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Original Article

DEVELOPMENT, CHARACTERIZATION AND PHARMACOKINETIC EVALUATION OF OPTIMIZED VILDAGLIPTIN SUSTAINED RELEASE MATRIX TABLET USING BOX-BEHNKEN DESIGN

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ABSTRACT

Objective: The principal objective of this research was to develop and optimize cost-effective sustained-release Vildagliptin (VLN) tablets using the wet granulation method.

Methods: The tablets were prepared by the non-aqueous wet granulation method. A Box-Behnken design was used to study the effect of the independent variables, i.e., HPMC K100 M, Eudragit RSPO and PVP K30, on the dependent variables swelling index, *in vitro* drug release at 8 and 12 h. The drug's physiochemical properties were investigated using ultraviolet (UV), Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC). The hardness, thickness, weight variation, content uniformity, swelling index, and *in vitro* drug release study of the formulated tablets were all evaluated. The optimized formulation Opt-VLD-SR was evaluated for pharmacokinetic parameters like AUC, C_{max}, t_{max} and MRT.

Results: The FTIR and DSC studies confirmed that no interaction occurred between the drug, polymers and excipients. The crystalline nature of VLN remained unchanged in the optimised formulation tablet, according to DSC studies. With the optimal concentration of both polymers, formulation Opt-VLN delayed drug release for up to 12 h. The formulated Optimized Sustained-release tablets (Opt-VLD-SR) showed significantly lower Cmax±3.01ng/ml) than conventional IR tablets (256.17±8.02ng/ml). In the pharmacokinetic study, the MRT for Optimized-VLD-SR is (7.40h) showed a better result than the Vildagliptin IR marketed product (3.70 h.), which leads to higher bioavailability of Vildagliptin.

Conclusion: Sustained release tablets of VLN with a combination of diffusion and erosion-controlled drug release mechanisms have been successfully developed.

Keywords: Vildagliptin, Box–behnken, Checkpoint, FTIR, DSC, Counter plots

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INTRODUCTION

Vildagliptin (VLN) an unique DPP-4 inhibitor drug, can efficaciously manage the endocrine phases in hypoglycaemia as well as hyperglycaemia and can be administered as monotherapy as well as in combination therapy for the treatment of T2DM [1]. Due to its rapid metabolism and short elimination half-life of 1.6–2.5 h, VLN is not effective for offering control over drug delivery with conventional oral dosage forms, triggering excessive fluctuations in plasma drug levels [2]. It is proposed that patients with T2DM need to stick precisely to the dosing interval and VLN should be taken at a dose of 50 mg twice a day. Upper respiratory tract infections, diarrhoea, nausea with hypoglycaemia and poor acceptability during chronic treatment are commonly seen side effects. The development of the VLN prolonged-release formulation for oral administration using biocompatible polymers might, therefore, significantly promote its duration and tolerability by lowering its dose frequency. Eudragit RSPO and HPMC K 100 as hydrophilic polymers were selected for the current study. These polymers enable pH-independent drug release in oral dosage forms, which can then be used to create sustained-release dosage forms. So in this work, the combination of polymers is used to get more sustained release action [3].

The design of an effective pharmaceutical formulation with a reasonable dissolving rate within a very short time and little testing was crucial for the development of a prolonged dose form. Surface response methodology (RSM) is one of the most important approaches for developing and optimising drug delivery systems. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, the generation of polynomial mathematical relationships and the mapping of the response over the experimental domain to select the optimum formulation [4].

The objective of this study was to develop a VLN sustained release formulation for long-term delivery by using a design of experiment approach. With RSM-based target release profiles and multiple response optimization using a quadratic polynomial equation, and to assess the utility of RSM in the development of VLN sustained-release dosage forms. In order to sustain the action of VLN, enabling a reduction in dosing interval for the treatment of hyperglycemia associated with T2DM. The independent variables for the present study were amount of release retardant polymers: HPMC K100M (X1), Eudragit RSPO (X2) and PVP K 30 (X3). To detect the burst impact and assure total drug release, the dependent variables evaluated were the swelling index and cumulative percentage release of medication at 8 and 12 h.

MATERIALS AND METHODS

Materials

VLN was acquired as a gift sample from Dr. Reddy Lab, Hyderabad, India. The excipients were as follows: Eudragit RSPO (Colorcon Asia Pvt. Ltd. Mumbai, India). PVP K30, magnesium stearate, and HPMC K100 M (CDH (P) Ltd. Bombay, New Delhi) (SD Fine Chemicals, India). The rest of the reagents and solvents were of analytical quality.

Compatibility of VLN with different excipients

Solid admixtures were made by mixing the drug with each formulation excipient separately in a 1:1 ratio and storing them in airtight containers at 30 2 C/65 5% RH to evaluate the compatibility of various formulation excipients with VLN. Using potassium bromide discs and differential scanning calorimetry, the solid admixtures were studied using Fourier transform infrared spectroscopy (FTIR-8400S, Shimadzu, Japan) in the range of 4000–400 cm^{-1} and differential scanning calorimetry (DSC-60, Shimadzu, Tokyo, Japan) The thermal analysis was performed in a nitrogen environment at a heating rate of 10 °C/min across a temperature range of 50–200 °C using a homogenised mixture (3 mg) in a DSC pan.

Experimental design

A three-level, three-factorial Box-Behnken experimental design was used in this study to assess the effects of selected independent

variables on responses, characterise the drug release process, and optimise the procedure. This design is appropriate for exploring quadratic response surfaces and building second-order polynomial models, assisting in process optimization by utilising a small number of experimental runs. Table 2 shows the dependent and independent variables chosen, as well as their low, medium, and high levels, which were chosen based on preliminary experimentation results. Table 2 shows the amounts of HPMC K 100M (X1), Eudragit RSPO (X2), and PVP K30 (X3) used to prepare each of the 15 formulations, as well as the observed responses. The Box–Behnken statistical screening design was used to optimise and evaluate the formulation ingredients' main effects, interaction effects, and quadratic effects on the *in vitro* release of VLN sustained-release formulations. With Design Expert®, a 3-factor, 3-level design is appropriate for exploring quadratic response surfaces and constructing second-order polynomial models (Version 12). The computer-generated nonlinear quadratic model is given as:

$$Y_0=b_0+b_1X_1+b_2X_2+b_3X_3+b_{12}X_1X_2+b_{13}X_1X_3+b_{23}X_2X_3+b_{11}X_1^2+b_{22}X_2^2+b_{33}X_3^2$$

Where Yo is the dependent variable, b_0 is an intercept, b_1–b_{33} are regression coefficients calculated from observed experimental Y values, and X_1–X_3 are independent variable coded levels. The interaction and quadratic terms are represented by the terms X1, X2, and Xi (I = 1, 2, or 3). (Box and Behnken, 1960) [5, 6].

