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Formulation and Evaluation of Controlled-release matrix Vildagliptin tablets

Balakrishnan M*, Sudarsanam P, Nethaji D U

Seshachala College of Pharmacy, Tirupathi – Chennai High way, Puttur-517 583, Chittoor (Dist), Andhra Pradesh, India

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ABSTRACT

Vildagliptin has a low biological half-life of 90 minutes along with having less bioavailability which requires multiple dosing daily, hence the current research study was intended to evolve a controlled release formulation of Vildagliptin to reduce the dose-related side effects and to reduce the dosage regimen. The present research project intended to develop a Control release matrix Vildagliptin tablets of the anti diabetic drug Vildagliptin, the present research comprising Vildagliptin useful for the management of type 2 diabetes. Polymers like Tamarind gum, Guar gum, and xanthan gum were used for controlling the drug release, and the polymers are mixed in a predetermined ratio. 9 formulations were prepared and assessed for pre-compression and post comparison criterion, and all the outcomes were found to be within the limitations. From the drug and excipients compatibility studies, the FT-IR it was confirmed that the drug and excipients not have any kind of interactions. The in vitro dissolution tests revealed that the F9 formulation possess 30% of Guar gum controls the drug release up to 24hours. So Guar gum containing F9 formulation was considered to be suitable for the formulation of Vildagliptin controlled release tablets at 30% concentration, and the drug clearance kinetics revealed that the F9 formulation shows a super case transport mechanism.

*Corresponding Author

Name: Balakrishnan M
Phone: +91 9490846668
Email: mbalakrishnan66@yahoo.com

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INTRODUCTION

Oral drug delivery is the broadly employed route of administration in comparison to all the routes that have been analyzed for the systemic release of drugs through the pharmaceutical products of various dosage forms [1]. The oral route is scrutinized as the most natural, appropriate, comfortable, and safe because of its ease of administration, patient acceptability, and budget friendly manufacturing procedure. Pharmaceutical products developed for the oral delivery are majorly immediate release or conventional type of drug delivery systems, which are outlined for the immediate release of drug for fast absorption [2]. Dosage forms that can lessen at the minimum of a twofold decrease in dosing regularity as in respective to the drug presented in a conventional form, like as solution or a elicit releasing conventional solid dosage form are coined as extended-release dosage forms. These products are prepared to make the contained medicament accessible over a long term after administration within its therapeutic index and therefore reduction in the dosing frequency in comparison to the conventional dosage forms [3].

MATERIALS AND METHODS

Vildagliptin became purchased free of charge sample from B.M.R Chemicals, Hyderabad; Tamarind gum, Xanthum gum & Guar gum was once purchased from Hi-media laboratory. Mumbai. PVP K 30, Mag-

nesium stearate and microcrystalline cellulose used to be a present sample of Lobachemiepvt.ltd, Mumbai, and other ingredients victimized in with Analytical grade.

Methodology

Compatibility Studies

Compatibility study along with excipients was executed by FTIR. The unalloyed drug and its preparations accompanying with the excipients were exposed to FTIR studies [Figures 1 and 2]. In the current study, the potassium bromide disc (pellet) method was applied [4].

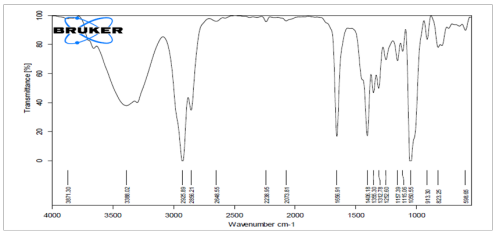

Figure 1: FTIR spectrum of pure Vildagliptin

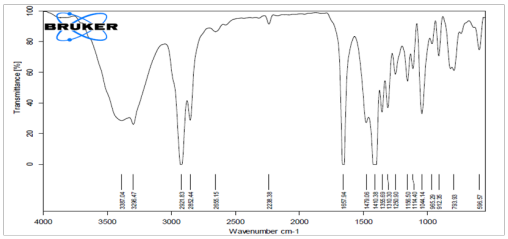

Figure 2: FTIR spectrum of Vildagliptin and Excipients

Preparation of Vildagliptin Controlled Release Matrix Tablets

Controlled release tablets of Vildagliptin were prepared by direct compression method using variable concentrations of different polymers Tamarind gum, Guar gum, and Xanthan gum. The direct compression method is a widely employed method for the production of compressed tablets. All the products were weighed individually [5]. The drug and the other excipients were allowed to pass through 40# sieve simultaneously and stirred for 10 minutes. The magnesium stearate was allowed to pass through 60# sieve and added to the mixture and then blended again for 5 minutes. The blended mixture of step 3 was compressed into the tablets by using 8.5mm, round punches, finally obtained controlled release matrix tablets [Table 1].

