

FORMULATION AND EVALUATION OF VILDAGLIPTIN SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

Vildagliptin belongs to a class of orally active anti-diabetic drug which inhibits dipeptidyl peptidase-4(DPP-4) and to potentiate the secretion of insulin in the β -cells, there by decreasing blood glucose level. Vildagliptin is a short half life drug so it needs to formulate into sustained release dosage form to reduce dose frequency for patient compliance. Among various techniques, formulation of matrix tablets using matrix formers is a simple and industrially useful technique in the design of sustained release drug delivery systems. In the present study, an attempt has been made to develop sustained release matrix tablets of Vildagliptin using hydrophilic polymers like HPMC (K15M, K100M) and Carbapol by using wet granulation method. Dissolution study was done by using type-II dissolution apparatus gave good results with combination of HPMC K100 M and Carbapol. Drug release from the formulation follows zero order, first order, Higuchi's equation, and korsmeyer's equation.

Keywords: Vildagliptin, Anti-diabetic drug, Sustained release dosage form, Matrix formers, Wet granulation.

INTRODUCTION

Sustained Release drug products constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. SR system generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval.[1,2]

The basic goal of this investigation is to achieve steady state blood level of Vildagliptin that is therapeutically effective and non-toxic for extended period of time. Sustained drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy and less side effects and reduced dosage regimen with less toxicity for treatment of many acute and chronic diseases. Vildagliptin belongs to a new class of oral anti-diabetic drugs and is a selective and reversible inhibitor of Dipeptidyl peptidase 4 (DPP-4), the enzyme which inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), hormones which significantly contribute to the maintenance of glucose homeostasis. It may be used either alone or in combination with other hypoglycemic agents. After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT). The biological half-life of Vildagliptin is 1.5 hours, In order to maintain the desired blood levels for an extended period of time and reduce the frequency of administration; Sustained release dosage forms are designed.

Keeping this in view the present investigation has aimed at designing a suitable sustained release matrix tablets using Hydrophilic polymer.

MATERIALS AND METHODS

Materials like HPMC (K15M, K100M), carbopol 971p, potassium dihydrogen phosphate, hydrochloric acid, sodium hydroxide, microcrystalline cellulose, PVP, magnesium stearate, aerosol, talc, and including vildagliptin all were gifted from the spectrum pharma Ltd.

Method of preparation:

In the present investigation sustained release matrix tablets were prepared by Wet granulation method. The Vildagliptin matrix tablets were prepared by employing different synthetic polymers such as HPMC K100M, HPMC K15M, Carbopol 971P and API, MCC, are mixed and passed through the #40 meshes. Then binder solution (PVP) is

added than again passed through the #20 mesh. After that it may allow for drying at 50°C-55°C by using tray dryer for 6 to 7 hrs till desired LOD is achieved. Dried granules were passed through #16 mesh sieve and loaded in a double cone blender. Magnesium stearate, and Aerosil was passed through #40 meshes and it was added to the contents of double cone blender and mixed for 10 min. Blended material was loaded in a hopper and compressed the powder into tablets by using compression machine with 10 standard flat punches.

Drug- Excipient Compatibility Studies by FTIR

Excipients that are likely to be used in the formulation will be identified. Appropriate quantities of the drug and excipients were weighed in different ratios as mentioned in table. The weighed drug and the excipients will be blended physically and will be transferred to glass vials and sealed. The sealed vials are placed inside stability chambers at 25°C/60%RH, 40°C/75%RH for a period of 4 weeks & Samples were analyzed for physical appearance, assay and the solid state property of the drug in the blended mixture ratios at predetermined time intervals. In the present study, the potassium bromide disc (pellet) method was employed.[6,7]

EVALUATION OF TABLETS³

a. Weight variation

Twenty tablets were collected randomly and the average weight and individual weight was calculated. The % weight variation was calculated with the following formula.

$$\% \text{Weight variation} = \frac{\text{Average weight} - \text{individual weight}}{\text{individual weight}} * 100$$

b. Thickness

The thickness of the ten tablets was measured in mm by using Vernier calipers.

c. Hardness

The hardness of the ten tablets was measured by using Tablet Hardness Tester and is given in the units of kg/cm².

d. % Friability

Ten tablets were carefully dedusted prior to testing and weighed accurately (Wo). The tablets were placed in the Friabilator. The friabilator was rotated for 100 times at a speed of 25rpm. The tablets were collected, re-dedusted and accurately weighed (W1). It is calculated from the following formula.

