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DEVELOPMENT AND EVALUATION OF EXTENDED-RELEASE VILDAGLIPTIN TABLETS USING QUALITY BY DESIGN

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ABSTRACT
Background: Extended-release dosage forms are designed to enhance patient compliance and decrease dosing frequency. However, commercially available extended-release tablets are made with synthetic or semisynthetic controlled-release polymer, which causes a ghost pill effect. The ghost pill effect is minimized by using natural polymers which are biodegradable. **Aim**: This study aimed to create extended-release vildagliptin tablets using natural polymer by employing the quality by Design. **Method**: The study involved preparing granules of vildagliptin by direct compression using co-processed polymer and other excipients and compressing them into tablets. **Results & Discussion**: The different micromeritic characteristics of granules were satisfactory for compressing them into tablets. The FTIR, DSC, and XRD analysis indicates no interaction between the drug and the other excipients. The drug release shows that the marketed formulation releases 97% of the drug in 8 hrs., Whereas the developed formulation extends the drug release >= 95% throughout 12hrs. Drug release kinetic study results reveal that the optimized batch obeys first-order kinetics with the Higuchi model. *In vivo* studies showed steady plasma levels over an extended period, achieving the objective of the current study. The stability study carried out as per the ICH guideline exhibited robustness of the formulation, with the drug content found between 96 % to 99 % at 30°C & 75 %RH and 40°C & 75 %RH. **Conclusion**: The extended-release formulation of vildagliptin could be successfully formulated using a combination of natural and semisynthetic polymers. This combination could prove to be effective, safe, and well tolerated, enhancing patient adherence and lowering overdose risks, thereby reducing overall diabetic treatment costs.

INTRODUCTION

More than 400 million people around the world are diabetic. It is projected that this number will increase to ~700 million by the year 2045 [1, 2]. Various oral anti-diabetic drugs are currently available on the market for the management of diabetes. The oral route is the most recommended for administering antidiabetic medications, as it is a long-term treatment. Vildagliptin is a BCS Class I drug with a short half-life, which makes it necessary to design an extended-release dosage form for such drugs to decrease dosing frequency, reduce dose, and increase patient

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compliance [3-6]. Various types of controlled-release (CR) synthetic, semi-synthetic, or natural polymers or their combinations can be selected to develop the extended-release formulation. However, the "ghost pill" is a commonly associated problem in which patients may see empty, intact shells of synthetic polymers in tablets or capsules in feces with controlled-release or extended-release formulations [7-9]. This problem may lead to mistrust and worry while taking medication for a longer period, which can hinder patient compliance. Natural polymers, which are environmentally safe and biodegradable, are known to reduce the ghost pill effect. Thus, it is essential to utilize natural polymers to create extended-release formulations while maintaining the formulation's effectiveness [10-12]. In addition, it is crucial to ensure that formulation and development are planned appropriately so that the chosen approach is efficient for time and resources. The design of the experiment (DoE) technique is a systematic methodology for determining the link between elements that impact the outcomes. It is a cost-effective approach to formulation development [3, 13].

Response surface methodology is a popular statistical technique for determining how different parameters affect formulation characteristics. It helps achieve the optimal formulation parameter values with minimal experimentation, thus making it more cost-effective than the traditional approach for developing formulations [14–17]. This research aims to eradicate the ghost pill effect by developing an extended-release tablet dosage form of vildagliptin utilizing a combination of co-processed natural polymers and semi-synthetic polymers using the Quality by Design approach [18, 19].

MATERIALS AND METHODS

Lee Pharma Limited, located in Andhra Pradesh, India, kindly supplied a free sample of vildagliptin. Seppic (La Garenne-Colombes, France) kindly provided a gift sample of Sepismart SR. Colorcon Ltd., India, provided Hydroxypropyl methylcellulose K4 M, while Dupont, India, provided Avicel® PH-200.

Colloidal silicon dioxide was obtained from Evonik Industries (India), while Magnesium stearate was provided by Amishi Drugs & Chemicals Pvt. Ltd., Ahmedabad, India. Instacoat Aqua III 40006 white was obtained from Ideal Cure India. All the chemicals utilized were of analytical grade. Double-distilled water was used throughout the experiment.

Pre-formulation studies

Organoleptic properties of vildagliptin, along with the determination of the melting point, ultraviolet-visible spectrophotometry and Fourier transform infrared spectroscopy (FTIR) analyses, were also carried out to confirm the purity of the obtained gift sample.

Quality Target Profile

It entails establishing goals and specifications based on the drug referenced in the list, encompassing aspects such as dosage form, administration method, strength, drug release, pharmacokinetic properties and stability.

Critical Quality Attributes (CQA)

A critical quality attribute (CQA) is a particular physical, chemical, biological, or microbiological aspect or characteristic that needs to be within a specific limit or distribution. To guarantee the intended quality of a product. Table 1 states the critical quality attributes of Vildagliptin extended-release tablets.

Critical Process Parameter

In pharmaceutical production, critical process parameters (CPPs) impact a critical quality attribute (CQA), necessitating their monitoring or management to ensure the medication product meets the desired quality standards. Table 2 and Figure 1 describe different manufacturing stages and critical process parameters.

Assessment of the risk associated with drug Substance characteristics

A risk assessment was performed to evaluate the potential impact of each characteristic of the drug substance on the critical quality attributes (CQAs) of the drug product. Table 3 presents a concise Summary of the evaluation result and the corresponding rationale. Every characteristic was classified as high, medium, or low risk in relative risk. Features with a high risk required further investigation, while attributes with low risk did not necessitate any additional inquiry. Using the current understanding, the medium risk level is deemed acceptable. To mitigate the risk, it may be essential to conduct more investigation into the medium level of risk. Table 3 provides a concise overview of the consistent utilization of the identical relative risk rating system for all aspects of the investigation. Table 4 presents the preliminary assessment of the potential risks linked to the drug substance's properties while considering the drug product's critical quality attributes (CQAs). Explanation for the initial assessment of risks related to the characteristics of the drug substance. This section provides the reasoning behind the preliminary evaluation of the risk linked to the attribute of the drug substance.

Table 1: Critical quality attributes (CQA)

Quality Attributes of Drug Product		Target		Is this CAQ?	Justification
Quality attributes for drug product	Physical Attributes	Appearance	White to off-white colored, capsule/ round shaped biconvex, film-coated tablet plain on both sides.	No	Physical attributes such as appearance, size, and shape do not directly correlate with safety and effectiveness; hence, they are not crucial factors.
		Size	10-12 mm		
		Shape	Round		
		Theoretical weight	500-600 mg		
		Coated/ uncoated	Film-coated		
	Identification	Positive for vildagliptin		Yes	Identification is critical for ensuring safety and effectiveness. Quality management can successfully handle this CQA.
	Dissolution	**Time Point**	**% DR**	Yes	Bioavailability can be affected if the dissolution specification is not met. Formulation and process variables impact the dissolving profile.
		1 hr.	20- 40%		
		8 hr.	60-80%		
		12 hr.	NLT 85%		
		16 hr.	NLT 95		

Table 2: **Critical process parameter**

Sr. No	Process	Critical parameters
1	Lubrication	Mixing time & blender speed

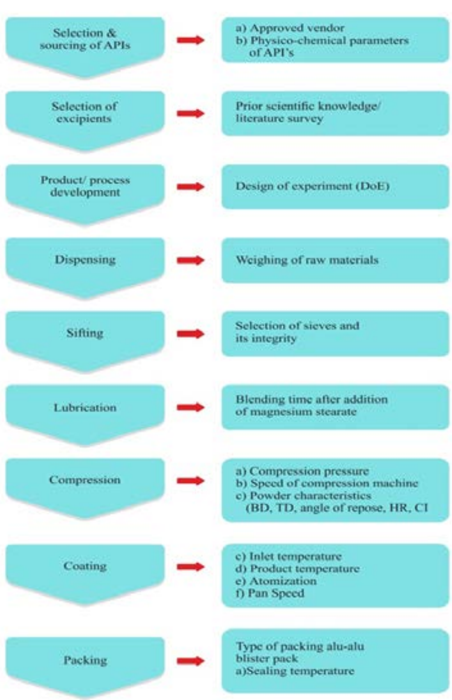


Figure 1: Manufacturing Process flow chart along with critical process parameters (CPP)

Table 3: Summary of the relative risk ranking framework

Low	The level of risk is deemed generally acceptable and further investigation is not required.
Medium	The acceptance of medium risk is acknowledged. Further investigations may be essential to alleviate the associated risk.
High	Risk is considered intolerable. Additional research is necessary to reduce the associated risk.

