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Research Article

Formulation Development and Evaluation of Vildagliptin Sustained Release Tablet

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ABSTRACT

Introduction: The present research work was to design and develop the sustained release 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: Sustained release tablets were prepared by direct compression technique, using polymers at different ratios. Powder blend was evaluated for bulk density, tapped density, angle of repose, Hausner's ratio, compressibility index. 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 10 h using 0.1 N HCl (1.2 pH) as a dissolution medium. Conclusion: The optimized formulation F-3 was shown maximum drug release 98.43 % in 10 h of dissolution studies.

Keywords: Vildagliptin, powder blend, Sustained release tablets, physicochemical properties, *In vitro* dissolution studies.

INTRODUCTION

Traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a formulation with control release that maintain a near-constant or uniform blood level. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[1]. 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[2].

Vildagliptin is a potent and selective inhibitor of dipeptidyl peptidase-IV (DPP-4), orally active, that improves glycemic control in patients with type 2 diabetes (T2DM) primarily by enhancing pancreatic (α and β) islet function. Thus Vildagliptin has been shown both to improve insulin secretion and to suppress the inappropriate glucagon secretion seen in patients with Type-2Diabetes Mellitus. Vildagliptin reduces HbA_{1c} when given as monotherapy, without weight gain and with minimal hypoglycemia, or in combination with the most commonly prescribed classes of oral hypoglycemic drugs: metformin, a sulfonylurea, a thiazolidinedione, or insulin[3].

An attempt has been made to develop Vildagliptin sustained release tablet formulation which will release the drug for 12 hrs. This delayed release will minimize side effects related to high serum levels that occur with immediate-release formulations. A sustained release formulation can lead to the reduction of the number of doses administered, leading to better patient compliance and less chances of overdose, in addition to which it can reduce the cost associated with treating diabetic symptoms.

MATERIALS AND METHODS

Vildagliptin was a gift sample NATCO Pharma, Hyderabad. HPMC and Eudragit grades were procured from SD fine chemicals Pvt Ltd, Mumbai, India, PVP-K 30, Magnesium Stearate and Talc were procured from Merck Specialties Pvt Ltd, Mumbai, India. All other reagents used were of analytical grade.

Methodology

Preformulation studies

Standard Calibration curve of Vildagliptin

100mg of Vildagliptin pure drug was dissolved in 100ml of 0.1 N HCl (stock solution)10ml of solution was taken and make up with100ml of 0.1 N HCl (100µg/ml). from this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5, 10, 15, 20,25µg/ml of Vildagliptin per ml of solution. The absorbance of the above dilutions was

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Table 1: Formulation composition of Vildagliptin sustained release tablet.

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F10	F11	F12
Vildagliptin	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	50	100	-	-	-	-	-	-	-	-	-	-
HPMC K15M	-	-	50	100	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	-	50	100	-	-	-	-	-	-
Eudragit L-100	-	-	-	-	-	-	50	100	-	-	-	-
Eudragit S 100	-	-	-	-	-	-	-	-	50	100	-	-
Eudragit RSPO	-	-	-	-	-	-	-	-	-	-	50	100
PVP K30	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total Weight	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Concentration and absorbance obtained for calibration curve of Vildagliptin in 0.1 N hydrochloric acid buffer (pH 1.2).

S. No.	Concentration (µg/ml)	Absorbance* (at 230 nm)
1	0	0
2	5	0.227
3	10	0.406
4	15	0.621
5	20	0.824
6	25	0.987

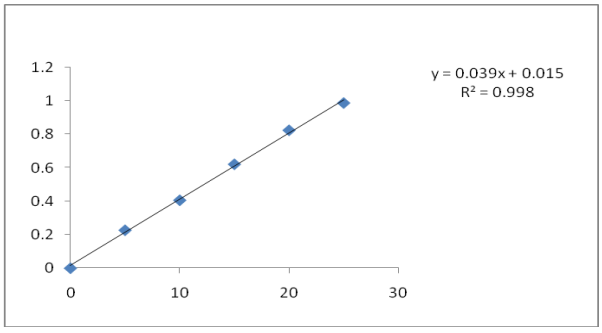

Figure 1 : Standard graph of Vildagliptin in 0.1 N HCl

Table 3: Observations for graph of Vildagliptin in p H 6.8 phosphate buffer (224nm).

