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ORIGINAL ARTICLE

Formulation and *In-Vitro* and *In-Vivo* Evaluation of Controlled Release Tablet of Sitagliptin Phosphate as an Antidiabetic Drug

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ABSTRACT
The present study aimed to develop and optimize a controlled release (CR) tablet of Sitagliptin phosphate to enhance glycemic control in type 2 diabetes mellitus (T2DM). The goal was to achieve controlled drug release, reduce dosing frequency, and improve patient compliance. CR tablets were formulated using HPMC K100M and Eudragit RS 100 as release-retardant polymers. A central composite design was employed to optimize polymer concentrations, with tablet hardness (Y_1) and 24-hour cumulative drug release (Y_2) as dependent variables. Formulations were evaluated for pre- and post-compression parameters, in-vitro drug release, release kinetics, and in-vivo hypoglycemic activity in diabetic Wistar rats. The optimized batch (KF8) containing 20% HPMC K100M and 15% Eudragit RS 100 demonstrated hardness of 7.4 kg/cm^2 and 97.5% drug release at 24 hours. Release followed zero-order kinetics (R^2 = 0.999). In-vivo studies confirmed a significant and sustained reduction in blood glucose levels (from 270.3 mg/dL to 108.2 mg/dL at 24 h). Accelerated stability testing over 3 months showed no significant changes in key attributes. The developed CR formulation of Sitagliptin phosphate offers a promising strategy for sustained glycemic control in T2DM, with excellent mechanical strength, release performance, in-vivo efficacy, and stability. This delivery system may enhance patient compliance and minimize plasma glucose fluctuations in long-term therapy.

Keywords: Sitagliptin phosphate, controlled release tablet, HPMC K100M, factorial design, in-vivo hypoglycemic study, type 2 diabetes.

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INTRODUCTION

Recently, type 2 diabetes has become a major health difficulty all over the world, currently affecting more than 537 million adults and projected to reach over 643 million by 2030 [1]. Insulin resistance or insulin deficiency which cause high blood sugar for long periods, greatly lead to illness and death [2]. It costs a lot, as healthcare spending globally climbed to USD 966 billion in 2021 which is more than three times the amount spent 15 years earlier [3]. Despite using many antidiabetic drugs, patients often still struggle with stable blood glucose, partly because the drugs don't stay in the system for long, require frequent dosing and some patients fail to stay compliant. Many physicians choose sitagliptin phosphate for its DPP-4 properties, even so, conventional preparations demand daily intake and commonly face swings in the blood level of the drug [4]. Thus, developing a controlled release formulation is very important for maintaining uniform treatment, lowering the number of daily doses and raising patient compliance as T2DM is managed [5,6].

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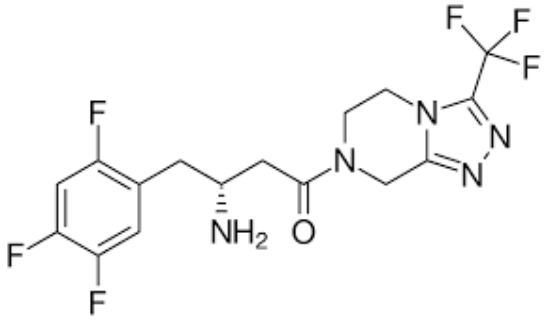

Figure 1: Chemical structure of Sitagliptin phosphate

Sitagliptin phosphate prevents digestive enzymes that lower insulin from working, so insulin is not released until glucose levels increase which also suppresses glucagon levels [7]. It is identified chemically as I-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine phosphate [8]. The fact that it has a molecular weight of 523.32 g/mol (as a monophosphate) and is very water-soluble leads to 87% bioavailability. Yet, since it is eliminated quickly from the body, the medicine needs to be given every day which sometimes makes it hard for some patients to follow the treatment plan closely [9]. Previous studies have shown that it works well by lowering HbA1c and fasting plasma glucose problems, without significant hypoglycemia. Also, the effects of the therapy can be reduced if patients do not use the drug regularly or if their drug levels change [10]. Controlled drug release over 24 hours (using a CR formulation) could overcome these problems and ensure the therapy stays active. The use of CR technology to deliver Sitagliptin phosphate could greatly improve glycemic management, making the drug more effective, safer and better for patients [11].

Unlike immediate-release tablets, the controlled release system keeps blood levels of drugs steady, extends their effects and ensures patients need to take medication less often [12]. Release of Sitagliptin phosphate can be regulated well by using a hydrophilic matrix made of polymers such as HPMC or ethylcellulose [13]. When they are exposed to stomach fluids, the matrices absorb liquid and turn into gel which controls how things can move and dissolve in the stomach. With recent progress in polymers and tablet engineering, it is now possible to adjust the release of antidiabetic agents to fit their needs [14]. Sitagliptin controlled release helps increase its bioavailability and reduces sharp changes in blood levels which cuts the risk of dangerous side effects. The idea behind this delivery method is especially fitting for diabetes, since patients require ongoing management and metabolic balance [15]. Moreover, these formulations improve the business side by helping to secure patents and support treatments that do not yet exist for managing blood sugar [16].

The goal of this work is to improve antidiabetic therapy by developing and reviewing a controlled release tablet of Sitagliptin phosphate. Objectives for drug development include better formulation methods, testing drug delivery in the lab and reviewing pharmacokinetics in real bodies. The aim is to help patients stick to their treatment plan, continue responding positively to therapy and connect conventional doses to successful blood sugar control by using a new delivery system.

MATERIAL AND METHODS

Materials

Sitagliptin phosphate was generously procured from Chemox Pharma, India. HPMC K100M and Eudragit RS 100 were obtained from Loba Chemie Pvt. Ltd., Mumbai. PVP K-30, magnesium stearate, talc, and lactose were of analytical grade and purchased from SD Fine Chemicals, India. All other reagents and solvents used were of analytical or pharmaceutical grade.

Methods

Calibration curve determination of sitagliptin phosphate

A calibration plot for Sitagliptin phosphate was prepared to test how accurately the drug responds to increasing concentrations in phosphate buffer 6.8. Sitagliptin phosphate (CAS number 845431-18-0, analytical grade from Sigma-Aldrich, USA) was dissolved in 100 mL of phosphate buffer 6.8 to produce a 100 µg/mL stock solution. From the stock solution, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mL were placed into 10 mL volumetric flasks and diluted to the marked volume with phosphate buffer 6.8 which gave final concentrations of 5, 10, 15, 20, 25 and 30 µg/mL. Measurements were taken at 267 nm by using the UV-1800 spectrophotometer (Shimadzu, Japan) with phosphate buffer 6.8 as the blank, in a 1 cm cuvette. All

experiments were carried out in three replicates (n=3) and by comparing the average absorbance to the concentration, we generated the calibration curve [17].

Solubility study of sitagliptin phosphate

Solubility studies involved the saturation shake-flask method in several solvents: phosphate buffer 6.8, ethanol, methanol, DMSO, DMF, chloroform, ethyl acetate, acetone, dichloromethane, 0.1 N NaOH and phosphate buffers (pH 6.8 and 7.4). For each solvent, 100 mg of the drug was added to 10 mL and mixed at 100 rpm in a mechanical shaker at a temperature of 25 ± 1°C for 48 hours. After filtering through a Whatman filter paper No. 41, I determined the solutions' concentration spectrophotometrically (UV-1800, Shimadzu, Japan) at 267 nm. Results were obtained three times for every sample and solubility was reported as mg/mL to identify differences that depend on the solvent [18].

Differential scanning colorimetry (DSC)

The compatibility and temperature behavior of Sitagliptin phosphate with the excipients were determined by carrying out differential scanning calorimetry (DSC). Samples of about 2–5 mg each from both the pure drug and the physical mixture were sealed in aluminum pans using a hermetic machine. Measurements were performed using the DSC-60 (Shimadzu, Japan) instrument, with a constant flow of nitrogen and a 10°C/min heating rate. Thermograms were created to check at what temperature the substance melts and changes. Each sample was analyzed three times (n=3) and the data were checked to see if any changes in peak shape, onset or disappearance of endothermic transitions suggested possible interactions [19,20].

Fourier-transform infrared (FTIR) spectroscopy

FTIR spectroscopy was used to examine if there are any chemical interactions between Sitagliptin phosphate and the various excipients in the mixture. Pure drug and physical mixtures were analyzed using an FTIR spectrometer (IRAffinity-1S manufactured by Shimadzu Japan) with a KBr pellet press. A transparent disc was formed after about 2 mg of sample was mixed with 100 mg of potassium bromide and the mixture was pressed using a hydraulic press. Spectra were recorded using a scanning range of 4000–400 centimeters per second at a 4-centimeter resolution. Identical conditions were used to scan each sample three times (n=3). Fingerprints of the peaks in Sitagliptin phosphate were checked and compared to the physical mixture to detect any changes, losses or new peaks that might represent interactions between the drug and excipients [21–23].

Experimental design

A central composite design (CCD) was utilized to optimize the controlled release tablet formulation of Sitagliptin phosphate, focusing on the effect of two independent variables: HPMC K100M (X_1: 15–25% w/w) and Eudragit RS 100 (X_2: 10–20% w/w). The experimental design was constructed using Design-Expert® software (Version 13.0, Stat-Ease Inc., USA), comprising a total of 10 runs, including axial points, factorial points, and 2 replicates at the center point to evaluate reproducibility and curvature. The dependent responses evaluated were tablet hardness (Y_1, kg/cm^2) and cumulative drug release at 24 hours (Y_2, %). The design matrix along with the coded levels of independent variables and corresponding responses is summarized in Table 1. The general form of the second-order polynomial regression model used for data analysis was:

$$Y=\beta0+\beta1X1+\beta2X2+\beta12X1X2+\beta11X12+\beta22X22$$

where Y represents the predicted response (hardness or drug release), X_1 and X_2 are the coded values of HPMC K100M and Eudragit RS 100 respectively, and the β terms are regression coefficients representing the effects of individual factors, their interaction, and their quadratic influence [24–26].

