraded vildagliptin definitions were oppressed for solidness examines including packing material and storage conditions.[33-35]

Stability Protocol

Packaging material

Tablets wrapped inside foil of aluminum.

Storage condition

Exposed the tablets for stability is shown in Table 5 according to conditions of ICH given in the following table. Kept the samples in the chamber of stability (Thermo lab, TH 200S).

Results and Discussion

Preformulation Studies

The drug identification had done by FTIR is similar to that of reference. Compatibility study concludes that there has no interaction in the drug and polymer.

FTIR Spectroscopy

The interpretation of FTIR spectrum of vildagliptin is displayed in Table 6 and spectra in Figure 2. The FTIR spectrum had compared with peaks mentioned in the literature which confirms the identification of vildagliptin with its functional groups.

FTIR Spectra of Vildagliptin and Excipients

FTIR of Vildagliptin with its excipients given in Table 7 and spectra in Figure 3 exhibits characteristic Interpretation of C-N stretching having peaks at wave number (cm^{-1}) 1253.43, N-H (amine)= 3423.24, C-N= 1253.43, C≡N-2236.23 which is match with standard FTIR of Vildagliptin exhibits characteristic interpretation of C-H stretching having peaks at wave number (cm^{-1}) 2900.7.

The FTIR spectra of physical mixture of Vildagliptin and Excipients showed the presence of characteristic peaks at 3452.09 cm^{-1}, 1929.62 cm^{-1}, 2885.25 cm^{-1}, 3562.08 cm^{-1}, 1312.25 cm^{-1}, and 2361.24 cm^{-1} which indicated no interaction in the drug and polymer when physically mixed in the ratio of 1:1 (drug to polymer).

Table 5: Storage conditions for the stability study

Description	*Storage conditions*
Accelerated testing	40°C / 75 % RH

Table 6: Functional groups and wavenumbers observed in FTIR

Functional group	*Wave number (cm^{-1})*	
	Reference	*Vildagliptin*
N-H (amine)	3500-3300	3423.24
C=O (amide)	1850 – 1800	1823.34
C-N (stretch)	1340-1250	1253.43
C≡N	2200-2400	2236.23

FTIR: Fourier transform infrared

Table 7: Functional groups and wavenumbers observed in FTIR

Functional group	*Wave number (cm^{-1})*	
	Reference	*Vildagliptin*
N-H (amine)	3500-3300	3452.09
C=O (Stretching)	1950–1800	1929.62
C-H	2900-2850	2885.25
O-H (Carboxylic Acid)	3650-3590	3562.08
C-N (stretch)	1340-1250	1312.25
C≡N	2200-2400	2361.24

FTIR: Fourier transform infrared

Drug-polymer Compatibility Study by DSC

The DSC thermogram of procured vildagliptin sample is shown in Figure 4. The thermogram of vildagliptin showed endothermic peak at 150.91°C that is MP of Vildagliptin. The MP matches with the standard MP of Vildagliptin as per reference.

Selection of Drug Delivery System

The selection of carrier for specific drugs based on the physiochemical properties of the drug as well as the disease for which the system is to be used. Factors, that is, chemical nature, partition coefficient of the drug, and stability as well as type of absorption enhancer selected influence the carrier selection.

Standard Curve of Vildagliptin

Determination of UV absorption maxima

The solution (10 mg/ml) of Vildagliptin was scanned between 200 and 400 nm using UV spectrophotometer. Absorption maxima was obtained in distilled water. The absorption maxima (λ max) had found to be 204 nm in the solvents (distilled water). The obtained λ max had used for the preparation of calibration curve which is in Table 8 and Figure 5.

Organoleptic Characteristics

Organoleptic properties are the aspects of creating experience through the senses–including taste, smell, and touch. Vildagliptin received which had examined for organoleptic characteristics, for example, color, odor, and appearance. The results are presented in Table 9.

Results of organoleptic characterization obtained confirmed that the obtained vildagliptin sample is pure; the results compared with reported standard results of the drug, which does not show any difference. The drug sample was white to light yellowish,

Table 8: Absorbance of vildagliptin solutions of varying concentrations at 204 NM

Concentration (µg/mL)	*Absorbance*
0	0
8	0.233
12	0.350
16	0.449
20	0.576
24	0.68
28	0.796
32	0.902

Table 9: Organoleptic characterization of drug

Identification test	*Observed results*	*Reported standard*
Color	White to light yellowish	White to light yellowish
Odor	Odorless	Odorless
Taste	Tasteless	Tasteless
Appearance	A crystalline solid	A crystalline solid