S. No.	Concentration (µg/ml)	Absorbance* (at 224 nm)
1	0	0
2	5	0.301
3	10	0.441
4	15	0.621
5	20	0.744
6	25	0.971

measured at 230 nm by using UV-Spectrophotometer ((Lab India UV-3000+). taking 0.1N HCl as blank.

The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Evaluation of Pre-compression parameters

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[4].

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[5,6].

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 was determined using the following formula[8].

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

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density/Bulk density

Preparation of Tablets

Vildagliptin Sustained release tablets were prepared by direct compression method. All the ingredients were weighed. Required quantity of drug and excipient mixed

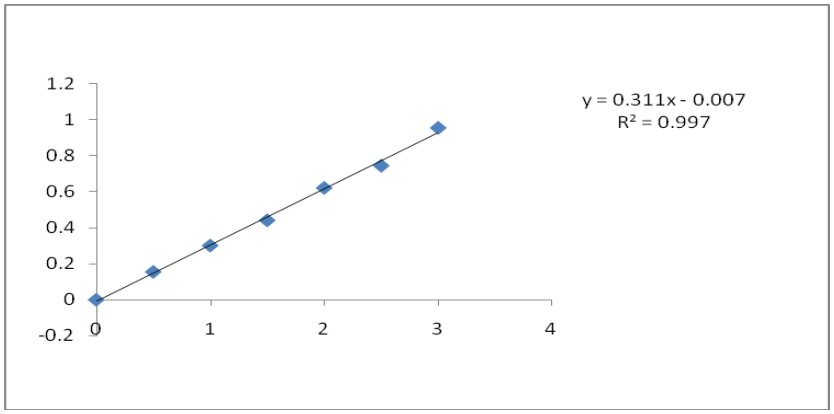

Figure 2: Standard graph of Vildagliptin in 6.8pH phosphate buffer.

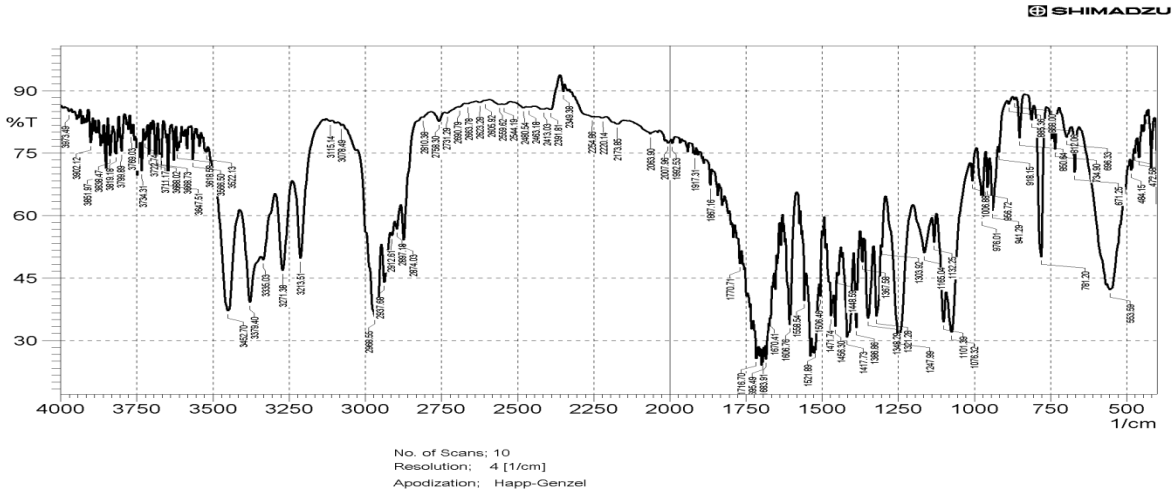

Figure. 3: FTIR spectrum of pure drug.

