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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF SITAGLIPTIN

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Abstract:

Diabetes mellitus is a metabolic illness with many symptoms defined by long-lasting hyperglycemia and variations in carbohydrate, lipid, and protein metabolism caused by insulin release and action abnormalities. Sustained rekease type of drug delivery system includes any drug delivery that achieve sustained release of drug over an extended period of time. The goal of the following research work is to formulate, develop ad evaluate sustained release formulation for anti-diabetic by using various polymers and excipients to enhance gastric retention. The tablets were formulated using a direct compression method and evaluated for their physicochemical properties, in vitro buoyancy, and drug release profiles. The optimized formulation (F4) showed a satisfactory floating lag time, buoyancy, and sustained release of Sitagliptin over 24 h. The release kinetics followed a zero-order model, and the mechanism of drug release was found to be Fickian diffusion. The results suggest that the developed sustained release tablets of sitagliptin can potentially improve patient compliance and therapeutic efficacy.

Key words: *Sustained release, sitagliptin, diabetes mellitus, glucose-dependent insulinotropic polypeptide, gastric retention, floating tablets.*

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INTRODUCTION:

Sustained release systems are customized medication delivery systems that can be utilized instead of traditional dosing systems. Patient compliance, avoidance of multiple dosages, cost-effectiveness, flexibility, avoidance of side effects, and the elimination of difficulties associated with conservative medication distribution systems are all advantages of the sustained release system.

Diabetes mellitus is a metabolic illness with many symptoms defined by long-lasting hyperglycemia and variations in carbohydrate, lipid, and protein metabolism caused by insulin release and action abnormalities. Sitagliptin inhibits the enzyme DPP-4, thereby slowing the degradation of incretin hormones such as GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). Incretins are secreted throughout the day and are further elevated in response to meals, playing a key role in maintaining glucose homeostasis [1-3].

The goal of the following research work is to formulate, develop ad evaluate sustained release formulation for anti-diabetic by using various polymers and excipients.

MATERIALS AND METHODS:

Sitagliptin is procured as a gift sample from Lupin Limited, Pune, India. All the chemicals and reagents used are analytical grade.

Preparation of calibration curve of sitagliptin in 0.1N HCl

Preparation of standard solution: The 100 mg of sitagliptin were carefully measured into a 100-milliliter volumetric flask and mixed with a little amount of 0.1 N hydrochloric acid. To achieve a concentration of 1000 µg/ml (SS-I), the volume was filled to the mark using 0.1 N HCl. To get a concentration of 10µg/ml (SS-II), 1 milliliter was taken and diluted with 100 milliliters.

Preparation of working standard solutions: Pipetted into 10 ml volumetric flasks were aliquots of 1, 2, 3, 4, and 5 milliliters from (SS-II). The final concentrations of 1, 2, 3, 4, and 5 µg/ml were achieved by adding 0.1N HCl to the volume in that order. UV-visible spectrophotometer (UV-1800 SHIMADZU) was used to quantify the absorbance with 0.1N HCl serving as the blank [4-6].

Drug-excipient compatibility studies

Fourier transform infrared spectroscopy (FTIR): Infrared spectra were acquired from the materials using an IR spectrophotometer using the KBr disk sample preparation technique, also known as the pressed pellet technique. A Fourier transform infrared spectrophotometer (SHIMADZU FTIR-8400s) was used to record the infrared spectra of both the pure medicines and all of the mixtures. Prior to analyzing the pure drug's spectrum, a baseline correction was performed using dried potassium bromide. The test sample and around 100 mg of spectroscopic-grade potassium bromide were carefully combined in a glass mortar. We got the infrared spectra by compressing the mixture into transparent disks in a moisture-free environment. We chose a scanning range of 4000 to 400 cm^{-1}.

Differential scanning calorimetry: All produced formulations and pure drug DSC thermograms were acquired using a DSC Refrigerated refrigeration system (Model Q1000, TA instruments, UK). Precisely measured samples ranging from 0.8 to 6.3 mg were placed in hermetically sealed aluminum pans and subjected to a constant purge of argon while they were heated for analysis. Indium and sapphire were used to calibrate the device before running the samples. The samples' thermal behavior was studied by scanning them from 0 to 300˚C at a rate of 10˚C/min [7-10].

Table 1: Formulation of sitagliptin tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	100	100	100	100	100	100	100	100	100
HPMC	50	100	150	---	---	---	---	---	---
Tamarind gum (TG)	---	---	---	50	100	150	---	---	---
Xanthan gum	---	---	---	---	---	---	50	100	150
MCC	145	95	45	145	95	45	145	95	45
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	350	350	350	350	350	350	350	350	350

Post-compression parameters

General appearance: Every single one of the tablets, regardless of its composition, were visually examined for things like size, shape, color, smell, surface roughness, physical imperfections, and consistency.