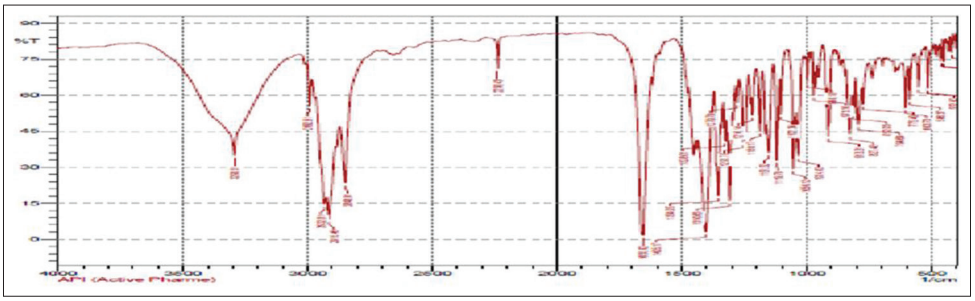

Figure 2: Fourier transform infrared spectra of vildagliptin at 75% RH, 40°C ± 2°C

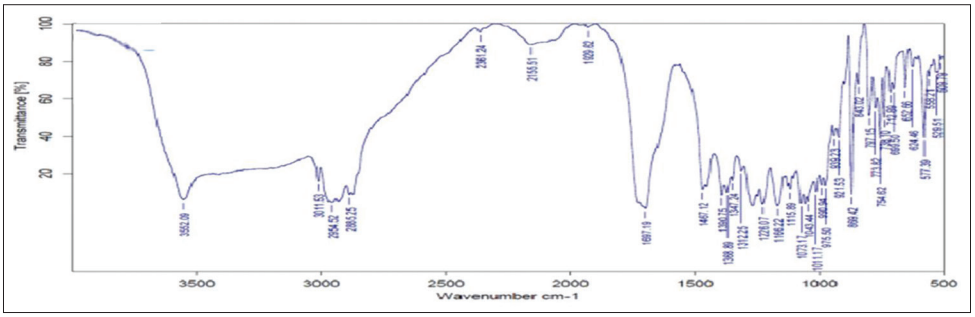

Figure 3: Fourier transform infrared spectra of vildagliptin and excipients at 75% RH, 40°C ± 2°C

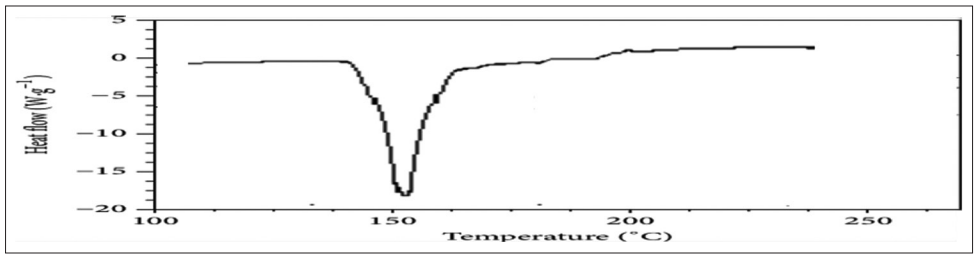

Figure 4: DCS thermogram of vildagliptin

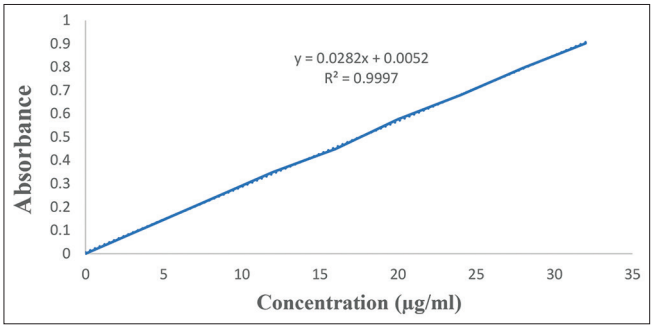

Figure 5: Calibration curve of vildagliptin

observed by naked eyes, it was odorless confirmed by smelling with nose simply, Taste shown tasteless and appeared to be a crystalline solid.

MP

An easily accessible MP physical parameter has significant potential for finding properties of the drug. MP is resolved in the capillary tube. The expression "melts about." implies that the temperature where the substance is melted, as showed by the disappearance of solid, will be nearby ±4°C from the expressed value, except if in any case demonstrated. MP of the drug by the capillary method in triplicate was performed, the average of these three determined, and results are mentioned in Table 10. As a MP study had done in triplicate, the average of these three reads is considered as a final result of the MP, which is compared with reported standard results, whereas no difference observed between them, it was 153 ± 1.5°C.

Solubility

It has the characteristic of a chemical substance that may be liquid, solid, or gas known as solute to break down in a solvent. Any drug's solubility was tested in various solvents, results are determined in (Table 11). Solubility was checked in water, ethanol, and PBS showed good results as per standard solubility of the drug. The drug was sparingly soluble in ethanol, freely soluble in water, that is, 20 mg/mL, and in PBS it showed 10 mg/mL that means practically insoluble.

Loss on Drying

The dampness in a strong could be communicated on a wet weight or dry wet premise. On a wet weight premise, the content

of water of material is determined as a level of the weight strong. This term is an outflow of dampness content on a wet weight basis. The dampness in a strong can be communicated on a wet weight or dry wet premise. On a wet weight premise, the water substance of material is checked as a level of the weight strong. This term is an outflow of dampness content on a wet weight premise. The average % loss drying was 0.723 ± 0.083%. The result of vildagliptin is determined in Table 12.

