

**FORMULATION AND EVALUATION OF VILDAGLIPTIN
IMMEDIATE RELEASE TABLET****Kausar Fatema*¹, Dr. S.R. Shahi¹, Dr. Zahid Zaheer² and Shaikh Tauqeer²**^{*1}Y.B. Chavan College of Pharmacy, Aurangabad.¹Government College of Pharmacy, Aurangabad.²Y.B. Chavan College of Pharmacy, Aurangabad.Article Received on
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Corresponding Author*Kausar Fatema**Y.B. Chavan College of
Pharmacy, Aurangabad.**ABSTRACT**

Vildagliptin is an oral anti-hyperglycemic agent (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Vildagliptin inhibits the inactivation 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. Vildagliptin has been shown to reduce hyperglycemia in type 2 diabetes mellitus. The immediate release tablet of vildagliptin were prepared and evaluated to increase bioavailability. The tablets were prepared by direct compression

method using simple excipients like microcrystalline cellulose, lactose anhydrous, disintegrant such as sodium starch glycolate and magnesium stearate were used in tablet formulation. The formulation were evaluated for various physical parameters, dissolution study and drug release profile. From all formulations the formulation F08 showed 102 % drug release within 45 minutes, which was highest drug release than other batches. The optimized immediate release tablet of formulation F08 showed no change in physical appearance, drug content or in dissolution pattern storage at 40 ± 20 C / 75 ± 5 % for 90 days. Finally it was concluded that F08 shows highest drug release, which was close similar to marketed product.

KEYWORDS: Immediate release tablet, Vildagliptin, Dissolution, Direct Compression.

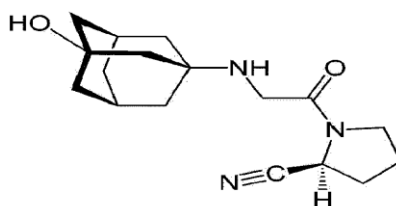
INTRODUCTION

Oral route is most common route of administration of drug because of its systemic effect, patient compliance, ease of manufacturing in production. Tablet provides accurate dosing of the drug in patient. Now a day's oral dosage form is popular compare to other dosage form for achieving its quick onset of action and it removes the drawbacks of conventional therapy. Above all it is easy to maintain its stability parameters throughout the shelf life.^[1-5]

The research work is concerned with the formulation and evaluation of immediate release tablet of Vildagliptin close similar to the reference product Galvus.

Vildagliptin is used for type 2 or non-insulin dependent diabetes. It increases the amount of insulin produced by the body. It also decreases the amount of glucagon which is produced by the body. Because of these effects, Vildagliptin can help to control blood sugar levels in people with diabetes. Vildagliptin is used in combination with other medicines which help to control blood sugar levels. DPP-IV inhibitors work by blocking the action of DPP-IV, an enzyme which destroys the hormone incretin.

There are two types of incretin hormones found in the body, called glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones are naturally produced by the body in response to food intake. Their function is to help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed. Vildagliptin works by binding to DPP-IV and preventing it from breakingdown the GLP-1 and GIP. This increases the levels of these hormones in the body and so increases their effect on controlling blood sugar.



Formula I

Its chemical name is (S)-{[(3-hydroxyadamantan-1-yl) amino] acetyl} pyrrolidine-2-carbonitril and its chemical structure is shown in the Formula I.^[6, 7]

Vildagliptin, previously identified as LAF237, is a new oral anti-hyperglycemic agent (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Vildagliptin inhibits the inactivation 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. It is currently in clinical trials in the U.S. and has been shown to reduce hyperglycemia in type 2 diabetes mellitus. While the drug is still not approved for use in the US, it was approved in Feb 2008 by European Medicines Agency for use within the EU and is listed on the Australian PBS with certain restrictions.^[8]

Vildagliptin chemistry information

Parameter	Property
Inn Name	Vildagliptin
Chemical Name	(2S)-1-{2-[(3-hydroxyadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile
Molecular Formula	C ₁₇ H ₂₅ N ₃ O ₂
Molecular Weight	303.4
CAS No	274901-16-5
Appearance	White to off-white powder.
Solubility	Soluble in DMSO ₄ & slightly soluble in water.

MATERIALS AND METHOD

MATERIALS

Vildagliptin was received as a gift sample from Megafine Pharma Ltd, Nasik India. Lactose Fast Flow, Sodium starch Glycolate, Microcrystalline cellulose Avicel PH112 /PH102, and magnesium stearate were received as a gift sample from Chempure Lab, Mumbai, India. All of them were of analytical grade.