Table 1: Variables and their levels in 3^2 full factorial design

Variables	**Levels**	
Independent variables	**Low**	**High**
(A) = HPMC K100M (%w/w)	15	25
(B) = Eudragit RS 100 (%w/w)	10	20
Dependent variables	**Goals**	
(R_1) = Hardness (kg/cm^2)	Maximize	
(R_2) = Cumulative drug release at 24 hr. (%)	Target	

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Table 2: Composition of Sitagliptin Phosphate Controlled Release Tablets

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Sitagliptin Phosphate	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
2	HPMC K100M	15.0	20.0	20.0	25.0	27.07	25.0	12.92	20.0	15.0	20.0
3	Eudragit RS 100	10.0	15.0	7.92	20.0	15.0	10.0	15.0	15.0	20.0	22.07
4	PVP-K30	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
5	Magnesium Stearate	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
6	Talc	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
7	Aerosil	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16
8	Lactose (q.s. to 100%)	47.04	36.04	44.12	25.04	29.94	36.04	43.12	36.04	36.04	29.94

All values are expressed as percentage by weight (% w/w), based on a total tablet weight of 400 mg.

Micromeritics study

The powder blends were characterized by tests for flowability and compressibility before making tablets. The fixed funnel method was applied to get the angle of repose by letting powder slide from the funnel to a flat surface and measuring the height as well as the diameter of the resulting cone. A 100 mL graduated cylinder was gently filled with 10 g of the PDF and the resulting void space was read; then, the cylinder was tapped 100 times using an apparatus and the void space was reread to determine particle density. Applying these values, Carr's index and Hausner's ratio were measured to determine the flow properties of the material. The measurements were carried out in triplicate (n=3) [27,28].

Formulation of Sitagliptin Phosphate Controlled Release Tablets

Sitagliptin phosphate-controlled release tablets were made using HPMC K100M and Eudragit RS 100 to control the release, as listed in Table 2. Sitagliptin phosphate, polymers, PVP-K30 and lactose were all accurately weighed and passed through a #60 mesh sieve to make the powder more uniform. A uniform blend of the dry ingredients was achieved by using geometric dilution. PVP-K30 was dissolved in a small amount of water and mixed gradually into the dry mixture to create a wet mass. Using a #16 mesh sieve, the wet mass was turned into granules which were dried in a hot air oven at 40 °C until their weight did not change. Following this, the dried granules were passed over a #20 mesh and blended with talc, magnesium stearate and aerosil. Lastly, all the blended powder was loaded into a machine that compressed the powder into tablets weighing 400 mg [29,30].

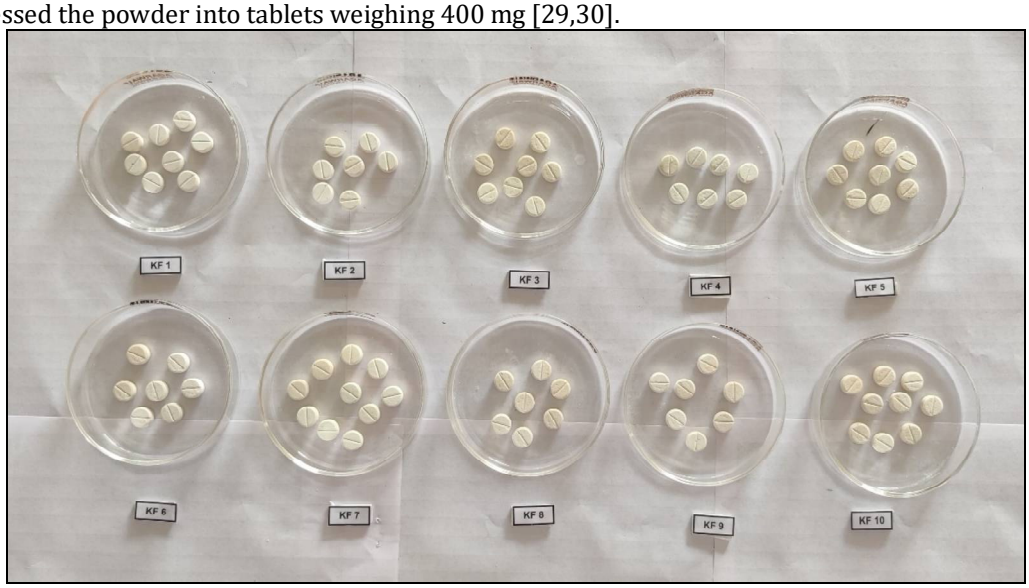

Figure 2: All formulated batches of sitagliptin phosphate-controlled release tablets

Evaluation of Sitagliptin Phosphate Controlled Release Tablets

Organoleptic Evaluation

The appearance and acceptability of each tablet were assessed through organoleptic evaluation after manufacturing Sitagliptin phosphate-controlled release tablets. Every batch was examined for color, perfect shape and texture, as well as any imperfections such as chips or cracks. Observations were made on the tablets using no special light source and their smoothness and uniformity were checked by feeling them [31].

Weight Variation Test

A weight variation test was performed to see if the tablets had the same weight in line with what is required by pharmacopeial guidelines. A total of twenty tablets from every batch were picked randomly and individually weighed on a Shimadzu AUX220 digital analytical balance. The average tablet weight was found and then each tablet's weight was measured against this average. The percentage deviation was checked for every tablet to confirm they were within the IP's set range for tablets weighing more than 250 mg (within ±5%). The evaluation showed that all batches had consistent compression and equal distribution of the formulation [32].

Thickness and Diameter

The size and thickness of each tablet were measured so they were all the same and met the specified requirements. A digital Vernier caliper from Mitutoyo (Japan) was used to randomly evaluate ten tablets from each batch. A measurement was taken for every tablet and the results for thickness and diameter were recorded using millimeters (mm). For packaging, handling and dosing to be consistent, these dimensions must be consistent. The tablets were evaluated to confirm that they met pharmacopeial requirements for even filling and pressure during production [33].

Hardness Test

Their mechanical strength and ability to withstand treatment and transport were tested by looking at their hardness. A Monsanto hardness tester (Cadmach, India) was used to test ten random tablets from each batch. Theaders was put between two anvils and force was exerted slowly until the tablet fractured. Each tablet's force needed for breakage was checked and then an average hardness value was determined. Similar hardness among batches showed that the tablets were properly pressed and the ingredients were evenly held together to ensure drug release and tablet quality [34].

Friability Test

Tablet friability was measured to find out how well they resist wear and breakage during handling, packaging and transport. For each batch, 6.5 grams of tablets (equal to 10 tablets) were taken and rotated in a Roche friabilator for 4 minutes to complete 100 revolutions at 25 rpm. The tablets were swabbed to collect dust and then reweighed after the test. The friability of each batch was determined and values less than 1% were accepted as according to the standards set by the pharmacopeia. Strong and solid formulated tablets were proved by their low friability [35].

Drug Content Uniformity

The drug content uniformity test was done to check that every tablet included the right amount of Sitagliptin phosphate. Ten capsules were picked at random from each batch, turned into a powder and weighed as needed to get 100 mg of Sitagliptin phosphate which was then put into a 100 mL flask. The powder was blended in a small amount of distilled water, sonicated for 10 minutes and afterward, brought to volume with the same solvent. Filtered samples were then diluted to capture a detection level suitable for the measurement in the calibration range. Sample absorbance was measured at 267 nm on a UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan) against a blank containing just the reagents. Each tablet was measured to determine its drug content, and the results were reported as the percentage of what the label said they should have. Each measurement was conducted three times (n=3) and we examined how well the content uniformity matched the standards set by the pharmacopeia (±5%) [36–38].

In-vitro Drug Release Studies

Drug release studies were carried out in the lab to identify how Sitagliptin phosphate is released from the tablets. During the study, the drug dissolved in 900 mL of phosphate buffer pH 6.8, in a USP type II (paddle) dissolution apparatus (TDT-08L from Electrolab, India). A single tablet was chosen from each batch and placed in the vessel, with 5 mL removed from it at preorganized times of 1, 2, 4, 6, 8, 12 and 24 hours. Each time a sample was taken, an equivalent volume of new pre-warmed dissolution medium was put back in to keep the sinkers in phosphate buffer 6.8. Samples were placed onto Whatman filter paper and dilution was done if required. At 267 nm, all samples were measured for absorbance using a UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan). All the experiments were done three times (n=3) [39].

Drug Release Kinetics Study

Release data for Sitagliptin phosphate in the laboratory were examined to determine the mechanism and pace of the controlled release. Suitable kinetic models for the release of the drug, including zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas, were determined using Microsoft Excel. The most suitable model was chosen according to its highest regression coefficient (R^2). With the Korsmeyer-Peppas model, we also calculate the release exponent (n) to determine the type of drug-diffusion process

it represents. All data for release kinetics studied was taken from in-vitro tests done three times (n=3) [40].

***In-Vivo* Evaluation of Hypoglycemic Activity**

Animals and ethical clearance

The experiment used twenty-four healthy Wistar rats weighing 180 to 220 grams to test for hypoglycemic activity directly in the body. Ethical permission to conduct this study was given by the IAEC of Dr. Vitthalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahilyanagar, under Proposal Number IAEC/M1/2024/12. All animals were held in clean, sterile; paddy husk-lined cages made of polypropylene under conditions of 22 ± 2°C, 55 ± 5% humidity and exposure to light and dark for 12 hours each day. The animals got standard pellet food and clean water anytime they wanted. All procedures for handling and caring for animals during the study period were conducted in accordance with CPCSEA standards [41].