$$\% \text{ Friability} = 1 - \frac{W_1}{W_0} * 100$$

% Friability of tablets is less than 1% was considered acceptable

e. Drug Content

Five tablets were weighed accurately and powdered. Powder equivalent to 100 mg of Vildagliptin was accurately weighed and transferred to a 100 ml volumetric flask. Initially some amount of pH 7.4 phosphate buffer was added to the volumetric flask and the flask was shaken for 10 min and then the mixture was sonicated. Finally the volume was made up to 100 ml with phosphate buffer and then filtered by using of 0.45µm membrane filter paper. The filtrate was suitably diluted with pH 7.4 phosphate buffers and analyzed against blank (pH 7.4 phosphate buffers) solution for the drug content by spectrophotometrically at 245 nm.

f. In vitro drug release studies of Vildagliptin sustained release matrix tablets

The in vitro dissolution study was carried out using dissolution test apparatus USP Apparatus II (paddle) type at 50 rpm in 900 ml simulated gastric fluid (pH 1.2) for first 2 hrs followed by simulated intestinal fluid (pH 7.4) from 2-24 hrs. Aliquots of 5 ml were withdrawn every one-hour and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted suitably, filtered and analyzed at 245 nm spectrophotometrically.

g. Curve fitting analysis (Kinetics of drug Release) [4,5]

The results of in vitro release data obtained for optimized formula was fitted in four popular models of data treatments as follows:

- Zero-order kinetic model (percentage drug release verses time).
- First-order kinetic model (log percentage drug remaining verses time).
- Higuchi's equation (percentage drug release verses square root time).
- Korsmeyer's equation (log percentage drug release verses log time).

RESULTS AND DISCUSSION

The solubility of Vildagliptin was found to be pH independent. The solubility studies data was shown in the **Table 1**. Vildagliptin showed highest solubility in distilled water which was around 20.36 mg/ml. The solubility of Vildagliptin in 0.1N HCl buffer was 19.12mg/ml where as in acetate buffer pH 4.5 the solubility was 15.14 mg/ml, 17.91 mg/ml pH 7.4 Phosphate buffer and 17.19 mg/ml in pH 6.8 Phosphate buffer. Controlling the drug release from the soluble drug thus is an important aspect in the formulation development.

Compatibility studies were performed by FTIR method. The FT-IR Spectrum of Vildagliptin as shown in the **Fig. 1** was compared with the FT- IR spectrum of Vildagliptin formulation shown in the **Fig. 2**. Thus the FT-IR studies indicated that there were no drug-excipient interactions and hence these polymers were selected in the present investigation. As shown in the **Table 2**. The peaks obtained in the spectrum of each formulation correlates with the peaks of drug's spectrum. This indicates that the drug is compatible with the formulation components.

The preformulation studies of Vildagliptin showed poor flow properties which was shown in the **Table 4**. Hence the flow properties of the formulations were improved by using glidants. The Vildagliptin granules were prepared by wet granulation method.

Vildagliptin granules of all the formulations were evaluated for the Micromeritic properties and the tablets were evaluated for various physico-chemical properties and obtained results were reported. The granules of the formulations F₁,F₂,F₃,F₄, F₅, F₆, F₇, F₈ and F₉ were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio and results were reported in **Table7**.

The angle of repose for these formulations ranged from 23.09-26.72, for bulk density ranged from 0.497g/ml to 0.596 g/ml and tapped density from 0.618-0.745g/ml. The compressibility index and Hausner's ratio were in the range of 17.75-21.80 and 1.215-1.278 respectively. From the above results all the formulations exhibited fair flow properties; it was also further supported by Carr's Index values and Hausner's ratio values.

The results of physicochemical evaluation of tablets were reported in **Table 8**. The %weight variation and Hardness of the tablets was in the range of 2.14 to 3.49 and 5.91 Kg/cm² to 7.23 Kg/cm². The % friability and thickness were found be in the range of 0.39-0.46 and 3.18-3.50 mm. The % drug content of the tablets was in the range of 95.11 to 102.51.

From the above results all the formulations shows % weight variation, hardness and friability were well within the limits. The percent drug content was found within in acceptable limits.

The In-Vitro dissolution studies of formulated Vildagliptin matrix tablets were carried in P^H1.2 buffer for two hours and in P^H7.4 buffer from 3- 24 hours by USP type II Dissolution apparatus. From the, the *in-vitro* dissolution data **Table 11**, It was found that the drug release from formulation containing CP (20%) (F1) 96% in 11 hrs, HPMC K15M (20%) (F2) 96.78% in 12 hrs, HPMC K 100M (20%)(F3) 98.89% in 16 hrs, CP (25%)(F4) 95.46% in 16 hrs, HPMC K15M (25%),(F5) 96.67% in 16 hrs, HPMC K 100M (25%)(F6) 90.26% in 20 hrs, where as incase of Combination of HPMC K 15M &CP (F7)98.45% in 16 hrs, HPMC K 100M & HPMC K15M (F8) 97.89% in 20 hrs and HPMC K100M&CP (F9) 98.78% in 24 hrs.