METHOD

Formulation of vildagliptin tablet

The simple manufacturing process for the Vildagliptin tablet manufacturing was selected. The Vildagliptin is mixed with excipients using direct compression technique, lactose fast flow was sifted with Vildagliptin using sieve of 595 um i.e. # 30 mesh, This blend is "active mix" then the microcrystalline cellulose and sodium starch glycolate was sifted through 400 um sieve i.e. # 40 mesh and mixed well with the above active premix.

After manual mixing magnesium stearate was sifted through 400 um sieve i.e. # 40 mesh and was mixed manually for homogenous blend formation.^[9,10]

The Powder blend is tested for the physical parameters like Bulk density, Tapped density, Carr's Index, Hausner's ratio. Finally the blends from each formulation were compressed by using 8 mm punch in single rotary compression machine and tablets were prepared.

The composition of various formulations of Vildagliptin immediate release tablet is shown in below Table 1.

Table 1: Unit composition of Vildagliptin.

VILDAGLIPTIN 50 MG TABLETS:		F01	F02	F03	F04	F07	F08
SN	Material	Qty/tab (mg)	Qty/tab (mg)	Qty/tab (mg)	Qty/tab (mg)	Qty/tab (mg)	Qty/tab (mg)
1	Vildagliptin	50.000	50.000	50.000	50.000	50.000	50.000
2	Lactose Anhydrous NF DC	69.500	69.500	75.000	60.000	89.000	50.000
3	Microcrystalline Cellulose AVICEL PH 102	69.500					
4	Microcrystalline Cellulose AVICEL PH 112		69.500	64.000	89.000	50.000	89.000
5	Sodium Starch Glycolate	10.000	10.000	10.000		10.000	10.000
6	Magnesium Stearate	1.000	1.000	1.000	1.000	1.000	1.000
	TOTAL TABLET WEIGHT	200.0	200.0	200.0	200.0	200.0	200.0

Evaluation of Vildagliptin Immediate release tablets: The tablets were subjected to evaluation for the following parameters.^[11, 12]

a) Tablet hardness

Tablet hardness is also known as tablet crushing strength. Monsanto Hardness tester was used to measure the tablet hardness. The prepared tablets were subjected to hardness test. It was carried out by using hardness tester and expressed in Kg/cm².

b) Friability test

Friability test was performed by taking 20 tablets. Pre weight of the individual tablet was taken before subjecting to friability test. Weighed tablet samples are transformed into friabilator and subjected to combined effects of abrasion and shock by revolving at 25rpm for 4min for 100 revolutions. Samples are withdrawn after set time completions and loose dust powder was removed from the tablet and final weight is noted and substituted in the formula.

$$\% \text{ friability} = (\text{Initial weight} - \text{Final weight}) / \text{Initial weight} \times 100.$$

c) Thickness

The thickness of the tablet was measured with Digital Vernier Caliper and the unit of thickness of tablet is in mm.

d) *In - vitro* Disintegration time

The disintegration test was performed using Electrolab disintegrating apparatus. Placed one tablet in each of the six tubes of the basket and operated the apparatus using water maintained at $37 \pm 0.5^\circ\text{C}$ as the immersion fluid. Then noted down the time to complete disintegration of tablets.

e) Content Uniformity

Weighed and transferred 1 tablet into a 100-ml volumetric flask. To it added 70 ml of diluent (mixture of water and acetonitrile in 90:10 ratio) and sonicated for 10 minutes with intermittent shaking to dissolve the contents. Shaken mechanically for 30 minutes, then diluted to volume with diluent and mixed well. Centrifuged a portion of the prepared solution for 10 minutes at 3000 rpm. Pipetted 5 ml of the clear solution into a 25-ml volumetric flask and diluted to volume with diluent and mixed well then injected the clear solution. (0.1 mg/ml)

Calculation of Vildagliptin

$$\text{Content of (Vildagliptin, \%L.C.)} = \frac{\text{Aspl} \times \text{Stdwt} \times 100 \text{ ml} \times 25 \text{ ml} \times \text{P}}{\text{Astd} \times 200 \text{ ml} \times 1 \text{ Tablet} \times 5 \text{ ml} \times 50 \text{ mg (L.C.)}}$$

Aspl= Peak area of Vildagliptin in the sample solution.

Astd = Peak area of Vildagliptin in the standard solution.