Thickness: Using a vernier caliper, we measured the thickness of the tablets from every batch. The tablet's thickness shouldn't deviate more than ± 5% from the reference value.

Hardness test: Tablets must possess a specific degree of toughness and resilience to endure mechanical shocks encountered throughout production, packing, and transportation. A device known as the "Monsanto Hardness Tester" is utilized to determine the hardness of the tablets. Six tablets from each batch were tested for hardness using a tablet hardness tester made by Monsanto.

Friability test: The tablets' friability was tested using a Roche friabilator, which spins a plastic container at 25 rpm, lowering the tablets six inches with each rotation, subjecting them to abrasion and shock. For tablets weighing 650 mg or less, it is recommended to take a full tablet sample that is as close to 6.5 g as possible for examination. The friabilator was turned on for 100 revolutions after dusting the weighed sample of entire tablets. The tablets were powdered again and weighed every rotation. The following calculation was used to compute the percentage loss:

$$\text{Percentage loss} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Weight variation test: To guarantee that each pill has the correct dosage of medication, their weight was assessed. For each batch, twenty pills were chosen at random, and their average mass was determined. Then, each tablet was weighed separately and the difference between the two was represented as a percentage deviation from the average weight.

Uniformity of drug content:

This is the procedure that was used to determine the amount of medication in every formulation. A hundred milliliters of simulated gastric fluid (SGF) with a pH of 1.2 was mixed with powder equal to the average weight of twenty randomly crushed pills. The solution was diluted to the appropriate concentration, filtered with whatmann filter paper no.41, and then spectrophotometrically measured at 207 and 258 nm for each sitagliptin independently, with SGF pH 1.2 serving as a blank.

Swelling index:

The measurement was taken at room temperature in a pH 1.2 simulated stomach fluid. The tablet's inflated weight was measured over the course of 24 h. The following equation was used to determine the swelling index (SI), which was given as a percentage [11-14].

$$SI = \frac{\text{Final weight of tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

***In vitro* buoyancy studies:** For this experiment, we used a beaker with 100 ml of pH 1.2 simulated stomach fluid as a testing medium and kept it at 37 ºC. We then randomly placed a tablet from each formulation into the beaker. When the tablet finally reached the surface, the amount of time it took for it to float there was recorded as the floating lag time (FLT). To find the total floating time (TFT), which includes floating lag time, we measured how long the tablet stayed on the medium's surface continuously. Each table displays the findings of an *in vitro* buoyancy study on a floating tablet of sitagliptin.

Stability studies: Stability testing is done to show how the medication formulation's quality changes over time in response to several environmental factors like light, humidity, and temperature. The study's findings provide light on the drug's ideal storage conditions, re-test intervals, and potential shelf life. In order to ensure that a product maintains its desired physical, chemical, and microbiological qualities over its specified storage and usage life, stability tests are conducted. A stability analysis was conducted on the optimized formulation. Packed in an airtight container, the chosen formulae were protected by aluminum foil. Their physical appearance, medication content, and solubility were assessed after they were stored at 40ºC with 75% relative humidity [15-19].

RESULTS AND DISCUSSION:

Preformulation tests

Investigating the potential of a combination of polymers to produce Sitagliptin floating tablets with prolonged release was the driving force behind this study. Research into drug release and assessments of physicochemical properties were conducted *in vitro* for every formulation. For Sitagliptin, the melting point was measured to be between 171 and 178°C. According to the authoritative pharmacopoeias, the melting points were determined to be the same. A loss of less than 0.5% was determined during drying. The poor angle of repose value is an indication of the drug's poor flow properties. A drug stock solution and an organic solvent mixture of methanol and chloroform (2:1 v/v) were prepared since the drug is soluble in both aqueous and non-aqueous solvents. Methanol was selected as the solvent.

Analytical method

The pH 1.2 simulated gastric fluid and the pH 6.8 phosphate buffer were used to generate the Sitagliptin graphs, which were taken at 258 nm, respectively.

Table 2: Observations for graph of sitagliptin in 0.1N HCl (258nm)

Concentration (µg/ml)	Absorbance
0	0
2	0.164
4	0.285
6	0.375
8	0.495
10	0.593
12	0.688
14	0.802

To make the sitagliptin calibration curve, we followed the steps in Table and utilized an acetate buffer with 0.1 N HCl. Figure 1, for the calibration curve that displays an absorbance at max of 258 nm, a regression coefficient of 0.9944, and a y intercept of 0.0552.