Physicochemical Evaluation of Bilayer Floating Tablet

All formulations remained smooth, white, and flat faced circular with no visible cracks. The results are displayed in Table 13. All the bathes displayed values within the prescribed limits for tests such as friability, thickness, hardness, weight variation, and drug content which indicate that the prepared tablets are of good standard quality.

Floating Lag Time and Duration of Floating of Factorial Batches

Gastro retentive buoyant tablets need to possess certain characteristics. Therefore, trials were done for buoyancy lag time as well as flotation period. Buoyancy lag time indicates how much time a tablet would take, under *in vitro* simulated conditions to float over the gastric fluid. All floating tablets had buoyancy lag time in the range of 72–55 s. The total floating time had obtained to be in the range of >12–6 h, indicating a stable gel layer formation by all polymers and sodium bicarbonate that persists for an extended time which is displayed in Table 14.

Table 10: The MP of the drug

Observation	*MP (Average)*	*Reported standard*
153±3.98°C 154±3.84°C 153±3.47°C	153–154°C	153±1.5°C

MP: Melting point

Table 11: The solubility of vildagliptin

Solvent	*Solubility*	*Solubility (mg/ml)*
Water	Freely Soluble	-
Ethanol	Sparingly soluble	20 mg/mL
Methanol	Freely soluble	-
PBS	Sparingly soluble	10 mg/mL
Chloroform	Soluble	-
Buffer 7.2	Slightly soluble	-

Table 12: Loss of drying of vildagliptin

Initial weight	*Final weight after 10 min*	*% loss of drying*	*Avg. % loss of drying*
5.011 g	4.977 g	0.67	0.723±0.083%
5.008 g	4.966 g	0.82	
5.006 g	4.971 g	0.68	

Tablet Swelling Ability

Investigation of polymer swelling as well as erosion has a valuable application to better recognize the relative significance of participating parameters and the mechanism of release. Swelling ratio shows the quantity of water which has enclosed within the hydrogel at equilibrium and has a function of network structure, ionization, and hydrophilicity of functional group. Swelling study had done on all the formulation of floating tablet for 24 h. The swelling index results have shown in Table 15, all the bilayer floating tablets swelled but remained intact without breaking throughout the period of swelling (24 h) in 0.1N HCl. The order of swelling index observed with different polymers was HPMC K100M (F9) > HPMC K15M (F6) > HPMC K4M.

In vitro Release Profile

From Figure 6, formulation F1 showed rapid burst release within 2–3 h F2 and F3 released the drug only for 6 h and 8 h only. And formulation F7 released drug totally in 12 h. Formulations F 5 and F 6 released the drug more than 80 % in 12 h. $NaHCO_3$ fixed concentration utilized for helping lightness and bio-adhesive property to the last preparation. F7 determines 99.66% discharge of medicate for 24 h shown in Table 16. It has huge % SI and furthermore kept up grid uprightness for 24 h. These estimations are in consistence with the capacity of HPMC to frame complex lattice organize which prompts multiplication in route of diffusion so diminishes medicate discharge.

F7 formulation had chosen for the optimized formulation in HPMC K15 formulation.

Optimization of OPTIMIZED BATCH (F7)

From the above results, it is clear that batch number F7 showed the best results, thus optimized for the further formulation. The optimization was performed based on reaction modeling on surface by utilizing the graphical and numerical advancement technique. Attractive quality is a target work that ranges from zero outside of the cutoff focuses to one at objective. Effect of DOE variables on the formulation and two ways ANOVA for FLT (floating lag time) has in Tables 17 and 18, respectively. The HPMC impact on FLT obtained to be greatly noteworthy and $NaHCO_3$ impact was again noteworthy.

HPMC K100M and $NaHCO_3$ impact on SI was observed highly significant.

T_{25} model

On placing data in Design Expert, Fit summary applied to information. Model had been proposed by the software so according to this model the condition is as per the following:

Table 13: Physicochemical parameters of core tablet

Batch code	*Hardness kg/cm²*	*Thickness (mm)*	*Friability (%)*	*Weight variation (%)*	*Drug content (%)*
F1	5.50±0.24	3.38±0.032	0.651	1.40	98.42±1.27
F2	5.65±0.18	3.32±0.011	0.661	1.02	97.65±0.90
F3	5.45±0.37	3.35±0.043	0.554	1.15	96.82±0.66
F4	5.55±0.54	3.53±0.129	0.417	1.15	95.08±1.80
F5	5.40±0.35	3.36±0.05	0.521	1.02	98.05±0.90
F6	5.50±0.48	3.1±0.083	0.431	1.15	96.65±0.64
F7	5.80±0.26	3.54±0.074	0.411	1.40	99.76±0.90
F8	5.45±0.25	3.12±0.012	0.521	1.40	97.34±0.56

In coded terms, model equation

Linear model followed by T_{25}

y=4.0666+0.6333 $NaHCO_3$ +0.6666HPMC K100M

Full and Reduced Models for Gastro-retentive tablet at T 25 model shows in (Figures 7-10) shows Normal % Probability v/s Internal standardized residual T, Generation of Contour plot of Optimized Batch, Generation of contour plot and response surface plot for response Y1 of Optimized Batch and 3-D Response plot of $T_{25\%}$ of Optimized Batch, respectively:

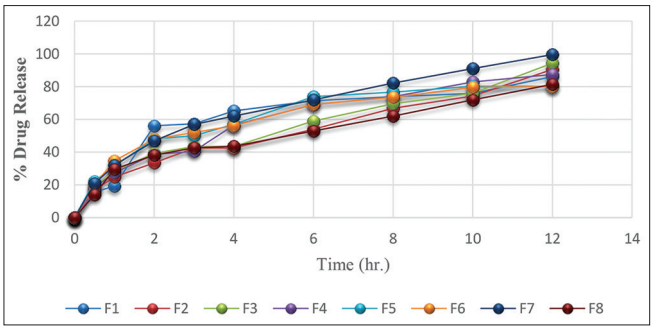

Figure 6: Percentage cumulative drug release of bathes

Table 14: Determination of the floating lag time and duration of floating tablets of preliminary batches

Batch No.	*Floating lag time (s)*	*Total floating time (h)*
F1	68±2.65	6
F2	57 ±1.54	9
F3	55±0.7	>12
F4	69±3.98	>12
F5	67±0.87	>12
F6	70±1.32	>12
F7	72±1.54	>12
F8	68±1.2	>12

Table 15: Swelling index of preliminary batches

Formulation	*% Swelling index (Avg.)*			
	4 h	*8 h*	*16 h*	*24 h*
F1	162.86±1.08	245.56±0.99	302.46±1.08	392.87±1.09
F2	169.63±0.99	232.44±0.91	319.31±0.91	464.00±1.08
F3	157.92±0.91	241.85±	291.46±0.99	452.35±1.04
F4	174.06±0.99	363.05±1.08	420.53±0.99	409.79±1.05
F5	166.12±0.51	245.56±0.56	324.34±0.98	405.22±0.87
F6	167.16±0.91	246.06±0.98	348.52±0.98	371.40±0.93
F7	195.99±0.98	281.78±0.91	385.97±1.08	525.44±0.99
F8	135.96±0.54	221.56±0.34	325.45±0.34	425.56±0.99

T_{90} model

On placing data in Design Expert, Fit summary applied to information in that direct model had been proposed by the software so according to this model the condition is as per the following:

Coded terms for model of equation

Model of linear kinetic followed by T_{90}

y=22.8111+5.6660$NaHCO_3$ +2.4660HPMC K100M

T90 model shown in Figures 11 and 12 which are 3-D Response plot of $T_{90\%}$ of Optimized Batch, and 3-D Response plot of % Drug Release of Optimized, respectively.

Consequence of numerous examinations of straight linear model regression conceals, $t_{25\%}$ is increased by increasing $NaHCO_3$ and HPMC K15M.

% Drug release model

2FI kinetic model is follow % drug release

Y=62.6166HPMC+442.5322

K100M-26.4483 $NaHCO_3$+18.4425HPMC K15M. $NaHCO_3$

% Drug release model is shown in Figure 12 -batch and 3-D response plot of FLT of optimized Batch. The consequence of numerous straight regression examinations (model of 2FI) exposes which has on enhancing HPMC- Percentage drug release is enhanced.

Model for FLT

On placing data in design expert, Fit summary applied to information in that direct model had been proposed by the software so according to this model the condition is as per the following:

Coded terms for model of equation- Model of linear kinetic followed by FLT

y=31.4444-9.3333HPMC K15M+10.3333$NaHCO_3$

Model for FLT3 d plot is shown in Figure 13. The consequence of numerous straight regression examinations (model of 2FI) exposes which has on enhancing HPMC- Floating lag time is enhanced.

X-ray Photographic Studies in Rabbits

Rabbit was placed upright posture for checking the position of tablet in gastric region using X-ray machine. X-rays had taken at

Table 16: Percentage cumulative drug release of factorial batches

Time(h)	*Formulations (mean±SD)*							
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*
0	0.0±000	0.0±000	0.0±000	0.0±000	0.0±000	0.0±000	0.0±000	0.0±000
0.5	15.522±0.624	16.786±0.554	18.149±1.574	18.259±0.548	22.146±0.122	19.991±0.963	20.813±0.852	13.925±0.684
1	19.276±1.032	24.831±0.87	28.746±1.245	27.519±1.574	31.586±0.189	34.725±0.842	32.004±0.864	29.563±0.843
2	56.049±1.894	33.457±1.089	39.293±1.124	38.519±1.099	48.055±0.587	47.961±0.258	46.917±0.589	38.172±1.555
3	57.332±0.956	42.48±0.933	43.424±0.965	40.566±1.099	50.055±0.587	51.961±0.258	56.917±0.589	42.712±0.666
4	65.240±0.789	42.48±0.933	43.424±0.965	56.483±1.359	57.078±0.344	56.118±1.027	62.046±1.024	43.623±0.479
6	71.412±0.867	53.974±0.795	58.959±0.687	69.019±2.011	73.929±0.988	69.216±0.521	71.988±0.279	52.933±0.589
8	73.900±0.815	66.825±0.952	69.585±1.65	73.88±0.981	76.745±0.789	73.571±0.159	82.277±0.455	61.980±0.861
10	75.848±0.762	74.348±1.07	76.076±0.942	82.915±1.842	80.281±0.555	79.602±1.089	91.120±1.087	71.907±0.357
12	86.12±.12	90.519±0.746	94.374±1.523	87.485±0.987	80.192±0.085	80.174±0.872	99.664±1.097	81.45±0.2