Stdwt = Weight of working standard taken, (mg)

Splwt = Weight of sample taken, (mg)

P = Potency of the working standard used (%)

L.C. = Label Claim (50mg)

f) Weight variation test

20 tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of Tablet's weight against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10%.

g) *In - vitro* release profile of formulated Vildagliptin tablet

Drug release studies were done by using USP type II apparatus (paddle type). For that 900ml of dissolution medium (0.01N HCl) was transferred into round bottomed beaker and the

temperature was maintained at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and Speed of Paddle was 50rpm. At regular time interval (5min.) 5ml sample was withdrawn and replaced with fresh dissolution medium. Removed sample was diluted and injected in HPLC and run at 210 nm with flow rate 0.3 ml/min column temp 35°C .

Sample Preparation: 6 tablets were taken individually in each dissolution vessel containing 900 ml of 0.01N HCl ($37^{\circ}\text{C} \pm 0.5$) at 50 rpm. After 45 minutes, withdrawn 10 ml aliquot of the solution under test and filtered with 0.2 μm GHP Acrodisc syringe filter by discarding the first few ml and injected the clear solution. (0.056 mg/ml).

Mobile Phase preparation: Prepared a mixture of Buffer Solution and Acetonitrile (previously filtered through 0.2 μm Nylon membrane filter) in the ratio 85:15 and sonicated to degas.

Buffer Solution preparation: Dissolved 1.15 g of ammonium dihydrogen orthophosphate and 0.23 g of di-ammonium hydrogen phosphate into 1 liter of purified water. Filtered through 0.2 μm Nylon membrane filter.

Procedure: Equilibrated the column for about 30 minutes with the mobile phase. Separately injected equal volumes (5 μl) of the sample solution into the chromatograph, recorded the chromatograms and measured the response of the major peak.

RESULT AND DISCUSSION

Precompression parameters

The Precompression parameters were the primary requirements to determine whether the specific material was suitable for the targeted formulation or not. The aim was to formulate the tablet formulation with direct compression method, so it was mandatory to know the bulk density, tapped density, Carr's index, Hausner's ratio as those were the official requirement while choosing any material for its dosage form formulation. Table 1 shows the unit different formulation trails for Vildagliptin. Table 2 shows the results of Evaluated parameters like Bulk Density, Tapped Density, Carr's index, Hausner's ratio for various tablet formulation. The result of evaluated clearly indicates its suitability to be the material of choice for formulation.

Table 2: Physical Properties of the Vildagliptin Blend

VILDAGLIPTIN 50 MG TABLETS:	F01	F02	F03	F04	F07	F08
BULK DENSITY	0.5	0.44	0.45	0.43	0.45	0.48
TAPPED DENSITY	0.64	0.59	0.64	0.60	0.64	0.58
HAUSNER'S RATIO = TD/BD	1.29	1.32	1.42	1.39	1.42	1.2
COMPRESSIBILITY RATIO = (TD - BD) / TD *100 (Carr's Index)	22	25	29	28	29	17
	POOR	POOR	POOR	POOR	POOR	FAIR

Post compression parameter

All the batches were subjected to compression and compression parameters were evaluated systematically. The results of all the batches were tabulated in Table 3. The results of all the trial batches were compared and found satisfactory, as per the reported specification. Finally the comparison parameters were keenly observed to finalize for selection of the optimized batch and formula. Hardness of tablets was found to be in the range of 2 to 8 kg/cm² as per Table 3.

The friability of all tablets was found to be in the range of 0.0 to 0.12 which is less than 1% that showed good mechanical strength.

Thus finally formulation F08 i.e. shows disintegration time 210 seconds and drug release 102% which is higher than other tablet formulations.

Table 3: Compression parameters for Vildagliptin formulation.

VILDAGLIPTIN 50 MG TABLETS:	F01	F02	F03	F04	F07	F08
Tablet Weight Average (mg)	201	199	200	201	201	199
Tablet Thickness (mm)	3.12	3.09	3.21	3.22	3.25	3.25
Tablet Hardness (kg/cm ²)	4 to 5	5 to 7	4 to 6	3 to 5	6 to 8	2 to 4
Tablet Fraibility (%)	0.00%	0.00%	0.06	0.08	0.09	0.12
Tablet Disintegration Test (Time)	6 min 30 sec	8 min 40 sec	5 MIN 30 sec	10 MIN 46 sec	10 min 40 sec	3 min 30 sec
Drug Content (%)	98.5	97.6	97.8	99.4	99.3	98.8

Note: All the batches were compressed using 8 mm Flat face punches

Drug Excipient Compatibility Study

Drug excipients compatibility studies were performed. The Spectrum of pure Vildagliptin was compared with the spectrum of drug-polymer mixture such as Vildagliptin and Lactose Anhydrous NF DC, Vildagliptin and Avicel PH 112, Vildagliptin and Sodium Starch Glycolate and Vildagliptin and Magnesium Stearate.

