RESEARCH ARTICLE

Formulation Development and Evaluation of Sustained Release Matrix Tablets of Vildagliptin - Synthetic and Natural Polymers

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Abstract

Aim: The present research work was to design and develop the sustained release matrix tablets of vildagliptin. It is having a short biological half-life (1.5 h) so it is considered as a suitable drug for the formulation of sustained release tablets to prolong its therapeutic action. Vildagliptin is an oral antihyperglycemic agent of the new dipeptidyl peptidase-4 inhibitor class of drug. **Materials and Methods:** Matrix tablets were prepared by wet granulation technique, using synthetic and natural polymers at different ratios. Granules were prepared and evaluated for bulk density, tapped density, Hausner's ratio, compressibility index. **Statistical Analysis Used:** The Fourier-transform infrared spectra of the vildagliptin and different polymers alone and in a combination show the compatibility of the drug with excipients. **Results:** The physicochemical properties of tablets were found within the limits. The prepared tablets were evaluated for weight variation, thickness, hardness, % friability, % drug contents, and *in vitro* release. *In vitro* dissolution studies (USP dissolution rate test apparatus II, 50 rpm, 37°C ± 0.5°C) was carried out for the first 2 h in 0.1 N HCl (1.2 pH) and followed 6.8 phosphate buffer for 10 h as a dissolution medium. **Conclusion:** The optimized formulation F-8 was shown maximum drug release 97.56 ± 0.72% in 12 h of dissolution. The release kinetic data of formulation F-8 shown zero order (R^2 = 9902).

Key words: Dipeptidyl peptidase-4 inhibitor, kinetics, SR Matrix, vildagliptin, wet granulation

INTRODUCTION

Sustained release dosage form is defined as "Any drug or dosage form modification that prolongs the therapeutic activity of the drug for an extended period of time." This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration to and below the minimum toxic level for the extended period of time. Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over the extended period of time after administration of a single dose.[1,2]

The objective in designing a sustained release system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. That is, release from the dosage form should follow zero order kinetics.[3]

Vildagliptin is an oral anti-diabetic drug of the dipeptidyl peptidase-4 (DPP-4) inhibitor class of drug. Vildagliptin

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inhibits the in activation of GLP-1 and GIP by DPP-4, allowing GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and suppress glucagon release by the alpha cells of the islets of Langerhans in the pancreas.

MATERIALS AND METHODS

Vildagliptin was a gift sample from MSN Laboratories Ltd., Hyderabad. HPMC grade was procured from signet chem. Mumbai and Sodium alginate, Chitosan, Xanthan gum, Guar gum, PVP-K 30, Aerosil, Magnesium Stearate, and Microcrystalline Cellulose were supplied by Yarrow Chem. Products, Mumbai, Maharashtra, India.

METHODOLOGY

Preformulation studies

Standardization of vildagliptin by UV-Visible spectrophotometry

In 0.1 N HCl solution

i. Preparation of stock solution: Stock solution 100 µg/ml vildagliptin was prepared in 0.1 N HCl solutions. This solution was suitably diluted with 0.1 N HCl to obtain a concentration of 10 µg/ml. The resultant solution was scanned in the range of 200-400 nm using UV double beam spectrophotometer (Lab India UV-3000+).
ii. Standard calibration of vildagliptin in 0.1 N HCl: 100 mg of vildagliptin was accurately weighed and dissolved in100 ml of 0.1 N HCl to obtain a concentration of 1000 µg/ml. From the above 10 ml was withdrawn and diluted to 100 ml to obtain a concentration of 100 µg/ml. From this stock solution aliquots of 0.5, 1, 1.5, 2, and 2.5 ml were diluted in 10 ml volumetric flask with phosphate buffer to give concentrations in the range of 5-25 µg/ml, respectively, absorbance was measured at 232 nm.

In pH 6.8 buffer

i. Preparation of stock solution: Stock solution 100 µg/ml of vildagliptin was prepared in phosphate buffer of pH 6.8. This solution was suitably diluted with phosphate buffer of pH 6.8 to obtain a concentration of 10 µg/ml. The resultant solution was scanned in the range of 200-400 nm using UV double beam spectrophotometer (Lab India UV-3000+).
ii. Standard calibration of vildagliptin in phosphate buffer of pH 6.8: 100 mg of vildagliptin was accurately weighed and dissolved in 100 ml of pH 6.8 phosphate buffers to obtain a concentration of 1000 µg/ml. From the above 10 ml was withdrawn and diluted to 100 ml to obtain a concentration of 100 µg/ml. From this stock solution aliquots of 0.5, 1, 1.5, 2 ml, and 2.5 ml were diluted in 10 ml volumetric flask with phosphate buffer to give concentrations in the range of 5-25 µg/ml, respectively, absorbance was measured at 227 nm.