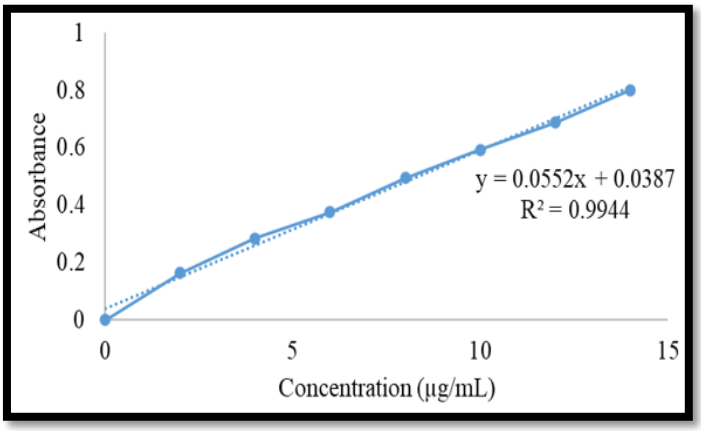


Figure 1: Standard graph of sitagliptin in 0.1N HCl

Solubility studies

A semi-quantitative analysis of the solubility was carried out by gradually introducing different solvents to a test tube that contained a set amount of solute, and vice versa.

Table 3: Solubility study of sitagliptin

S. No	Solvents/Medium	Solubility (mg/mL)
1	Water	0.0403
2	0.1N HCl	10.475
3	Phsophate Buffer pH 6.8	42.13
4	Phsophate Buffer pH 6.8 + 1% SLS	59.62
5	Acetone	21.46
6	Methanol	60.27
7	Ethanol	65.38

Melting point

They found the drug's melting point using the capillary method. Conforming to both the DSC results and the published literature (171-178°C), the drug's melting point was determined to be close to 175.36 ± 0.48 ºC.

Compatibility studies

FT-IR: Utilizing an FT-IR spectrometer, investigations into the compatibility of drugs and excipients were conducted. The FTIR spectra reveal the stretching bonds, which prove the medicine and excipients are compatible under acceleration conditions. The well-known peaks of sitagliptin can be attributed to various processes: O-H stretching at 3310 cm-1, Ar-H stretching at 3080 cm-1, C-H stretching at 2880 cm-1, C-N stretching at 1600 cm-1, N-H bending at 1597 cm-1, C-H bending at 1340 cm-1, C-C stretching at 1070 cm-1, -C-O-C group at 1030 cm-1, and substituted benzene ring at 791 cm-1.

