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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF VILDAGLIPTIN

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ABSTRACT

The purpose of this research work was to establish Vildagliptin sustained release matrix tablets of 50mg. Vildagliptin is an anti diabetic drug of the new dipeptidylpeptidase-4 (DPP-4) inhibitor class of drug. The tablets were prepared by wet granulation technique using different grades of Hydroxy Propyl Methyl cellulose (HPMC K 100 LV, HPMC K15M and HPMC K4M) as extended release polymer. Tablets were evaluated for different parameters such as thickness, hardness, friability, weight variation, *in vitro* dissolution studies and FT-IR studies. The physico-chemical property of the finished product compiles with the internal specification limits. *In vitro* release from the formulation was studied as per the USP and IP dissolution procedure. The formulation gave a release of 98.5 % for 24 hr and the data best fitted into Higuchi model. From the present study it was concluded that the vildagliptin sustained release tablets can extend drug release and improve the bioavailability of vildagliptin.

Key words: Vildagliptin, HPMC (K 100 LV, K100M, K15M & K4M), sustain release matrix tablets.

INTRODUCTION

Diabetes a global public health problem is a chronic disease and is now growing as an epidemic in both developed and developing countries. Around 150 million people suffer from diabetes in the world out of which above 35 million are Indians. "Genetics loads the Gun, Life style pulls the trigger". There are many diseases that are caused due to genetic disorders, and are one of the causes for Diabetes Mellitus[1]. Diabetes Mellitus (DM) is a group of syndromes and chronic metabolic disorder characterized by hyperglycaemia, altered metabolism of lipids, carbohydrates and proteins because of a lack of, or ineffective use of the hormone insulin and associated with reduced life expectancy, significant morbidity due to specific diabetes related micro vascular complications and diminished quality of life[2]. A fasting blood glucose level of 126 mg /dl and 200mg/dl post prandial (oral Glucose load) is considered as indication of DM. Current drugs used for managing TYPE II Diabetes and its precursor syndromes, such as insulin resistance, fall into different classes of compound such as the biguanides, thiazolidinediones, the sulfonylureas peptide analogus and alpha glucosidase inhibitors[3]. Vildagliptin is an oral anti diabetic drug from the peptide analogues (DPP-4 inhibitor class) class[4]. The aim of any drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration. In the recent years sustained release[5] (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reactions. In general the goal of sustained release dosage form is to maintain therapeutic blood or tissue level of the drug for extended period of time[6]. This is generally accomplished by attempting to obtain "zero order" release from the dosage form. Zero order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system. Sustained release system generally do not

attain this type of release and usually try to mimic zero order release by providing drug in slow "first order" fashion (i.e. concentration dependent)[7]. Vildaglliptin, chemically is (*S*)-1-[*N*-(3-hydroxy-1-(S)-adamantyl)glycyl]pyrrolidine-2 carbonitrile is a potent new oral antihyperglicemic agent that reduces insulin resistance in patients with type 2 diabetics by inhibits the inactivation of GLP-1 by DPP-4, allowing GLP-1 to potentiate the secretion of insulin in the beta cells.

MATERIALS AND METHODS

Vildagliptin was purchased from affine chemicals Ltd., Hydroxy Propyl Methyl Cellulose diff grades like K100 LV, K 4M, K15M and K100M were gifted from Dow chemical's Ltd., All other ingredients used were of analytical grades.

Preparation of Matrix Tablets: Matrix tablets were prepared by aqueous wet granulation method. The composition of various formulations was given in table1. The API, different grades of HPMC polymers like K100 LV, K 4M, K15M and K100M and microcrystalline cellulose was mixed in a polythene bag and the mixture was passed through mesh (No .40). Granulation fluid was prepared using a PVP K-30 in sufficient water. This granulating fluid was added to the above mixture. Thereafter, the wet mass was passed through mesh (No. 16). Dry the wet granules at 60^0 C until LOD is 1-3 % w/w. pass the dried granules through multimill fitted with 1mm screen. Add microcrystalline cellulose pH 102 to the dried granules. Finally dried granules were mixed with magnesium stearate and talc (passed through sieve No.60) for 5 min. Tablets were compressed at 50mg weight on a on the 16 station rotary tablet compression machine using 8.0 mm round standard convex punches[8,9,10].

Drug – Excipients compatibility studies: Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minima (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards. The polymer and the drug compatibility were evaluated by spectral as show in fig 1.