Table 1: Variables in box–behnken design

Independent variable	Levels used actual (coded)		
	Low	Mid	High
X1= HPMC K100 M (mg)	30(-1)	40(0)	50(+1)
X2= Eudragit RSPO (mg)	20(-1)	35(0)	50(+1)
X3=PVP K 30 (mg)	30(-1)	45(0)	60(+1)
Response variables			
Y1= Swelling Index	Maximize		
Y2=DR % at 8h	Moderate		
Y3= DR% at 12h	Maximize		

Preparation of sustained-release matrix tablets of VLN

Table 1 lists the components of VLN sustained-release tablets. The non-aqueous wet granulation method was used to prepare the tablets because it is more efficient than other processes. All of the ingredients were screened via mesh size 180 microns (ASTM #80) to obtain a powder mass with uniform particle size, accurately weighed (table xx), and mixed uniformly with the addition of 1 percent w/v IPA solution (1 percent w/v, granulating liquid) to obtain a wet mass. Further granules were obtained by having to pass the wet mass through a mesh size of 850 microns (ASTM #20), followed by 1 hour of drying at 60 °C in a hot air oven (Bio Technics India, Mumbai, Maharashtra, India). A tablet punching machine was used to compress the granules (Karnavati) the maximum punch compaction pressure employed was 160 kg/cm^2 [7].

Table 2: Observed responses in the box-behnken design for vildagliptin SR tablets

Formulation	Independent variable			Dependent variable		
	X1	X2	X3	Y1	Y2	Y3
VLSR1	50	50	45	81	38.75	87.18
VLSR2	40	35	45	83	42.31	81.14
VLSR3	40	35	45	76	51.33	86.14
VLSR4	30	35	60	82.5	49.12	93.31
VLSR5	50	20	45	81.7	65.14	85.14
VLSR6	40	35	45	83.01	68.17	92.17
VLSR7	40	20	30	80	60.12	93.16
VLSR8	50	35	30	82.14	62.34	87.12
VLSR9	30	50	45	79	55.45	87.14
VLSR10	30	20	45	81	69.14	81.13
VLSR11	40	50	60	82	62.31	90.25
VLSR12	30	35	30	89	71.34	98.04
VLSR13	50	35	60	80	56.31	85.14
VLSR14	40	50	30	83	49.14	92.47
VLSR15	40	20	60	81	50.42	93.34

X1= HPMC K100 M (mg), X2= Eudragit RSPO (mg), X3=PVP K 30 (mg), Y1= Swelling Index, Y2=DR % at 8h, Y3= DR% at 12h

Characterization of tablets

The *in vitro* characteristics of the compressed matrix tablet, such as hardness, friability, weight variation, and content uniformity, were calculated as per IP. Hardness was determined by using a Monsanto hardness tester. Friability was determined using Roche friability testing apparatus. Weight variation, drug release % and content uniformity of the drug were performed according to the IP procedures [8].

***In vitro* drug release study**

Dissolving investigations were carried out using the USP 2, basket technique (Lab India DS 8000) at 37.50 °C and 100 rpm with 0.1 percent Tween 80 as a dissolution medium using simulated stomach fluid (pH 1.2) and intestinal fluid (pH 6.8). Tween was used to make a water-insoluble medication more wet table in the medium. The stirring speed was set to 100 rpm. VLN pills were dissolved in 900 ml of stomach solution and kept at 37 °C. At regular intervals, five millilitre samples were obtained. The pH of the dissolving media was altered from 1.2 to 6.8 after 2 h by adding 50 ml of concentrated phosphate buffer with pH 12 to obtain the target intestinal fluid pH of 6.8 and the experiment was then run for the duration given. At 208 nm, the samples were analysed using an ultraviolet/visible spectrophotometer (Lab India, UV-3200). Each formulation required at least 6 tablets to be determined. The dissolved percent mean and standard deviation were calculated [9].

Swelling and erosion studies

The matrix tablets were studied for swelling and erosion under the same conditions as the dissolution testing. The basket-matrix system was withdrawn from the dissolution vessel at regular intervals,

blotted with tissue paper to remove excess water, reweighed, and then dried in a hot air oven at 50 °C to a constant weight.

The following equation was used to calculate the percentage water uptake (i.e., the degree of swelling due to absorbed medium) and matrix erosion (E) at time t [10].

$$\text{Degree of swelling} = \frac{\text{Wet weight} - \text{Remaining dry weight}}{\text{Orginal dry weight}}$$

$$\text{Erosion (\%mass loss)} = \frac{\text{Orginal weight} - \text{Remaining dry weight}}{\text{Orginal weight}} \times 100$$

Scanning electron microscopy (SEM)

SEM was used to examine the surface morphology of the tablets following *in vitro* dissolution for 2 h in 0.1 N HCl and 12 h in phosphate buffer, pH 6.8. (JSM 6400, JEOL, Tokyo, Japan). Tablets were removed, gently wiped with tissue paper to remove surface water then mounted onto double-sided adhesive tape that had been fastened on copper stubs and coated with platinum before analysis [11].

Optimization data analysis and validation of optimization mode

The swelling index %, Drug release % at 8 hr. and 12h (responses) of all model formulations were treated by Design-Expert software. (Version 12). The best-fitting mathematical model was selected based on the comparisons of several statistical parameters, including the coefficient of variation (C. V.), the multiple correlation coefficient (R^2), the adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS), proved by Design-Expert software. Among them, PRESS indicates how well the model fits the data, and for the chosen model it should be small relative to the other models under consideration [12, 13].

Stability study

Stability testing of the improved formula was carried out according to ICH recommendations at 40 °C±2 °C/75% RH±5% RH. The tablets were visually examined after 1, 3, and 6 mo to detect any physical changes and were tested for drug content and *in vitro* release profiles [14].