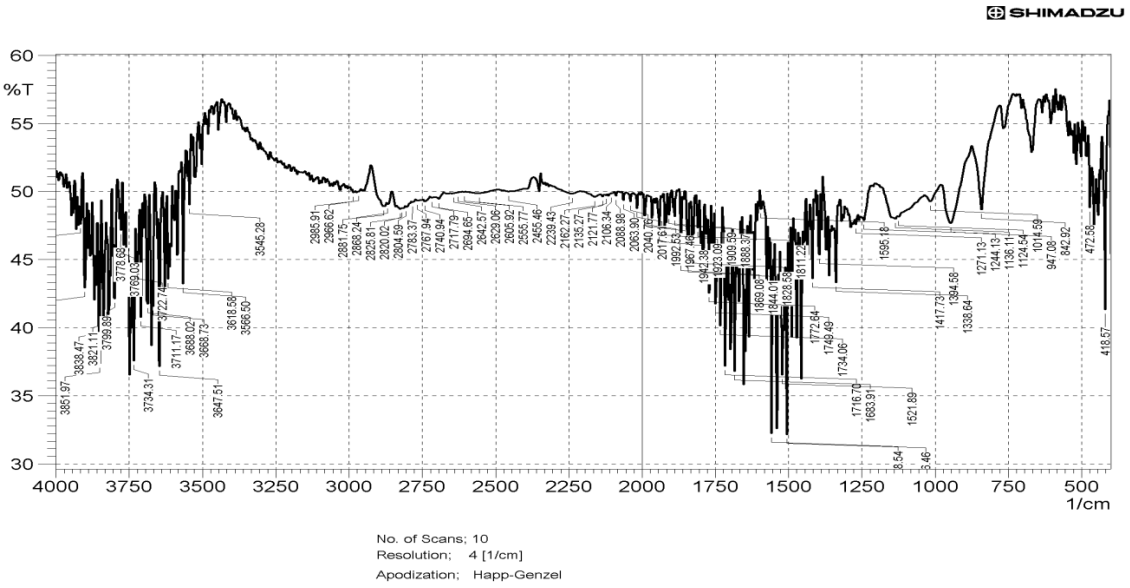

Figure 4: FTIR spectrum of optimized formulation.

thoroughly and the blend is compressed using rotary tablet press.

Evaluation of Tablets

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical strength while handling. The hardness of the

Table 4: Pre-compression parameters.

Pre-compression parameters					
Formulations	Bulk Density (gm/ml)	Tap Density (gm/ml)	Carr's Index(%)	Hausner's ratio	Angle Of Repose(Ɵ)
F_1	0.45 ±0.18	0.55 ±0.23	18.18 ±0.45	1.22 ±0.24	27.91 ±0.12
F_2	0.47 ±0.26	0.55 ±0.32	14.54 ±0.37	1.17 ±0.31	28.23 ±0.41
F_3	0.50 ±0.15	0.58 ±0.40	13.79 ±0.42	1.16 ±0.21	29.34 ±0.64
F_4	0.46 ±0.11	0.55 ±0.24	16.36 ±0.29	1.19 ±0.29	26.71 ±0.23
F_5	0.50 ±0.24	0.58 ±0.37	13.79 ±0.35	1.16 ±0.08	29.34 ±0.22
F_6	0.47 ±0.23	0.55 ±0.12	14.54 ±0.09	1.17 ±0.52	28.23 ±0.10
F_7	0.50 ±0.29	0.58 ±0.08	13.79 ±0.24	1.16 ±0.23	29.34 ±0.54
F_8	0.41 ±0.16	0.50 ±0.15	18 ±0.12	1.21 ±0.39	26.78 ±0.29
F_9	0.41 ±0.10	0.50 ±0.13	18 ±0.37	1.21 ±0.51	26.78 ±0.42
F10	0.42 ±0.28	0.51 ±0.31	18.24 ±0.29	1.20 ±0.27	26.68 ±0.30
F11	0.48 ±0.21	0.56 ±0.20	18.12 ±0.31	1.21 ±0.45	26.70 ±0.52
F12	0.41 ±0.30	0.54 ±0.25	18.11 ±0.52	1.22 ±0.64	26.71 ±0.28

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

Table 5: Post-compression parameters.