Table 4: The initial evaluation of the possible risk associated with the active pharmaceutical ingredient's characteristics considering the drug product's critical quality attributes (CQAs)

Critical Quality Attributes of Drug Products	**Attributes of active pharmaceutical ingredients.**				
	Solid state form	Size Distribution of Particles	Solubility	Chemical Stability	Flow Properties
Assay	Low	Low	Low	High	Medium
Dissolution	Low	Medium	Low	Low	Low

Table 5: Explanation for the initial assessment of risks related to the attributes of the drug substance

Attributes of API	**Critical Quality Attributes of Drug Products**	**Explanation**
Solid state form	Assay	The tablet assay is unaffected by the drug solid state.
	Dissolution	The dissolution is not affected by the solid-state form.
Particle Size Distribution (PSD)	Assay	The drug material is in crystalline form and has good flow properties therefore the risk is limited.
	Dissolution	As a BCS class I drug, vildagliptin is not expected to be significantly influenced by PSD in terms of its dissolution properties. The risk level associated with this drug is categorized as medium.
Solubility	Assay	The solubility does not affect the tablet assay.
	Dissolution	Vildagliptin is a BCS class I molecule. The dissolution is unaffected by its solubility.
Chemical Stability	Assay	There is a strong relationship between temperature and the degradation reaction. At higher temperatures, the degradation rate increases significantly.
	Dissolution	Particle size distribution and drug material solubility have the most effect on tablet dissolution. The chemical stability of the medicinal ingredient has no impact on tablet disintegration. There is minimal risk.
Flow Properties	Assay	Poor flow can significantly influence test results, affecting the uniformity of material. The level of risk is medium.
	Dissolution	The drug substance's flowability does not depend on its degradation mechanism or solubility, so the assessed potential risk is low.

Drug excipient compatibility studies

The study of compatibility between the drug and excipients was carried out by storing the physical mixture in a sealed vial at 40 °C with a relative humidity of 75% for 28 days.

Fourier transforms infrared spectroscopy (FTIR)

Drug compatibility with the chosen excipients was determined utilizing Fourier Transforms Infrared Spectroscopy (Shimadzu IR Affinity 1S). In the potassium bromide powder, 2 mg of vildagliptin was individually dispersed along with a mixture of lubricated granules derived from the optimized formulation. Distinct scanning procedures were conducted on both the lubricated granules of the optimized formulation and the pure drug. The resulting spectra from these two samples (the pure drug and the lubricated granules) were analyzed to verify the compatibility between the drug and the excipients.

Differential scanning calorimetry (DSC)

Precisely 5mg of vildagliptin was weighed and transferred to an aluminum differential scanning calorimetry pan, which was then subjected to a temperature scan between 25 and 300°C to get thermograms. The process was repeated to blend the optimized formulation. The obtained thermograms were then compared to understand the interaction between the drug and excipients (if any).

X-ray diffraction (XRD)

The drug and polymer samples were analyzed using a Bruker D2 Phaser (Benchtop) X-ray diffractometer to get their X-ray diffraction spectra. The patterns were gathered between the 2θ ranges of 10 to 50. The scan rate was set at 100 per minute and step size was 0.020 [1].

Formulation and development of vildagliptin extended-release tablets using design expert

Experimental Design

In the formulation of vildagliptin extended-release tablets, 3^2 full factorial designs were implemented to optimize the concentrations of the extended-release polymers like supersmart SR and Hydroxypropyl methylcellulose K4M. The concentration of Sepismart SR and the concentration of Hydroxypropyl methylcellulose K4M were chosen as independent variables. The responses (dependent variables) chosen were the percentage of drug release at 1 hour, 8 hours, 12 hours, and 16 hours (R_{1hr}, R_{8hr}, R_{12hr}, and R_{16hr}, respectively). The significance terms were selected at a 95% confidence interval ($p<0.05$) for the equations. In developing the vildagliptin extended-release tablet formulation, three levels of factor A (Sepismart SR) were explicitly utilized at concentrations of 210, 230, and 250 mg, in conjunction with three levels of factor B (Hydroxypropyl methylcellulose K4M) at 30, 45, and 60 mg per tablet. Following a 3^2-factorial face-centered design, nine experimental formulations were created using chosen combinations of the two factors, A and B. Table 6 states the formula for the experimental batches. These formulations were then evaluated to determine the significance of A and B's combined effects and the optimal combination and concentration required to produce an extended-release of the drug from the dosage form. The statistical optimization and ANOVA study were performed using a design expert.

Table 6: Formula for experimental batches using design of experiment software

S. No.	Ingredients	Quantity Per Tablet (in mg)								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
A. Formula for core tablets										
1.	Vildagliptin	50	50	50	50	50	50	50	50	50
2.	Sepismart SR	230	230	210	250	210	250	250	210	230
3.	Hydroxypropyl methylcellulose K4M	45	30	30	45	45	30	60	60	60
4.	Colloidal silicon dioxide	5	5	5	5	5	5	5	5	7
B. Formula for film coating										
5.	Instacoat Aqua III 40006 white	15	15	15	15	15	15	15	15	15
6.	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Preparation of vildagliptin extended-release tablets

The measured quantity of vildagliptin IP was sifted through the 60-mesh stainless steel sieve (Atlanta) separately. Further co-processed natural polymer (Sepismart SR), Hydroxypropyl methylcellulose K4M, colloidal silicon dioxide, and microcrystalline cellulose (Avicel® PH-200) were sifted through a 40-mesh sieve (Atlanta). Lubricant magnesium stearate was sifted through a 60-mesh sieve separately. The drug and excipients, after being sifted, were placed into an octagonal blender (Gansons, Model: 2/5/10 LTR), excluding the lubricant, and mixed for 10 minutes at 10 revolutions per minute. Sifted magnesium stearate was transferred to a blender, and the mixture was blended for another 3 minutes at 10 revolutions per minute to obtain lubricated granules. The prepared lubricated granules were compressed in 12 mm standard concave plain upper and lower punches and corresponding dies (from Bombay Pharma Tools) of a 10-station 'D' Tooling tablet compression machine (General Machinery: GMC Jaguar). An adequate quantity of Aqua III White 40006 was added to purified water in a suitable capacity stainless steel vessel under continuous stirring for 45 minutes. The obtained coating suspension was filtered using a 40-mesh nylon cloth. The core tablets were coated using Gansons Benchtop Coater 275/250" using coating suspension prepared per the formula in Table 6 [20].

Evaluation of pre-compression parameters

The micromeritic characteristics like tapped and untapped density, Carr's compressibility index, Hausner's ratio, loss on drying, and angle of repose of granules were studied to determine the suitability of the developed granules for compression.

Method of determination of micrometric properties of granules

Bulk density

The powder sample (Lubricated granules of optimized formulation) was prepared by ensuring it was free from lumps and agglomerates. Using a balance, a suitable quantity of the powder sample was measured. The weighed powder was carefully moved into a graduated cylinder without compacting it. Letting the powder settle naturally without using any outside pressure was crucial. To prevent parallax errors, the volume that the powder occupied in the graduated cylinder once filled was measured at eye level. This measurement indicated the powder's bulk volume. The bulk density (BD) was determined by utilizing the formula.

$$BD = \frac{\text{Mass}}{\text{Volume}}$$

Tapped density was determined using a precision balance; 30 grams of the powder sample (Lubricated Granules of optimum formulation) was weighed. The sample was mixed correctly to achieve homogeneity and was made sure to be dry and free-flowing. The tapping density apparatus's graduated cylinder was filled with the weighed powder sample. The powder's initial volume (V0) was measured without any tapping. The tapping was carried out using the procedure described in USP. The tapping continued until no more discernible drop in volume, usually after 500 taps. Following the tapping procedure, the powder's final volume (Vt) in the cylinder was noted. Using the following formula, the tapped density (ρt) was determined.

$$\rho\text{t} = \frac{\text{M}}{Vt}$$

Where ρt = Tapped density (g/ml)

M = Mass of powder sample (g)

The compressibility index

The compressibility index (CI) was calculated using the formula:

$$CL = \frac{V0 - Vf}{V0} \times 100$$

V0 = initial bulk volume, Vf = final tapped volume

Hausner's ratio

Hausner's ratio (HR) was determined by dividing the tapped density by the bulk density:

$$HR = \frac{\rho\text{t}}{\text{BD}}$$

ρt = Tapped density, BD: Bulk Density

The micrometric characteristics of lubricated granules are essential for enhancing the direct compression technique in tablet manufacturing. These characteristics directly influence flowability, compressibility, mechanical strength, drug content uniformity, and the final product's overall stability.