Pharmacokinetic study

Pharmacokinetic research was conducted in 6 healthy rabbits weighing 2.0 to 2.5 kg to investigate the safety and efficacy of the produced Pure drug of VLN and SR tablets containing 100 mg of VLN. The study's procedure was approved by the animal ethics committee at the university. 0.5 ml of blood was extracted from the rabbits' marginal ear vein using sterilised disposable syringes at specified time intervals of 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, and 24.0 h. To isolate plasma, blood was deposited in a vial containing anticoagulant (11 percent sodium citrate solution) and centrifuged at 4,000 rpm for 4 min. After that, the plasma was separated from the protein using an equal volume of 10% perchloric acid and vortexed for 2 min. The supernatant liquid was separated and stored in a freezer (-70 °C) after centrifugation at 4,000 rpm for 4 min. To assess the drug concentration in plasma samples, a repeatable analytical technique was established [15]. Phoenix WinNonlin Software was used to calculate pharmacokinetic parameters (Cmax, t_{max}, $t_{1/2}$, Kel, AUCo-t, and AUCo-∞).

RESULTS AND DISCUSSION

IR spectroscopy and DSC were used to test the compatibility of drug excipients. When VLN was mixed with excipients, there were no significant changes in its IR peaks (fig. 1), indicating that it had no interaction with the excipients. To determine the thermal changes of polymers and drug, DSC thermograms of the drug (fig. 2) and the physical mixture of drug-excipients were recorded. When VLN was blended with various excipients, the endotherm values did not differ significantly from those of pure VLN. The absence of an interaction between the medicine and the excipients is further supported by the IR spectra results. As a result, the excipients chosen for this investigation are VLN-inert and acceptable for formulation development.

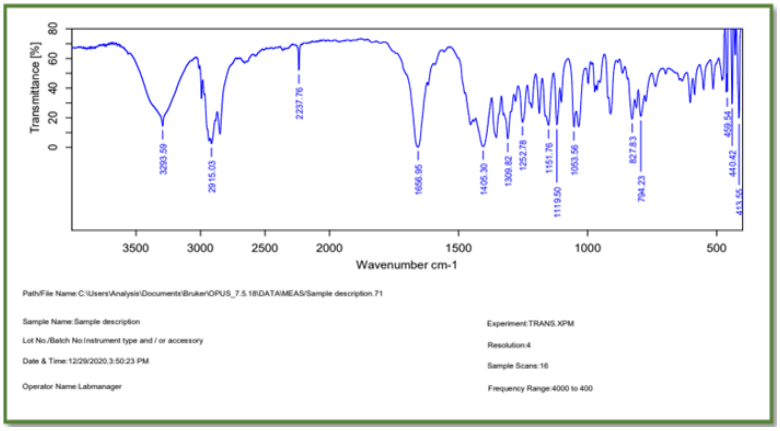


Fig. 1: FTIR of pure drug vildagliptin

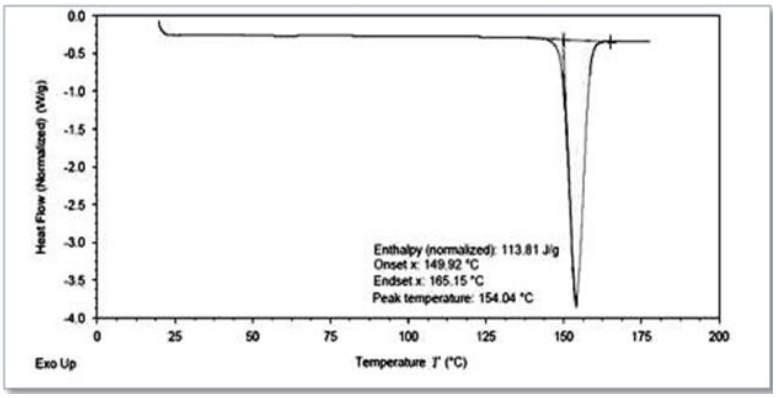


Fig. 2: DSC of pure drug vildagliptin

Post-compression parameters of the vildagliptin SR tablet

According to the process provided in the Indian Pharmacopoeia, the weight variation, friability, hardness, and content homogeneity of Matrix tablets of various formulations were subjected to various evaluation procedures. The weight fluctuation and friability, respectively, were less than 4% and 0.4 percent. The drug content of several batches of tablets was found to be quite consistent, and the drug content was over 95%.

Table 3: Post compression parameters for VLN sustained release tablet

Formulation	Average weight (mg±SD)	Hardness of tablet (kg/cm²±SD)	Thickness in (mm ± SD)	Friability (%±SD)	Drug content (%±SD)
VLSR1	251.01±0.14	7.50±0.21	4.111±0.01	0.410±0.44	96.32±0.52
VLSR2	250.02±0.53	7.42±0.12	4.144±0.16	0.503±0.42	95.42±0.61
VLSR3	250.02±0.25	8.10±0.11	4.134±0.11	0.312±0.14	96.52±0.42
VLSR4	250.01±0.29	8.54±0.25	4.241±0.03	0.110±0.23	97.22±0.21
VLSR5	250.01±0.60	7.84±0.40	4.231±0.11	0.124±0.21	96.12±0.82
VLSR6	249.04±0.34	8.14±0.87	4.156±0.13	0.142±0.54	95.37±0.71
VLSR7	251.04±0.20	8.10±0.65	4.144±0.28	0.451±0.44	97.09±0.48
VLSR8	250.02±0.20	8.21±0.71	4.146±0.11	0.102±0.20	95.32±0.65
VLSR9	250.06±0.03	8.25±0.87	4.241±0.42	0.201±0.26	96.32±0.73
VLSR10	250.04±0.16	7.94±0.21	4.142±0.51	0.410±0.31	98.02±0.55
VLSR11	250.01±0.14	7.84±0.42	4.200±0.45	0.406±0.51	95.33±0.88
VLSR12	250.00±0.12	8.08±0.38	4.204±0.36	0.562±0.21	96.02±0.78
VLSR13	251.01±0.02	8.08±0.55	4.210±0.44	0.610±0.51	97.07±0.76
VLSR14	251.02±0.15	7.98±0.78	4.211±0.21	0.208±0.11	95.32±0.66
VLSR15	250.03±0.14	8.02±0.83	4.203±0.51	0.422±0.21	96.02±0.56