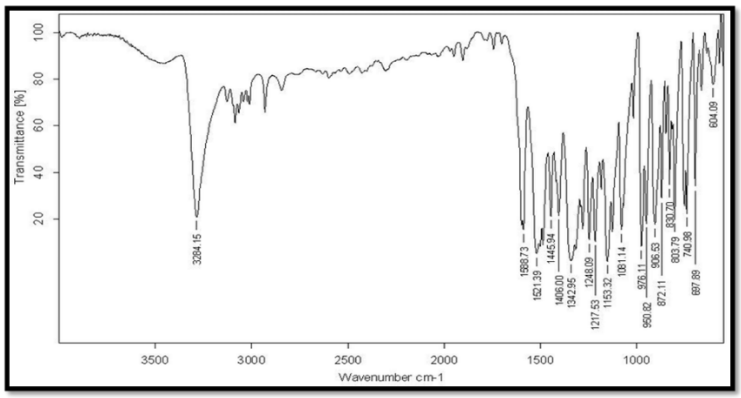


Figure 2: FTIR spectrum of pure drug

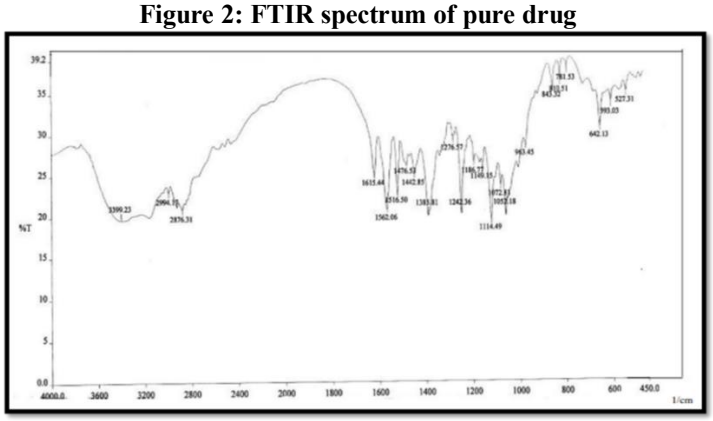


Figure 3: FTIR spectrum of optimized formulation

Differential scanning calorimetry: A defining feature of every chemical is its endothermic or exothermic peak. Using the determination of temperature variation and energy phase transition, it is a valuable tool for analyzing crystallization and interaction between excipients. For sitagliptin, the thermogram revealed a distinct exothermic peak at 173.64°C. Concurrently, the thermogram for TG showed a peak at 183.03°C, defining its properties. The temperature for MCC was 149.32°C.

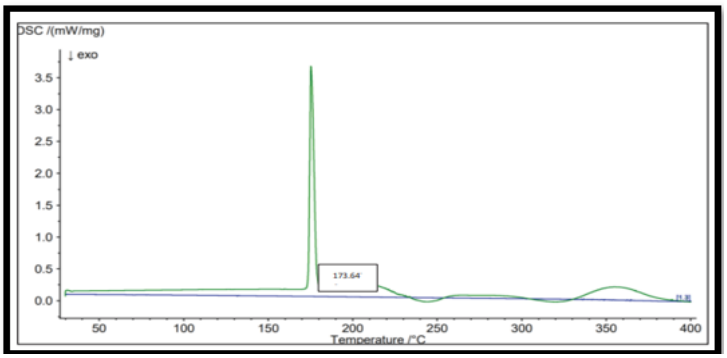


Figure 4: Differential scanning calorimetry of sitagliptin

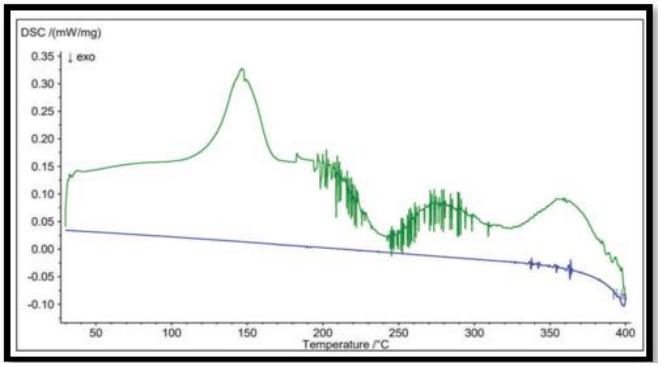


Figure 5: Differential scanning calorimetry of physical mixture

Evaluation of pre-compression parameters of sitagliptin

Several requests led to the pre-formulation of a tablet powder mixture. The statistics on the angle of repose show that the powder blend has great flow properties. All of the formulations' bulk densities ranged from 0.52 to 0.71 (gm/cm^3), suggesting that the powder has adequate flow characteristics. All of the formulations' tapped densities fell within the range of 0.65 to 0.81, which means the powder had adequate flow characteristics. Compressibility indices ranging from 10.52 to 20.22 across all formulations suggest that the powder has outstanding flow properties. The powder has great flow properties, as shown by the Hausner's ratio, which falls between 1.11 and 1.25. This is correct regardless of the formulation.

Table 4: Pre-formulation parameters of core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	22.59	0.56	0.68	17.647	1.21
F2	31.24	0.69	0.81	14.814	1.17
F3	30.46	0.67	0.79	15.189	1.17
F4	28.95	0.59	0.72	18.05	1.22
F5	34.57	0.65	0.78	16.66	1.2
F6	36.51	0.71	0.89	20.22	1.25
F7	28.94	0.68	0.76	10.52	1.11
F8	26.73	0.64	0.74	13.51	1.15
F9	24.15	0.52	0.65	20.00	1.25

Post compression parameters

Shape: Tablets from every formulation batch were found to be round and crack-free upon microscopic analysis.

Tablet dimensions: The range of tablet mean thicknesses was 4.20 mm to 4.65 mm, which was nearly constant across all formulations.

Weight variation: The weight variation test was passed by all the tablets because their percentage of weight fluctuation was within the limitations set by the Pharmacopoeia. Low standard deviation values were observed for the tablet weights, which were determined to be uniform. The average weight of the tablets was not significantly different from the weight of the individual tablets. All batches of tablets were determined to be within the specified USP limits for weight.

Hardness: The tablet needs to be sturdy enough to resist breaking when handled, which means it needs to be hard enough and resistant to friability. But it also affects how drugs dissolve in water and how tablets break down. Each batch's measured hardness of tablets ranged from 4.50 to 5.60 kg/cm^2, as shown in the table. All the formulations were consistent in terms of tablet hardness.