Experimental Design and In-vivo Hypoglycemic Activity

Six healthy Wistar rats were assigned randomly to four groups to test in-vivo hypoglycemic activity of the Sitagliptin phosphate-controlled release formulation. The normal control animals in Group I were fed vehicle (distilled water) and Group II was the group given treatment for diabetes. Group II, III and IV were made diabetic using an intraperitoneal STZ injection of 50 mg/kg. After 72 hours, fasting blood glucose was measured again and the rats with levels greater than 200 mg/dL were accepted as diabetic and continued in the study. All rats in Group III received a standard immediate-release Sitagliptin, given at 2 mg per rat. Those in Group IV were given a 2 mg Sitagliptin phosphate-controlled release mini tablet, with the l tablet composition changed, just as in the original 40 mg design. With the use of oral gavage, all treatments were given by mouth. A drop of blood from the tail was collected and used with a glucometer (Accu-Chek Active, Roche Diagnostics, India) to check blood glucose at 0, 1, 2, 4, 8, 12 and 24 hours after the dose was given. Analyses were performed to determine the duration and extent of low blood sugar symptoms after administration of each treatment [42].

Figure 3. *In-vivo* study procedures for evaluating hypoglycemic activity in diabetic Wistar rats. (A) Oral administration of Sitagliptin phosphate formulation using an oral gavage needle; (B) Measurement of blood glucose level from the tail vein using a glucometer.

Stability Study

The stability of the designed Sitagliptin phosphate-controlled release tablets was examined under accelerated conditions, according to the guidelines from ICH (Q1A[R2]). A total of three months of testing at 40 ± 2°C and 75 ± 5% relative humidity in a stability chamber (ThermoLab, India) involved placing tablets in amber-colored containers. Samples were taken at 0, 1, 2 and 3 months to analyze their appearance, test hardness, see if drugs are present and check drug release under simulation. Any noticeable changes in the results were detected by comparing them with the initial values. All measurements were repeated three times (n = 3) to make sure results could be reproduced [43].

Statistical Analysis

Results from all experiments were reported as the mean ± SD and a one-way analysis of variance (ANOVA) was used with post hoc Tukey's tests to find significant differences among groups. It was believed a p-value less than 0.05 had a strong statistical significance. Data analysis and making graphs were carried out on GraphPad Prism (version 9.0, GraphPad Software, USA) and Microsoft Excel [44].

RESULTS AND DISCUSSION

RESULTS

Results of precompression study

All batches were found to have good flow properties before compression. All results show acceptable compressibility and flow, ranging from 25.66° to 29.04° for angle of repose, 0.45 to 0.49 g/cm^3 for bulk density and 12.50% to 16.36% for Carr's index (Table 3). The Hausner Ratio results verified the material filled the bottle easily and flowed smoothly.

Table 3: Pre-compression parameters of powder blends for Sitagliptin phosphate-controlled release tablets

Batch	Angle of Repose (°)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio
KF1	27.45 ± 0.12	0.48 ± 0.01	0.56 ± 0.01	14.29 ± 0.32	1.17 ± 0.02
KF2	26.38 ± 0.15	0.46 ± 0.01	0.53 ± 0.01	13.21 ± 0.28	1.15 ± 0.01
KF3	28.12 ± 0.17	0.47 ± 0.01	0.55 ± 0.02	14.55 ± 0.25	1.17 ± 0.02
KF4	25.66 ± 0.20	0.49 ± 0.02	0.56 ± 0.01	12.50 ± 0.30	1.14 ± 0.01
KF5	27.89 ± 0.18	0.46 ± 0.01	0.54 ± 0.02	14.81 ± 0.33	1.17 ± 0.01
KF6	26.73 ± 0.14	0.47 ± 0.01	0.54 ± 0.01	12.96 ± 0.29	1.15 ± 0.01
KF7	29.04 ± 0.16	0.45 ± 0.01	0.53 ± 0.01	15.09 ± 0.35	1.18 ± 0.01
KF8	25.89 ± 0.11	0.48 ± 0.01	0.55 ± 0.01	12.73 ± 0.26	1.15 ± 0.01
KF9	28.65 ± 0.13	0.46 ± 0.02	0.55 ± 0.01	16.36 ± 0.30	1.20 ± 0.02
KF10	26.15 ± 0.12	0.47 ± 0.01	0.54 ± 0.01	12.96 ± 0.28	1.15 ± 0.01

Values are expressed as mean ± SD; n = 3

Calibration curve determination

The graph of Sitagliptin phosphate in phosphate buffer 6.8 was linear between 5 and 30 µg/mL at 267 nm. The equation A = 0.029x + 0.001 and the correlation coefficient R^2 = 0.999 indicate that the estimated values fit the data very well (Figure 4).

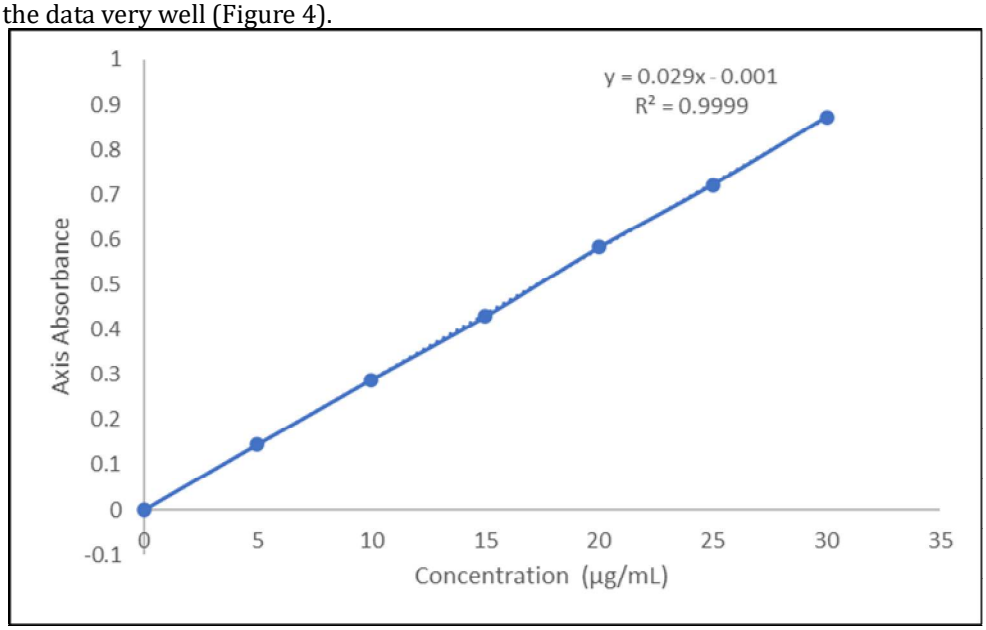

Figure 4: Calibration curve determination of Sitagliptin Phosphate in phosphate buffer 6.8.

Differential scanning colorimetry analysis

DSC measurements indicated the presence of crystals by showing a clear endothermic peak for Sitagliptin phosphate at 216.79 °C. Similar peaks for the physical mixture at 215.30°C and minor shifts indicate that the drug and excipient interact little and can be heated safely together (Figure 5). No new peaks showed up when the substances were mixed.

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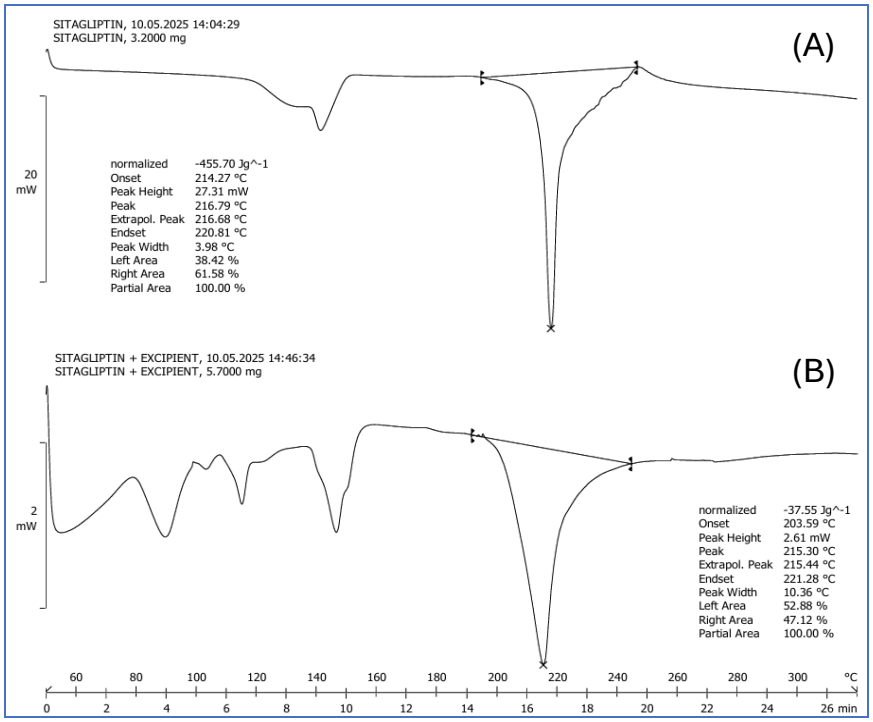

Figure 5: Differential Scanning Calorimetry (DSC) thermograms of (A) pure Sitagliptin phosphate and (B) Sitagliptin phosphate with excipients.