Physicochemical properties of tablets:

Thickness: The thickness of the tablets was determined using vernier calipers. Tablet thickness should be controlled within ±5 % variation of standard value. Five tablets from each batch were used, and average values were calculated.

Weight Variation Test: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Sartorius), and the test was performed according to the official method.

Hardness and Friability: For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cad-mach, Ahmedabad, India) and the Roche friabilator (Camp-bell Electronics,Mumbai, India), respectively.

Drug content: To determine tablet assay (drugs content) twenty tablets were powdered and accurately weighed quantity of powder containing drug equivalent to 50 mg was transferred to 100 ml volumetric flask and dissolved with appropriate amount of solvent with the aid of sonicator. After which the solution was filtered through whattman filter paper (90 mm diameter). The total amount of the drugs within the tablets was analyzed after appropriate dilution of test solution by using UV spectrophotometer (labindia UV-3200 double beam Spectrophotometer) against the reference solution with suitable dilution at 245 nm.

***In vitro* drug release:** *In vitro* drug release study from 6 tablets of each formulation, in triplicate, was determined using the USP II (paddle) apparatus(labindia DS-8000) where 900 ml of pH 6.8phosphate buffer were used as dissolution media maintained at 37^0 C (±0.5) 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at times 1, 4, 8, 12, 16, 20 & 24 hours and the samples were replaced with the fresh dissolution medium. The samples were passed through Whattmann filter paper and estimation was carried out by UV-Visible double beam spectrophotometer, while keeping the dissolution media as a blank at 245 nm.

RESULTS AND DISCUSSION

FT-IR study was carried to study the incompatibility between the formulation ingredients. The typical FTIR peaks data obtained from FTIR scans. Examination of all FTIR peaks reveals that there is no interaction between drug and polymers used for the drug formulation.

The flow properties of granules were done and results was placed in **table 2**. Bulk density and tapped density for Vildgliptin sustained release granules were found to be between 0.480±0.02 to 0.694± 0.09

and 0.625±0.1 to 0.834±0.09 respectively. Carr's index and Hausner's ratio were obtained in the range of 12.45±0.13 to 23.6±0.16 and 1.15±0.21 to 1.33±0.14 respectively. Angle of repose was observed in the range of 32^0 5 ±0.14to 38^0 5±0.23. Moisture content was found to be between 6.1± 0.16 to 6.5±0.15.

The tablets of different formulations were subjected to various evaluation tests, such as thickness, diameter, weight variation, drug content, hardness, friability, and *in vitro* dissolution. The thickness of the tablets ranged from 5.48 ± 0.2 to 5.52± 0.2 mm. Drug content was found to be uniform among different batches of the tablets and ranged from 95.5 ± 1.5 to 105 ± 2.1. The hardness and percentage friability of the tablets of all batches ranged from 6.50 ± 0.2 to 7.01 ± 0.2 kg/cm ^{2} and 0.15 to 0.34%, respectively (Table **3**). All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 250 mg is ± 5 %. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 95%. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

The results of dissolution studies of formulations F1-F8 composed of varying concentration of different HPMC polymers like K100 LV, K100M, K15M, and K4M, and prepared using PVPK30 as granulating agent, are shown in Table 5 and fig 2.

In vitro dissolution study of the formulations containing polymer in different concentrations were compared. In formulation F-1 to F-4 formulations consists of HPMC K100M, HPMC K4M, HPMC K15M and HPMC K 100 LV in the constant concentration of 35% with respect to the average weight and weight of the tablet was balanced with microcrystalline cellulose PH 101.The release of the drug in the F-1 to F-4 was not found to be within the specification limits. The release of the drug was found to be below than the specification limits as shown in Table 5.

In order to retard the release of the drug, the combination of polymers were used .The polymer HPMC K4M concentration was kept constant for formulations F-5 to F-8.The HPMC K4M polymer was 14% constantly used for F-5 to F-7 formulations. The polymer of HPMC K 15M in the concentration of 25% in formulation F-5.But the release of the drug at 8 hr and 20 hr was 38.5 and 66.7 below to the desired release pattern. To meet the required release profile of the drug, HPMC K 100M concentration of 25% in formulation F-6. But the release of the drug at 8 and 20 hr was 31.8 % and 55%, below the desired release pattern. To meet the required release profile of the drug, HPMC K 100LV concentration of 25% in formulation F-7.But the release of the drug at 24 hr was 91.4%. To meet the required release profile of the drug, HPMC K 100LV,HPMC K15M and HPMC K4M concentration of 40%,27% and 8.6%in formulation F8 and was found to be satisfactory where the release of the drug 24 hr was found to be 98.6%. The F8 formulation was found to be zero order[11] (r^2=0. 985) as show in fig 3 and first order[12] (r^2=0.815) as show in fig 4, mechanism of drug release Higuchi[13] (r^2=0.994) as show in fig 5, Korsmeyer-peppas(r^2=0. 990) as show in fig 6 and Hixon-Crowell cube root plot [14](r^2=0. 873) as show in fig 7.