Friability: In order to ensure that the tablets were mechanically stable, the percentage of friability was NMT 1% throughout all formulations. This means that the formulations have demonstrated sufficient resilience to handle.

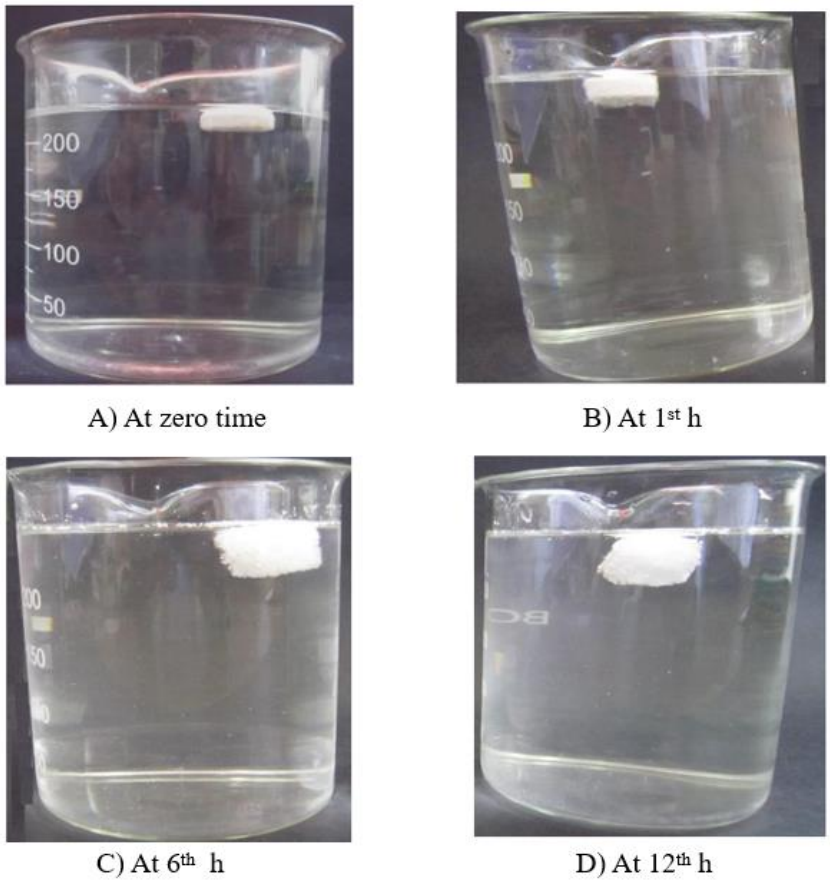
Content uniformity: The permissible range for the percentage of drug content in sitagliptin floating tablets was determined to be between 97.38±0.35 and 102.58±0.76.

Floating lag time and total floating time: The idea behind floating medication delivery devices is to float on the gastric juice once the stomach is filled. Sodium bicarbonate and citric acid were used as gas-developing salts in a swellable hydrophilic matrix to provide the buoyancy in sitagliptin tablets. This specific matrix is entirely made of hydrophilic polymers that can swell. The process begins when the dissolving medium is absorbed into the tablet matrix. This interaction between the fluid and the effervescent base creates a swelling gel and traps carbon dioxide gas. As a result, the matrix expands, causing the density to decrease and the buoyancy to increase. The floating lag time decreased as the percentage of sodium bicarbonate increased in the case of sitagliptin, which is a gas-generating effervescent base. This finding has important implications for the lag time of the system buoyancy. A higher sodium bicarbonate percentage may be responsible for this effect since it produces more effervescence. All of the formulations stay afloat for at least 12 h in the case of sitagliptin and above 24 h in all cases.

Swelling index: You can see the swelling percentages of all the formulations from F1 to F9, in which were derived from water imbibition investigations. We found that the swelling index of sitagliptin-containing formulations increased as the concentration of the polymer, TG, rose, and that

changes in the sodium bicarbonate content had minimal impact on tablet swelling.

***In vitro* buoyancy studies:** The low density polypropylene foam powder produced excellent buoyancy *in vitro* and eliminated floating lag time (Zero) in all of the formulations. In order to achieve their stomach retention capabilities, the pills stayed buoyant for over 12 h.