Evaluation of granules

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using the following formula.[4]

$\tan \Theta = h/r$

Where, "h" is the height of the heap and "r" is the radius of the heap of granules.

Carr's compressibility index

The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 ± 2/min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume.

Carr's compressibility index was calculated using the following formula.[5,6]

Carr's compressibility index (%) = [(Tapped density-Bulk density) ×100]/Tapped density

Bulk Density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends were determined using the following formula.[7]

Bulk density = Total weight of powder/Total volume of powder

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powder blends were determined using the following formula.[8]

TBD = Total weight of powder/Total volume of tapped powder

Preparation of matrix tablets

Vildagliptin tablets with synthetic and natural polymer at different concentrations were prepared by the wet granulation method.

Wet granulation method

All the powders were passed through 80 mesh. Required quantities of all ingredients were mixed thoroughly, and a sufficient volume of granulating agent (isopropyl alcohol) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40°C for 12 h. Once, dry the granules retained on 44 mesh were mixed with 10% of fine granules that passed through 44 mesh. Talc and magnesium stearate were added as glidant and lubricant. In all formulations, the amount of the active ingredient is equivalent to 50 mg of vildagliptin (Table 1).

Evaluation of tablets

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical strength while handling. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm^2. 10 tablets were randomly picked from each formulation and the mean and standard Deviation values were calculated.[9,10]

Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). 10 tables were initially weighed (Wt. initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions.[11] The tablets were weighed again (Wt. final). The percentage friability was then calculated by,

% F = (loss in weight/initial weight) × 100

% Friability of tablets less than 1% are considered acceptable.

Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The US Pharmacopoeia allows a little variation in the weight of a tablet. To study weight variation, 20 tablets of each formulation were weighed using an electronic balance Aqua and the test was performed according to the official method.[12]

Drug content (Assay)

Drug content of the tablets was determined by UV Spectrophotometrically.

Uniformity of thickness

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier caliper.[13-15]

In vitro dissolution studies

In vitro drug release studies from the prepared vildagliptin SR matrix tablets were conducted using USP type II apparatus at 37°C at 50 rpm. Dissolution mediums used were 900 ml of 0.1 N HCl and phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for first 2 h and changed to phosphate buffer (pH 6.8) for next

Table 1: Composition of vildagliptin sustained release matrix tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Vildagliptin	50	50	50	50	50	50	50	50	50	50
HPMC K 15 M	50	75	-	-	-	-	-	-	-	-
HPMC K 100 M	-	-	50	75	-	-	-	-	-	-
Sodium alginate	-	-	-	-	75	100	-	-	-	-
Chitosan	-	-	-	-	-	-	50			-
Xanthan gum	-	-	-	-	-	-	-	50	75	-
Guar gum	-	-	-	-	-	-	-	-	-	75
PVP-K 30	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
IPA	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Aerosil	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5
MCC	127.5	102.5	127.5	102.5	102.5	77.5	127.5	127.5	102.5	102.5
Total weight (mg)	250	250	250	250	250	250	250	250	250	250

HPMC: Hydroxypropyl methylcellulose, IPA: Isopropyl alcohol, MCC: Microcrystalline cellulose

Table 2: Absorbences of vildagliptin in 0.1 N HCl

Concentration (mcg/ml)	Absorbance (nm)
0	0
5	0.098
10	0.203
15	0.306
20	0.399
25	0.501

Table 3: Absorbences of vildagliptin in 6.8 pH phosphate buffer

Concentration (mcg/ml)	Absorbance (nm)
0	0
5	0.13
10	0.262
15	0.381
20	0.516
25	0.648

10 h time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analyzed by UV-Visible Spectrophotometer (Lab India 3000+). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time curve.