Table 17: Two-way ANOVA for % drug release

Source of variation	*Sum of squares*	*Degree of freedom*	*Mean square*	*F ratio*
Model	1163.3	2	581.67	167.07
HPMC K15M	522.67	1	522.67	150.13
$NaHCO_3$	640.67	1	5640.67	184.02
Residual	20.89	6	3.48	---
Source of variation	*P-value summary*		*Significant*	
HPMC	*** (P<0.0001)		Yes	
$NaHCO_3$	*(P<0.0001)		Yes	

HPMC: Hydroxypropyl methylcellulose

Table 18: Two ways ANOVA for FLT

Source of variation	*Sum of squares*	*Degree of freedom*	*Mean square*	*F ratio*
Model	29082	3	9694.22	69.02
HPMC K15M	23525	1	23525	167.5
$CaCO_3$	3197	1	4197	29.88
AB	1360.5	1	1360.5	9.69
Residual	702.25	5	140.45	-
Source of Variation	*P-value summary*		*Significant?*	
Model	*** (P=0.0002)		Yes	
HPMC	*** (P<0.0001)		Yes	
$NaHCO_3$	*** (P=0.0028)		Yes	
AB	*** (P=0.0265)		Yes	

HPMC: Hydroxypropyl methylcellulose, FLT: Floating lag time

Table 20: Correlation coefficients (r^2) values of different kinetic models

Formulation	R^2			
	Zero	*First*	*Higuchi*	*Peppas*
Optimized batch	0.954	0.873	0.989	0.99

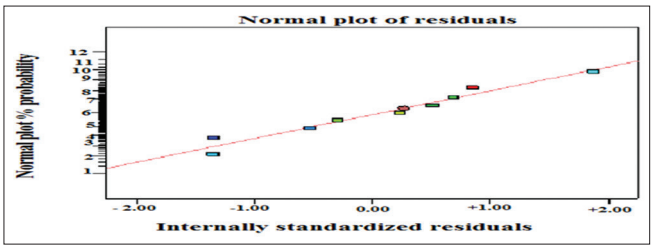

Figure 7: Normal % probability versus internal standardized residual T

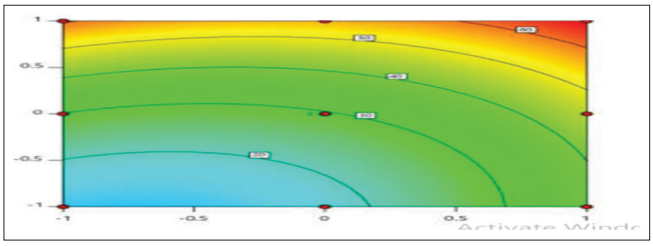

Figure 8: Generation of contour plot of optimized batch

various time intervals such as 1 h, 2 h, 4 h, and 8 h. X-ray imaging studies results showed that tablet was float more than 8 h in gastric region of the Albino rabbits as shown in Figures 14 and 15.

Data Analysis

Data analysis of optimized batch is as in Table 19 and data analysis of optimized batch was fitted into first-order, zero-order, Higuchi matrix, and Korsmeyer-peppas model and based on the r value and showed zero-order - 0.954, First order - 0.873, Higuchi matrix - 0.989, and Korsmeyer-peppas model - 0.99.

Comparison with Marketed Formulation

The promising formulation obtained by evaluation studies had compared with marketed formulation. The comparative IV-dissolution study of optimized batch and marketed product have displayed in below Figure. The result of comparison study indicated for the optimized formulation and which has better control on release rate by comparison to the commercial product. With the help of the dissolution data, we conclude that tablet release 15.45 ± 0.87% of drug within 0.5 min while floating tablet release only 2.31% of drug within first 0.5 min. Furthermore, it maintains the continuous release of drug from the formulation for 12 h with 99.89 ± 0.49% of total drug release, while tablet releases only 78.98% of total drug in the same time period shown in Figure 16.

Accelerated Stability Studies

Stability study of optimized final formulation was performed for 4 weeks and the formulation was evaluated for appearance, thickness, hardness, FLT, absorption maxima, and percentage drug content, results obtained are determined below in Table 20.

From table, thickness of optimized formulation was 3.32 ± 0.6 mm. Weight of tablet had obtained to be 180 ± 0.16 mg. Uniformity of tablets had 99.96 + 0.85. Short-term stability study had completed for optimized formulation. The outcomes for the dissolution profile have as showed in the diagram.