From the results it was observed that, increasing the amount of polymer in the formulations resulted in slower rate and decreased amount of drug release from the tablet. Comparison among the formulations containing HPMC K15M, HPMC K100 M, CP and the combination of HPMC K15 M, HPMC K100M and CP based tablets, Release of drug from the CP based tablet, we found to be faster as compared to HPMC K15 M and HPMC K100 M, and their combination.

Order of retardation of different formulations is in the following sequence:

CP < HPMC K 15 M < HPMC K 100 M

Table 1: Solubility studies of Vildagliptin in different media

Media	Solubility(mg/ml)
Distilled water	20.36
0.1 N HCl	19.12
pH 4.5 Acetate Buffer	15.14
pH 7.4 Phosphate Buffer	17.91
pH 6.8 Phosphate buffer	17.19

Table 2: Comparison of IR Spectrum of Pure drug & Formulation

S. No.	Wave number of functional groups in formulation (cm ⁻¹)	Wave number of functional groups in pure drug (cm ⁻¹)	Functional groups present
1	2937.00	3057.36	CH stretching alkane
2	1615.82	1632.17	C=N Stretching
3	1387.09	1370.06	CH bending(alkane)
4	1149.13	1146.80	CN Vibrations
5	3056.36	3057.36	C-H stretching(aromatic)
6	1668.96	1667.99	C=O stretching

Table 3: Physical Compatibility Results

Material	Sample Status After 1 month, kept at 25°C /60%RH & 40°C/75%RH
Vildagliptin + HPMC K 15M	No Change
Vildagliptin+HPMC K 100M	No Change
Vildagliptin +aerosol	No Change
Vildagliptin +Carbopol	No Change
Vildagliptin+MCC	No Change
Vildagliptin +Magnesium Stearate	No Change
Vildagliptin +Talc	No Change

Table 4: Flow properties of Vildagliptin pure drug

S. No.	Parameter	Observation
1	Polymorphic State	Crystalline
2	bulk density	0.645
3	Tapped Density	0.827
4	Carr's index	22.92
5	Hausner's ratio	1.28
6	Angle of Repose (θ)	41.96
7	Result	Poor Flow

Table 5: Standard Calibration Data of Vildagliptin in 0.1N HCl

Concentration ($\mu\text{g/ml}$)	Absorbance($\bar{x} \pm \text{sd}$)
0	0
5	0.129 \pm 0.01
10	0.261 \pm 0.02
15	0.384 \pm 0.01
20	0.512 \pm 0.02
25	0.631 \pm 0.03
30	0.763 \pm 0.01

Table 6: Standard Calibration Data of Vildagliptin in 7.4 P^H phosphate buffer

Concentration ($\mu\text{g/ml}$)	Absorbance($\bar{x} \pm \text{sd}$)
0	0
5	0.117 \pm 0.03
10	0.222 \pm 0.02
15	0.332 \pm 0.04
20	0.445 \pm 0.01
25	0.542 \pm 0.02
30	0.646 \pm 0.03

Table 7: Micromeritic properties of the granules of Vildagliptin formulation

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Angle of repose(θ)	Compressibility Index (%)
F1	0.509	0.630	1.237	23.09	19.20
F2	0.522	0.639	1.224	24.98	18.30
F3	0.497	0.618	1.241	25.01	19.57
F4	0.556	0.690	1.239	23.33	19.42
F5	0.545	0.697	1.278	25.67	21.80
F6	0.565	0.687	1.215	23.45	17.75
F7	0.516	0.655	1.269	24.58	21.22
F8	0.526	0.661	1.258	25.03	20.42
F9	0.596	0.745	1.251	26.72	20.73