Dependent-model method (Data analysis)

To describe the vildagliptin release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: Zero order, first order, Higuchi, Korsmeyer–Peppas. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The release of drugs from the matrix tablets can be analyzed by release kinetic theories. To study the kinetics of drug release from matrix system, the release data were fitted into Zero order as cumulative amount of drug release versus time (Equation 3), first order as log cumulative percentage of drug remaining versus time (Equation 4), Higuchi model as cumulative percent drug release versus square root of time (Equation 5). To describe the release behavior from the polymeric systems, data were fitted according to well-known exponential Korsmeyer–Peppas equation as log cumulative percent drug release versus log of time equation (Equation 6).[16-19]

(i) Zero order kinetics

$$Qt=K0t \quad (3)$$

Where,

Q = Amount of drug release in time t

K0 = Zero order rate constant expressed in unit of concentration/time

t = Release time

(ii) First order kinetics

$$\text{Log } Q = \text{Log } Q_0 - k_t/2.303 \quad (4)$$

Where,

Q_0 = is the initial concentration of drug

k = is the first order rate constant

t = release time

(iii) Higuchi kinetics

$$Q=k_{t1/2} \quad (5)$$

Where,

k = release rate constant

t = release time, hence the release rate is proportional to the reciprocal of the square root of time.

(iv) Korsmeyer–Peppas

First 60% *in vitro* release data was fitted in equation of Korsmeyer *et al*. to determine the release behavior from controlled release polymer matrix system. The equation is also called as power law,

$$M_t/M_\infty = K_t\, n \quad `(6)$$

Where,

M_t = amount of drug released at time t

M_∞ = amount of drug released after infinite time

M_t/M_∞ = fraction solute release

t = release time

K = kinetic constant incorporating structural and geometric characteristics of the polymer system

n = diffusional exponent that characterizes the mechanism of the release of traces. The magnitude of the release exponent "n" indicates the release mechanism (i.e., Fickian diffusion, non-Fickian, supercase II release). For matrix tablets, values

of n of near 0.5 indicate Fickian diffusion controlled drug release, and an n value of near 1.0 indicates erosion or relaxational control (case II relaxational release transport, non-Fickian, zero order release). Values of n between 0.5 and 1 regarded as an indicator of both diffusion and erosion as overall release mechanism commonly called as anomalous release mechanism.[20]

RESULTS AND DISCUSSION

Vildagliptin Standard graph Preparations: (Tables 2 and 3)

The absorption maximum for Vildagliptin was found to be 232 nm in 0.1N HCl and 227 nm in pH 6.8 Phosphate buffer. The concentrations in range of 5µg/ml to 25µg/ml respectively, Regression Coefficient R^2 Values of Vildagliptin was found to be in 0.1N HCl is $R^2 = 0.9998$ and in pH 6.8 Phosphate buffer is $R^2 = 0.9998$.

Drug excipient compatibility studies - Fourier-transform infrared (FTIR)

Drug-excipient compatibility studies by FTIR revealed no interaction between drug and the polymers used in the formulation thus showing compatibility [Figures 1, 2 and 3].

Physical characteristics of blends and Tables 4 and 5

The Pre compression parameters such as Bulk density, Tapped density, Hausner ratio, Carr's index and Angle of repose of the all formulations (F1-F10) were found to be in between the range of 0.326±0.98 to 0.59±0.36 g/ml., 0.477±0.23 to 0.614±0.11 g/ml., 1.193±0.99 to 1.321±0.08., 17.04±0.06 to 22.27 ±0.05 and 22.05±0.03 to 27.23±0.17 respectively.

The Post compression parameters such as Weight variation, Thickness, Hardness, Friability, Drug content of the all formulations (F1-F10) results was found to be Within the Pharmacopoeial specifications.

In vitro dissolution studies (Tables 6 and 7)

The tablets were evaluated for in vitro dissolution studies in acid buffer (pH-1.2) for 2 hours followed by pH 6.8 buffer for 10 hours. The results of in-vitro drug release revealed that the vildagliptin was released in a controlled manner from all the formulations where formulation F8 showed maximum drug release i.e. 97.56±0.72% at the end of 12th hour.