A) At zero time B) At 1st h

C) At 6th h D) At 12th h

Figure 6: Matrix tablet formulation dimensional changes and *in vitro* floating behavior photographs

Table 5: Post-compression parameters

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	499.56	4.54	0.19	4.29	96.53
F2	475.86	4.82	0.24	4.31	97.02
F3	486.31	4.69	0.35	4.36	96.85
F4	501.23	5.09	0.42	4.45	98.46
F5	497.52	5.18	0.56	4.51	97.86
F6	492.16	5.23	0.48	4.32	99.02
F7	485.63	5.46	0.39	4.58	98.67
F8	489.13	4.75	0.27	4.31	99.01
F9	490.65	4.68	0.31	4.22	98.46

Water uptake studies: The pace at which the tablets absorb water from the dissolving media is indicated by their swelling behavior. The swelling of floating tablets became worse over time because the weight gain of the tablets was directly related to the rate of hydration up to 6 h, and the matrix looked swelled practically immediately after incorporation. Swelling subsided after a while as a result of the outer gelled coating of pills dissolving. After 6 h, the swelling was fully resolved. The percentage of swelling for each formulation was examined in a pH 1.2 HCl buffer; and pictures of swelling at various time intervals, which is also graphically depicted. A higher concentration of TG caused the edema to increase, while a lower concentration of MCC had the opposite effect. The drug's diffusion was greatly affected by the tablet's water content. This might be since the amount of water in the system had a significant impact on how mobile the polymer chains were. When the water content is high, the system swells significantly because the polymer chains relax and the volume expands. The lowest proportion of swelling was observed in formulation F6, which had the largest quantity of TD and the lowest amount of sodium bicarbonate. The percentage of swelling was directly related to the release of the drug.

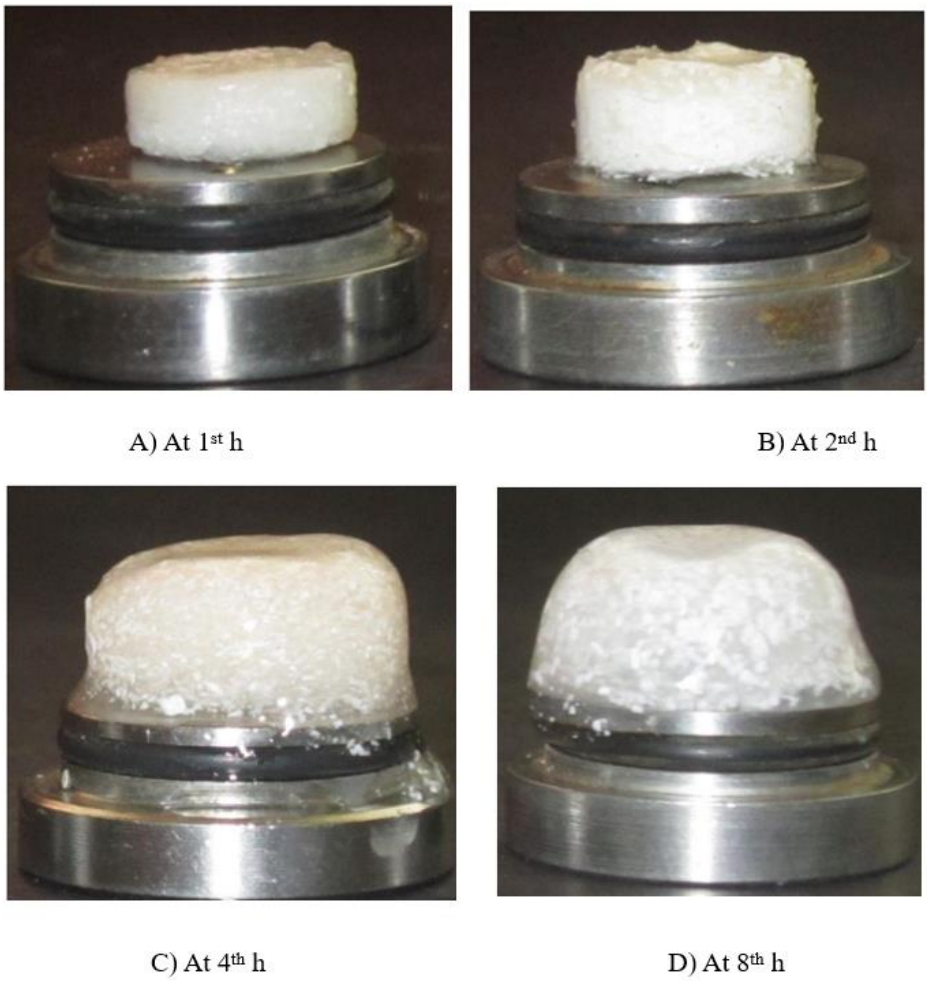


Figure 7: The floating matrix tablet formulation swells in a pH 1.2 HCl buffer, as shown in the photographs