Results of solubility determination in different solvents

Sitagliptin phosphate exhibited the best solubility in both 0.1N HCl and distilled water which means it is freely soluble in these two media. The substance exhibited moderate degrees of solubility in methanol and ethanol (18.5 and 12.7 mg/mL, respectively). It was barely soluble in chloroform and n-hexane (<0.1 mg/mL each) (Table 4).

Table 4: Solubility of Sitagliptin Phosphate in Various Solvents

Sr. No	Solvent	Solubility (mg/mL)	Result
1	Distilled water	85.3 ± 2.4	Freely soluble
2	Ethanol	12.7 ± 0.6	Sparingly soluble
3	Methanol	18.5 ± 0.9	Sparingly soluble
4	Acetone	2.1 ± 0.3	Slightly soluble
5	0.1N HCl	91.8 ± 2.0	Freely soluble
6	Phosphate buffer pH 6.8	72.4 ± 2.1	Freely soluble
7	Chloroform	0.02 ± 0.01	Practically insoluble
8	n-Hexane	0.06 ± 0.01	Practically insoluble

All values are expressed as mean ± SD, n=3.

Fourier Transform Infrared Spectroscopy analysis

The Infrared spectrum showed important peaks in pure Sitagliptin phosphate at 3365 cm^{-1} (for N–H stretch), 1682 cm^{-1} (C=O stretch) and 1290 cm^{-1} (C–N stretch). The peaks from the original PVC/PEVA blend did not change shape or vanish after adding HPMC K100M and Eudragit RS 100. Further excipients like 1105–1120 cm^{-1} (C–O–C stretch) were seen in the spectrum, confirming drug and polymer did not interact (Figure 6; Table 5).

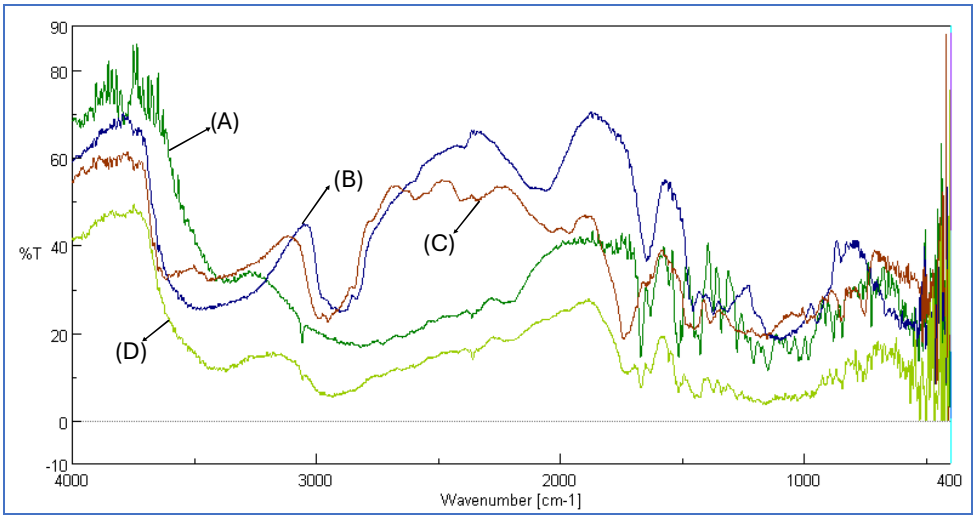

Figure 6: FTIR spectra of (A) Sitagliptin phosphate (pure drug), (B) HPMC K100M, (C) Eudragit RS 100, and (D) Physical mixture.

Table 5: FTIR Interpretation of Sitagliptin Phosphate, Excipients, and Physical Mixture

Functional Group	Standard Wavenumber (cm^{-1})	Pure Drug (A)	HPMC (B)	Eudragit (C)	Physical Mixture (D)
N–H Stretch (Primary amine)	~3300–3400	3365	—	—	3362
C=O Stretch (Amide/Carboxyl)	~1650–1700	1682	1685	1687	1681
C–N Stretch	~1250–1350	1290	—	—	1289
C–O–C Stretch (Ether)	~1050–1150	—	1105	1120	1106
O–H Stretch (Broad)	~3200–3550	3390 (broad)	3400	3395	3392
Aliphatic C–H Stretch	~2850–2950	2930	2928	2925	2927

Organoleptic evaluation

No tablet batches were spotted with capping, chipping or discoloration and they all had a white, smooth and round appearance. The examination of tablet size, surface appearance and texture through visual and touch inspection showed that all formulations were of similar quality and could be consistently made. Every batch was free of physical problems when inspected.

Table 6: Organoleptic Evaluation of Sitagliptin Phosphate Controlled Release Tablets

Batch	Color	Shape	Surface Texture	Physical Defects	Overall Appearance
KF1	White	Round	Smooth	No capping or chipping	Acceptable
KF2	White	Round	Smooth	No capping or chipping	Acceptable
KF3	White	Round	Smooth	No capping or chipping	Acceptable
KF4	White	Round	Smooth	No capping or chipping	Acceptable
KF5	White	Round	Smooth	No capping or chipping	Acceptable
KF6	White	Round	Smooth	No capping or chipping	Acceptable
KF7	White	Round	Smooth	No capping or chipping	Acceptable
KF8	White	Round	Smooth	No capping or chipping	Acceptable
KF9	White	Round	Smooth	No capping or chipping	Acceptable
KF10	White	Round	Smooth	No capping or chipping	Acceptable

Results of evaluation of Weight Variation, Thickness, Diameter, and Friability

All of the tablets met the pharmacopoeial guidelines for their weight and the average size was between 399.5 and 401.0 mg. Their thickness measured 3.09–3.18 mm and diameters were within the 8.98–9.04 mm range. Mechanical strength and resilience to abrasion are very good, as the friability values were below 0.42% (Table 7). None of the batches had cracks or problems at the edges.

Table 7: Results of evaluation of Weight Variation, Thickness, Diameter, and Friability of Sitagliptin Phosphate Controlled Release Tablets

Batch	Avg. Weight (mg)	Thickness (mm)	Diameter (mm)	Friability (%)
KF1	400.5 ± 2.3	3.12 ± 0.05	9.02 ± 0.03	0.36 ± 0.01
KF2	399.8 ± 2.0	3.15 ± 0.04	9.01 ± 0.02	0.39 ± 0.02
KF3	400.2 ± 1.8	3.10 ± 0.03	8.99 ± 0.04	0.41 ± 0.01
KF4	401.0 ± 2.5	3.18 ± 0.06	9.03 ± 0.03	0.35 ± 0.01
KF5	399.5 ± 1.7	3.14 ± 0.05	9.00 ± 0.02	0.38 ± 0.02
KF6	400.4 ± 2.1	3.11 ± 0.04	9.01 ± 0.03	0.37 ± 0.01
KF7	399.7 ± 2.2	3.09 ± 0.05	8.98 ± 0.04	0.42 ± 0.01
KF8	400.6 ± 1.9	3.13 ± 0.04	9.02 ± 0.02	0.36 ± 0.02
KF9	400.1 ± 2.4	3.17 ± 0.06	9.04 ± 0.03	0.39 ± 0.02
KF10	399.9 ± 1.6	3.12 ± 0.03	9.00 ± 0.02	0.37 ± 0.01

All values are expressed as mean ± SD; n = 20 for weight, n = 10 for thickness and diameter, n = 10 for friability.

Results of Hardness and Drug Content Uniformity

Designers at Fibrotex assigned tablets a hardness of 6.0 to 6.8 kg/cm^2, showing the tablets are strong enough to be packaged and handled without fear of breaking. Each batch showed a uniformity of drug content within a good range, between 97.6% and 99.3%. Each batch stayed inside the range set by the pharmacopoeia, proving the formulation is accurate.

Table 8: Hardness and Drug Content Uniformity of Sitagliptin Phosphate Controlled Release Tablets

Batch	Hardness (kg/cm^2)	Drug Content (%)
KF1	6.2 ± 0.15	98.6 ± 1.2
KF2	6.5 ± 0.18	99.3 ± 1.0
KF3	6.1 ± 0.20	97.9 ± 1.4
KF4	6.8 ± 0.22	98.7 ± 1.1
KF5	6.6 ± 0.17	99.1 ± 1.3
KF6	6.4 ± 0.16	98.4 ± 1.0
KF7	6.0 ± 0.14	97.6 ± 1.5
KF8	6.3 ± 0.19	98.8 ± 1.2
KF9	6.7 ± 0.21	99.2 ± 1.1
KF10	6.4 ± 0.18	98.9 ± 1.0

Values are expressed as mean ± SD; n = 10 for hardness, n = 3 for drug content uniformity.

In-vitro Drug Release Profile

A study carried out under laboratory conditions showed Sitagliptin phosphate was released slowly throughout the day. Each batch displayed controlled release, with the last total amount of drug released varying between 95.0% and 97.5% (see Table 9). The highest release observed in Batch F8 (97.5%) was very close to the study prediction. All formulations were found to perform in a similar pattern from the release groups.