Evaluation Parameters

Pre Compression Parameters

The blended mixture was evaluated for the flow properties as follows.

Angle of repose: $\theta = \tan^{-1}$ (h/r)

Bulk density = Weight of powder/ Bulk volume

Tapped density = Weight of powder/ Tapped volume

Carr's Index (I) = (Tapped Density - Bulk Density)/ (Tapped Density) x100

Hausner's ratio = Tapped density/ Bulk density [Table 2] [6].

Post Compression Parameters

Thickness and Diameter

The physical parameters of the tablets including compactness and diameter are vital for consumer acceptability and tablet size uniformity [7]. The thickness and diameter of the tablets were studied by using Vernier calipers. It is measured in millimeters (mm).

Hardness

The tablet hardness was calculated with the help of using Monsanto hardness tester. The tablet was placed in between the affixed and moving jaw. The scale was regulated to zero; the load was gently raised until the tablet was break down [8]. The value of the load at that point results the estimation of the hardness of the tablets. Hardness was measured in Kg/cm^2.

Friability

In Roche Friabilator tablet strength was measured. Previously weighed tablets were allowed for100 revolutions (4min), taken out, and were deducted. The percentage of weight reduction was calculated by rewriting the tablet weights [9].

Weight Variation Test

The weight of the tablets is being made to measure generally to confirm that a tablet possess the proper quantity of a drug. The USP weight variation test was carried out by measuring the weight of 20 tablets separately. Then calculate the average weight, and then compare the independent weights to the average weight [10].

The tablets meets the USP test if not more than 2 tablets are beyond the percentage limits and if no tablets differ by greater than 2times the percentage limit.

Drug Content

10 tablets were picked up randomly. Each tablet was shifted into a 50mL volumetric flask, dissolved and then diluted to 50 mL with phosphate buffer pH 6.8. 1 ml of this solution was diluted to 100 ml with phosphate buffer of pH 6.8 [11]. The quantity of the drug present in each tablet was evaluated by UV spectroscopy at 266 nm.

Table 1: Composition of different formulations of Vildagliptin controlled release tablets

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Vildagliptin	50	50	50	50	50	50	50	50	50
Tamarind gum	25	50	75	-	-	-	-	-	-
Xanthan gum	-	-	-	25	50	75	-	-	-
Guar gum	-	-	-	-	-	-	25	50	75
PVP K30	15	15	15	15	15	15	15	15	15
Micro. Cellulose	154	129	104	154	129	104	154	129	104
Mg stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total weight.(mg)	250	250	250	250	250	250	250	250	250

Table 2: Pre-Compression Parameters of Vildagliptin controlled release matrix Tablets

Formulation Code	Angle of Repose (θ)	Bulk density (g.mL)	Tapped density (g.mL)	Hausner's ratio (HR)	Carrs index (%)
F1	27.52±0.26	0.312±0.33	0.366±0.30	1.17±0.59	14.75±0.23
F2	28.63±0.56	0.284±0.26	0.325±0.23	1.14±0.35	12.62±0.21
F3	27.85±0.48	0.286±0.32	0.334±0.26	1.17±0.26	14.37±0.15
F4	27.59±0.75	0.298±0.21	0.342±0.21	1.15±0.15	12.87±0.63
F5	29.26±0.85	0.293±0.25	0.338±0.17	1.15±0.48	13.31±0.24
F6	27.63±0.52	0.321±0.36	0.369±0.58	1.15±0.57	13.01±0.26
F7	26.18±0.12	0.312±0.32	0.352±0.25	1.13±0.59	11.36±0.59
F8	26.25±0.56	0.289±0.45	0.332±0.21	1.15±0.26	12.95±0.51
F9	25.15±0.03	0.266±0.52	0.301±0.50	1.13±0.26	11.63±0.28

Table 3: Post-Compression Parameters of Vildagliptin controlled release matrix Tablets

Formulation Code	Avg.Wt (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	248.74±1.54	3.37±1.26	8.54±0.04	0.22±0.48	91.14±0.98
F2	249.85±0.26	3.22±0.58	8.92±0.12	0.16±0.02	92.54±0.46
F3	248.53±0.54	3.75±0.68	9.12±0.25	0.54±0.16	91.26±0.84
F4	247.52±0.11	3.65±0.84	8.26±0.36	0.28±0.48	94.64±0.38
F5	248.41±0.28	3.73±0.12	8.54±0.98	0.10±0.25	91.41±0.78
F6	249.52±0.36	3.63±0.69	9.20±0.54	0.46±0.66	95.26±0.54
F7	247.41±0.28	3.29±0.22	8.86±0.87	0.29±0.22	93.14±0.69
F8	248.81±0.54	3.83±0.36	8.24±0.22	0.84±0.48	94.12±0.89
F9	249.42±0.05	3.85±0.14	8.26±0.16	0.12±0.25	97.64±0.94