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	205±0.98	4.5±0.18	3.59±0.13	0.43±0.12	97.23±1.21
F2	204±0.88	4.6±0.21	3.64±0.15	0.34±0.14	98.55±1.05
F3	210±0.97	4.5±0.32	3.59±0.14	0.49±0.09	98.16±0.98
F4	209±0.96	4.6±0.25	3.58±0.21	0.47±0.22	99.34±0.92
F5	199.4±1.12	4.3±0.15	3.59±0.25	0.49±0.12	98.16±1.09
F6	202±1.30	4.7±0.19	3.64±0.52	0.34±0.16	98.55±1.03
F7	201±0.97	4.5±0.21	3.59±0.28	0.49±0.19	98.16±1.11
F8	207±0.87	4.6±0.18	3.56±0.32	0.34±0.28	99.25±2.12
F9	202±0.89	4.5±0.24	3.56±0.29	0.34±0.26	99.25±1.76
F10	203±1.02	4.4±0.26	3.55±0.21	0.43±0.37	98.6±1.68
F11	202.4±1.39	4.8±0.32	3.45±0.32	0.54±0.31	98.7±1.45
F12	198.5±1.65	4.5±0.23	3.54±0.25	0.43±0.46	98.5±1.26
	n=20	n=5	n=10	n=10	n=5

Table 6: Dissolution profiles of formulations (F1-F6).

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	20.22±0.65	14.26±0.86	15.02±1.12	17.21±0.69	14.66±0.54	16.22±0.54
2	32.65±0.98	20.65±1.23	22.55±1.02	29.53±0.78	28.44±0.68	25.45±0.28
3	49.68±0.32	39.29±1.21	40.89±1.24	40.12±0.59	43.85±0.78	36.89±0.32
4	55.24±1.21	59.55±1.18	48.22±0.95	56.84±1.69	65.88±0.59	42.83±0.41
5	60.35±0.96	77.58±1.25	54.48±0.68	66.85±0.78	79.25±0.87	58.46±0.26
6	74.24±0.89	80.65±0.96	59.77±1.12	76.63±1.21	96.12±0.69	62.70±0.45
7	88.28±1.12	98.63±1.14	66.62±1.42	85.12±1.35		75.23±0.62
8	97.55±1.25		74.35±0.98	97.70±1.29		84.26±0.85
9			88.99±1.14			97.99±1.12
10			98.43±1.35			

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

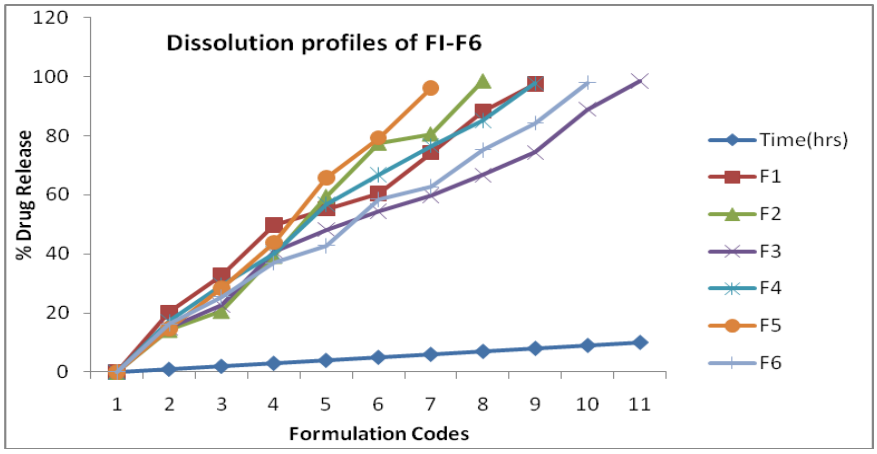

Figure 5: Dissolution profile of formulation F1-F6.

Table 7: Dissolution profiles of formulations (F7-F12).