Table 9: In-vitro Drug Release Profile of Sitagliptin Phosphate Controlled Release Tablets

Time (hr.)	KF1	KF2	KF3	KF4	KF5	KF6	KF7	KF8	KF9	KF10
1	4.2 ± 0.15	3.8 ± 0.10	4.1 ± 0.14	4.0 ± 0.13	4.1 ± 0.12	4.2 ± 0.16	4.3 ± 0.15	4.0 ± 0.14	4.1 ± 0.13	4.1 ± 0.11
2	8.6 ± 0.22	7.9 ± 0.18	8.4 ± 0.20	8.1 ± 0.19	8.3 ± 0.21	8.6 ± 0.23	8.5 ± 0.22	8.2 ± 0.18	8.3 ± 0.19	8.4 ± 0.20
4	17.3 ± 0.28	16.1 ± 0.25	17.1 ± 0.30	16.4 ± 0.27	16.8 ± 0.26	17.4 ± 0.31	17.0 ± 0.29	16.6 ± 0.28	16.9 ± 0.27	17.0 ± 0.30
6	26.0 ± 0.35	24.4 ± 0.32	25.8 ± 0.34	25.1 ± 0.33	25.5 ± 0.36	26.1 ± 0.38	25.6 ± 0.33	25.2 ± 0.34	25.7 ± 0.35	25.9 ± 0.36
8	35.2 ± 0.40	33.5 ± 0.38	34.9 ± 0.39	34.0 ± 0.37	34.5 ± 0.41	35.3 ± 0.43	34.6 ± 0.39	34.1 ± 0.38	34.7 ± 0.40	34.8 ± 0.41
12	52.8 ± 0.48	51.2 ± 0.45	52.1 ± 0.47	51.5 ± 0.46	51.9 ± 0.49	52.7 ± 0.51	52.0 ± 0.47	51.6 ± 0.46	52.2 ± 0.48	52.5 ± 0.49
24	95.2 ± 0.55	97.5 ± 0.60	96.3 ± 0.58	97.5 ± 0.62	97.0 ± 0.59	96.4 ± 0.57	95.0 ± 0.53	97.5 ± 0.61	96.0 ± 0.56	97.02 ± 0.60

Values represent cumulative % drug release; mean of n = 3.

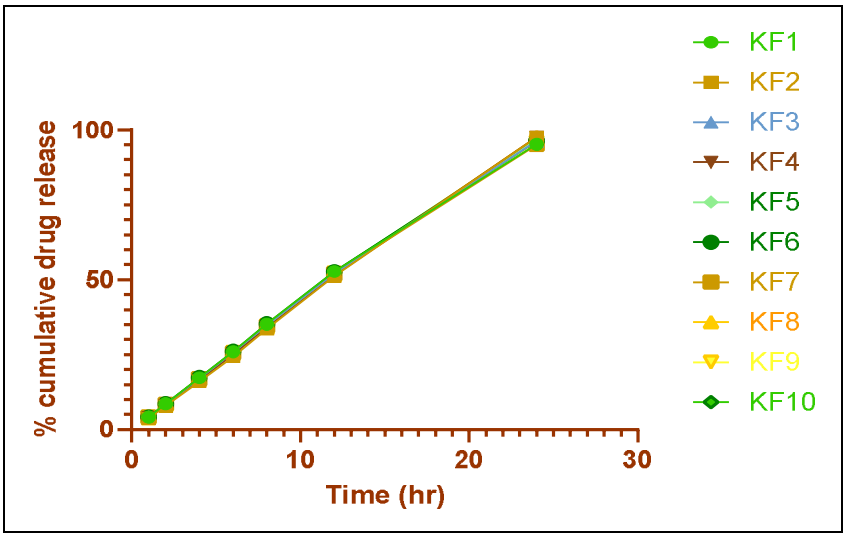

Figure 7: In-vitro Drug Release Profile of Sitagliptin Phosphate Controlled Release Tablets

Optimization of formulations

Effect on Tablet Hardness (Y_1)

The quadratic model for tablet hardness was found to be statistically significant (p = 0.00049), with a high adjusted R^2 value of 0.911 and predicted R^2 of 0.971, confirming excellent model fit and predictability (Table 10). The lack of fit was non-significant (p = 0.972), further supporting the adequacy of the model. According to the ANOVA summary (Table 11), the most influential factors were HPMC K100M (A) and Eudragit RS 100 (B), both contributing significantly to tablet hardness with F-values of 104.85 (p = 0.00051) and 33.10 (p = 0.00453), respectively. Additionally, the quadratic terms A^2 and B^2 were highly significant, with F-values of 103.16 (p = 0.00053) and 147.46 (p = 0.00026), indicating non-linear effects of both polymers. The interaction term AB was not statistically significant (p = 0.3645), suggesting minimal synergistic effect.

The derived quadratic polynomial equation for hardness (Y_1) in terms of coded factors is:

7.4 + 0.194816 * A + -0.109461 * B + -0.0275 * AB + -0.255625 * A^2 + -0.305625 * B^2

As observed in the contour and 3D surface plots (Figure 8: A, B), hardness increased progressively with the rise in concentrations of both HPMC K100M and Eudragit RS 100. The curvature of the response surface was convex, peaking in the central region where both polymers were present at mid-to-high levels, confirming the influence of quadratic terms. The design space revealed an optimal formulation zone that achieves a balanced increase in tablet hardness without exceeding compressibility limits.

Effect on Cumulative Drug Release at 24 Hours (Y_2)

The quadratic model applied for cumulative drug release was also statistically significant (p = 0.00138), with an adjusted R^2 of 0.903 and a predicted R^2 of 0.969, indicating excellent fitting and prediction accuracy (Table 10). The lack of fit was non-significant (p = 0.969), affirming the model's adequacy. According to ANOVA (Table 11), both polymer concentrations had a significant effect on drug release. HPMC K100M (A) exhibited the strongest influence with an F-value of 145.12 (p = 0.00027), followed by Eudragit RS 100 (B) with an F-value of 40.44 (p = 0.00313). The quadratic effects of A^2 (F = 101.29, p = 0.00055) and B^2 (F = 32.67, p = 0.00463) were also highly significant, highlighting non-linear effects. The AB interaction remained non-significant (p = 0.4076), similar to the hardness model.

The final quadratic polynomial equation for drug release (Y_2) is:

97.5 + 0.691053 * A + 0.364779 * B + 0.075 * AB + -0.76375 * A^2 + -0.43375 * B^2

Contour and 3D response surface plots (Figure 8: C, D) showed a dome-shaped profile, where drug release peaked around mid-levels of both HPMC and Eudragit concentrations. At low polymer levels, insufficient matrix formation led to reduced release, while at excessively high concentrations, tighter gel networks restricted diffusion. The optimal zone was visually aligned with maximum drug release (~97.5%), validating the model predictions and supporting selection of ideal formulation parameters within the central design space.

Table 10: Model Fit Summary for Quadratic Models of Sitagliptin Phosphate Controlled Release Tablets

Response	Model	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	Model Suggestion
Hardness (kg/cm^2)	Linear	0.1394	—	0.2677	0.1438	—
	2FI	0.8587	—	0.1505	-0.1258	—
	Quadratic	0.0005	—	0.9719	0.9112	Suggested
	Cubic	0.0874	—	0.9951	0.9302	Aliased
Drug Release at 24 h (%)	Linear	0.0305	—	0.5254	0.3948	—
	2FI	0.8345	—	0.4507	0.2338	—
	Quadratic	0.0014	—	0.9694	0.9033	Suggested
	Cubic	0.0575	—	0.9965	0.9500	Aliased

Suggested models are based on p-values < 0.05, high R^2, and non-significant lack of fit.

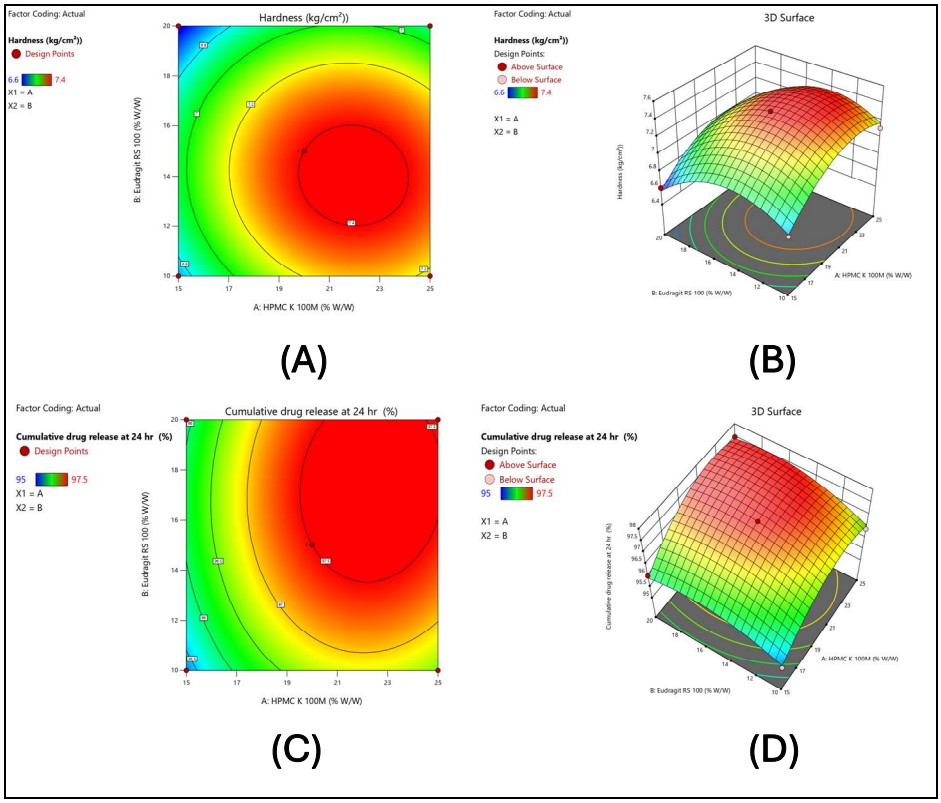

Figure 8: Contour and 3D surface response plots showing the effect of HPMC K100M (X_1) and Eudragit RS 100 (X_2) on tablet hardness (Y_1) and cumulative drug release at 24 hours (Y_2). (A) Contour plot for hardness showing optimal zone around mid-to-high levels of both polymers with a peak hardness of 7.4 kg/cm^2; (B) 3D surface plot for hardness illustrating a convex response surface with a prominent increase in hardness at central polymer concentrations; (C) Contour plot for drug release at 24 h demonstrating a high-response region (up to 97.5%) corresponding to the combined mid-levels of X_1 and X_2; (D) 3D surface plot validating a quadratic drug release pattern with a dome-shaped surface, indicating reduced release at extreme low or high polymer concentrations.