***In vitro* drug release:** For the *in vitro* release investigation, two distinct dissolving media were used: first, 0.1N HCl (an acidic buffer with a pH of 1.2) for 2 h, and second, simulated intestinal fluid (a phosphate buffer with a pH of 6.8 over the following 24 h). After 2 h in 0.1N HCl, the amounts of drug released by the pure drug solution, optimized tablet, and commercial formulation were 89.35%, 15.36%, and 24.59%, respectively. Due to the lack of retardant TG in the pure drug solution formulation, nearly all of the drug was released after 2 h. Optimal sustained release tablets released 39% of the drug after 12 h, whereas the commercial formulation released 62.59% after 12 h. The results demonstrated that when the concentration of TG increased in each formulation, the drug release from the formulations reduced. The optimized formulation Table 6 reveals that the medication release is slower than any other formulations. Formulation F4, which releases 92.35% of the drug after 24 h, was deemed the optimal formulation according to the drug release profile.

Table 6: *In vitro* drug release profile of formulations

Time (h)	Pure drug solution	Optimized formulation (F4)	Marketed formulaion
0	0	0	0
1	37.68	5.96	7.59
2	75.94	14.75	18.69
3	98.26	36.98	43.26
4	--	43.28	62.59
6	--	55.47	78.34
8	--	64.03	80.76
10	--	72.47	90.34
12	--	83.16	103.28
14	--	93.51	

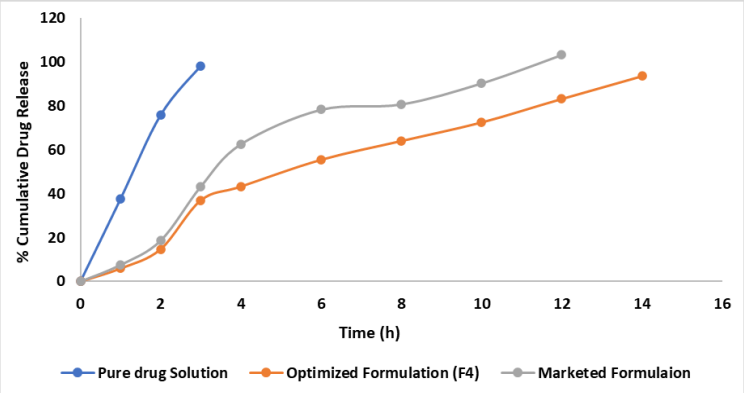


Figure 8: *In vitro* drug release studies

Release kinetics:

Graph showing curve fitting results of the intended formulation's release rate profile; this provides insight into the release rate and mechanism. By comparing the values for the kinetic model and the drug equation, we can see that the optimized formulations F4 follow the release kinetics model proposed by Higuchi with regression values of 0.9884. This conclusion was reached after fitting the release rate data to various models.