Table 8: Physico-Chemical Evaluation of Vildagliptin Tablets

Formulation Code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm ²)	% Friability	%Drug Content	Disintegration time
F1	3.00 \pm 0.02	3.4 \pm 0.02	7.04 \pm 0.05	0.45 \pm 0.09	98.12 \pm 0.03	Non-disintegrating
F2	2.99 \pm 0.03	3.50 \pm 0.05	6.88 \pm 0.03	0.41 \pm 0.03	102.14 \pm 0.05	Non-disintegrating
F3	2.97 \pm 0.02	3.44 \pm 0.03	6.92 \pm 0.07	0.39 \pm 0.06	98.64 \pm 0.03	Non-disintegrating
F4	3.01 \pm 0.04	3.39 \pm 0.05	6.79 \pm 0.02	0.46 \pm 0.04	97.49 \pm 0.05	Non-disintegrating
F5	3.21 \pm 0.05	3.50 \pm 0.08	6.71 \pm 0.09	0.21 \pm 0.02	102.51 \pm 0.08	Non-disintegrating
F6	2.31 \pm 0.06	3.45 \pm 0.06	6.95 \pm 0.02	0.25 \pm 0.03	101.26 \pm 0.06	Non-disintegrating
F7	3.04 \pm 0.08	3.36 \pm 0.07	6.26 \pm 0.04	0.31 \pm 0.07	96.35 \pm 0.07	Non-disintegrating
F8	3.49 \pm 0.03	3.18 \pm 0.08	7.23 \pm 0.06	0.29 \pm 0.09	97.49 \pm 0.08	Non-disintegrating
F9	2.14 \pm 0.05	3.46 \pm 0.06	5.91 \pm 0.06	0.46 \pm 0.06	99.71 \pm 0.06	Non-disintegrating

Table 9: Finalized formula (F9) stability data

Condition	Parameter	Initial data	Data after one month
Accelerated(40°C ± 2°C/75% RH ± 5 % RH)	Hardness (N)	5.91	5.45
	Friability (%)	0.46	0.41
	Assay (%)	99.71	98.63

Table 10: Invitro dissolution profile of (F9) at 40°C/75% RH

Time (hr)	Cumulative % drug released	
	Initial F9	Percentage of Drug release at 40°C±2°C/75% ± 5% RH F9
0.0	0	0
1	13.89	15.65
2	20.67	23.46
3	26.58	28.43
4	31.89	34.26
5	35.87	38.86
6	39.39	42.49
7	43.59	47.53
8	46.79	50.21
9	50.8	52.8
10	54.6	56.6
11	60.51	63.05
12	64.56	68.14
16	77.29	74.46
20	84.89	88.26
24	98.78	99.06

Table 11: In vitro dissolution studies results

Time(hrs)	Cumulative % drug released(X= ± SD) (n = 3)									
	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉	
0	0	0	0	0	0	0	0	0	0	
1	33.98 ± 1.2	25.45±1.5	20.13±2.12	23.45±1.6	18.78±1.45	16.23±1.87	20.32±1.34	16.89±1.56	13.89±1.6	
2	42.64 ± 1.56	35.01±0.67	27.96±1.69	29.45±2.12	22.98±0.89	24.45±0.89	30.76±0.56	23.45±1.23	20.67±1.45	
3	49.56 ± 2.43	43.89±2.23	34.45±1.43	37.16±2.12	28.46±2.12	30.58±2.13	36.56±2.45	29.27±0.78	26.58±0.23	
4	55.23 ± 1.89	49.67±2.43	43.76±2.23	43.56±2.12	33.67±1.87	35.26±2.45	40.06±3.12	35.69±1.45	31.89±1.23	
5	60.26 ± 0.76	56.61±0.67	48.23±1.65	49.24±2.34	39.96±1.76	39.86±2.12	44.56±2.45	40.46±1.73	35.87±1.87	
6	65.67 ± 1.34	62.09±0.23	53.89±0.78	54.16±2.45	50.16±1.34	44.56±3.45	49.53±1.45	44.89±1.06	39.39±0.89	
7	70.67 ± 1.76	68.23±1.23	59.23±2.65	59.36±2.65	56.41±1.45	49.53±1.45	55.01±2.67	48.71±1.89	43.59±1.34	
8	76.78 ± 1.45	75.03±2.12	65.23±1.92	65.67±2.87	60.99±2.12	56.21±1.56	60.12±1.87	52.56±1.67	46.79±1.87	
9	82.13 ± 1.67	79.56±1.89	71.45±1.78	70.67±1.78	64.16±2.89	58.8±0.91	65.89±2.13	56.56±2.56	50.8±1.45	
10	88.89 ± 1.23	84.89±1.45	76.56±1.67	74.98±1.89	71.27±1.19	64.6±1.76	71.12±2.45	61.68±0.87	54.6±0.78	
11	96 ± 1.45	89 ± 0.72	80.89±0.78	79.98±1.73	75.99±1.10	68.05±2.12	77.34±2.76	66.78±1.65	60.51±0.81	
12		96.78±0.65	84.89±1.45	84.89±2.12	81.89±2.45	71.14±3.14	84.45±1.67	71.56±1.45	64.56±1.67	
16			98.89±0.92	95.46±1.67	96.67±0.67	81.45±3.45	98.45±1.45	84.52±2.12	77.29±1.65	
20						90.26±1.2		97.89±2.23	84.89±1.93	
24									98.78±0.99	