CONCLUSION

Vildagliptin is used for the treatment and relief of diabetes mellitus-type II. Drug release from the matrix was found to depend on the combination of polymer concentration, where as the polymer concentration was employed from 20-50%w/w of the average tablet weight. HPMC K100LV, HPMC K15M, HPMC K4M required to channelize the drug release was optimized to 95 to 99%. In conclusion, a stable sustained release matrix tablet formulation of vildagliptin was successfully developed and in vitro drug release pattern up to 24 hours. Among all formulations, F8 was found to be the most suitable sustained release formulation. The best linearity was found in zero order release and mechanism of release was fitted to Higuchi diffusion.

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Table 1: Formulation summary of Vildagliptin matrix tablets (50mg tablet)

INGREDIENTS (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8
VILDAGLIPTIN	50	50	50	50	50	50	50	50
MCC Ph101	130	130	130	130	130	130	130	—
HPMC K 100LV	—	—	—	120	—	—	50	148
HPMC K 15M	—	120	—	—	50	—	—	100
HPMC K 100 M	—	—	120	—	—	50	—	—
HPMC K4M	120	—	—	—	90	90	90	32
Povidone K 30	12	12	12	12	12	12	12	12
MCC Ph 102	20	20	20	20	20	20	20	20
TALC	4	4	4	4	4	4	4	4
Magnesium	4	4	4	4	4	4	4	4
WATER	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	**340**	**340**	**340**	**340**	**360**	**360**	**360**	**370**

Table 2: The evaluation results of flow properties of granules

Formulation code	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	Angle of repose
F-1	0.48±0.02	0.625±0.1	21.23±0.21	1.32±0.14	38.5±0.23
F-2	0.583±0.15	0.745±0.21	23.60±0.16	1.27±0.05	38.5±0.15
F-3	0.490±0.12	0.635±0.31	22.45±0.31	1.33±0.08	37.2±0.26
F-4	0.581±0.01	0.714±0.14	16.67±0.25	1.2±0.16	36.5±0.09
F-5	0.654±0.21	0.802±0.26	15.07±0.31	1.19±0.21	35.4 ±0.21
F-6	0.694±0.09	0.834±0.09	16.09±0.16	1.21±0.18	34.5±0.19
F-7	0.510±0.06	0.641±0.28	17.74±0.17	1.22±0.22	35±0.17
F-8	0.582±0.01	0.714±0.13	12.45±0.13	1.15±0.24	32.5±0.14

Table 3: Physical properties of sustained release matrix tablets of vildagliptin

Batch code	Weight variation(mg) n=20	Thickness (mm) n=10	Hardness (Kg/cm²) n=5	Friability (%w/w) n=10	Assay (%) n=5	Water Content (%)
F1	340±3.01	5.52±0.2	6.5±0.02	0.15±0.01	96.5±0.9	6.39±0.01
F2	340±2.89	5.48±0.2	7.0±0.2	0.18±0.01	96.0±1.8	6.35±0.21
F3	340±3.05	5.5±0.2	6.5±0.2	0.21±0.01	95.5±1.5	6.45±0.15
F4	340±2.98	5.52±0.2	6.8±0.2	0.19±0.01	105±2.1	6.58±0.21
F5	360±3.00	5.48±0.2	6.9±0.02	0.34±0.01	97.5±1.4	6.15±0.18
F6	360±2.95	5.52±0.2	6.9±0.2	0.19±0.02	96±0.9	6.38±0.24
F7	360±2.99	5.48±0.2	7.0±0.01	0.22±0.01	98±0.51	6.55±0.09
F8	370±2.97	5.52±0.2	7.1±0.2	0.21±0.01	99.8±0.84	6.13±0.16