(n=3), *All the values are expressed as mean±SD

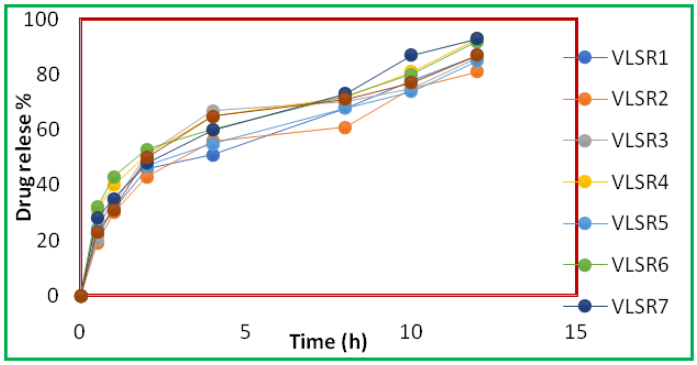


Fig. 3*: In vitro* dissolution of study of vildagliptin sustained release tablets (VLSR1-VLSR8)

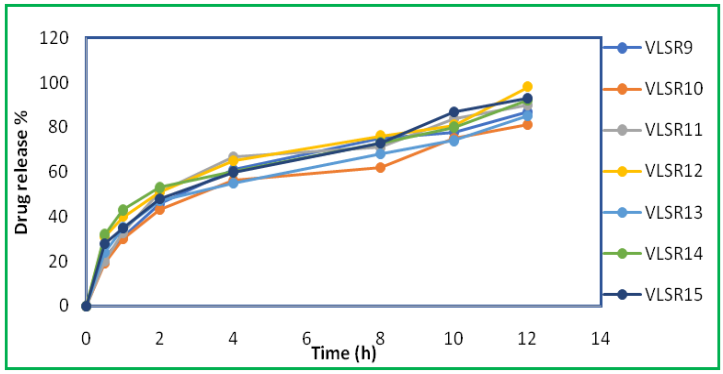


Fig. 4*: In vitro* dissolution of study of vildagliptin sustained release tablets (VLSR9-VLSR15)

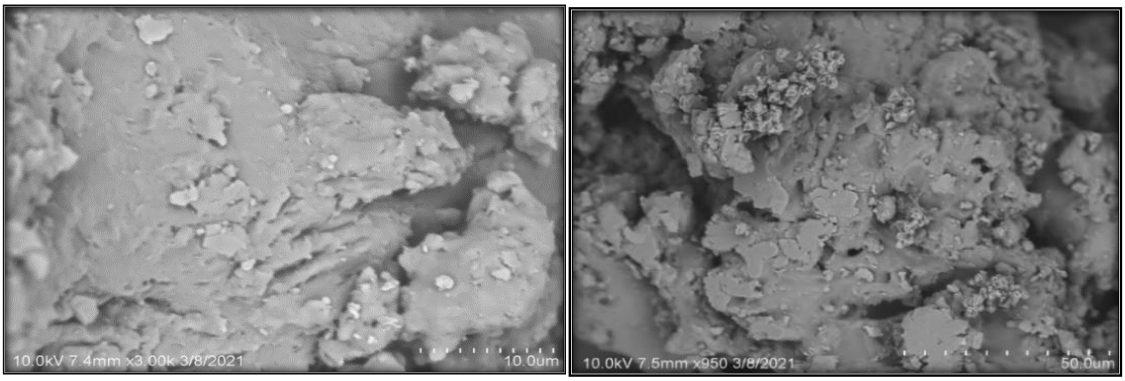
***In vitro* release profile**

Fig. 3 and 4 depict the VLN release pattern from various batches of prepared matrix tablets. When compared to other tablets, those containing (VLSR12) HPMC K100 and Eudragit RSPO (1:1) had a slower release of VLN (>98 percent in 12 h). Batch VLSR4, VLSR6 and VLSR7 (fig. 3) containing Eudragit RSPO and HPMC K100M released more than 90% (<95%) of the medication in 12 h. VLSR12 release more than 70% of drug in 8h.

Surface morphology

SEM analysis confirmed that both the diffusion and erosion mechanisms were active during drug release from the optimised batch of matrix tablets. SEM photomicrographs of the matrix tablet taken at various time intervals following the dissolution experiment revealed that the matrix was intact and pores had formed throughout the matrix (fig. 5). SEM photomicrographs of the tablet surface at various time intervals also revealed that

matrix erosion increased with time. A SEM photomicrograph of the surface of a fresh tablet (Revealed no pores). As a result, the formation of both pores and a gelling structure on the tablet surface suggests that both erosion and diffusion mechanisms are involved in the sustained release of VLN from formulated matrix tablets.



(a) Acidic media at 2h **(b) Basic media at 12h**

Fig. 5: SEM photomicrographs showing surface morphology of hydrated matrix tablets in (a) acidic media, 2h and (b) basic media, 12h

After being placed in the dissolution media, the matrices clearly swelled and eroded at the same time. Because swelling and erosion occur concurrently in the matrix, constant release can be obtained in such matrices. Constant release occurs in such cases because the increase in diffusion path length caused by swelling is compensated for by continuous matrix erosion (table 4).

Table 4: Swelling % and erosion % studies of vildagliptin sustained release tablets

Formulation	Swelling index % at 12th h	Degree of swelling at 12th h	Erosion % at 12thh
VLSR1	81.990.31	0.29±0.18	22±0.22
VLSR2	83.87±0.34	0.30±0.82	24±0.25
VLSR3	76.47±0.11	0.27±0.41	20±0.37
VLSR4	82.51±0.61	0.25±0.61	24±0.13
VLSR5	81.70±0.31	0.27±0.31	22±0.38
VLSR6	83.01±0.44	0.30±0.42	20±0.26
VLSR7	80.47±0.38	0.25±0.71	24±0.38
VLSR8	82.14±0.41	0.29±0.51	19±0.74
VLSR9	84.14±0.34	0.23±0.62	20±0.44
VLSR10	81.45±0.31	0.22±0.71	24±0.38
VLSR11	82.33±0.37	0.26±0.61	22±0.29
VLSR12	91.14±0.47	0.32±0.52	23±0.38
VLSR13	80.14±0.30	0.22±0.41	21±0.55
VLSR14	83.24±0.32	0.21±0.62	22±0.26
VLSR15	81.41±0.22	0.27±0.61	24±0.28

(n=3), *All the values are expressed as mean±SD

Optimization of formulation

In order to evaluate the effect of formulation ingredients on the dissolution pattern, the causal factor and response variables were related using a polynomial equation with statistical analysis. All the responses observed for the 15 formulations prepared were simultaneously fitted to different models using Design-Expert®. The comparative values of multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R2), S. D, and % C. V. are presented in table 5. Responses Y1 Swelling Index, Y2 CDR% at 8 hr and Y3 CDR% at 12 hr were found to follow the quadratic model because its PRESS was the smallest. All statistically significant ($p<0.05$) coefficients are included in the equations. The Predicted residual sum of squares (PRESS) is a measure of the fit of the model to the points in the design. The model showed a statistically insignificant lack of fit. The adequacy of the model was also confirmed with residual plot tests of regression models. Analysis of variance (ANOVA) was applied to estimate the significance of the model at the 5% significance level.