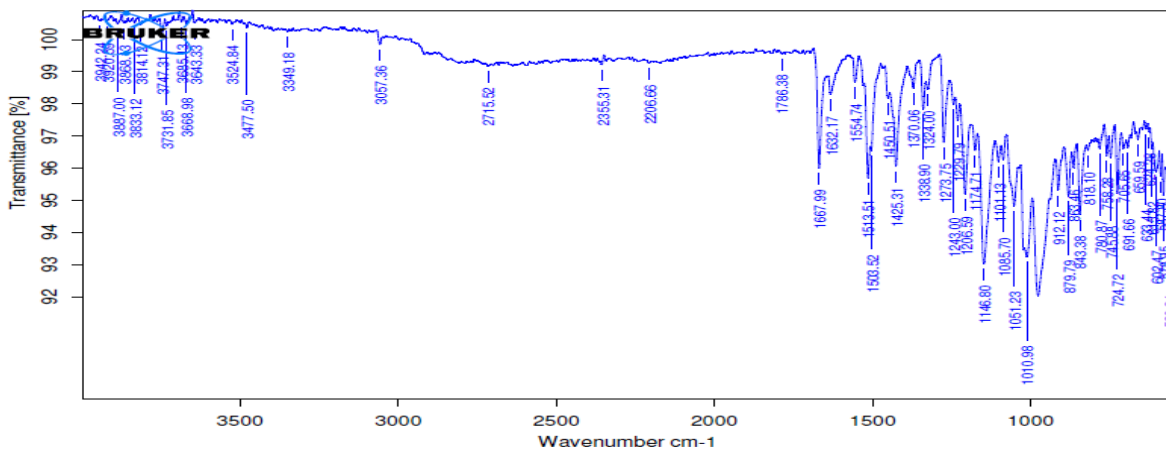


Fig. 1: FT-IR Spectrum of Vildagliptin

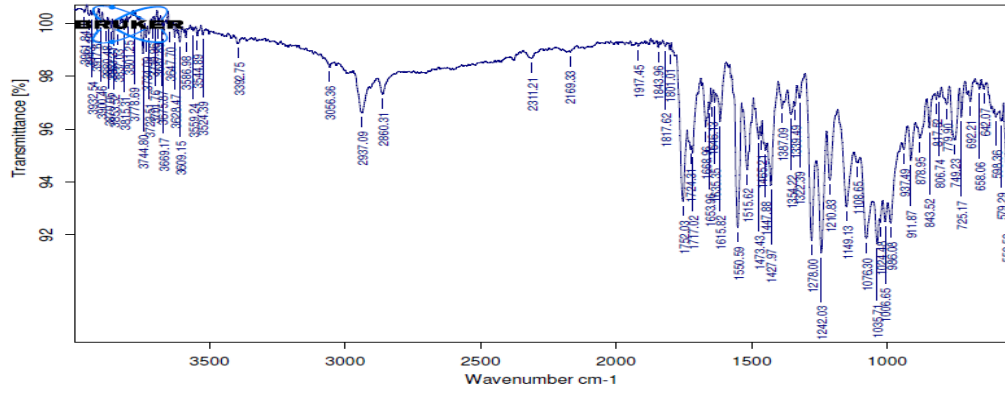


Fig. 2: FT-IR Spectrum of Vildagliptin Formulation

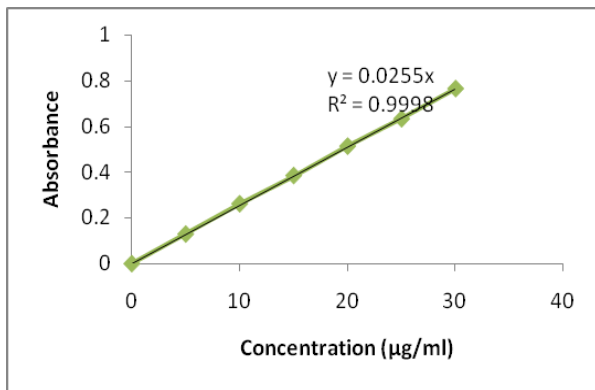


Fig. 3: Calibration curve of Vildagliptin in 0.1N HCl

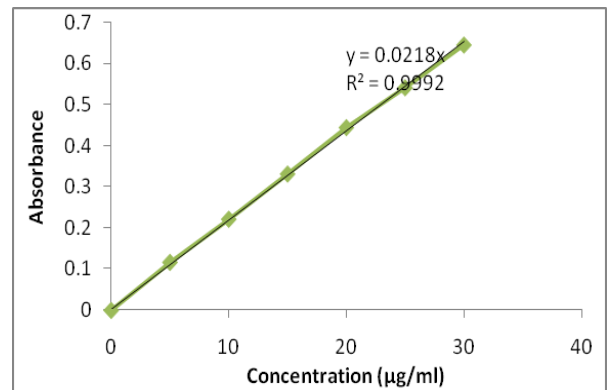


Fig. 4: Calibration curve of Vildagliptin in 7.4pH Phosphate buffer

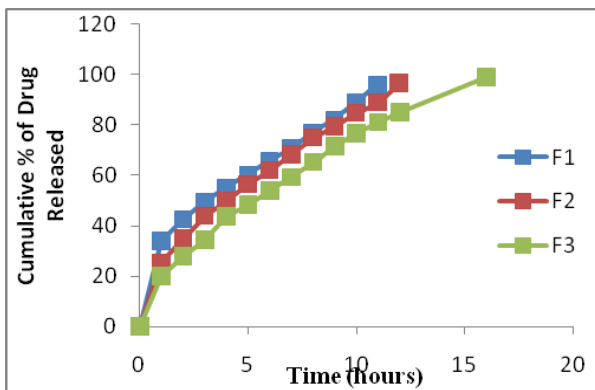