Evaluation of post-compression parameters

The hardness of the tablets was evaluated, and any chips, cracks, or other undesirable features were identified. A random sample of 20 tablets was chosen, and the weight of each tablet was measured along with the mean weight of all the tablets. Each group of 20 tablets was measured using a digital vernier caliper, and the average thickness in mm was recorded. The mean hardness of 10 tablets was measured using an electrolab digital hardness tester and expressed in Newton (N). A total of 6.5 grams of tablets were subjected to testing in a Roche friabilator, where they were rotated for 100 revolutions at a speed of 25 revolutions per minute. Following this process, the tablets were dedusted and subsequently reweighed. The percentage of friability was then determined using the formula provided below:

$$\%\, \boldsymbol{friability} = \frac{\boldsymbol{A - B}}{\boldsymbol{B}} \times \mathbf{100}$$

Where A = Initial weight of tablets, B = Final weight of tablets after 100 revolutions

Drug content

20 tablets were weighed to calculate their average weight. The tablets were then crushed into a fine powder, which was weighed accurately. This powder, corresponding to 50 mg of vildagliptin, was placed into a 100 ml volumetric flask. Subsequently, 10 ml of methanol was added, and the mixture was sonicated for 15 minutes to fully dissolve the contents. The solution was then adjusted to a total volume of 100 ml with water. Filtration was carried out using Whatman No. 1 filter paper, with the initial few ml of filtrate discarded before collection. Finally, 6 ml of the filtrate was diluted to a total volume of 100 ml with water. [The concentration of vildagliptin was 30 parts per million (ppm)]. The absorbance of the standard and sample preparations was measured at 202 nm by taking water as a blank. The percentage

assay of vildagliptin was calculated using the procedure in the official compendia [21].

In vitro drug release and drug kinetic study

The drug release studies of film-coated vildagliptin extended-release tablets 50 mg were conducted using a dissolution testing apparatus USP type II (paddle type) (Electrolab) (Model: TDL-08 L). The dissolution test was performed over 16 hours, utilizing 900 ml of water maintained at 37°C and a rotational speed of 75 rpm. At 1, 8, 12, and 16 hours, a 5 ml sample was extracted from the dissolution apparatus, with an equivalent volume of fresh dissolution medium added to ensure the maintenance of sink conditions. The Whatman filter paper was used to filter the samples, and the corresponding medium was then used to dilute it to the appropriate concentration. The absorbance of the sample was measured at 202 nm using a UV-visible spectrophotometer (Meta Spec Pro, Labman) [22, 23].

***In vivo* studies**

The pharmacokinetic characteristics of the drug were examined through in vivo studies, which also validated the results obtained from the in vitro drug release study. An *in vivo study was* carried out at the organization's IACE. The first animal study protocol was approved vide letter no. (Approval No. Biotox/IAEC/02/2023/RP-10). The study involving animals was conducted under the guidelines established by the Committee for Control and Supervision of Experiments on Animals (CPCSEA). A rabbit model was used to conduct an in *vivo* study. The experiments were performed on female white rabbits with weights ranging from 2.0 to 2.5 kg. Before the initiation of the study, the rabbits were divided into two groups of six and subjected to an overnight fasting period, although they had unrestricted access to drinking water. The first group (test) received the optimized formulation in intact tablet form, while the second group received the marketed product (As intact tablets) via gastric intubation. Blood was collected via the ear vein while the animals were restrained with rabbit restraints. Blood samples were taken into heparinized tubes at predefined intervals of 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 16 hours post-administration. The plasma was extracted from collected blood samples by centrifugation at 500 RPM and 4 °C for five minutes. The test plasma samples were stored at -20 °C until they could be further analyzed after being separated. A high-performance liquid chromatography (HPLC) technique was employed to determine the amount of the drug in plasma. The samples were analyzed using a Cosmosil C18 (250mm x 4.6ID, particle size: 5µ) column. The mobile phase consists of acetonitrile: 10 mM KH_2PO_4 buffer (70:30) delivered at a flow rate of 0.8 ml/min, UV detection at 205 nm, and a 20 µL injection volume. The analysis operations and data interpretation were conducted using Lab Solutions software. Table 7 outlines the HPLC parameters utilized for sample analysis [24-25].

Table 7: HPLC parameters used in the analysis of plasma

Mobile Phase	ACN:10mM KH_2PO_4 Buffer (70:30)
Flowrate	0.8ml/min
Wavelength	202nm
Injection Volume	20uL
Pressure	12-13MPa

Stability studies

Stability batches were prepared with a batch size of 1000 tablets as per the optimized formula stated in Table 13 on the outcome of the response surface design (face-centered design) and method of preparation as disclosed above. These tablets were packed in an alu-alu Blister Pack (Accupack: Blislab-100). The stability of the samples was assessed over six months in a stability chamber (Newtronic: NLWH34238U) under accelerated conditions, which included temperature and humidity variations of 40°C±2°C with 75%±5% humidity and 30°C±2°C with 75%±5% humidity. Periodic evaluations were carried out at 1, 2, 3, and 6 months. Samples were removed and were analyzed for hardness, percent assay, and percent dissolution [26, 27].

RESULTS

The extended-release formulation has been prepared for most antidiabetic drugs, which were initially required to be taken twice daily. Now, because they are required to be taken only once, it has been proved that they are compliant and adhere to therapy as well. John A. Romley et al., 2019, have given the extended-release formulation and medication adherence along with different drugs, including antidiabetic drugs like Glipizide and metformin [28].

Pre-formulation studies

The physical characteristics revealed that vildagliptin was a white, odorless, and colorless powder. Its melting point has been identified as ranging from 151 to 153°C. The FTIR spectra from the gifted sample matched the previously published FTIR spectra of vildagliptin, showing a high degree of comparability. In addition, the UV spectrometric analysis showed a λ max of 202 nm, which is consistent with the λ max values found in the literature for this compound. This Preformulation data is crucial for establishing the purity of the drug.

Drug excipient compatibility studies

FTIR analysis confirmed the compatibility of the drugs with the chosen excipients, indicating the absence of any interactions. Figure 2 shows the IR spectra of (A) Vildagliptin API, (B) Sepismart SR, (C) Magnesium Stearate (D) and HPMC K4M (E), Lubricated Granules of Vildagliptin extended release Tablets (F), Colloidal Silicon Dioxide (G) and Avicel PH 200. Vildagliptin characteristic peak at 1658 cm^{-1} is being preserved in all physical mixtures with chosen excipients, which reveals drug compatibility with the excipients. Furthermore, the pure drugs and the optimized formulations were subjected to DSC analysis, resulting in thermograms obtained at 155.2°C and 152.39°C, respectively. This data further corroborates the compatibility between the drug and the excipients, as no significant displacement in the endothermic peak was observed in the DSC thermograms. (Figure 3). X-ray diffraction (XRD) determines the fundamental properties of materials, such as crystal structure, crystallite size, and strain. The overlay X-ray diffraction graph clearly showed that the vildagliptin maintained its nature unchanged during processing. Vildagliptin's sharp peak at shows at 2θ 17.464 showed vildagliptin is crystalline in nature. A sharp peak at 2θ 17 in the lubricated granules of the extended-release tablets indicates no alteration in the form of vildagliptin (Figure 4).