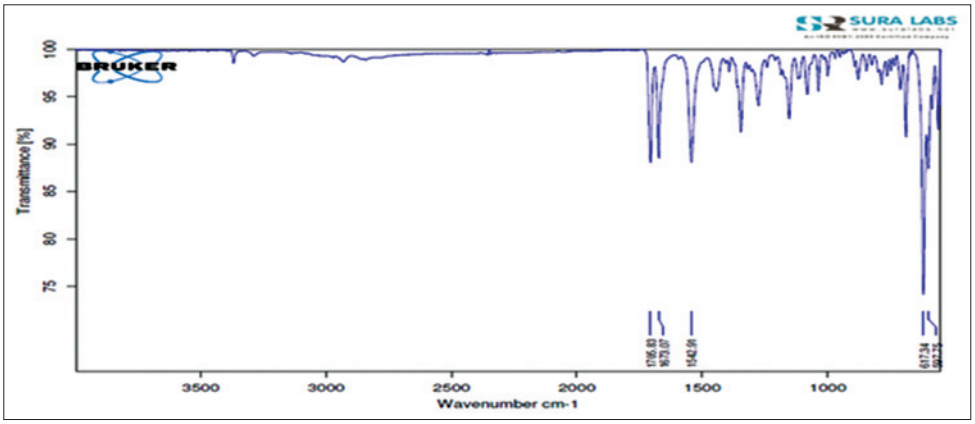


Figure 1: Fourier-transform infrared spectra of vildagliptin

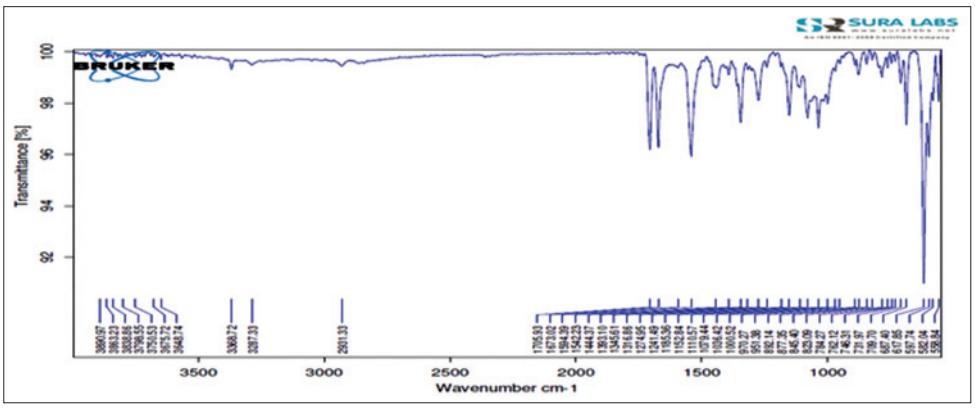


Figure 2: Fourier-transform infrared spectra of vildagliptin + Xanthan gum

Table 4: Pre-compression parameters

F code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's compressibility index (%)	Angle of repose (Θ)
F1	0.59±0.36	0.592±0.16	1.321±0.08	17.19±0.18	24.22±0.64
F2	0.451±0.07	0.481±0.18	1.266±0.17	19.93±0.26	22.05±0.03
F3	0.394±0.16	0.603±0.04	1.193±0.99	21.15±0.15	26.54±0.09
F4	0.491±0.29	0.542±0.17	1.206±0.12	18.99±0.09	25.99±0.15
F5	0.326±0.98	0.596±0.02	1.276±0.16	17.04±0.06	27.23±0.17
F6	0.402±0.09	0.477±0.23	1.303±0.08	20.04±0.03	24.77±0.18
F7	0.513±0.12	0.498±0.19	1.299±0.04	19.21±0.11	23.53±0.05
F8	0.481±0.05	0.517±0.06	1.313±0.16	18.92±0.14	26.21±0.19
F9	0.511±0.03	0.614±0.11	1.276±0.12	22.27±0.05	24.19±0.16
F10	0.432±0.14	0.506±0.01	1.298±0.44	17.54±0.17	22.59±0.33

The data are presented as mean value ±SD (*n*=3). SD: Standard deviation

Table 5: Post-compression parameters

F code	Weight variation (mg)*	Thickness (mm)ω	Hardness (kg/cm²)€	Friability (%)†	% drug content‡
F1	250±0.99	3.14±0.18	4.48±0.31	0.38±0.24	99.12±0.08
F2	249±1.21	3.97±0.44	4.99±0.05	0.67±0.05	98.59±0.22
F3	248±1.97	3.23±0.27	5.01±0.13	0.44±0.12	101.54±0.98
F4	250±0.26	3.53±0.63	4.17±0.94	0.51±0.03	98.94±0.66
F5	250±0.94	3.98±0.74	4.04±1.26	0.27±0.22	99.06±0.03
F6	249±1.44	3.99±0.19	4.55±0.37	0.31±0.54	97.55±0.95
F7	250±0.88	3.34±0.06	4.96±0.14	0.57±0.16	98.86±0.24
F8	250±0.12	4.03±0.05	4.88±0.06	0.49±0.08	99.68±0.13
F9	249±0.57	3.71±0.55	5.12±0.02	0.45±0.12	99.21±0.28
F10	250±0.14	3.66±0.51	4.15±0.19	0.29±0.25	99.03±0.03