Table 5: Results summary of regression analysis for response Y1, Y2 and Y3

Summary of regression analysis for responses Y1, Y2 and Y3					
Responses	**R^2**	**Adjusted R^2**	**%CV**	**S.D**	**Model suggested**
Swelling Index (Y1)	0.9478	0.8412	3.63	3.45	Quadratic
CDR% at 8h (Y2)	0.9181	0.7601	4.49	2.74	Quadratic
CDR% at 12h (Y3)	0.9881	0.9601	0.370	0.48	Quadratic

$Y1=80.67+0.8325A+0.1625B-1.08C+0.3250AB+1.09AC-0.5000BC+0.9575A^2-0.952B^2+1.78\ C^2$

$Y2=53.9-2.81A-4.90B-3.10C-3.18AB+4.05\ AC+5.72\ BC+3.73\ A^2-0.5483B^2+2.11\ C^2$

$Y3=84.15-1.79A-0.9663B-1.51C-0.7425AB+4.76AC+1500BC+0.6650A^2-0.1.09B^2+4.49\ C^2$

Effect of Independent Variables on Swelling Index %

Swelling index is a vital evaluation parameter for the sustained release action of tablets. Fig. 6 and 7 depict the effect of Eudragit RSPO and HPMC K100M on swelling index by counterplots (fig. 8) and 3D plots (fig. 9). From the equation given in table 5, it is clear that Eudragit RSPO and HPMC K100M have a synergistic effect on swelling index %.

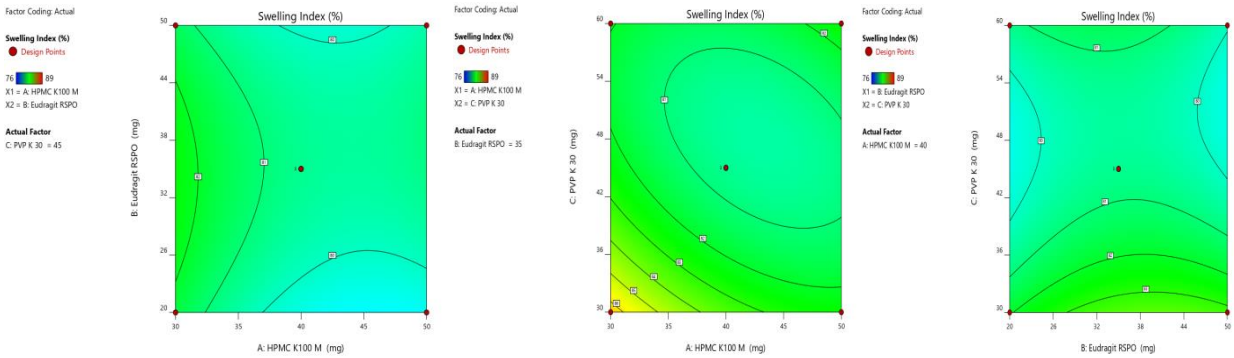


Fig. 6: Counter plots of swelling index %

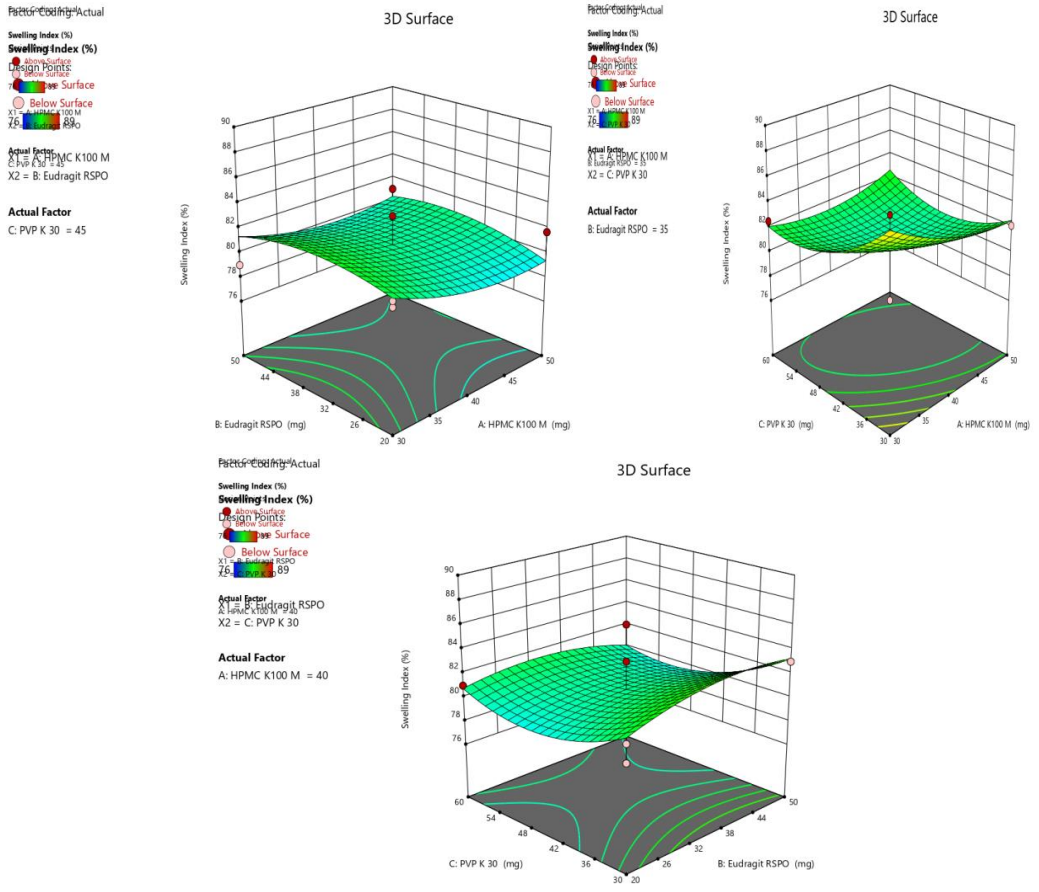


Fig. 7: Response surface plot or 3D plots for swelling index

This result was similar to earlier studies by [16], which reported that the hydrophilic material can stimulate water penetration into the inner parts of the matrices, which leads to swelling and release modification of the drug.