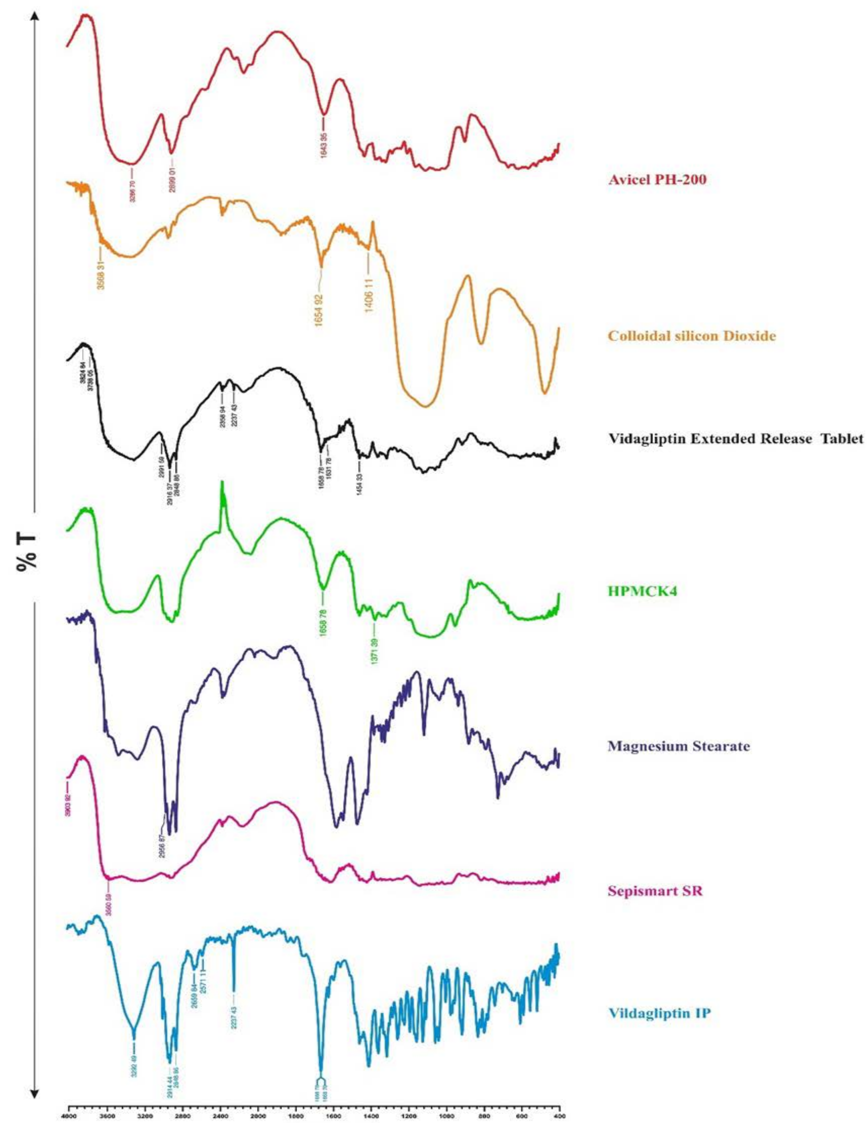


Figure 2: FTIR spectra of vildagliptin API and other excipients

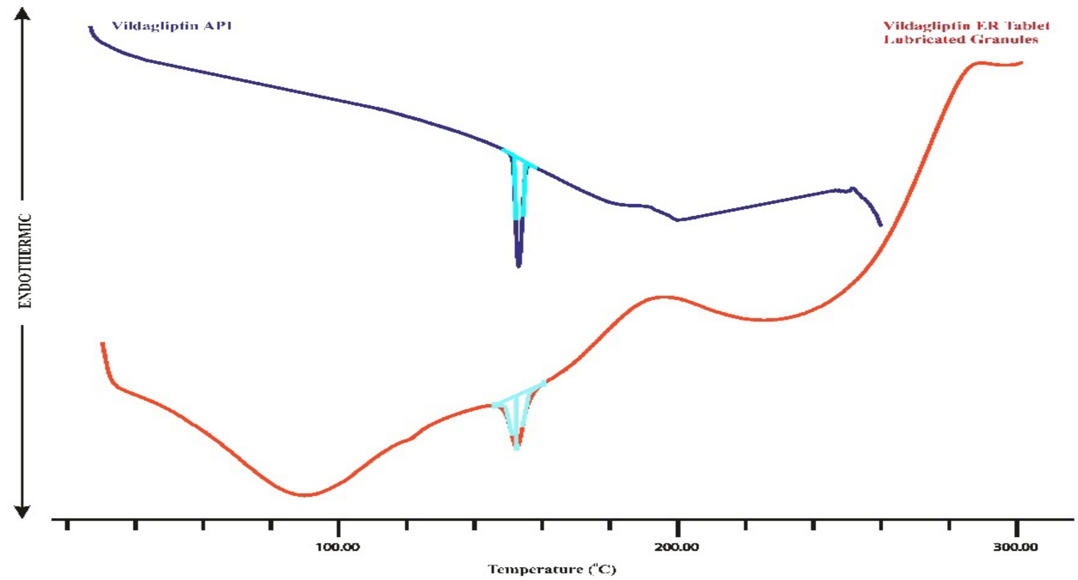


Figure 3: DSC thermogram of vildagliptin API & lubricated blend of vildagliptin extended release tablet

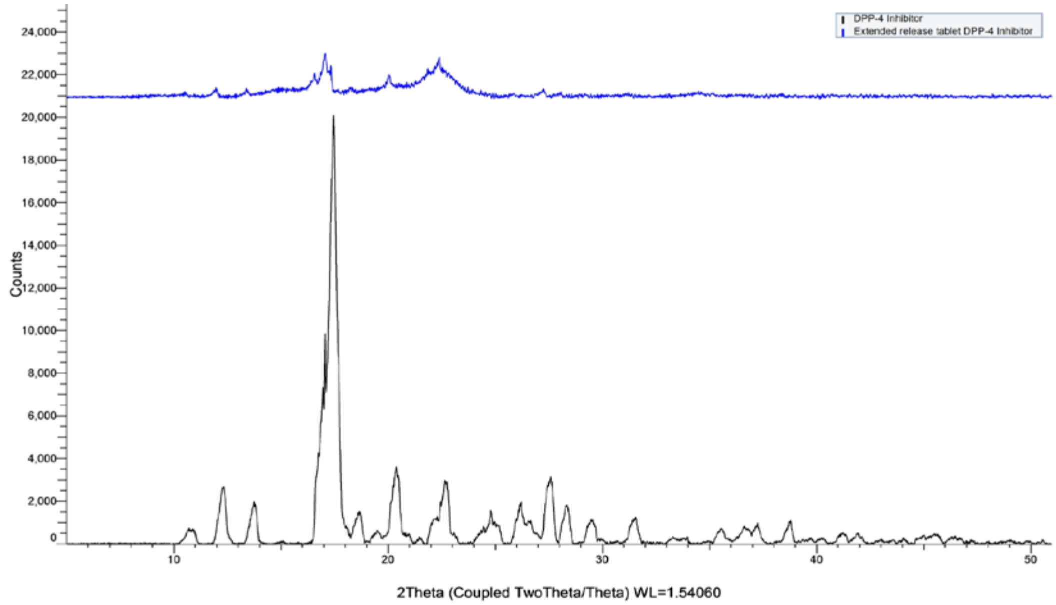


Figure 4: XRD thermograms of vildagliptin and lubricated granules of extended release tablet of vildagliptin

Table 8: Physical parameters of core tablets of experimental batches

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
A) Physical parameters of core tablets of experimental batches									
Average Weight (mg)	525	525	525	525	525	525	525	525	525
Hardness (N)	150 - 160	145 - 163	140 -155	160 -165	150-160	155- 169	140-155	150- 170	161-169
Thickness (mm)	4.90-5.0	4.90-5.0	4.90-5.0	4.90- 5.0	4.90- 5.0	4.90-5.0	4.90- 5.0	4.90- 5.0	4.90-5.0
B) Physical parameters of coated tablets of experimental batches									
Average Weight (mg)	540	540	540	540	540	540	540	540	540
Hardness (N)	140-150	130-140	176-182	150-160	130-140	140-150	160-170	150-165	140-155
Thickness (mm)	5.00-5.15	5.00-5.15	5.00-5.15	5.00-5.15	5.00-5.15	5.00-5.15	5.00-5.15	5.00-5.15	5.00-5.15

Evaluations of vildagliptin extended-release tablets

Evaluation of pre-compression parameters

Before compression, the physicochemical properties of the granules were evaluated to formulate tablets via direct compression. The bulk and tap density results, which were used to calculate the compressibility index, showed that the granules in all the batches had good flow properties. The bulk density ranged from 0.401 to 0.421 g/ml, and the tapped density ranged from 0.590 to 0.610g/ml. The angle of repose ranged between 40º and 30º, exhibiting acceptable flowability of the blend. The Hausner ratio was found to be between 1.40 and 1.52. The evaluation of micromeritic data concludes that the granules tend to have free-flowing characteristics.