Table 4: Dissolution profile of all formulations

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
1	5.6±0.5	6.7±0.4	3.5±0.3	30.5±1	5.8±0.4	4.9±0.4	5.5±0.5	6.9±0.5
4	32.2±1.3	28±1.1	19.9±0.8	65.1±1.2	30.1±1.4	23.9±1.1	30.7±1.4	28.4±1.1
8	46.3±1.6	36.6±1.5	35.2±1.8	86.9±1.9	38.4±1.1	31.5±0.7	52.5±1.2	44.6±1.5
12	55.2±0.8	49.6±1.9	42.4±1.3	95.4±0.6	49.3±1.1	38.9±1.2	69.1±1.8	58.9±1.1
16	72.4±0.5	58±0.7	46.7±1.5	99±1.1	57±1	43.6±1.5	81.5±0.8	72.9±0.9
20	80.8±2	67.2±0.8	50.1±1	-	66.7±1.9	57.5±0.8	99.4±0.8	87.5±0.6
24	85.3±1.3	73.2±2.3	55.6±1.3	-	71.1±0.4	62.2±1.3	-	98.6±1

* S.D= ± n=3,

Table: 5 Kinetics studies of optimized formulation (F-8):

Release kinetics	**R^2**
Zero order	0.985
First order	0.815
Higuchi	0.994
Korsmeyer-peppas	0.990
Hixon-Crowell cube root plot	0.873