Effect of independent variables on drug release% at 8h

The effect of HPMC K100M, Eudragit RSPO and PVK 30 on drug release at 8 h is presented by counter plot and a 3D surface response graph (fig. 8 and 9). The coded equation (Y2) for drug release% at 8h (table 5) showed that there is an antagonistic relation between polymers and drug release% at 8h. This happens due to swelling that takes place at high concentrations of polymers, which retards the drug release from the formulations.

Effect of independent variables on drug release % at 12h

Drug release % at 12h is vital from a therapeutic point of view. The influence of HPMC K100 M, Eudragit RSPO, and PVK 30 on drug release % at 12h is presented by a counter plot and a 3D surface response graph (fig. 10 and 11). The coded equation (Y3) for drug

release % at 12 h (table 5) showed that there is an antagonistic relation between polymers and drug release % at 12 h. This happens due to swelling that takes place at high concentrations of polymers, which retards the drug release from the formulations.

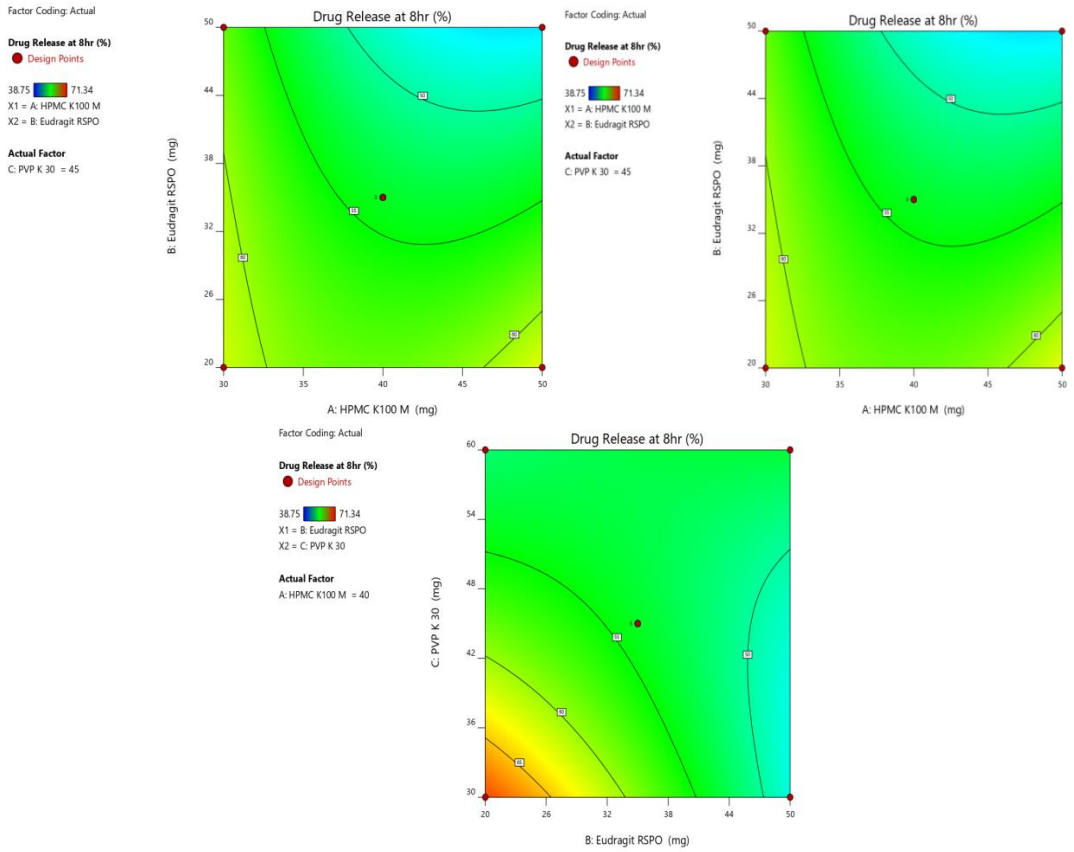


Fig. 8: Counter plots of drug release% at 8h

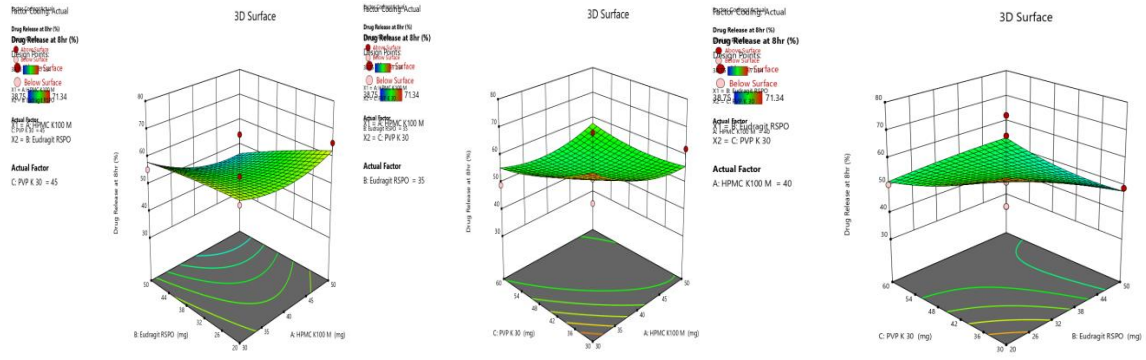


Fig. 9: Response surface plot of drug release% at 8h

Moreover, the interaction effects of polymers and MCC (BC, AC and ABC) were not significant. The value of the positive coefficient of X3 was larger, which showed that the effect of PVP K30 was the increasing influence factor on the drug release from extended-release matrix tablets. This result was similar to earlier studies [17], which reported that the hydrophilic material can stimulate water penetration into the inner parts of the matrices, thus resulting in drug release from the matrix at a later stage.