Evaluation of post-compression parameters

The core and coated tablets were evaluated for weight, thickness, hardness, and % friability variations. Table 8 illustrates the satisfactory results obtained from these evaluations of core tablets & coated tablets. The weight variation results show that each formulation remains within the permissible range of ±7.5%. All samples of tablets had a uniform thickness ranging from 5.09 to 5.30 mm. Tablets of every batch showed a hardness in the range of 150 to 160 Newton. All samples of tablets had friability between 0.03% to 0.135. The data obtained from the post-compression parameter evaluation confirm the developed formulation's suitability for further coating process.

Drug content

The drug content analysis of the coated tablets reveals that the values of drug content were between 97.95 to 103.9%. Table 9 summarizes the drug content of coated tablets in the experimental batches. The values obtained for drug contents were all within the specification as per the pharmacopoeial limit. Table 10 states the drug content of optimized and market formulation coated tablets.

In vitro drug release and drug kinetic study

The dissolution profiles of all nine formulations (F1 to F9) are depicted in Table 11 and Figure 5. It is clear from the dissolution profiles of the experimental batches that the F7 formulation shows better results as compared to the other batches. The dissolution data of experimental batches helped us to get the solution for the optimized batch with the help of the DoE software. Results from the optimized formulation OTP-01 dissolution study reveal that the release was extended for 16 hours. Table 12 illustrates the findings of the optimized formulation compared to the market sample and Figure 6, and the results reveal that the market formulation released the drug within eight hours, whereas the optimized formulation could extend the release up to 16 hours. This proves that Batch No.OTP-01 can maintain therapeutic levels of the drug in the body for a more extended period, potentially leading to better efficacy and reduced dosing frequency. Batch No. OTP-01 shows a consistent drug release rate over 16 hours, whereas the market formulation has a rapid initial release followed by a decline. This suggests that Batch No.OTP-01 can provide a more stable and predictable drug release profile, which may result in improved therapeutic outcomes and reduced side effects. The optimized formulation was used to calculate and assess the amount of drug released, employing various drug release kinetics such as zero order, first order, Higuchi, and Korsmeyer-Peppas. Linear graphs were generated using MS Excel 2016 and yielded regression equations for each graph. The linearity was assessed using a regression coefficient (r2) value. The model resulting in the most linear graph was selected as the most appropriate for the drug release data. The drug release constant (k), correlation coefficient (r), and Peppas diffusion exponent (n) were determined using the kinetic equation. Based on the correlation coefficient value, i.e., 0.9598, which is closer to 1, it concludes that it follows first-order kinetics, where drug release depends on the remaining concentration. Though drug solubility is higher, it depends on the remaining drug concentration as the matrix formed is sufficient to release slowly. The Higuchi model describes the release of drugs from a polymeric matrix, such as xanthan gum, through a diffusion-controlled mechanism. The model assumes that the drug is uniformly distributed throughout the polymer matrix. The release occurs through diffusion, where the drug molecules migrate out of the matrix and into the surrounding environment.

Table 9: Drug content of coated tablets of experimental batches

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug Content (%) (Limit as per Indian Pharmacopeia) (95 % to 105 %)	99.32	98.67	101.65	98.89	97.95	99.38	98.48	98.94	100.56

Table 10: Drug content of coated tablets of optimized formulation

Parameters	Batch No. OTP-01 (Optimized Formulation)	Market Formulation
Drug Content (Limit: 95 % to 105 %)	99.62%	97.87%

Table 11: Dissolution profile of experimental batches of vildagliptin extended-release tablets

Batch No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
R_{1hr}	32.5	40.3	65	30.2	58.2	42.3	20.5	53.2	24.7
R_{8hr}	89	95	99.13	80	97.84	88	72	92	81
R_{12hr}	96.2	100	105	92	100.3	91	92	95	95.7
R_{16hr}	103.22	109	110	99	109.7	104	95	108.3	100.6

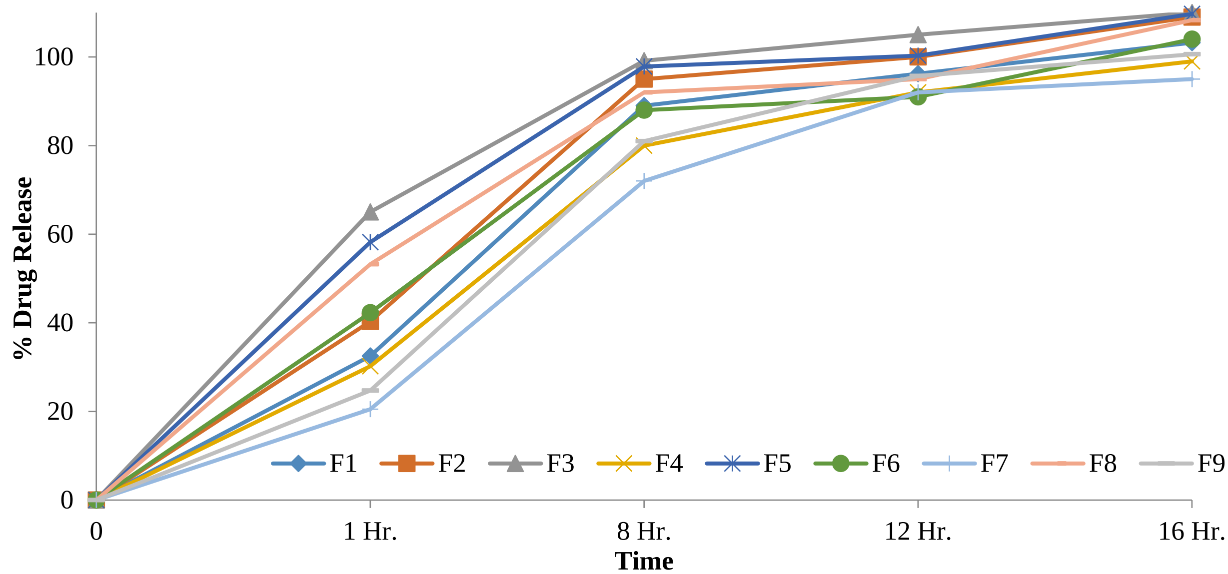


Figure 5: Dissolution profile of experimental batches

Table 12: Dissolution profile of vildagliptin extended-release tablets Vs. market formulation

Time (Hours)	Vildagliptin extended-release tablets (optimized formulation)	Market formulation
R_{1hr}	30.2	22.75
R_{8hr}	76.8	97.1
R_{12hr}	91.2	99.1
R_{16hr}	102.1	99.4

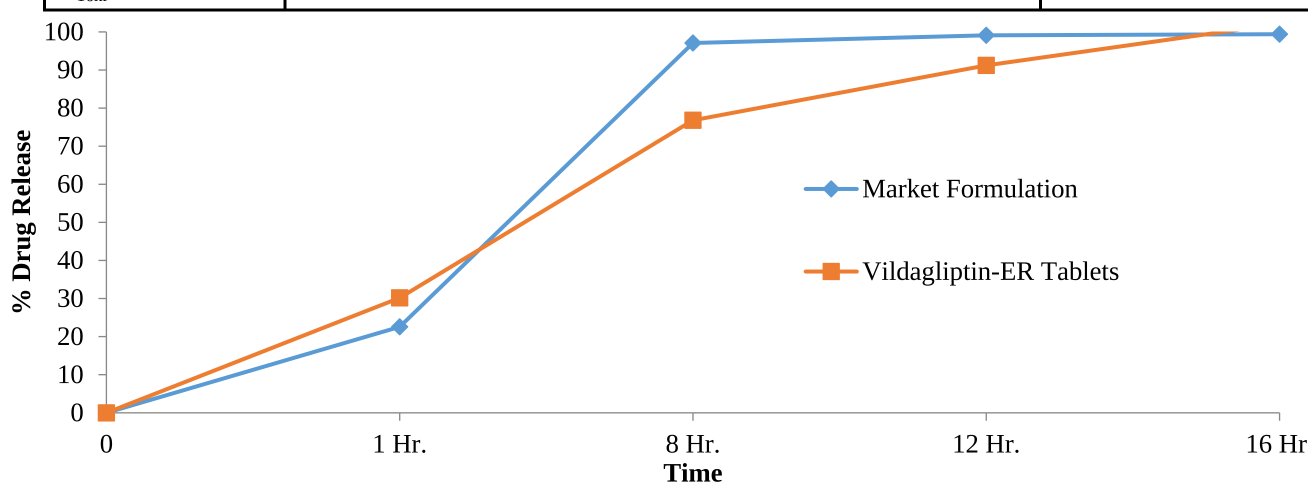
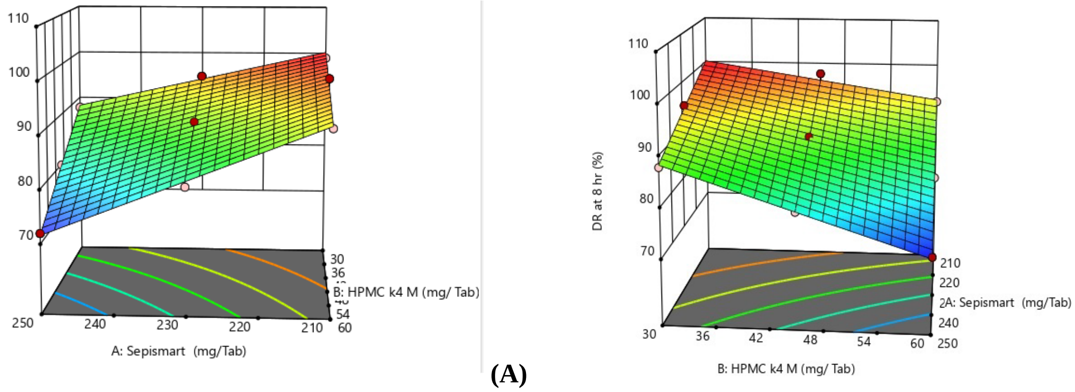