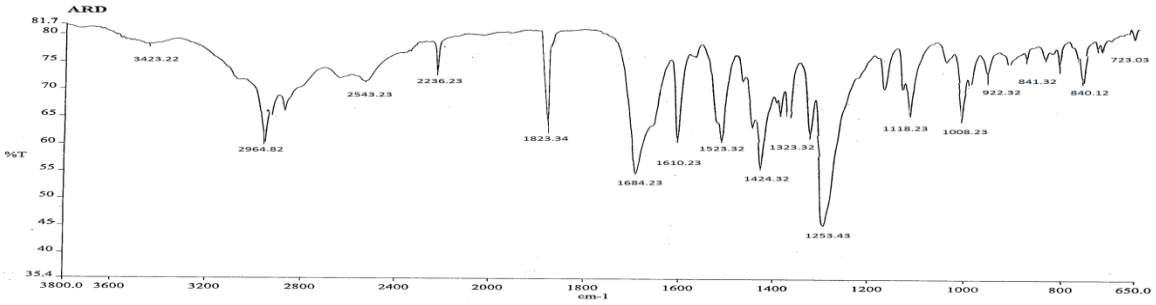

Fig.1. FT-IR SPECTRUM OF VILDAGLIPTIN-STD

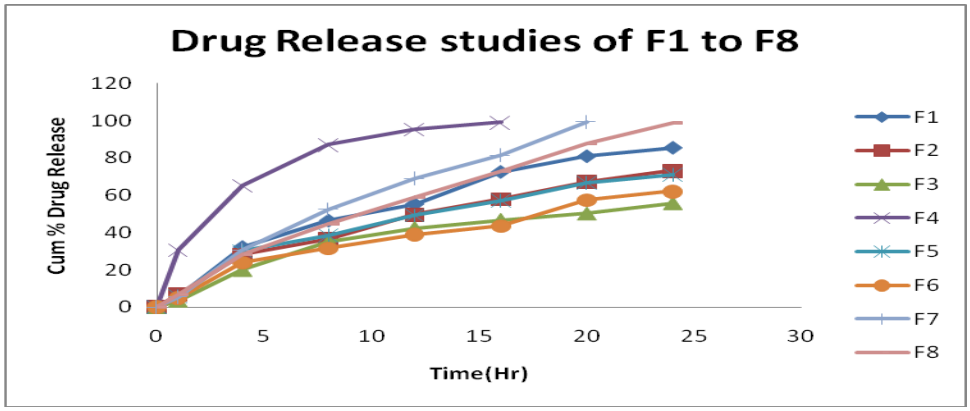

Fig2. CDR Profile of all formulations

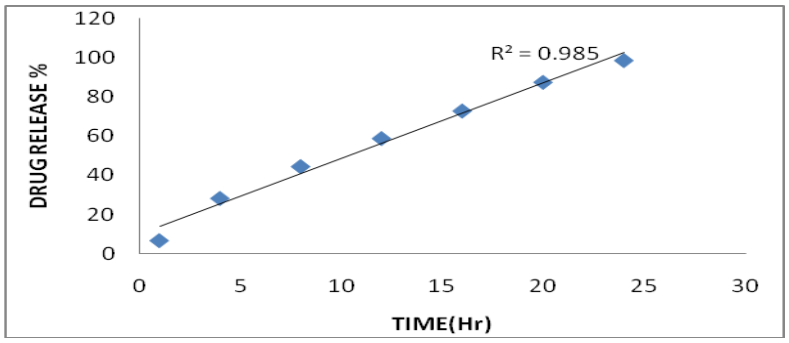

Fig3. Zero Order Release Kinetics of F8

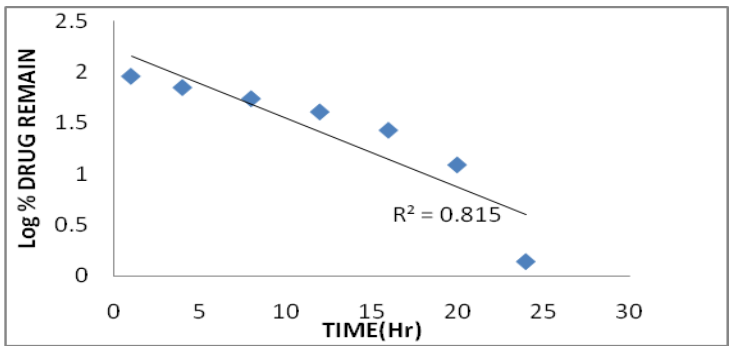

Fig.4. First Order Release Kinetics

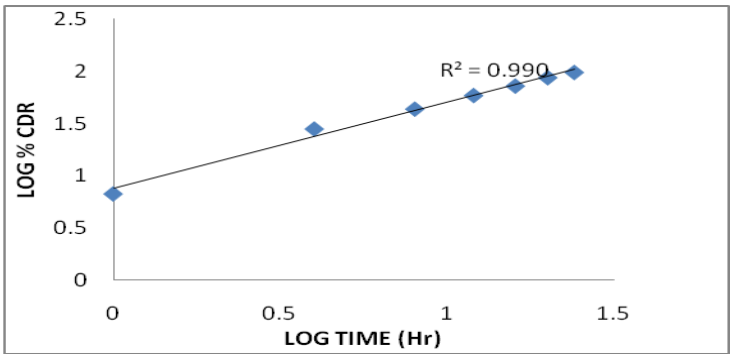

Fig.5. Korsmeyer –Peppas Diffusion Kinetics

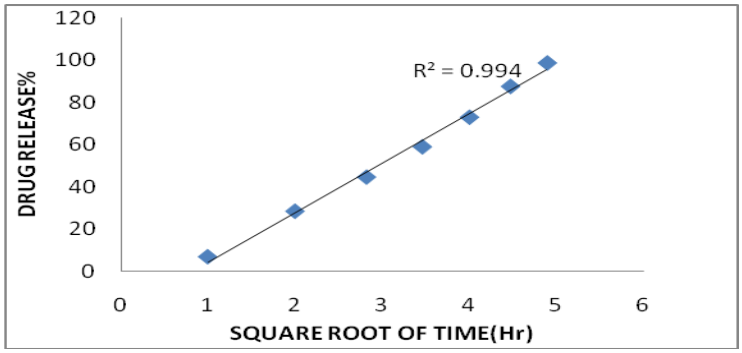

Fig.6. Higuchi Plot of Release

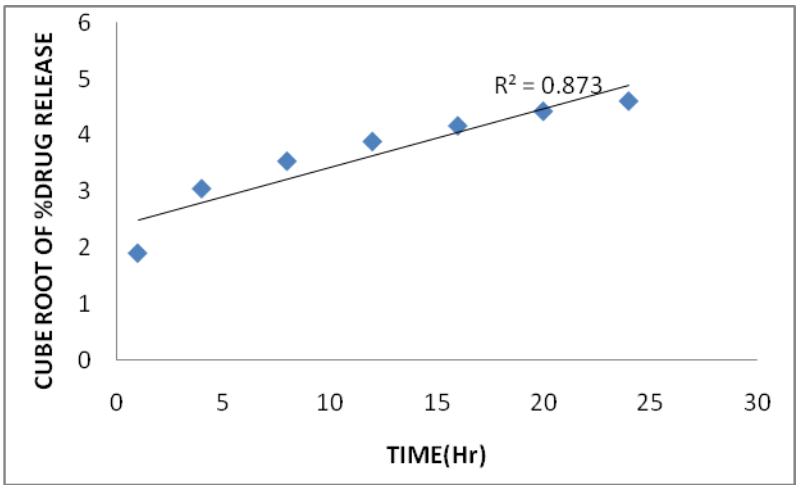

Fig.7. Hixon-Crowell Drug Release

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