Fig. 5: Comparative Dissolution plots of Vildagliptin SR matrix tablets (F1-F3)

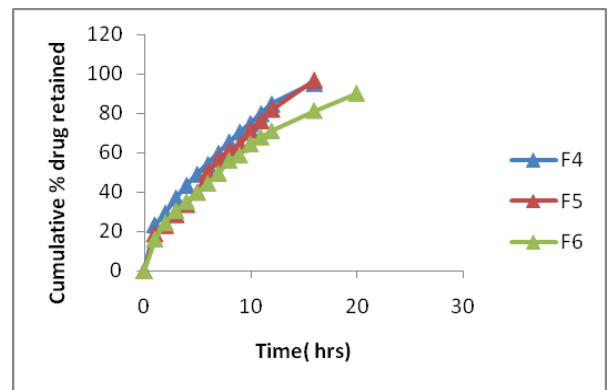


Fig. 6: Comparative Dissolution plots of Vildagliptin SR matrix tablets (F4-F6)

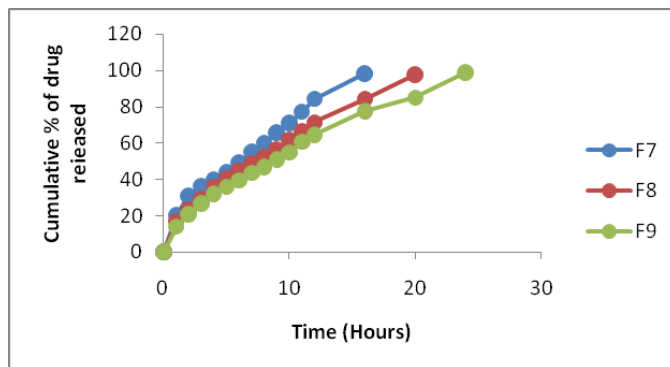


Fig. 7: Comparative Dissolution plots of Vildagliptin SR matrix tablets (F7-F9)

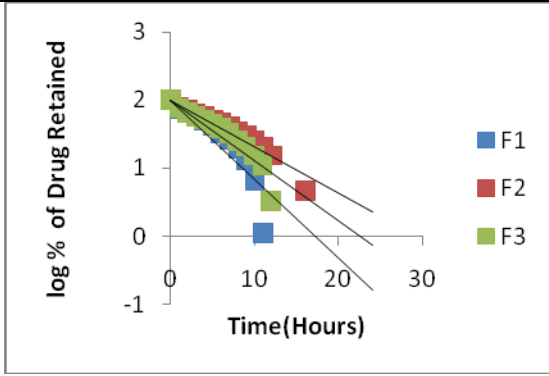


Fig. 8: Comparative first order plots of Vildagliptin sustained release matrix tablets (F1-F3)