Checkpoint analysis and validation of optimized formulation

The optimum values of the variables were obtained by graphical and numerical analyses using the Design-Expert® software and based on the criterion of desirability [18]. The optimum response was found with Y1 (80.2%), Y2 (81.33%) and Y3 (98.66%), at X1, X2 and X3 values of 50 mg,35 mg and 30 mg, respectively. To verify these values, the optimum formulation was prepared according the above values of the factors at X1, X2 and X3 and subjected to the Swelling index test and the dissolution test.

Kinetics modelling of drug release for optimized formulation (Opt-VLD-SR)

Model-dependent approaches the drug dissolution profile data of optimized formulation were fitted to different drug release mathematical kinetic models of zero order, first order, Higuchi, and Korsmeyer-Peppas. Drug release data was the best fitted in Higuchi with r^2= 0.999 and Krosmayer Peppas with r^2=0.998, the

critical value of n=0.86 as compared to Zero order r^2= 0.918 and first order r^2=0.989 which indicating that the mechanisms of drug release were anomalous diffusion or diffusion coupled with erosion. Hence, the drug release was controlled by more than one process; the current study is similar to the historical data studies by [19].

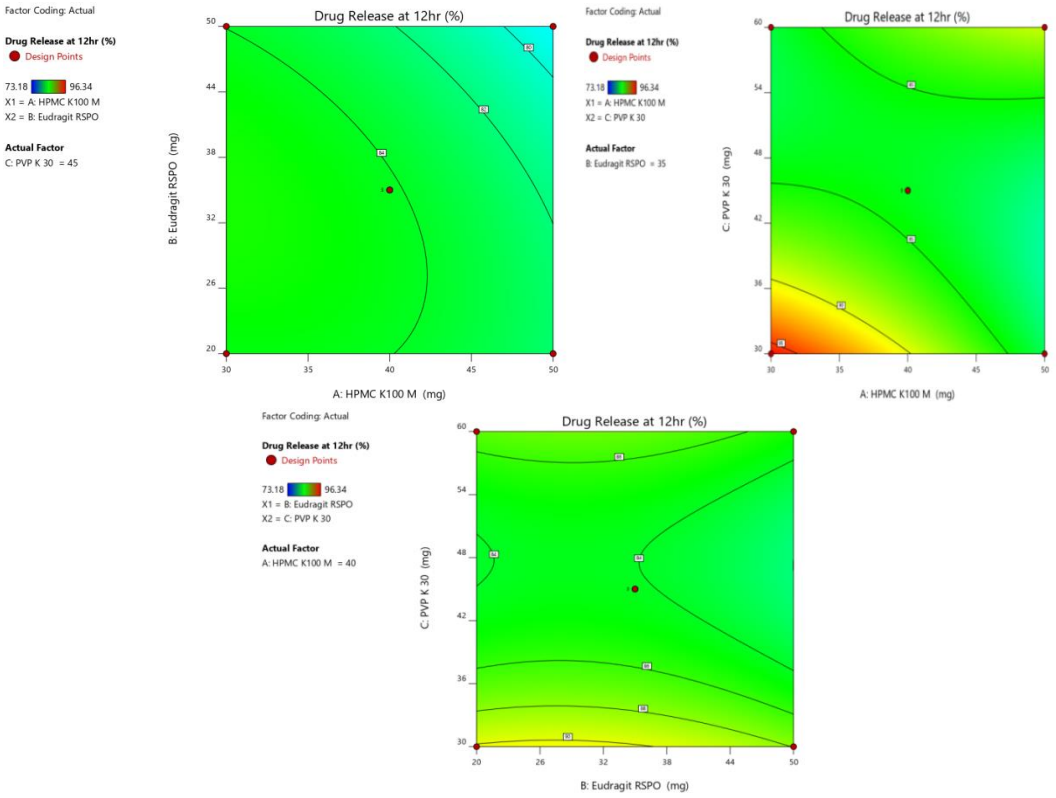


Fig. 10: Counter plots of drug release % at 12h

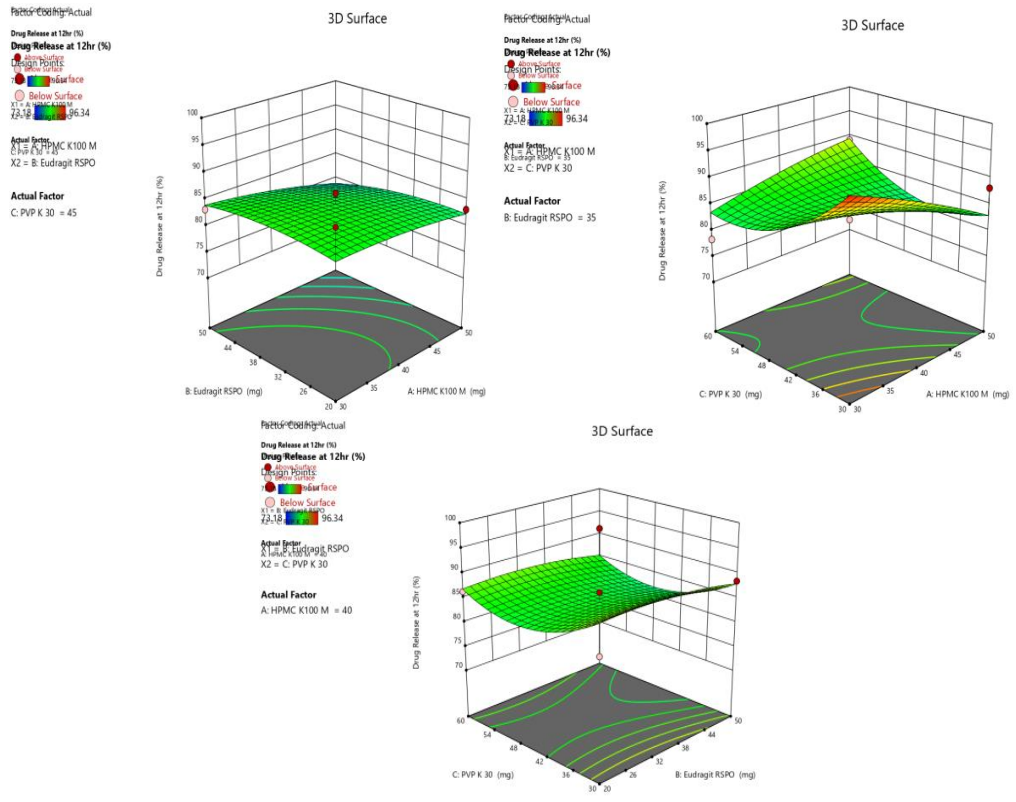


Fig. 11: Response surface plot of drug release % at 12h

Table 6: Composition of optimum checkpoint formulations, the predicted and experimental values of response variables and percentage prediction error of VLD sustained release matrix tablets