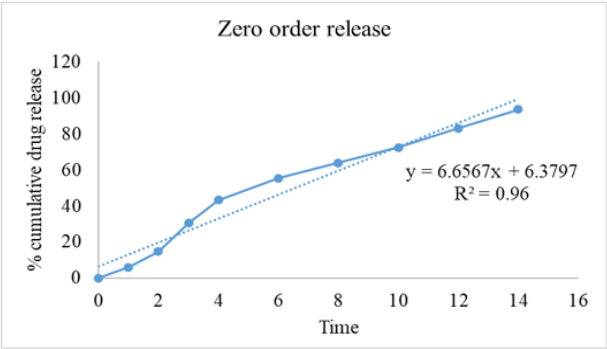


Figure 9: Release rate kinetics of zero order reaction

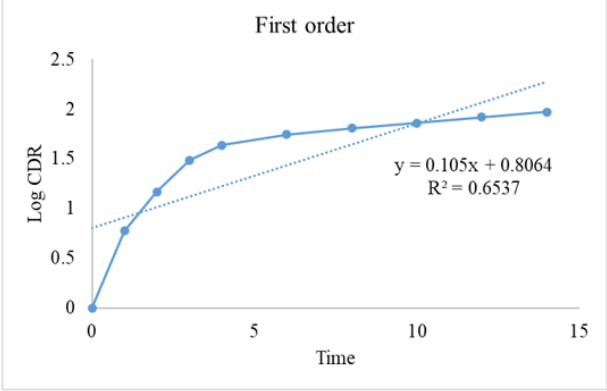


Figure 10: Release rate kinetics of First orders

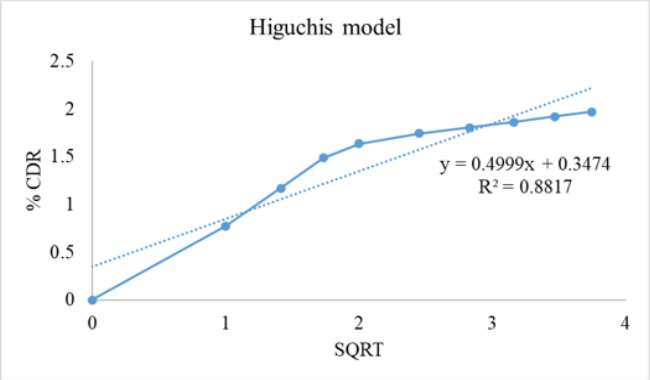


Figure 11: Release rate kinetics of Higuchis Model

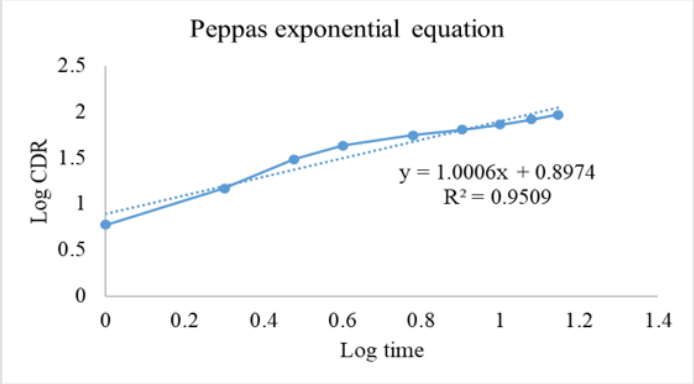


Figure 12: Release rate kinetics of Peppas exponentional equation

The *in vitro* release of sustained release tablets was studied using many models, including zero-order, first-order, Higuchi's equation, and Korsmeyer-Peppas equation. Formulations' zero-order plots were supposed to be linear, with high regression values indicating this. That being the case, we know that pellets release drugs according to either first-order or second-order kinetics. Even though they are all straight, the slopes of the first order curves are different, therefore they cannot be used to predict the second order. As a result, the data was calculated and plotted using Higuchi's and korsmeyer-peppa's equations in order to validate the precise method of medication release from the polymer films.

The release mechanism varied depending on the kind and amount of polymer in the matrix, although it was higher for medicines with higher water solubility. There is a noticeable on-release mechanism due to the polymer type used. The precise and accurate management of the amount released over a specified duration was of utmost importance. The hydrophilic nature of the polymers employed in the dissolution study had a significant impact on the amount of polymer that changed, and the study provided numerous factors to regulate in future batches. The release of the medication decreased as the concentration of the polymer increased. The optimal batch (F4) had a r^2 value of 0.8817 according to Higuchi's model. The r^2 values for first order and zero order were 0.6537 and 0.96, respectively, while the korsmeyer-peppas r^2 value was determined to be 0.9509. These findings provide credence to the hypothesis that non-Fickian diffusion is the mechanism by which drugs released from sustained-release pellets follow a zero-order distribution pattern.

CONCLUSION:

From the current investigation, there was no chipping, capping, or sticking observed in the gastro retentive effervescent floating tablets of sitagliptin that were made using TG produced by the direct compression method, the powder mix of the drug formulations exhibited good micromeritic qualities, according to the results of the precompression parameters. All of the tablet formulations were identical concerning the medication content. The medication appears to be distributed uniformly throughout the matrices, as indicated by the low standard deviation values. The medicine is found to be compatible with the excipients according to DSC and FTIR testing. Results showed that the drug-polymer ratio affected the formulations' drug release rates. It has shown that medication release rates decrease with increasing polymer levels. The polymer's viscosity grades (Tg) also affected the drug release. A decrease in medication release was seen when the polymer's viscosity rose. The floating lag time is affected by the amounts of citric acid and sodium bicarbonate. To achieve buoyancy, a concentration of at least 10% sodium bicarbonate was determined. While the QP formulations stayed afloat for over 12 h, all of the other formulations

(F1–F9) floated for over 24 h. It was discovered that the drug was released from F1 to F9 through fickian diffusion in the optimized formulation F4, which exhibited first-order release rather than zero-order release in the optimized formulation. The F4 optimized formulation including Sitagliptin features a zero-order drug release profile and a Fickian diffusion for drug release.

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