Figure 6: Dissolution Profile of market formulation Vs. vildagliptin extended release tablets

Optimization of vildagliptin extended-release tablets

In the optimization of vildagliptin extended-release tablets, a 3^2-factorial design was employed, focusing on two independent variables: the concentrations of Sepismart SR (A) and Hydroxypropyl methylcellulose K4M (B). These variables were assessed at three concentration levels: high, medium, and low. The ranges of the variables were -1, 0, and +1, as illustrated in Figure 7.



(A) **(B)**

Figure 7: Graphical representation of effect of concentration of sepismart SR & HPMCK4M

The effect of these independent variables on the percentage of drugs released at one, eight, twelve, and sixteen hours was evaluated as the four optimization response parameters (dependent variables). Tablets were manufactured by the direct compression process using the formula shown in Table 6. A reduced quadratic model was obtained for the response parameter (DR-1hr), and two-factor interaction (2FI) models were obtained for the remaining three response parameters. The model equations obtained for the response parameters were as follows:

$$R_{1hr} = 34.07 - 13.57A - 7.87B + 11.17A^2$$

[R^2 *= 0.98, F-value = 83.32, p-value = 0.0001*]

$$R_{8hr} = 88.22 - 8.16A - 6.19B - 2.22AB$$

[R^2 *= 0.99, F-value = 175.84, p-value < 0.0001*]

$$R_{12hr} = 96.36 - 4.22A - 2.22B + 2.75AB$$

[R^2 *= 0.96, F-value = 45.70, p-value = 0.0005*]

$$R_{16hr} = 104.31 - 5.00A - 3.18B - 1.83AB$$

[R^2 *= 0.98, F-value = 72.66, p-value = 0.0002*]

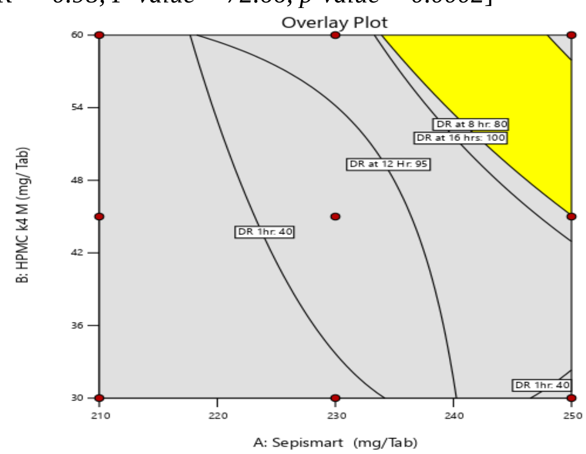


Figure 8: Overlay plot (design space) for the concentration of sepismart SR & HPMC K4M

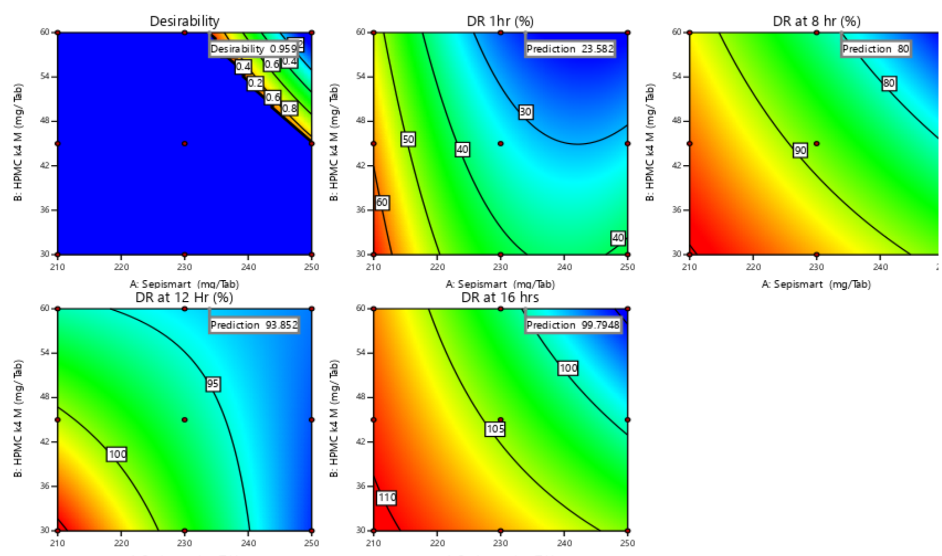


Figure 9: Graphical representation of predicted drug release at different time points

The graph from Figures 7 A and 7B and Table 11 clearly shows that an increase in the concentration (mg/tab) of Sepismart SR leads to a decrease in the dissolution rate. The observed effect may be attributed to the rise in polymer density corresponding with higher concentrations of Sepismart SR. This phenomenon results in a more compact and denser matrix, thereby diminishing porosity and enhancing the tortuosity of the diffusion pathway. As a result, the drug molecules have to travel a longer distance to diffuse out of the matrix, leading to a slower release. Higher molecular weight polymers have a more complex structure, reducing the drug molecules' mobility and slowing their release. As the concentration of Sepismart SR increases, the polymer chains form a stronger and more rigid matrix. This entanglement reduces the flexibility of the polymer chains making it more difficult for the drug molecules to diffuse out, leading to a slower release. Sepismart SR is a hydrophilic polymer that forms hydrogen bonds with water molecules. As the concentration increases, the number of hydrogen bonds also increases, leading to a stronger and more stable matrix. This reduces water penetration and matrix swelling, resulting in slower drug release. Increasing the concentration of Sepismart SR also increases the viscosity of the polymer solution. Higher-viscosity solutions have a slower diffusion rate, leading to slower drug release. Whereas graph 7B reveals that dissolution is retarded as the concentration (mg/tab) of Hydroxypropyl methylcellulose K4M was increased. Figure 8 graph is an overlay plot of the design space, which shows the optimum concentration of Sepismart SR and Hydroxypropyl methylcellulose K4M to achieve the desired dissolution profile. Figure 8 demonstrates that through different predictions using various constraints concerning polymers Sepismart SR and Hydroxypropyl methylcellulose K4M and drug release at different time points, 50 solutions were suggested by design expert software, out of which 1 solution was selected that had a higher desirability value, i.e., 0.959 for the verification batch having the desired drug release profile. Table 13 shows the formula for the verification (optimized) batch as suggested by DoE. It can be seen that the predicted and experimentally observed drug release values were similar.