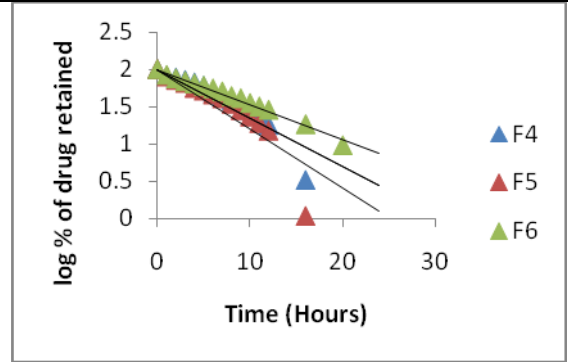


Fig. 9: comparative first order plots of Vildagliptin sustained release matrix tablets (F4-F6)

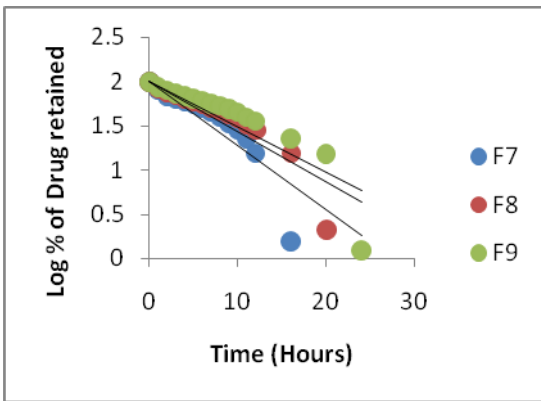


Fig. 10 Comparative first order plots of Vildagliptin sustained release matrix tablets (F7-F9)

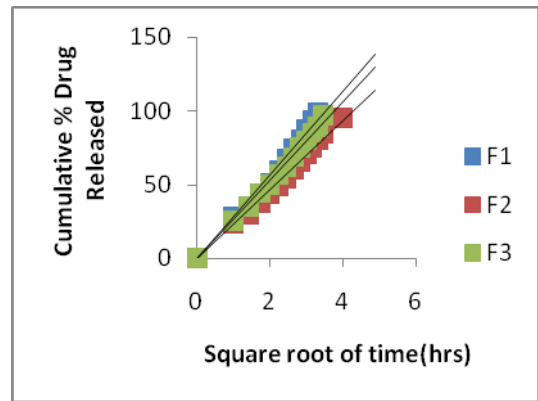


Fig. 11: Comparative Higuchi plots of Vildagliptin sustained release matrix tablets (F1-F3)

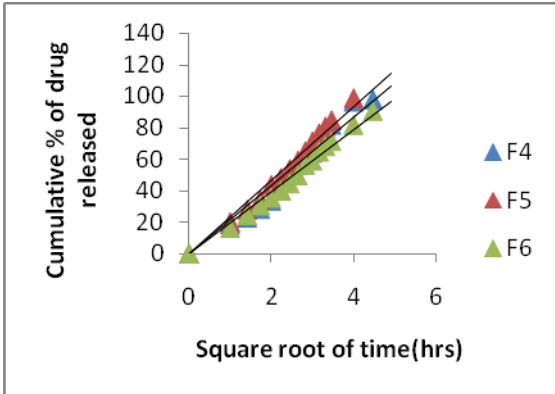


Fig. 12: Comparative Higuchi plots of Vildagliptin sustained release matrix tablets (F4-F6)

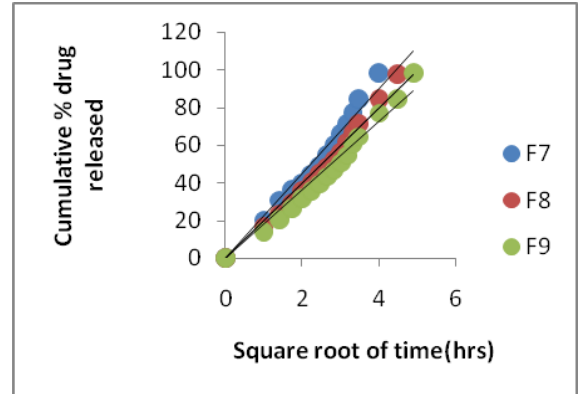


Fig. 13: Comparative Higuchi plots of Vildagliptin sustained release matrix tablets (F7-F9)