Table 11: ANOVA Summary for Quadratic Models

Response	Source	Sum of Squares	df	Mean Square	F-value	p-value	Significance
Hardness (kg/cm^2)	Model	0.9165	5	0.1833	63.30	0.0007	Significant
	A – HPMC K100M	0.3036	1	0.3036	104.85	0.0005	Significant
	B – Eudragit RS100	0.0959	1	0.0959	33.10	0.0045	Significant
	AB	0.0030	1	0.0030	1.04	0.3645	NS
	A^2	0.2987	1	0.2987	103.16	0.0005	Significant
	B^2	0.4270	1	0.4270	147.46	0.0003	Significant
	Residual	0.0116	4	0.0029	—	—	—

Drug Release (%)	Model	7.6375	5	1.5275	58.02	0.00080	Significant
	A – HPMC K100M	3.8204	1	3.8204	145.12	0.00027	Significant
	B – Eudragit RS100	1.0645	1	1.0645	40.44	0.00313	Significant
	AB	0.0225	1	0.0225	0.85	0.4076	NS
	A^2	2.6666	1	2.6666	101.29	0.00055	Significant
	B^2	0.8601	1	0.8601	32.67	0.00463	Significant
	Residual	0.1053	4	0.0263	—	—	—

NS = Not Significant ($p > 0.05$)

Statistical optimization of formulation

A central composite design in Design-Expert® software (version 13.0) helped find the KF8 formulation as the best with 20% HPMC K100M and 15% Eudragit RS 100. A good fit was found for the model, with both hardness (adjusted $R^2 = 0.911$) and drug release (adjusted $R^2 = 0.903$) having an excellent fit (Table X). The expected outcomes from the theory agreed with actual results very well, with errors less than 0.25% (Table 12).

Table 12: Statistical optimization of formulation

F. Code	Composition	Amount (%W/W)	Response	Predicted Value	Experimental Value	Relative Error (%)
KF8	HPMC K4M	20	Hardness	7.415	7.4	0.202
	Eudragit RS 100	15	In-vitro Drug Release at 24 hr (%)	97.557	97.5	0.058

Release kinetics models

The optimized formulation data (KF8) show that the release of the drug follows a zero-order model, meaning the drug was released at a constant rate for the entire 24-hour experiment (Figure 9). Compared to the others, the Hixson–Crowell model ($R^2 = 0.951$) was seen to better fit the data, whereas Higuchi ($R^2 = 0.908$), first-order ($R^2 = 0.892$) and Korsmeyer–Peppas ($R^2 = 0.834$) were less well fitted.

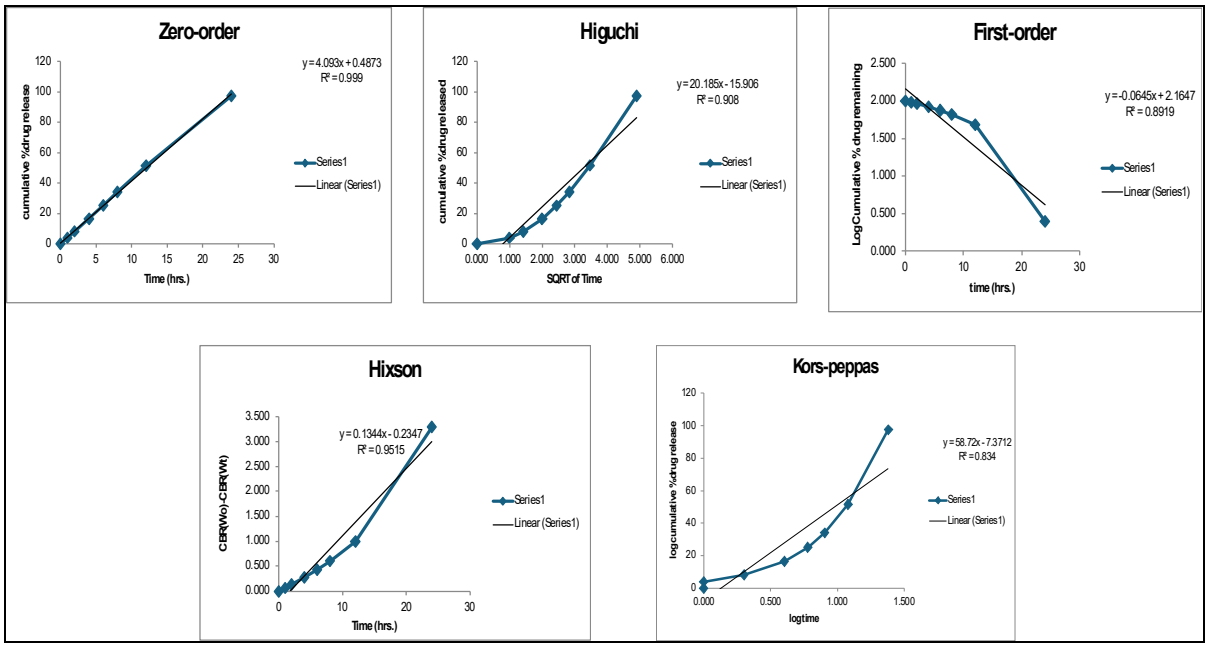

Figure 9. Drug release kinetics of the optimized formulation showing best fit to zero-order model ($R^2 = 0.999$), followed by Hixson–Crowell ($R^2 = 0.951$), Higuchi ($R^2 = 0.908$), first-order ($R^2 = 0.892$), and Korsmeyer–Peppas ($R^2 = 0.834$).

Results of In-vivo Hypoglycemic Activity

There was continued lowering of blood glucose in diabetic rats with the new formulation, as their blood sugar decreased from 270.3 mg/dL at 0 h to 108.2 mg/dL at 24 h (Table 13: Figure 10). Unlike administration with the standard formulation, administration with the controlled release system showed an initial lowering of glucose then a rise at 24 h.

Table 13: In-vivo Hypoglycemic Activity – Blood Glucose Levels (mg/dL) at Different Time Intervals

Time (h)	Group I (Normal Control)	Group II (Diabetic Control)	Group III (Standard)	Group IV (Test CR Mini-tablet - F8)
0	92.3 ± 4.2	272.6 ± 5.8	268.9 ± 6.1	270.3 ± 5.6
1	90.7 ± 3.9	271.5 ± 5.5	210.3 ± 5.7	240.8 ± 5.3
2	89.2 ± 4.1	270.8 ± 6.0	178.6 ± 6.2	215.7 ± 5.9
4	88.5 ± 3.8	272.3 ± 5.7	145.2 ± 5.4	180.6 ± 6.1
8	89.1 ± 4.0	271.9 ± 5.9	160.8 ± 5.6	140.4 ± 5.8
12	90.3 ± 4.2	272.5 ± 6.3	190.1 ± 6.0	115.6 ± 5.2
24	91.0 ± 4.4	273.1 ± 6.5	248.3 ± 5.7	108.2 ± 5.0

Values are expressed as mean ± SD (n = 6).

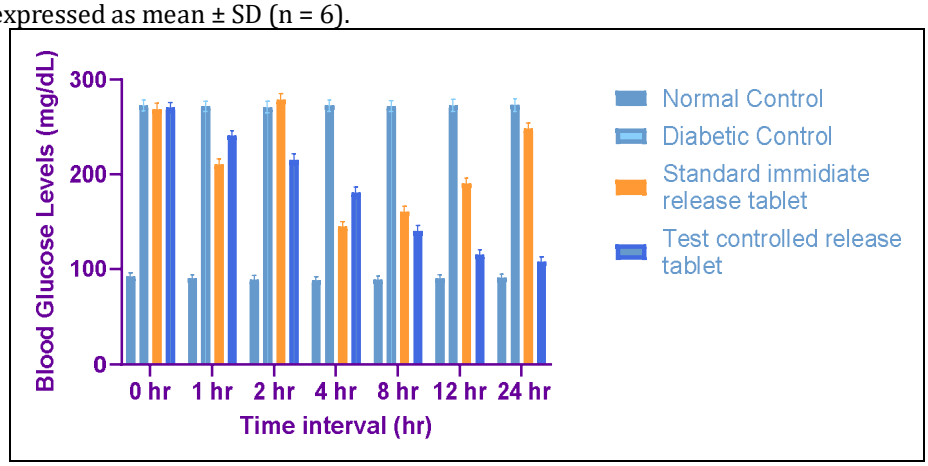

Figure 10: Blood glucose levels over 6 hours showing sustained reduction with the test-controlled release tablet compared to standard, diabetic, and normal control groups.

Accelerated stability study.

Over 3 months at 40 ± 2°C and 75 ± 5% RH, the F8-optimized group showed the same appearance, hardness, content and release of drugs. The formulation remained stable, as hardness was 6.0 kg/cm^2, drug content was 97.4% and drug release was 96.4%, according to Table 14.

Table 14: Accelerated Stability Study Results of Optimized Batch KF8

Time Point	Appearance	Hardness (kg/cm^2)	Drug Content (%)	% Drug Release at 24 hr
0 Month	White, smooth	6.3 ± 0.19	98.8 ± 1.2	97.5 ± 0.61
1 Month	No change	6.2 ± 0.21	98.4 ± 1.0	97.3 ± 0.58
2 Months	No change	6.1 ± 0.20	97.9 ± 1.1	96.9 ± 0.60
3 Months	No change	6.0 ± 0.22	97.4 ± 1.3	96.4 ± 0.63

All values are expressed as mean ± SD, n=3.