*n=20, ωn=10, €n=5, †n=10, ‡n=5

Table 6: Dissolution release profiles of formulations (F1-F5)

Time (h)	Cumulative % drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	7.23±0.56	7.13±0.27	7.65±0.41	8.59±0.72	9.21±0.49
2	13.24±0.43	16.71±0.81	19.76±0.56	17.56±0.67	18.98±0.25
3	29.06±0.35	20.24±0.72	29.82±0.39	25.70±0.82	29.85±0.45
4	37.25±0.36	23.16±0.63	37.36±0.53	39.05±0.46	40.51±0.31
5	49.98±0.58	33.44±0.79	45.48±0.27	44.9±0.17	52.28±0.42
6	54.57±0.87	38.16±0.51	59.94±0.19	58.54±0.27	59.84±0.51
7	69.67±0.77	51.34±0.67	67.82±0.22	63.54±0.63	68.87±0.35
8	72.50±0.65	62.36±0.44	70.13±0.81	65.47±0.33	73.11±0.68
9	81.60±0.63	73.35±0.52	74.36±0.42	70.17±0.64	81.29±0.59
10	87.34±0.51	79.81±0.49	80.04±0.36	74.36±0.67	87.74±0.47
11	90.17±0.72	86.54±0.87	83.29±0.47	79.67±0.58	91.66±0.35
12	93.23±0.49	91.55±0.23	89.13±0.45	85.75±0.69	94.56±0.26

The data are presented as mean value ±SD (*n*=3). SD: Standard deviation

Table 7: Dissolution release profiles of formulations (F6-F10)

Time (h)	Cumulative % drug release				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	9.28±0.25	9.22±0.51	9.54±0.65	8.66±0.17	10.30±0.34
2	13.40±0.41	17.97±0.76	13.28±0.58	10.92±0.43	17.92±0.47
3	19.75±0.29	28.22±0.25	24.26±0.41	22.15±0.26	28.63±0.65
4	26.05±0.36	37.35±0.36	36.62±0.5	30.55±0.69	37.36±0.58
5	30.58±0.52	44.10±0.39	42.72±0.64	38.47±0.85	44.65±0.21
6	40.04±0.55	53.34±0.46	50.73±0.12	50.82±0.76	50.73±0.65
7	47.96±0.42	62.23±0.62	62.48±0.25	59.83±0.45	61.81±0.84
8	58.45±0.37	68.76±0.55	73.68±0.37	70.02±0.37	73.24±0.34
9	66.11±0.36	73.38±0.38	82.30±0.54	78.95±0.66	77.86±0.22
10	72.74±0.59	79.45±0.72	87.74±0.48	82.11±0.4	80.24±0.19
11	80.04±0.67	84.56±0.89	90.19±0.66	88.24±0.17	86.55±0.27
12	84.74±0.83	90.12±0.43	97.56±0.72	93.23±0.55	91.79±0.48