In vivo studies

A 500 µl test plasma sample was combined with an internal reference in a centrifuge tube. It was mixed and shaken for one minute. 100 µl of acetonitrile was added to this mix to make it precipitate. The resulting mixture was vigorously agitated and then subjected to centrifugation at a speed of 3000 rpm for 20 minutes. The next step involved filtering and collecting the supernatant. The filtrate obtained was considered a plasma sample for the HPLC analysis. Subsequently, a volume of 20 µl of the test sample was injected into the HPLC system for analysis. The 'peak area ratio' values were derived by analyzing all test plasma samples with the same HPLC parameters. The corresponding drug concentrations for the 'peak area ratio' values obtained were determined by employing the drug calibration curve illustrated in Figure 10. The data gathered on plasma drug concentrations across different time points was analyzed to identify vital pharmacokinetic parameters including the peak plasma concentration (Cmax), the time necessary to reach Cmax and the area under the curve (AUC). Two peaks at various times of retention that match the internal standard and vildagliptin were seen in the chromatogram produced by the developed HPLC technique. The constructed standard graph of vildagliptin in rabbit plasma demonstrates high linearity according to the Beer-Lambert equation. Figure 10 displays the drug concentration-time profile that was produced employing the predetermined calibration curve. The calculated pharmacokinetic (PK) parameters are shown in Tables 15 and 16. The mean C_{max} values of the optimized formulation and market sample were 227 ng/ml and 212 ng/ml, respectively. The plasma drug concentration peaked in the market sample after 10 hours of administration. This result confirms the rapid drug absorption from the reference solution. The first and second groups of rabbits exhibited mean AUC values of 318599.7 ng.hr/ml and 169552 ng.hr/ml, respectively. Compared to commercially available products, the developed formulation has demonstrated the most compelling and beneficial advantages. The plasma drug concentration in ng/ml for both the market formulation and vildagliptin extended-release tablets in rabbits is illustrated in Figure 11.

Table 13: Optimized formula for vildagliptin extended-release tablets

S No.	Ingredients	Quantity (mg/Tablets
1.	Vildagliptin	50
2.	Sepismart™ SR	234
3.	HPMC K4M	60
4.	Colloidal silicon dioxide	5
5.	Magnesium stearate	7
6.	Avicel- PH-200	169
	Tablet weight of core tablet	525

Table 14: Physical parameters of core & coated tablets of optimized formulation

Parameters	Batch No. OTP-01
A) Physical parameters of core	
Average weight of core Tablet (mg)	525.00
Hardness (N)	150-160
Thickness (mm)	4.90-4.95
Friability (%)	0.17
B) Physical Parameters of coated tablets of optimized formulation	
Average weight of core Tablet (mg)	540.00
Hardness (N)	150-160
Thickness (mm)	5.05 -5.15 mm

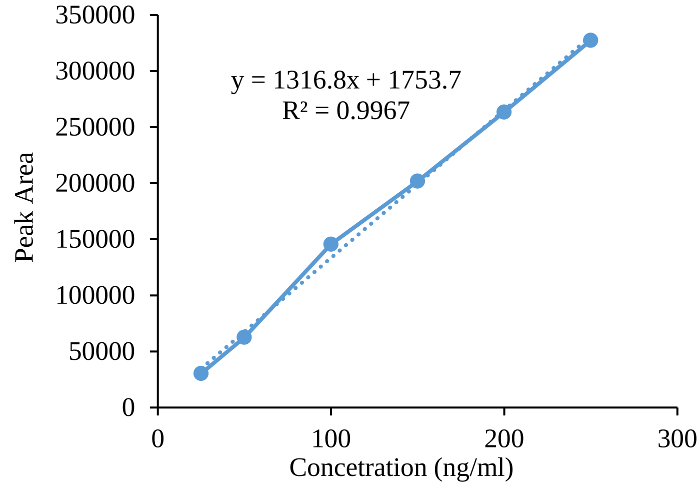


Figure 10: Standard calibration curve of vildagliptin in Rabbit plasma (HPLC Method)

Table 15: Plasma drug concentration of vildagliptin extended-release tablets

Time	**Sample Area**						**Mean**	**Conc. (ng/ml)**
	1	**2**	**3**	**4**	**5**	**6**		
30 min	22663	22968	22458	21953	22010	22356	22401.33	15.98674
1hr	55849	55246	54825	54912	55026	55689	55257.83	39.43481
2hr	115492	114565	115865	116254	115237	115425	115473	82.40743
4hr	142432	141954	142521	142983	141546	142857	142382.2	101.6112
6hr	154054	154252	153555	153625	154877	155011	154229	110.0657
8hr	177633	178524	177425	178322	177569	178245	177953	126.9964
10hr	232273	233145	236451	233214	234121	234291	233915.8	166.9343
12hr	296155	294521	295363	296541	294587	295314	295413.5	210.8222
14hr	318911	318246	319254	317422	318542	319657	318672	227.4206
16hr	319578	318627	316254	319522	318465	319152	318599.7	227.369
20 hr								

Table 16: Plasma drug Concentration of market formulation

Time	**Sample Area**						**Mean**	**Conc. (ng/ml)**
	1	**2**	**3**	**4**	**5**	**6**		
30 min	21337	21452	22652	21549	22455	23488	22155.5	27.72576
1hr	37492	37569	36915	36714	38121	39254	37677.5	47.15025
2hrs	57099	57814	58215	57141	58141	59625	58005.83	72.58946
4hrs	80310	80302	81874	79844	79104	80252	80281	100.465
6hrs	117114	116542	117896	116524	116329	117484	116981.5	146.3926
8hrs	170046	168592	169547	170112	170983	169988	169878	212.5881
10hrs	169937	169524	169325	170212	170953	171484	170239.2	213.0401
12hrs	167952	170252	170212	171036	169854	169323	169771.5	212.4549
14hrs	166140	168748	169555	170258	169716	169784	169033.5	211.5313
16hrs	169579	168121	170236	169425	170121	169832	169552.3	212.1806

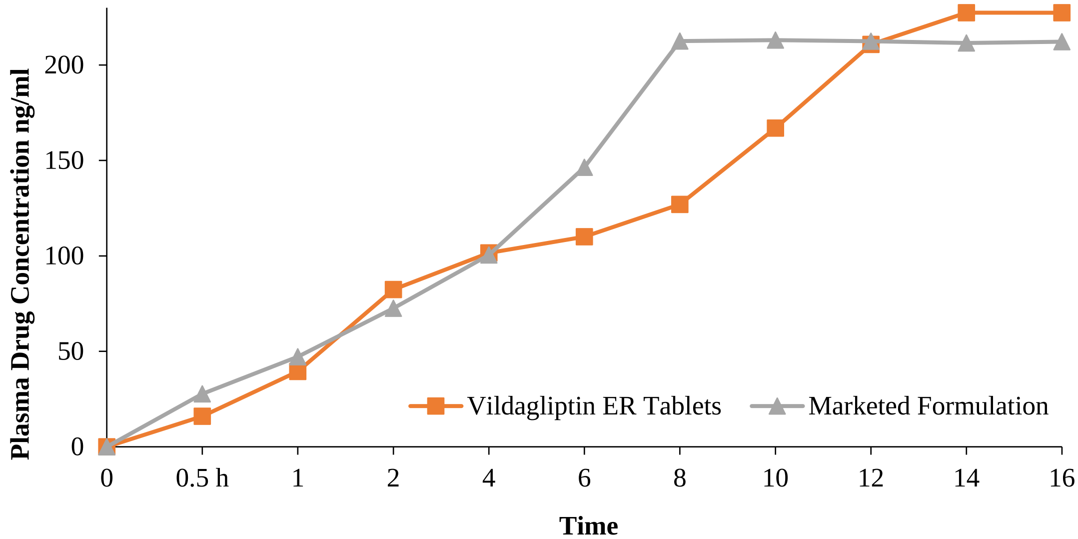


Figure 11: Plasma drug concentration ng/ml of vildagliptin extended-release tablets & market formulation in rabbit

The developed extended-release tablets exhibit a distinctive plasma drug concentration-time profile characterized by a gradual increase in plasma drug concentrations (C_{max}) over a prolonged absorption phase (T_{max}) followed by a sustained plateau phase lasting 12 hours. In contrast, the marketed formulation displays a shorter absorption phase (T_{max}) and a more rapid decline in plasma drug concentrations, resulting in a shorter therapeutic level. This prolonged plasma drug concentration profile offers several pharmacokinetic advantages.

- Increased area under the curve (AUC): The extended plasma drug concentrations result in a greater AUC, indicating enhanced drug exposure.
- Prolonged mean residence time: The extended-release formulation increases the mean residence time, reflecting a longer duration of drug action.
- Reduced peak-to-trough fluctuation: The slower absorption and sustained release minimize peak-to-trough fluctuation, ensuring a more stable therapeutic effect.
- Improved steady-state pharmacokinetics: The prolonged plasma drug concentration profile enables a more consistent and predictable steady-state profile.