DISCUSSION

The authors produced a CR tablet formulation of Sitagliptin phosphate by following a well-designed approach to help patients better control their blood sugar and increase adherence to the drug. Results of micromeritic testing indicated that the powder blends had favorable flow and compression, with slight differences in angle of repose and Carr's index around 12.50–16.36%, supporting direct compression (Table 3) [45]. Hausner's ratio confirmatory tests were stable and maintained values inside the acceptable flow range (1.14–1.20). Significant levels of dissolution and absorption in the gut are made possible by the high solubility of the drug in aqueous and acidic media, especially in distilled water and 0.1N HCl (Table 4). Country A had an excellent calibration curve with high linearity in the range of 5–30 µg/mL at 267 nm, giving an R^2 value of 0.999 (Figure 4), so it could easily be used for quantitative analysis [46].

Sitagliptin phosphate and the selected polymers proved to be compatible by DSC and FTIR studies. Figure 5 demonstrates that there is almost no shift in the melting point of the drug from pure to physical mixture. Likewise, no big shifts or missing peaks (N–H, C=O and C–N) were found in the FTIR measurement (Figure 6, Table 5), indicating the materials were chemically compatible. All batches of the

formulated tablets were pharmaceutically elegant and displayed uniform organoleptic qualities (Table 6) [47]. Consistency in the thickness of the discs (3.09–3.18 mm) and diameter of the core (8.98–9.04 mm) was confirmed by a uniform development in each batch. A hardness rating of 6.0–6.8 kg/cm^2 (see Table 8) was found for the materials, making them strong and reliable during transportation and packing. The drug content was very similar (97.6–99.3%) in each regimen, showing good homogeneity [48].

The study on how the drug is released in the lab showed that each formulation sustained drug release for 24 hours, with results ranging from 95.0% to 97.5% (See Table 9). Of the batches examined, KF8 was found to release the most (97.5%) and thus was identified as the optimized formulation. Figure 7 demonstrates that the material successfully molded the manner in which drug release occurred. Running the optimization method with a central composite design led to significant quadratic models for hardness and drug release, both with adjusted R^2 values over 0.90 (Table 10). ANOVA indicated that the responses were strongly influenced in a linear and quadratic way by HPMC K100M (A) and Eudragit RS 100 (B) (Table 11) [49]. The equations predicted that results were best when both polymers were at mid-levels. Figures 8A–D represent the outlined design space and prove that hardness and drug-release behaviors are strong. KF8, made with 20% HPMC K100M and 15% Eudragit RS 100, had a very small difference between the values we calculated and the observed values for both hardness and drug release (Table 12). Simulations verified that the optimization process had produced correct and valid results [50].

Using kinetic modeling, it was seen that the optimized formulation released the medication continuously at the same rate each hour (R^2 = 0.999). It is an ideal property in CR because it allows proper and continuous levels of the drug in the blood. According to the model, erosion controlled the release of drugs, with poorer correlations seen for Higuchi, first-order and Korsmeyer–Peppas models representing diffusion [51]. Using diabetic rats, we showed that the KF8 formulation maintained lowered glucose levels for 24 hours. Conversely, those on the initial-release group had early low blood sugar, followed by higher-than-normal sugar levels at 24 h. This confirms that the CR matrix continued to work throughout (Table 13; Figure 10). Because of its pharmacodynamic profile, the formulation is able to keep glucose in the therapeutic range and improve blood sugar control. We observed that the physical and chemical properties of the KF8 batch did not change over three months in the accelerated stability study. All findings indicate that the capsules are stable for the full 12 months under different stress conditions [52].

CONCLUSION

The study effectively produced and optimized a controlled release tablet of Sitagliptin phosphate using HPMC K100M and Eudragit RS 100 as matrix systems. KF8 had excellent release of the drug over 24 hours, was mechanically stable and showed uniform drug content, along with strong control of blood sugar levels in living subjects. Results from statistical modeling showed the study is reliable and repeatable, while accelerated stability studying confirmed the formula's suitability for the shelf-life. The system helps improve patient compliance, allows for smaller doses and lowers ups and downs in blood glucose. More work is needed in the form of detailed pharmacokinetic and long-term animal experimentation to demonstrate that these drugs are safe and effective for clinical use.

Abbreviations

ANOVA: Analysis of Variance; FTIR: Fourier-transform Infrared Spectroscopy; UV: Ultra-violet Spectroscopy; DSC: Differential Scanning Calorimetry; HPMC: Hydroxypropyl Methylcellulose; PVP: Polyvinylpyrrolidone; SD: Standard Deviation; IP: Indian Pharmacopoeia; RH: Relative Humidity; STZ: Streptozotocin; CR: Controlled Release; IR: Immediate Release; IAEC: Institutional Animal Ethics Committee; CPCSEA: Committee for the Purpose of Control and Supervision of Experiments on Animals; ICH: International Council for Harmonization; R^2: Regression Coefficient; n: Number of observations; df: Degree of Freedom.

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Authors contribution

All authors contributed equally.

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Conflict of interest
The authors declare no conflict of interest.

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REFERENCES
1. Alam, M.M. (2021). Prevalence of Type 2 Diabetes Mellitus complications in human. Thesis, Chattogram Veterinary & Animal Sciences University.
2. Lynch, P. (2022). Type 2 diabetes mellitus. Med. Indep., (Accessed May 24, 2025).
3. Burakoti, A.K., Roy, R.K. & Dubey, H. (2023). Safety of opicapone use in Parkinson's disease: Review of literature and real-world safety data. World J. Curr. Med. Pharm. Res., 5(5):202–209.
4. Su, J., Luo, Y., Hu, S., Tang, L. & Ouyang, S. (2023). Advances in research on Type 2 Diabetes Mellitus targets and therapeutic agents. Int. J. Mol. Sci., 24(17):13381.
5. Hossain, M.J., Al-Mamun, M. & Islam, M.R. (2024). Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. Health Sci. Rep., 7(1): e2004.
6. Tamboli A, D. Tayade S. (2025). In-Depth Investigation of Berberine and Tropane through Computational Screening as Possible DPP-IV inhibitors for the Treatment of T2DM. J Pharm Sci Comput Chem;1.
7. Alqahtani, Q.H., Alshehri, S., Alhusaini, A.M., Sarawi, W.S., Alqarni, S.S., Mohamed, R. et al. (2023). Protective effects of sitagliptin on streptozotocin-induced hepatic injury in diabetic rats: A possible mechanism. Diseases, 11(4):184.
8. Ali, D.M., Ahmed, S.M., Abd el Hafez, S.M.N., Welson, N.N. & Abdelzaher, W.Y. (2023). Mitigating function of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in silver nitrate experimentally induced pancreatic toxicity: The role of HIF-1α. Minia J. Med. Res., (In press).
9. Chang, X.M., Xiao, F., Pan, Q., Wang, X.X. & Guo, L.X. (2021). Sitagliptin attenuates endothelial dysfunction independent of its blood glucose controlling effect. Korean J. Physiol. Pharmacol., 25(5):425–437.
10. Patel, R., Parmar, N., Palit, S.P., Rathwa, N. & Begum, R. (2023). A novel combination of sitagliptin and melatonin ameliorates T2D manifestations: Studies on experimental diabetic models. J. Endocrinol. Invest., 46(8):1597–1612.
11. Ansari, P., Hannan, J.M.A., Choudhury, S.T., Islam, S.S., Talukder, A., Seidel, V. et al. (2022). Antidiabetic actions of ethanol extract of Camellia sinensis leaf ameliorates insulin secretion, inhibits the DPP-IV enzyme, improves glucose tolerance, and increases active GLP-1 (7–36) levels in high-fat-diet-fed rats. Medicines, 9(11):56.
12. Singh, G.R. (2022). Design, development and evaluation of controlled-release formulation of freely phosphate buffer 6.8-soluble drugs. Thesis, Institute of Pharmacy, Nirma University, Ahmedabad.
13. Kumar, A., Jain, S.K., Mishra, D.K. & Gautam, R. (2024). Influence of drug properties and routes of drug administration on design of sustained and controlled release systems. In: Yadav, A.K. & Jain, K. (Eds.), Novel Carrier Systems for Targeted and Controlled Drug Delivery, Springer Nature, Singapore, pp. 1–46.
14. Gupta, D., Pandey, M., Maiti, A. & Pujari, N.M. (2023). Bilayer tablet technology: A concept of immediate and controlled drug delivery. J. Pharm. Negat. Results, 14(S1):503–512.
15. Bchkol, D.H.K. & Mohammed, O.S. (2025). Review of the controlled drug delivery method, dosage form categorization, and therapeutic impact on the human body. Span. J. Innov. Integr., 39(1):88–109.
16. [No author]. (n.d.). [No title found]. Int. J. Pharm. Sci. Res., 12(1).
17. Kosman, V.M., Karlina, M.V., Faustova, N.M., Makarov, V.G. & Makarova, M.N. (2022). Comparison of biomarker and chromatographic analytical approaches to pharmacokinetic study of sitagliptin. Biopharm. Drug Dispos., 43(1):3–10.
18. Cong, Y., Du, C., Xing, K., Bian, Y., Li, X. & Wang, M. (2022). Research on dissolution of actarit in aqueous mixtures: Solubility determination and correlation, preferential solvation, solvent effect and thermodynamics. J. Mol. Liq., 358(1):119141.
19. Sakkal, M., Arafat, M., Yuvaraju, P., Beiram, R., Ali, L., Altarawneh, M. et al. (2024). Effect of hydration forms and polymer grades on theophylline controlled-release tablet: An assessment and evaluation. Pharmaceuticals, 17(3):271.
20. Wang, H., Vemula, S.K., Bandari, S. & Repka, M.A. (2023). Preparation of core-shell controlled release tablets using direct powder extrusion 3D printing techniques. J. Drug Deliv. Sci. Technol., 88(1):104896.
21. Israr, M., Pugliese, N., Farid, A., Ghazanfar, S., Di Cerbo, A., Muzammal, M. et al. (2022). Preparation and characterization of controlled-release floating bilayer tablets of esomeprazole and clarithromycin. Molecules, 27(10):3242.
22. Mustafa, M.A., Khan, A.M., Ali, N., Ahmed, F., Latif, M.U., Shahid, Z. et al. (2023). Formulation and in vitro evaluation of pH dependent colon targeted controlled release tablet of mesalamine containing Cyamopsis tetragonoloba gum and sodium alginate. Int. J. Pharm. Investig., 13(3):476–484.
23. Jadhav S, Dighe P, Kumbhare M. (2025). Synthesis In Vitro Evaluation and Molecular Docking Studies of Novel Pyrazoline Derivatives as Promising Bioactive Molecules. J Pharm Sci Comput Chem;1.