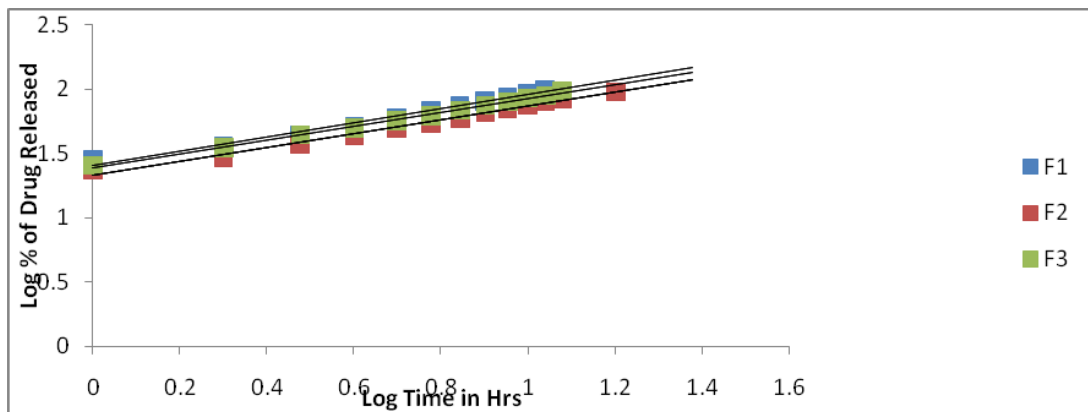


Fig. 12: Comparative Korsmeyer-Peppas plots of Vildagliptin sustained release matrix tablets (F1-F3)

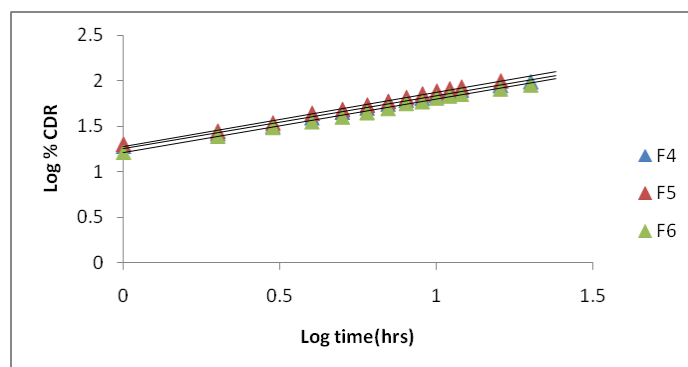


Fig. 13: Comparative Korsmeyer-Peppas plot of Vildagliptin sustained release matrix tablets (F4-F6)

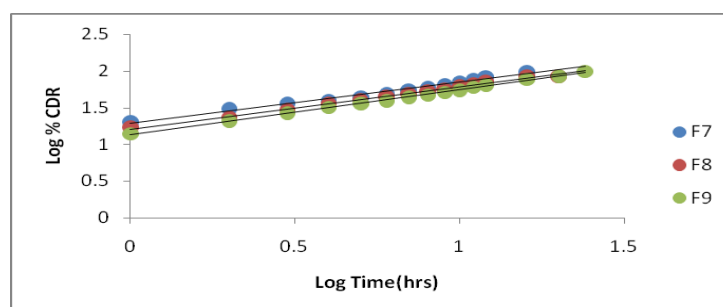


Fig. 14: Comparative Korsmeyer-Peppas plot of Vildagliptin sustained released matrix tablets (F7-F9)

STABILITY STUDIES

The results of the stability studies revealed that no visible changes were observed in the tablets after storage. The drug content was found to be uniform as shown in the **Table 09**, revealed that results were within the prescribed limits even after storage at $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{RH}$. The drug release data was shown in **Table 10** indicated that there are no significant changes in the drug release even after storage at $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{RH}$. The slow drug release characteristics of the product were found to be stable and unaltered.

CONCLUSION

The following conclusions were drawn from the present investigation

- Drug - excipients compatibility studies were conducted by FT-IR spectroscopy, results indicated that the Vildagliptin and polymers were found to be compatible.
- The micromeritic properties of granules were evaluated, all the formulations exhibited good flow properties.
- The evaluation parameters for the prepared tablets such as % weight variation, hardness, % friability, thickness and drug content were found to be in satisfactory limits.
- The maximum drug release was found to be 98.78% over a period of 24 hours in HPMC K100M & CP based tablets. This indicates combination of HPMC K 100M & CP required to prepare the sustained release matrix tablets of Vildagliptin.
- The effect of different hydrophilic polymers on release rate was studied. The order of release retardation was HPMC K 100M > HPMC K 15 M > CP
- All the formulations were also subjected to model fitting analysis to know the order and mechanism of drug release from the formulations by treating the data according to Zero order, First order, Higuchi and Peppas Equations, The data clearly shows that, the release kinetics revealed that the formulations containing HPMC K15M, HPMC K 100M and CP

follows zero order release kinetics and release rate was controlled by Non-Fickian diffusion.

- Thus in the present investigation, finally concluded that sustained release tablets of Vildagliptin were successfully designed by wet granulation method and evaluated. It can be concluded that HPMC K100M and CP combination can be used as an effective matrix former to sustain the release of Vildagliptin for the period of 24 Hours.

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