Short-term accelerated stability reports gotten for final preparation exposed medication content, hardness, thickness, and *in vitro* dissolution had inside the satisfactory limit. All outcomes obtained had conforms to the official values and *in vitro* drug release study of final preparation (F7) in Table 21 and dissolution study of final batch is shown in Figure 17. As per the results of dissolution studies after, 0 and 4th weeks of the stability studies are shown in Table 22. It is clearly seen that no difference was seen in drug release profile of the formulation. Thus, it can be stated as a stable batch after 4 weeks.

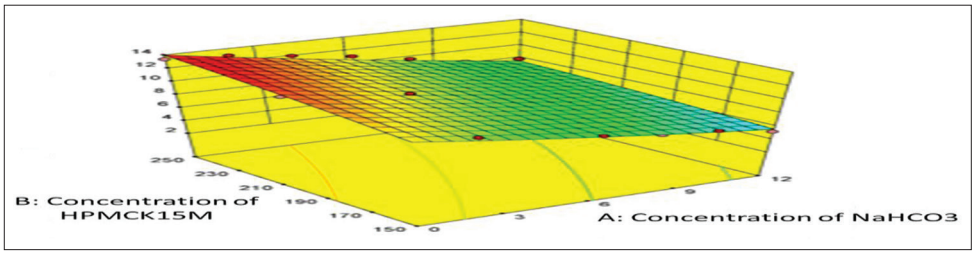

Figure 9: Generation of contour plot and response surface plot for response Y1 of optimized batch

Table 21: Evaluation of final formulation kept for stability at 40°C/75%RH

Parameter	*0 week*	*1 week*	*2 week*	*3 week*	*4 week*
Appearance (Color)	White to light yellowish	White to light yellowish	White to light yellowish	White to light yellowish	White to light yellowish
Thickness (mm)	3.32±1.89	3.32±1.39	3.32±1.29	3.32±1.38	3.32±1.67
Hardness (kg/cm^2)	5.31±0.37	5.31±0.37	5.31±0.90	5.2±0.85	5.2±0.19
FLT(s)	72±0.12	70±0.19	71±0.84	69±0.26	71±0.16
λ max (nm)	244	244±3.09	244±3.89	244±3.10	244±3.28
Drug content (%)	99.96±1.56	99.97±1.86	99.86±1.97	99.9±2.37	99.88±2.98

Table 22: *In vitro* drug release study of final preparation (f7) kept for stability at 40°C/75% RH

Time (h)	*0 week*	*4 week*
0	0.0±000	0.0±000
1	18.46±0.85	19.96±0.16
2	38.7±0.7	36.94±0.43
4	58.13±0.97	58.29±0.20
6	69.87±1.47	66.26±0.40
8	75.79±1.14	76.29±0.14
10	91.63±0.36	90.5±0.25
12	99.09±0.68	98.52±0.52

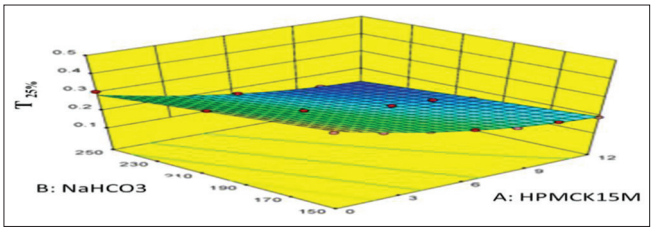

Figure 10: Three dimensional response plot of $T_{25\%}$ of optimized batch

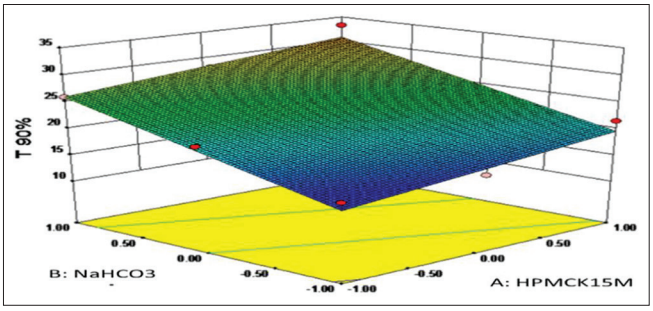

Figure 11: Three-dimensional response plot of $T_{90\%}$ of optimized batch

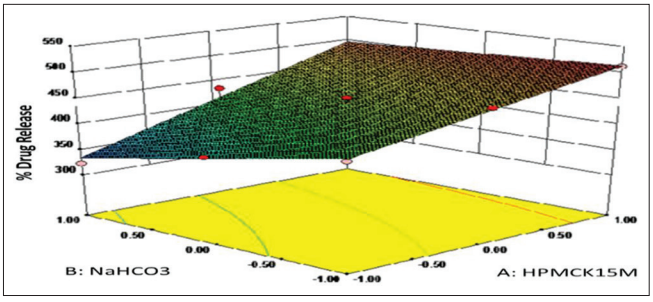

Figure 12: Three-dimensional response plot of % drug release of optimized batch

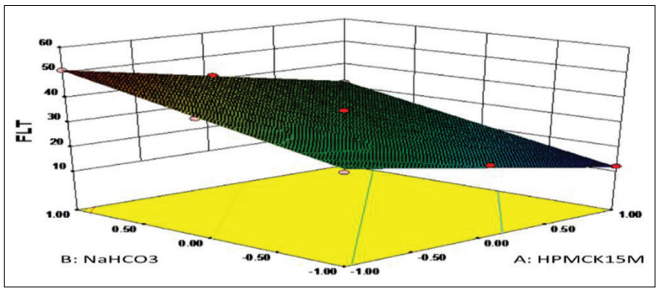

Figure 13: Three-dimensional response plot of floating lag time of optimized batch