Time(hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	21.10±0.65	19.50±0.69	23.54±0.96	21.01±1.02	12.14±1.32	21.15±1.21
2	32.86±0.96	31.88±0.36	38.33±0.89	36.01±0.68	18.24±1.28	29.45±1.02
3	43.24±1.10	49.28±1.23	44.25±0.29	40.22±1.21	22.24±1.02	35.48±1.29
4	66.49±1.21	61.11±1.35	51.01±0.36	43.15±1.14	32.14±1.21	45.15±0.68
5	74.85±1.14	78.96±1.57	66.86±0.56	46.57±0.68	42.15±0.69	52.47±1.29
6	84.25±1.30	82.58±1.42	78.98±0.68	51.22±0.78	51.21±1.14	61.48±0.78
7	95.57±1.28	94.66±1.15	84.26±0.65	61.21±1.29	62.14±0.32	68.24±0.65
8			96.99±0.29	72.15±1.14	73.15±0.65	72.15±0.45
9				81.22±1.26	79.24±0.82	82.14±0.68
10				89.54±1.45	82.55±0.78	91.25±1.14

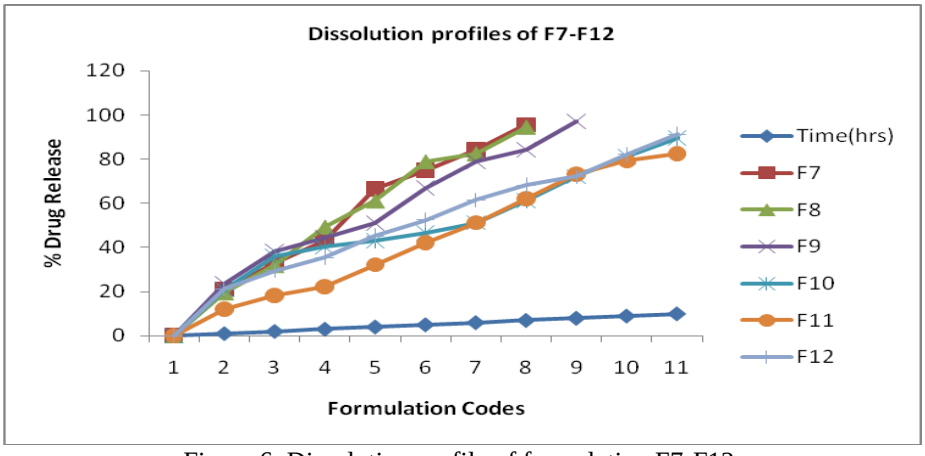

Figure 6: Dissolution profile of formulation F7-F12.

To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated[12].

% weight variation = (WA–WI) x 100/ WA

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 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 10 h time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh

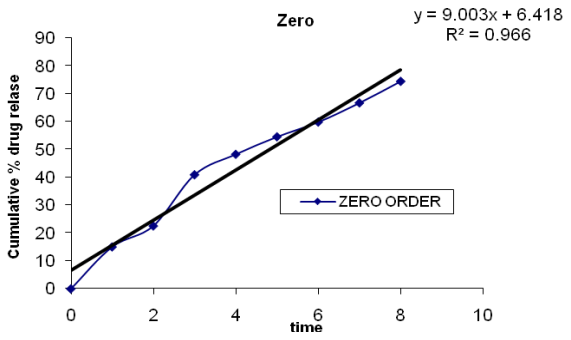

Figure 7: Zero order

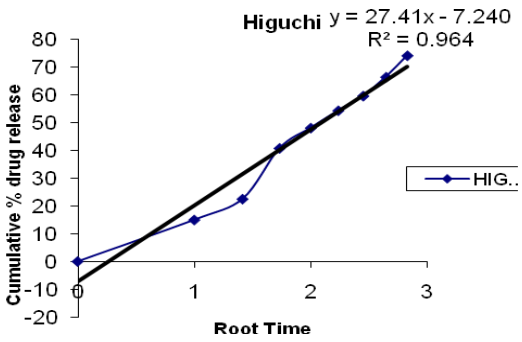

Figure 8 : Higuchi plot

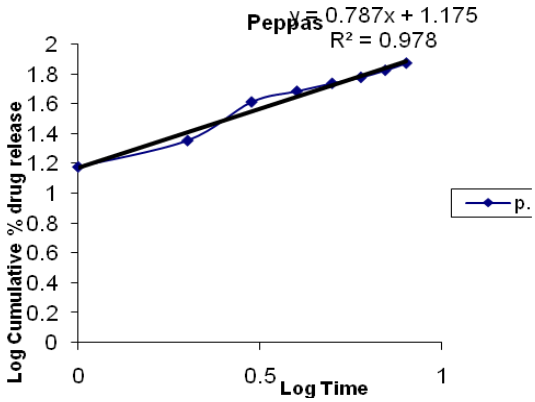

Figure 9: Korsmeyer–Peppas

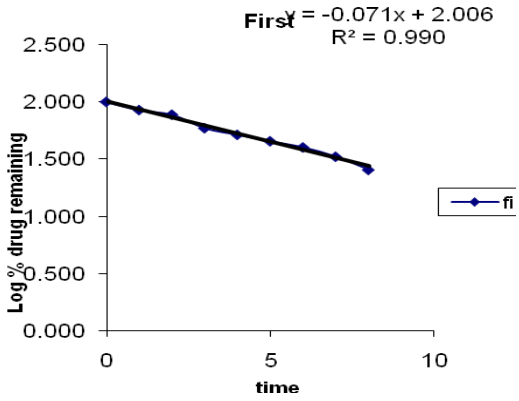

Figure 10: First order

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[2].

Kinetics of drug release

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[2].

RESULTS AND DISCUSSIONS

Preparation of standard Calibration curve of Vildagliptin

The absorption maximum for Vildagliptin was found to be 230 nm in 0.1N HCl and 224 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 $R^2 = 0.998$ and in pH 6.8 Phosphate buffer is R2 = 0.997.

Drug- excipient compatibility studies using FTIR

Drug-excipient compatibility studies by FTIR revealed no interaction between drug and the polymers used in the formulation thus showing compatibility [Figures 3 and 4].

Evaluation of Pre-compression parameters

The Pre compression parameters such as Bulk density, Tapped density, Carr's index, Hausner ratio and Angle of repose of the all formulations (F1-F12) were found to be in between the range of 0.41±0.30 to 0.50±0.29 g/ml., 0.50±0.13 to 0.58±0.37 g/ml., 13.79±0.24 to 18.24±0.29., 1.16±0.08 to 1.22±0.0.64 and 26.68±0.30 to 29.34±0.64 respectively.

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

In vitro dissolution studies

The tablets were evaluated for in vitro dissolution studies in acid buffer (pH-1.2) for 2 hours followed by pH 6.8 buffers for 8 hours. The results of in-vitro drug release revealed that the Vildagliptin was released in a controlled manner from all the formulations where formulation F3 showed maximum drug release i.e. 98.43±1.35 % at the end of 10th hour.

Release Kinetics for Optimized formulation F3

From the graphs it was evident that the formulation F3 was followed Zero order release kinetics.

The results of the stability studies revealed that no visible

Table 8: Results of Stability Studies for optimized formulation (F3).

Condition	Parameters	Initial Data	After 30 days
Accelerated(40°C ± 2°C/75% RH ± 5 % RH)	Hardness(kg/cm^2)	4.5±0.32	4.32±0.59
	Friability (%)	0.49±0.09	0.46±0.12
	Assay (%)	98.16±0.98	97.32±1.12

changes were observed in the Table 7, 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 ^{0}C ±2°C / 75% ± 5% 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 ^{0}C ±2°C / 75% ± 5% RH.

CONCLUSION

The Sustained Release matrix tablets of Vildagliptin were prepared by direct compression technique. FTIR spectra indicated the absence of probable chemical interaction between the drug and polymers; hence these polymers were selected in the present investigation. 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 tablets were formulated with different grades of HPMC (HPMC-K4M, HPMC-K15M, HPMC-K100M), Eudragit (Eudragit L-100, S-100, RSPO) other Polymers like PVP K-30, Microcrystalline cellulose, Magnesium Stearate. Among 12 formulations, F-3 is optimized based on the cumulative % drug release is 98.43±1.35 % at the end of 10th hour. The *in vitro* drug release data was plotted for various kinetic models. The R^2 value for optimized formulation F3 for zero order was found to be 0.9902.

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