Table 4: *In-vitro* dissolution studies of Vildagliptin controlled release matrix Tablets F1-F5

Time (Hrs)	F1	F2	F3	F4	F5
0	0	0	0	0	00
1	31.70±0.89	26.48±0.36	20.62±0.24	25.56±0.26	18.48±0.56
2	43.84±0.21	35.81±0.25	28.98±0.20	37.92±0.23	27.40±0.22
3	55.98±0.56	45.15±0.21	37.34±0.36	45.28±0.14	36.32±0.55
4	68.12±0.54	54.48±0.29	45.70±0.22	57.64±0.25	45.24±0.64
6	80.26±0.59	63.82±0.67	54.06±0.19	68.50±0.63	54.16±0.69
8	92.40±0.25	73.16±0.95	62.42±0.18	79.36±0.6	63.08±0.3
10	98.23±0.36	82.49±0.14	70.78±0.25	90.22±0.95	72.00±0.25
12	-	91.83±0.56	79.14±0.36	98.08±0.45	80.92±0.26
14	-	98.56±0.62	87.50±0.25	-	89.84±0.02
16	-	-	97.86±0.36	-	98.76±0.01

Table 5: *In vitro* dissolution studies of Vildagliptin controlled release matrix Tablets F6 – F9

Time (Hrs)	F6	F7	F8	F9
0	0	0	0	0
1	8.45±0.98	6.26±0.23	5.60±0.68	3.24±0.32
2	16.56±0.06	17.52±0.24	14.64±0.33	10.56±0.12
3	24.67±0.01	28.78±0.01	23.68±0.36	17.88±0.01
4	32.78±0.23	40.04±0.26	32.72±0.35	25.20±0.15
6	40.89±0.01	51.30±0.24	41.76±0.26	32.52±0.26
8	49.00±0.23	62.56±0.18	50.80±0.24	39.84±0.35
10	57.11±0.51	73.82±0.59	59.84±0.25	47.16±0.66
12	65.22±0.86	85.08±0.54	68.88±0.59	54.48±0.59
14	73.33±0.48	92.34±0.47	77.92±0.61	61.80±0.47
16	81.44±0.52	97.60±0.69	86.96±0.56	69.12±0.55
18	89.55±0.36	-	96.00±0.25	76.44±0.41
20	97.66±0.32	-	99.04±0.36	83.76±0.14
24	-	-	-	98.12±0.52

Table 6: Release order kinetics of Vildagliptin controlled release matrix Tablets

	R^2 values				n values
Formulation	Zero order	First order	Higuchi	Korsmeyer-Peppas	Korsmeyer- Peppas (n)
F9	0.990	0.790	0.962	0.906	1.169

In-vitro dissolution studies

The dissolution test was executed in USP Apparatus Type II (paddle) with 900 ml of 0.1 N Hydrochloric acid as the dissolution medium which is maintained at temperature 37±2^{o}C. Paddle was allowed to rotate at 5 rpm [12].

Kinetic Treatment

The data acquired of the in vitro dissolution studies obtained the kinetic track record analysis [13].

Zero-order kinetics: $Q_t = Q_o + K_o t$

First-order kinetics: $Q_t = \log Q_o + K_1 t/2.303$

Higuchi model: $Q_t = K_H \cdot t^{1/2}$; Korsmeyer-Peppas release model: $Mt / Mo = Kt^{1/2}$

RESULTS AND DISCUSSION

Compatability Studies

Characterization of Drug

The average weight of the Vildagliptin tablet was

obtained to be in the range of 247.52 to 249.85 mg. The thickness of the Vildagliptin tablet was obtained to be in the range of 3.22 to 3.85mm. The hardness of the Vildagliptin tablet was obtained to be in the range of 8.24 to 9.20 kg/cm^2. Friability of the Vildagliptin tablet was obtained to be in the range of 0.10 to 0.84%. The drug content of the Vildagliptin tablet was obtained to be in the range of 91.14 to 97.64% [Table 3].