24. Khamkat, P., Barik, V., Barik, B.B., Chakraborty, A., Patra, D., Mondal, P. et al. (2023). Formulation and evaluation of propranolol hydrochloride sustained release matrix tablets using different grades of HPMC and MCC. Int. J. Pharm. Investig., 13(4):763–771.
25. Khan, K.A., Ahmad, A., Marini, C., Nicotra, M., Di Cerbo, A., Fazal-Ur-Rehman et al. (2024). Formulation and preparation of losartan-potassium-loaded controlled-release matrices using Ethocel grade 10 to establish a correlation between in vitro and in vivo results. Pharmaceutics, 16(2):186.
26. Patel, R.P., Paliwal, H. & Patel, A. (2023). Investigating the influence of HPMC K4M and Eudragit L 100-55 on guanfacine-loaded extended-release tablets. Dissolution Technol., 30(1):22–29.
27. Dwivedi, M. & Sharma, N. (2025). Development and evaluation of natural gum-based sustained-release tablets for levosulpiride and alprazolam. Curr. Res. Pharm. Sci., 15(1):1–7.
28. Muthudoss, P., Kumar, S., Ann, E.Y.C., Young, K.J., Chi, R.L.R., Allada, R. et al. (2022). Topologically directed confocal Raman imaging (TD-CRI): Advanced Raman imaging towards compositional and micromeritic profiling of a commercial tablet components. J. Pharm. Biomed. Anal., 210(1):114581.
29. Denduyver, P., Vervaet, C. & Vanhoorne, V. (2024). Studying the API distribution of controlled release formulations produced via continuous twin-screw wet granulation: Influence of matrix former, filler and process parameters. Pharmaceutics, 16(3):341.
30. Venkatesh, D.N., Meyyanathan, S.N., Kovacevic, A., Zielińska, A., Fonseca, J., Eder, P. et al. (2022). Effect of hydrophilic polymers on the release rate and pharmacokinetics of acyclovir tablets obtained by wet granulation: In vitro and in vivo assays. Molecules, 27(19):6490.
31. Sierra-Vega, N.O., Alsharif, F.M., O'Connor, T., Ashraf, M. & Zidan, A. (2024). Characterizing a design space for a twin-screw wet granulation process: A case study of extended-release tablets. Int. J. Pharm., 650(1):123681.
32. Shamim, R., Shafique, S., Hussain, K., Abbas, N., Ijaz, S. & Bukhari, N.I. (2024). Surfactant-assisted wet granulation-based matrix tablets without exceptional additives: Prolonging systemic exposure of model BCS class II ketoprofen. AAPS PharmSciTech, 25(1):241.
33. Vodeti, R., Chalmale, N., Mujawar, T., Lohiya, G.V., Vilangalil, A., S, S. et al. (2025). Formulation and assessment of natural polysaccharide-based matrix tablets for colon-specific epigallocatechin gallate delivery via wet granulation technique. Cuest. Fisioter., 54(4):1373–1386.
34. Khan, N.A., Khan, A., Ullah, R., Ullah, M., Alotaibi, A., Ullah, R. et al. (2022). Preparation and characterization of hydrophilic polymer based sustained-release matrix tablets of a high dose hydrophobic drug. Polymers, 14(10):1985.
35. Khan, A. (2021). Prediction of quality attributes (mechanical strength, disintegration behavior and drug release) of tablets on the basis of characteristics of granules prepared by high shear wet granulation. PLOS ONE, 16(12): e0261051.
36. Naguboyina, T., Lakkala, P., Munnangi, S.R., Vemula, S.K. & Repka, M. (2025). Evaluation of process parameters for continuous manufacturing of quetiapine fumarate immediate release tablets using twin screw wet granulation. Pharm. Res., 42(3):685–696.
37. Chinthaginjala, H., Ahad, H.A., Bhargav, E. & Pradeepkumar, B. (2021). Central composite design aided formulation development and optimization of clarythromycin extended-release tablets. Indian J. Pharm. Educ. Res., 55(2):395–406.
38. Singh, S., Dadabhau, G.D. & Singh, K. (2023). Formulation, development and investigation of matrix type sustained release tablet of antiulcer drug by using soluble polymer as a drug release retarding agent. Int. J. Membr. Sci. Technol., 10(4):2593–2603.
39. Faizan, M. (2024). Novel extended-release carbamazepine oral suspension: Formulation, evaluation and drug-release kinetic study. Pak. J. Pharm. Sci., (In press).
40. Prohit P, Pakhare P, Pawar V, Dandade S, Waghmare M, Shaikh F, et al. (2025). Formulation and Comparative Evaluation of Naproxen-Based Transdermal Gels. J Pharm Sci Comput Chem;1
41. Xie, L., Yu, D., Li, Y., Ju, H., Chen, J., Hu, L. et al. (2022). Characterization, hypoglycemic activity, and antioxidant activity of methanol extracts from Amomum tsao-ko: In vitro and in vivo studies. Front. Nutr., 9:869749.
42. Elmoghayer, M.E., Saleh, N.M. & Abu Hashim, I.I. (2024). Enhanced oral delivery of hesperidin-loaded sulfobutylether-β-cyclodextrin/chitosan nanoparticles for augmenting its hypoglycemic activity: In vitro-in vivo assessment study. Drug Deliv. Transl. Res., 14(4):895–917.
43. González-González, O., Ramirez, I.O., Ramirez, B.I., O'Connell, P., Ballesteros, M.P., Torrado, J.J. et al. (2022). Drug stability: ICH versus accelerated predictive stability studies. Pharmaceutics, 14(11):2324.
44. Belayneh, T., Gebremichael, S., Chinchkar, A.V., Berhanu, T., Singh, A. & Upadhyay, A. (2022). Comparative study on chemical composition and antioxidant properties (GraphPad Prism approach) of wild Ethiopian Z. spina-christi and Indian Z. jujube fruit species. Food Anal. Methods, 15(10):2224–2237.
45. Thrivikraman Nair, S., Kamalasanan, K., Moidu, A., Shyamsundar, P., Nair, L.J. & P, V. (2021). Ethyl cellulose coated sustained release aspirin spherules for treating COVID-19: DOE led rapid optimization using arbitrary interface; applicable for emergency situations. Int. J. Biol. Macromol., 182(1):1769–1784.
46. Charoenying, T., Patrojanasophon, P., Ngawhirunpat, T., Rojanarata, T., Akkaramongkolporn, P. & Opanasopit, P. (2021). Design and optimization of 3D-printed gastroretentive floating devices by central composite design. AAPS PharmSciTech, 22(6):197.

47. Triboandas, H., Pitt, K., Bezerra, M., Ach-Hubert, D. & Schlindwein, W. (2022). Itraconazole amorphous solid dispersion tablets: Formulation and compaction process optimization using quality by design principles and tools. Pharmaceutics, 14(11):2398.
48. Hassan, H., Adam, S.K., Alias, E., Meor Mohd Affandi, M.M.R., Shamsuddin, A.F. & Basir, R. (2021). Central composite design for formulation and optimization of solid lipid nanoparticles to enhance oral bioavailability of acyclovir. Molecules, 26(18):5432.
49. Wang, L., She, X., Chen, Z., Quan, S., Liu, Y., Mai, X. et al. (2021). Preparation and characterization of a chiral molecularly imprinted polymer with a novel functional monomer for controlled release of S-sulpiride. Int. J. Pharm., 601(1):120526.
50. Martín-Illana, A., Chinarro, E., Cazorla-Luna, R., Notario-Perez, F., Veiga-Ochoa, M.D., Rubio, J. et al. (2022). Optimized hydration dynamics in mucoadhesive xanthan-based trilayer vaginal films for the controlled release of tenofovir. Carbohydr. Polym., 278(1):118958.
51. Đuranović, M., Obeid, S., Madžarević, M., Cvijić, S. & Ibrić, S. (2021). Paracetamol extended release FDM 3D printlets: Evaluation of formulation variables on printability and drug release. Int. J. Pharm., 592(1):120053.
52. Mukherjee, K., Dutta, P. & Giri, T.K. (2023). Al^{3+}/Ca^{2+} cross-linked hydrogel matrix tablet of etherified tara gum for sustained delivery of tramadol hydrochloride in gastrointestinal milieu. Int. J. Biol. Macromol., 232(1):123448.

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