The data are presented as mean value ±SD (*n*=3). SD: Standard deviation

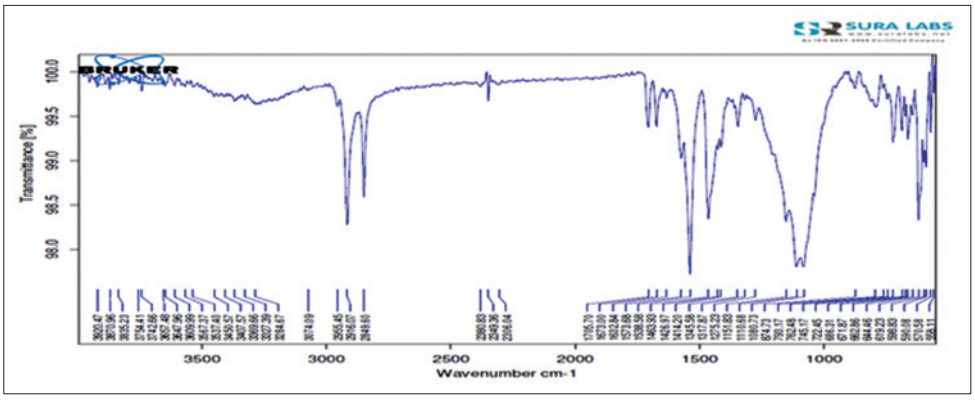
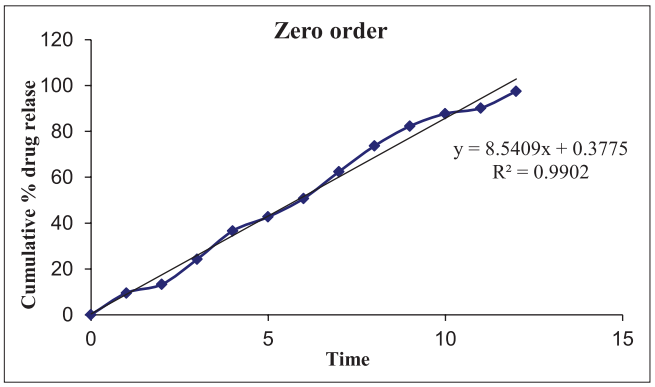
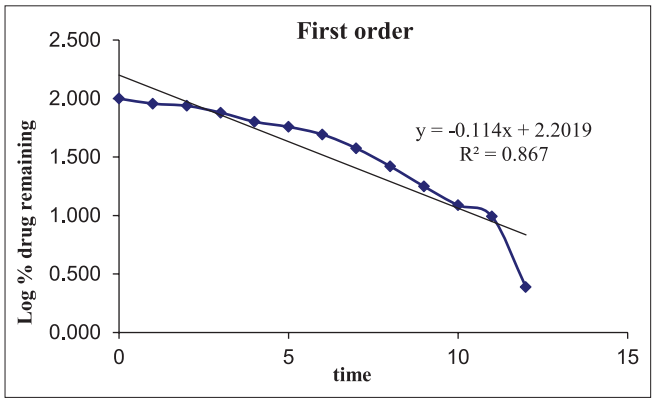


Figure 3: Fourier-transform infrared spectra of optimized formulation (vildagliptin + Xanthan gum + PVP-K 30 + Isopropyl alcohol + Aerosil + Magnesium Stearate + Microcrystalline Cellulose)

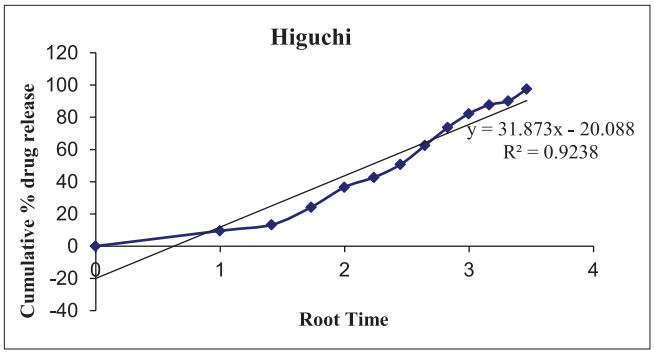
Release Kinetics for Optimized formulation F8

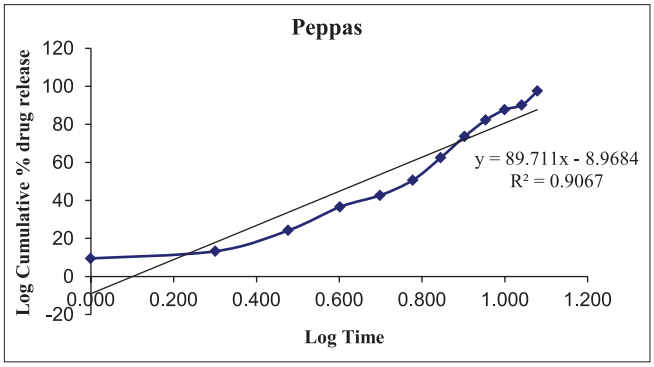




CONCLUSION

The Sustained Release matrix tablets of vildagliptin were prepared by Wet granulation technique. FTIR spectra indicated the absence of probable chemical interaction between the drug and polymers. Vildagliptin SR matrix tablets were formulated with different grades of HPMC such as HPMC-K15M, HPMC-K100, and other Polymers like Sodium alginate, Chitosan, Xanthan gum, Guar gum. The Drug to Polymer ratio 1:1 (Vildagliptin:Xanthan gum) is





optimized. Among 10 formulations, F-8 is optimized based on the cumulative % drug release is 97.56 ± 0.72% in 12 hrs. The *in vitro* drug release data was plotted for various kinetic models. The R^2 value for optimized formulation F8 for zero order was found to be 0.9902.

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