Optimized formulation composition (X1:X2:X3) (Opt-VLD-SR)	Response variable	Experimental value	Predicted value	Prediction Error (%)
HPMC	Y1	80.2%	80.31%	1.50
K100M: Eudragit	Y2	81.33%	81.43%	1.34
RSPO: PVP K30, 50:35:30	Y3	98.66%	98.71%	0.87
*Predicted Error (%)=(Experimental value-Predicted value)/Predicted value ×100 %				

Stability study

Stability study of Optimized formulation Opt-VLD-SR was conducted for 6 mo; the weight variation, hardness, thickness, Friability and % Dissolution was evaluated and summarised in table 7.

Pharmacokinetic study

Plasma concentration and pharmacokinetic parameters after oral administration of formulated sustained-release matrix tablets (Opt-VLD-SR) and the marketed tablet vildaily (50 mg) are summarised in table 8 and fig. 12. No sustained blood level of marketed Vildagliptin was evident after oral administration of the conventional formulation. The formulated Optimized Sustained release tablets (Opt-VLD-SR) showed significantly lower Cmax (184±3.01ng/ml) than conventional IR tablet (256.17±8.02ng/ml) and required significantly more time to reach Cmax (t_{max} 6.48±0.12h) as compared with conventional tablets (t_{max} 2.99±0.03h). However, these tablets maintained a constant plasma concentration for up to 12 h. The lower AUC (969.4±11.03) was observed with conventional tablets, whereas the Optimized Sustained release tablets (Opt-VLD-SR) showed a higher AUC value (1289.56±8.22), indicating increased the Bioavibility of Vildagliptin SR tablet. Opt-VLD-SR formulation exhibited a lower elimination rate constant (K_e) In comparison to conventional tablets. The MRT for optimized-VLD-SR is 7.40 h higher than the Vildagliptin IR marketed product (3.70 hr) , which leads to higher bioavailability of Vildagliptin. The pharmacokinetic data obtained with the IR and SR formulations in the current study is similar to the historical data [20, 21].

Table 7: Stability studies of optimized vildagliptin sustained-release tablets

S. No.	Parameter	Test			
		0 mo	1st mo	2nd mo	6th mo
1.	Description	White-colored circular and flattened	White-colored circular and flattened	White-colored circular and flattened	White-colored circular and flattened
2.	Weight (mg)	250.00±0.12	251.56±0.21	252.02±0.09	252.15±0.32
3.	Hardness (kg/cm²)	8.08±0.13	7.78±0.56	7.56±0.016	7.54±0.078
4.	Thickness (mm)	4.204±0.24	4.25±0.15	4.55±0.09	4.58±0.13
5.	Friability (%)	0.56±0.02	0.57±0.12	0.576±0.26	0.58±0.14
6.	Dissolution (%) at 12h	98±1.34	98±1.24	98±1.11	98±1.01

(n=3), *All the values are expressed as mean±SD

Table 8: Pharmacokinetic parameters of marketed vildagliptin and VLD-SR

Parameter	Vildaily-50 IR (Marketed vildagliptin)	VLD-SR
$t_{1/2}$ (h)	1.75±0.01	3.82±0.16
C_{max} (ng/ml)	256.17±8.02	184±3.01
T_{max} (h)	2.99±0.03	6.48±.12
K_e (h^{-1})	0.39	0.18
$AUC_{0-\infty}$ (ng/ml. h)	969.4±11.03	1289.56±8.22
$AUMC_{0-\infty}$(ng/ml. h^2)	3591.95±20.07	9547.19±11.44
MRT(h)	3.70	7.40

*Average of three observations (n=3), *All the values are expressed as mean±SD

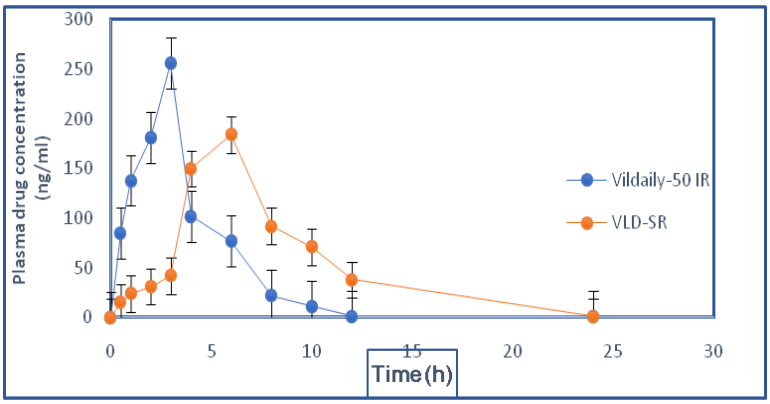


Fig. 12: Plasma drug concentration and time profile of marketed vildagliptin and VLD-SR. Error bars indicates standard deviation of triplicate studies

CONCLUSION

It can be concluded from the present research that the box-behnken experimental design can effectively optimise sustained release matrix tablet formulation with minimum run as it offers the advantages of minimum cost and time. Despite the differences in PK profiles, the results from this study confirm the therapeutic equivalence between the immediate and sustained-release formulations with respect to DPP-4 enzyme inhibition over time. Furthermore, the results provide a scientific rationale for the use of the new SR formulation of vildagliptin (100 mg SR QD) in India as a therapeutic alternative to the already approved 50 mg IR BID tablets. This study confirms the therapeutic equivalence of vildagliptin IR and SR formulations for DPP-4 enzyme inhibition over time. The study supports vildagliptin 100 mg SR QD as a useful therapeutic alternative to the 50 mg IR BID formulation to potentially improve patient adherence and compliance.

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AUTHORS CONTRIBUTIONS

All the authors contributed equally.

CONFLICTS OF INTERESTS

There is no conflict of interest among authors.

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