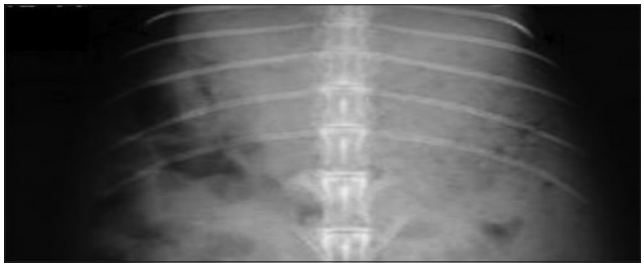

Figure 14: X-ray without tablet in rabbit of optimized batch

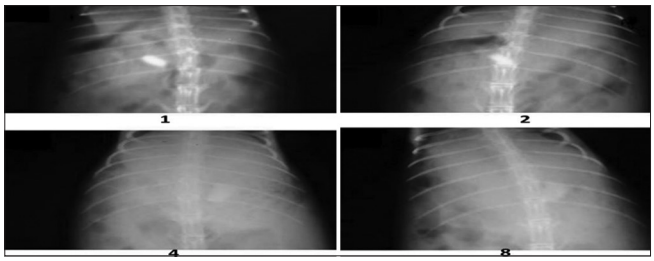

Figure 15: X-rays had taken at various time intervals such as 1 h, 2 h, 4 h, and 8 h of optimized batch

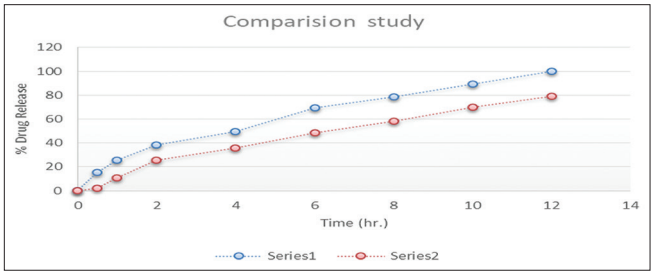

Figure 16: Comparison with marketed formulation

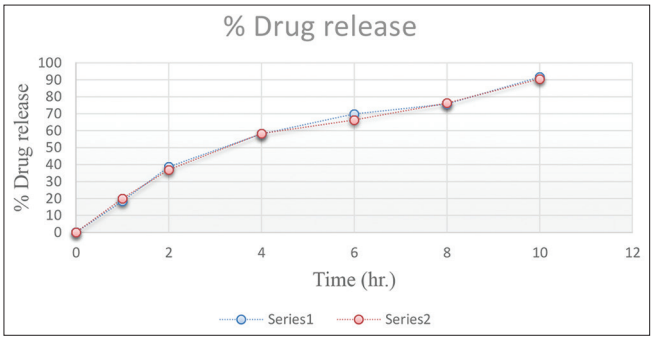

Figure 17: Dissolution study of optimized batch before after 0 and 4 weeks time interval

Conclusion

From the study, it was concluded that HPMC K15M and sodium alginate might be a promising combination for the formulation of GRDDS. Among all formulation batches, F7 reported good drug release pattern with appropriate swelling index and *in vitro* drug release. Hence, the formulation batch F7 was selected as optimized formulation and was kept for further studies. QbD approach can be successfully prepared by direct compression techniques using selected polymer for the better patient compliance and effective therapy.

Acknowledgment

The authors thank Beaukev Pharma International Pvt. Ltd., Mumbai for providing gift samples to carry out this work. The authors are thankful to the principal and Dr. A. G. Jadhav, Sandip Foundation's, Sandip Institute of Pharmaceutical Sciences, Nashik for providing required facilities to carry out this research work.