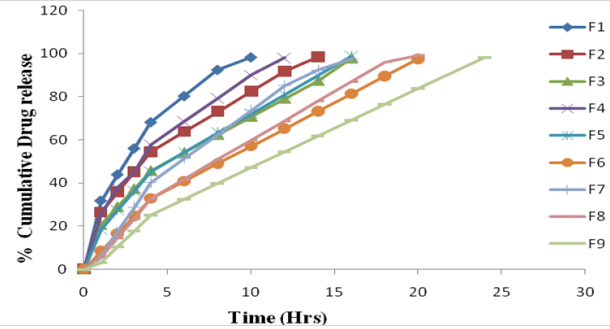

Figure 3: *In Vitro* Drug Release Studies of F1-F9 Formulations

In-vitro drug release studies

In-vitro drug release studies were executed by using USP XXII dissolution apparatus type II (Lab India DS 8000) at 50rpm. The dissolution medium containing of 900ml of phosphate buffer, maintained at 37±0.5^{o}C [Tables 4 and 5]. The drug release at various time intervals was determined at 266 nm using an ultraviolet-visible spectrophotometer. The study was performed in triplicate [Figure 3].

From the in vitro, drug release studies of Vildagliptin controlled-release tablets using Tamarind gum, Guar gum, and Xanthan gum in different polymer ratios using MCC as a filler and PVP K30 as a binder. Among all 9 trails F1-F3 trails were formulated using Tamarind gum with the ratio of 10, 20, and 30%, the drug release was reduced with an elevation in the polymer concentration. F1 formulation containing 10% of Tamarind gum shows 98.23% of drug release at the margin of 10hours, while F2 formulation containing 20% of Tamarind gum shows 98.56% of drug release at the margin of 14hours, whereas F3 formulation containing 30% of Tamarind gum shows 97.86% of drug release at the margin of 16hours. Among all the F1-F3 preparations, none of the formulations control the drug release for 24hours even at 30% concentration. So, further formulations were prepared using Xanthan gum. Then F4-F6 trails were formulated using Xanthan gum in three different ratios like 10, 20, and 30% the drug release was reduced with an elevation in the polymer concentration. F4 formulation containing 10% of Xanthan gum shows 98.08% of drug release at the margin of 12hours, while F5 formulation containing 20% of Xanthan gum shows 98.76% of drug release at the margin of 16hours, whereas F6 formulation containing 30% of Xanthan gum shows 97.66% of drug release at the margin of 20hours. Among all the three preparations of Xanthan gum, none of the formulations control the drug release for 24hours even at 30% concentration. So, further formulations were prepared using Guar gum. Then F7-F9 trails were formulated using Guar gum in two different ratios like 10, 20, and 30% the drug release was reduced with an elevation in the polymer concentration. F7 formulation containing 10% of Guar gum shows 97.60% of drug release at the margin of 16hours, while F8 formulation containing 20% of Guar gum shows 99.04% of drug release at the margin of 20hours, whereas F9 formulation containing 30% of Guar gum shows 98.12% of drug release at the margin of 24hours. Among all the 10 preparations F9 preparation containing 30% of Guar gum controls the drug release up to 24hours. So Guar gum was considered to be suitable for the formulation of Vildagliptin controlled-release tablets at 24% concentration. So the drug release kinetics was carried out for the F9 preparation [Table 6].

The in-vitro dissolution details for best preparation F10 were applicable in different kinetic models i.e., zero order, first order, Higuchi, and Korsmeyer-Peppas equation. Optimized preparation F9 reveals an r^2 value of 0.990. As its value closer to the '1', it is verified as it follows the Zero-order release. The process of drug release is further verified by the Korsmeyer and Peppas plot, if n = 0.45 it is known as Case 1 or Fickian diffusion, 0.45 to 0.89 is for atypical practice or non-Fickian transport, n = 0.89 for case II transport. The 'n' value is 1.168 for the optimized preparation (F9) i.e., the n value was 0.89 which suggests super case transport.

CONCLUSION

The pre and post-compression parameters show that the values were calculated to be allowable within the angle. Various specifications like hardness, friability, weight variation, drug content uniformity, in-vitro drug release were analyzed. Among all 10 formulations F9 preparation possess 30% of Guar gum controls the drug release up to 24 hours. So Guar gum was considered to be suitable for the formulation of Vildagliptin controlled-release tablets at 24% concentration. So the drug release kinetics was carried out for the F9 preparation. Based on these outcomes, preparation F9 was determined to be the most promising preparation. The In-vitro dissolution details for best prepa-

ration F9 were applicable in various kind of kinetic models i.e., zero order, first order, and Higuchi and Korsmeyer-Peppas equation. Optimized preparation F9 shows an r^2 value of 0.990.

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Conflict of Interest

The authors attest that they have no conflict of interest in this study.

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