The drug remains effective for extended periods, providing patients with better glucose control and convenience. It reduced peak-to-trough fluctuation. The slower release reduces the extreme highs and lows in drug levels, leading to a more stable therapeutic effect. It improved patient compliance. The extended-release reduces dosing frequency, making it easier for patients to adhere to their treatment regimen. This is happening due to Sepismart SR, a specially designed co-processed extended-release natural polymer, which forms a strong and cohesive matrix that releases the drug slowly & regulates water uptake, preventing rapid swelling and drug release. It maintains a consistent release profile, ensuring a stable therapeutic effect. Combining xanthan gum and gum acacia (Sepismart SR) creates a robust and extended-release system, resulting in a more effective and patient-friendly formulation. Sepismart SR forms a robust and cohesive matrix that resists breakage and cracking, preventing core separation and enhancing adhesion between the tablet matrix and the core, creating a strong bond that minimizes the risk of core separation. Sepismart SR releases the drug in a controlled and sustained manner, maintaining a consistent release profile. The passage of intact, undigested, or insoluble drug housing shells into feces is sometimes known as “the ghost pill or ghost tablet. The "ghost pill" effect is often observed in extended-release tablets formulated with synthetic polymers. In contrast, the developed formulation utilizes a blend of xanthan gum and gum acacia (Sepismart SR) as the matrix-forming excipients. A non-ionic polysaccharide, Xanthan gum forms a strong and cohesive gel network upon hydration, providing an extended drug release. Gum acacia, a complex polysaccharide, enhances the gel strength and stability while contributing to the expression mechanism. The unique combination of xanthan gum and gum acacia in Sepismart SR enables a dual-release mechanism.

- Diffusion-controlled release: The drug diffuses through the hydrated xanthan gum network, providing a sustained release profile.

- Expression-controlled release: The swelling of the gum acacia component creates pressure that pushes the drug out of the tablet, supplementing the diffusion mechanism and ensuring a consistent release profile. This synergistic combination minimizes the ghost pill effect. Vildagliptin has gained significant popularity as a commonly used medication for the management of type II diabetes. Traditionally, patients had to take conventional immediate-release tablets twice a day, which could lead to missed doses. However, with the development of extended-release formulations, patients can take the medication just once a day, reducing the frequency of dosing and improving patient compliance with the treatment plan. While many anti-diabetic drugs are available in extended-release forms, the focus is on selecting a drug that is widely utilized in treating diabetes. Therefore, Vildagliptin was chosen for the development of an extended-release formulation.

Compared with other classes of antidiabetic medications, such as metformin, sulfonylureas, thiazolidinediones (TZDs), and SGLT2 inhibitors, vildagliptin's unique characteristics become apparent.

Metformin: While metformin is often considered first-line therapy due to its efficacy and safety profile, it primarily acts through different mechanisms (e.g., reducing hepatic glucose production). An extended-release formulation exists for metformin; however, it does not provide the same incretin-based approach as vildagliptin.

Sulfonylureas: These agents stimulate insulin secretion but carry a higher risk of hypoglycemia and weight gain than vildagliptin.

SGLT2 Inhibitors: While effective in promoting glycosuria and weight loss, these medications can cause urinary tract infections and dehydration.

Thiazolidinediones: These agents improve insulin sensitivity but are associated with weight gain and cardiovascular risks. Vildagliptin's favorable pharmacokinetics, combined with its efficacy in managing blood glucose levels while minimizing side effects, make it an excellent candidate for development into an extended-release tablet formulation

Control strategy

The control strategy for vildagliptin extended-release tablets is derived from thorough investigations that have enhanced the understanding of the product and its production methods. In the preliminary risk assessment, these investigations assessed the material properties and process variables identified as high-risk factors affecting the therapeutic product's critical quality attributes (CQAs). This control strategy embodies a comprehensive framework that ensures quality by leveraging established processes and accumulated product knowledge. The control strategy of Vildagliptin Extended Release is studied during the stability batches. The control strategy includes drug substances and excipient material attributes to be controlled, which are controlled through raw material specifications for each drug substance and excipient. In-process controls and high-risk process parameter ranges were studied during development batches, and the proposed operating ranges for stability batches were set.

Stability studies

Accelerated stability studies conducted for the optimized batch of vildagliptin extended-release tablets showed that temperature and humidity do not affect the tablets' hardness. The drug content and dissolution profile of vildagliptin are satisfactory, and the formulation has been stable for over six months. The stability study results are depicted in Table 17.

Table 17: Stability study results

Tests	Limits				30°C/75%RH			40°C/75%RH		
		Initial	1M	2M	3M	6M	1M	2M	3M	6M
*Description	To be comply	Complies					Complies			
Hardness	140±30	170±5	160±5	163±5	160±5	150±5	164±5	160±5	150±5	140±5
Assay										
Vildagliptin	90- to 110%)	99.62	98.4	98.5	97.5	96.85	98.1	98.3	97.2	96.0
Dissolution										
R_{1hr}.	20- 40%	31.1	29.4	29.1	33.0	32.69	30.2	28.1	26.4	31.67
R_{8hr}	60-80%	72.0	70.3	71.0	74.1	76.71	73.9	71.6	74.3	73.56
R_{12hr}	NLT 85%	90.3	86.7	88.1	90.4	92.0	90.7	88.4	88.2	90.0
R_{16hr}	NLT 95 %	98.1	98.4	95.7	100.3	96.65	98.6	96.8	97.3	98.5

*NLT= Not Less Than ***** White to white, Round Shape, biconvex film-coated tablets, plain on both sides.

CONCLUSION

A comprehensive understanding of formulation and process variables via research and a risk-oriented methodology yields a product with the desired qualities and characteristics while utilizing cost-effective techniques. Quality by design is an outstanding approach to accomplishing this objective. The current study demonstrated Quality by Design (QbD) principles in developing and optimizing vildagliptin extended-release tablets. These tablets were formulated with a combination of natural polymers, specifically co-processed gums of Xanthan and Acacia (Sepismart SR), and hydroxypropyl methylcellulose K4M. This formulation resulted in an extended drug release for 16 hours, reducing dosing frequency and improving patient compliance. This research proved that vildagliptin can develop into a stable extended-release dosage form. This extended-release formulation would address the issue of the ghost pill effect by utilizing a combination of natural and semisynthetic polymers. It would also minimize the occurrence of side effects associated with high serum levels that are commonly seen with immediate-release formulations. Furthermore, this formulation has proven effective, safe, and tolerated. Additionally, it has the potential to reduce the frequency of doses administered, resulting in improved patient compliance and a decreased risk of overdose. Ultimately, this can lead to a reduction in the overall cost of treating diabetic symptoms. The present study provides the direct compression method to prepare tablet dosage. The pharmaceutical industry needs to form a pharmaceutical composition formulated as a tablet using a direct compression method using natural polymer. Wet granulation involves multiple steps, and the need for additional time, space, and equipment in wet granulation can increase production costs. Loss of materials during various processing stages in wet granulation can impact tablet production's overall yield and efficiency, potentially affecting the cost-effectiveness of manufacturing vildagliptin extended-release tablets. Direct compression requires fewer unit operations than wet granulation, leading to labor, time, and resource cost savings. This economic advantage is particularly beneficial for large-scale production. Direct compression involves using minimum equipment and reducing power consumption and space requirements. Tablets manufactured through direct compression are less likely to experience changes in dissolution profiles during storage than wet granulation tablets. This ensures consistent release of vildagliptin over time, maintaining its therapeutic effectiveness. The present invention disclosed using natural polymer and formulation by direct compression, which is indeed needed for large-scale production. Thus, the present invention is inventive and possesses the inventive step. The present invention carefully selects the combination of natural gums, i.e., Xanthan Gum & Gum Acacia, which allows it to swell immediately in water and form a thick gel layer around the tablet. As a result, the soluble active ingredients like vildagliptin diffuse slowly through the gel layer, whereas the insoluble ones are released gradually by tablet erosion. This helps to avoid the ghost pill effect, which is a major cause of non-compliance by the patient using extended-release composition.

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NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Atul K Pund was responsible for the study's conception and design, the manuscript's writing, and the research work's execution, including contributions to data collection. Atishkumar S. Mundada reviewed and edited the manuscript to improve its technical clarity, grammatical correctness, and consistency.

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