References

1. Gupta A, Garg S, Khar RK. Mucoadhesive buccal drug delivery systems. Indian Drugs Bombay 1992;29:586.
2. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: A Treatise. New Delhi: Vallabh Prakashan; 2005.
3. Desu PK, Pasam V, Kotra V. Formulation and *in vitro* evaluation of superporous hydrogel based gastroretentive drug delivery system of vildagliptin. Marmara Pharm J 2019;23:873-85.
4. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, *et al*. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2197-223.
5. Zhou B, Lu Y, Hajifathalian K, Bentham J, Di Cesare M, Danaei G, *et al*. Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4 4 million participants. Lancet 2016;387:1513-30.
6. Suh S, Song SO, Kim JH, Cho H, Lee WJ, Lee BW. Effectiveness of vildagliptin in clinical practice: Pooled analysis of three Korean observational studies (the VICTORY Study). J Diabetes Res 2017;2017:5282343.
7. Kleppinger EL, Helms K. The role of vildagliptin in the management of Type 2 diabetes mellitus. Ann Pharmacother 2007;41:824-32.
8. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007;132:2131-57.
9. Idris I, Donnelly R. Dipeptidyl peptidase-IV inhibitors: A major new class of oral antidiabetic drug. Diabetes Obes Metab 2007;9:153-65.
10. Halimi S, Schweizer A, Minic B, Foley J, Dejager S. Combination treatment in the management of Type 2 diabetes: Focus on vildagliptin and metformin as a single tablet. Vasc Health Risk Manage 2008;4:481.
11. Sunkara G, Sabo R, Wang Y, He YL, Campestrini J, Rosenberg M, *et al*. Dose proportionality and the effect of food on vildagliptin, a novel dipeptidyl peptidase IV inhibitor, in healthy volunteers. J Clin Pharmacol 2007;47:1152-8.
12. Mathieu C, Kozlovski P, Paldánius PM, Foley JE, Modgill V, Evans M, *et al*. Clinical safety and tolerability of vildagliptin insights from randomised trials, observational studies and post-marketing surveillance. Eur Endocrinol 2017;13:68.
13. Hoffmann P, Bentley P, Sahota P, Schoenfeld H, Martin L, Longo L, *et al*. Vascular origin of vildagliptin-induced skin effects in cynomolgus monkeys: Pathomechanistic role of peripheral sympathetic system and neuropeptide Y. Toxicol Pathol 2014;42:684-95.
14. Vummaneni V, Nagpal D, Surapaneni S. Formulation and optimization of famotidine floating tablets using 23 factorial design. J Pharm Res 2012;5:5280-4.
15. Kuldeep V, Sheetal M, Jitendra S, Masheer K. Formulation and evaluation of once a day dual component gastro retentive drug delivery system. Asian J Sci Technol 2018;10:10247-54.
16. Swarbrick J. In: Nash RA, Wachter AH, editors. Pharmaceutical Process Validation. New York: Marcel Dekker; 2003.
17. Jickells S, Negrusz A. Clarke's analytical forensic toxicology. In: Annales de Toxicologie Analytique. Vol. 20. Les Ulis, France: EDP Sciences; 2008. p. 233-4.
18. Senthil A, Kumar PS, Raju CH, Mohideen S. Formulation and evaluation of gastric oral floating tablet of glipizide. Int J Biol Pharm Res 2010;1:108-13.
19. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Philadelphia: Lea and Febiger; 1976.
20. Camarco WR, Druffner A. Selecting superdisintegrants for orally disintegrating tablet formulations. Pharm Technol 2006;34:S28.
21. Balasubramaniam J, Bee T. The influence of superdisintegrant choice on the rate of drug dissolution. Pharm Technol 2009;21:S1-2.
22. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: Formulation and *in vitro* evaluation. Aaps Pharm Sci Technol 2004;5:77-82.
23. Fita CA, Lupuliasa DU, Hirjau V, Sala GA, Karampelas O, Saramet G. The influence of formulation factors on the release of the metoprolol tartrate from extended release tablets. Farmacia 2012;60:905-14.
24. Chandira M, Bhavesh VB, Jayakar B, Bhowmik D, Chiranjib KK. Studies on formulations and evaluation of floating tablets containing anti-ulcer drugs. Pharm Lett 2009;1:102-14.
25. Jiménez-Castellanos MR, Zia H, Rhodes CT. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm 1994;105:65-70.
26. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm 2003;253:13-22.
27. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. Aaps Pharm Sci Technol 2005;6:E372-90.
28. Atram SC, Udavant YK, Salunke R, Neb GB, Shahi SR, Gulecha BS, *et al*. Formulation of bilayer tablet containing metoprolol succinate and amlodipine besylate as a model drug for antihypertensive therapy. J Pharm Res 2009;2:1335-47.
29. Kulkarni A, Bhatia M. Development and evaluation of regioselective bilayer floating tablets of atenolol and lovastatin for biphasic release profile. Iran J Pharm Res 2009;8:15-25.
30. Hilton AK, Deasy PB. *In vitro* and *in vivo* evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate. Int J Pharm 1992;86:79-88.
31. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983;15:25-35.
32. Karkhile VG, Karmarkar RR, Sontakke MA, Badgujar SD, Nemade LS.

Formulation and evaluation of floating tablets of furosemide. Int J Pharm Res Dev 2010;1:1-9.
33. Mazzo DJ, editor. International Stability Testing. Boca Raton, Florida: CRC Press; 2020.
34. Purnima DA, Namita SR. Formulation and evaluation of extended release nimesulide tablets. Indian Drugs Bombay. 2008;45:105.
35. Carstensen JT, Rhodes CT. Drug Stability, Revised, and Expanded: Principles and Practices. Boca Raton, Florida: CRC Press; 2000.