Compatibility of Vildagliptin with excipients used in the formulation was investigated and studied by using Differential Scanning Calorimeter (DSC). The individual components i.e active substance, excipients and the mixture of the active Vildagliptin with each excipient were investigated by DSC with temperature range from 25°C to 300°C, by comparing the results “from each figure” for the individual components and the mixture, it can be seen that there is no thermal effect or changes on the Vildagliptin in the presence of any of the excipients.

All the excipients used in the formulation were found to be compatible with the active ingredient “Vildagliptin”.

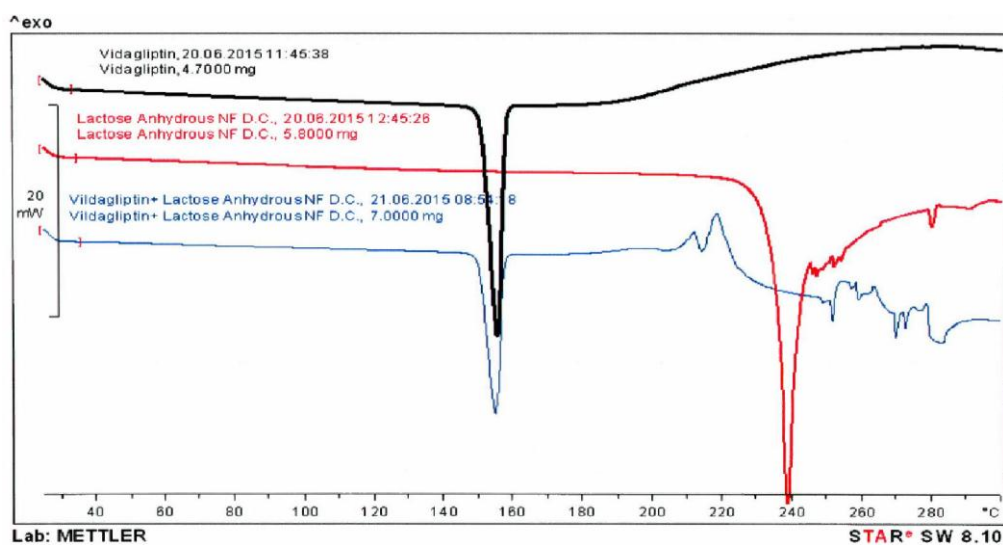


Figure 1: DSC Graph of Vildagliptin and Lactose Anhydrous NF DC.

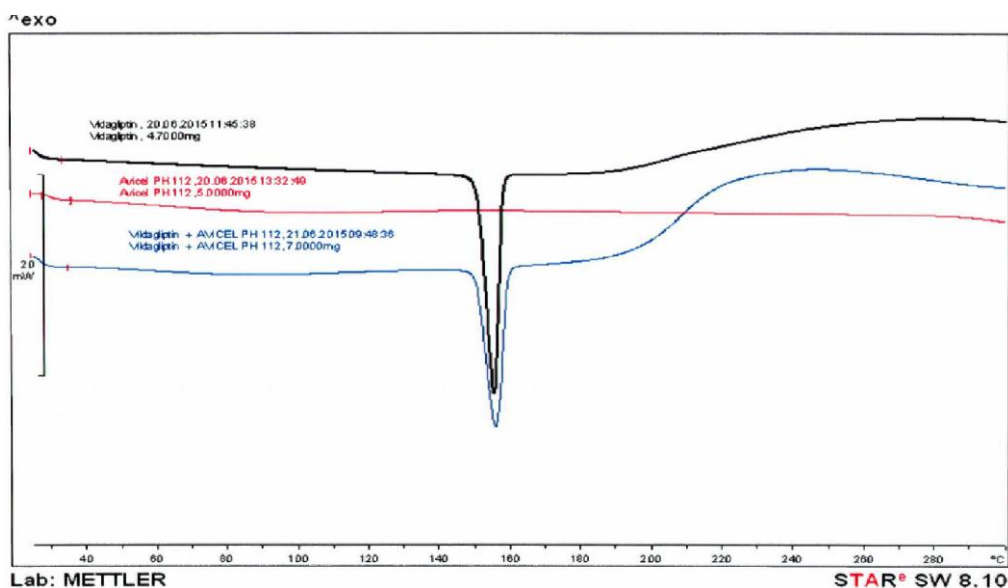


Figure 2: DSC Graph of Vildagliptin and Avicel PH 112.

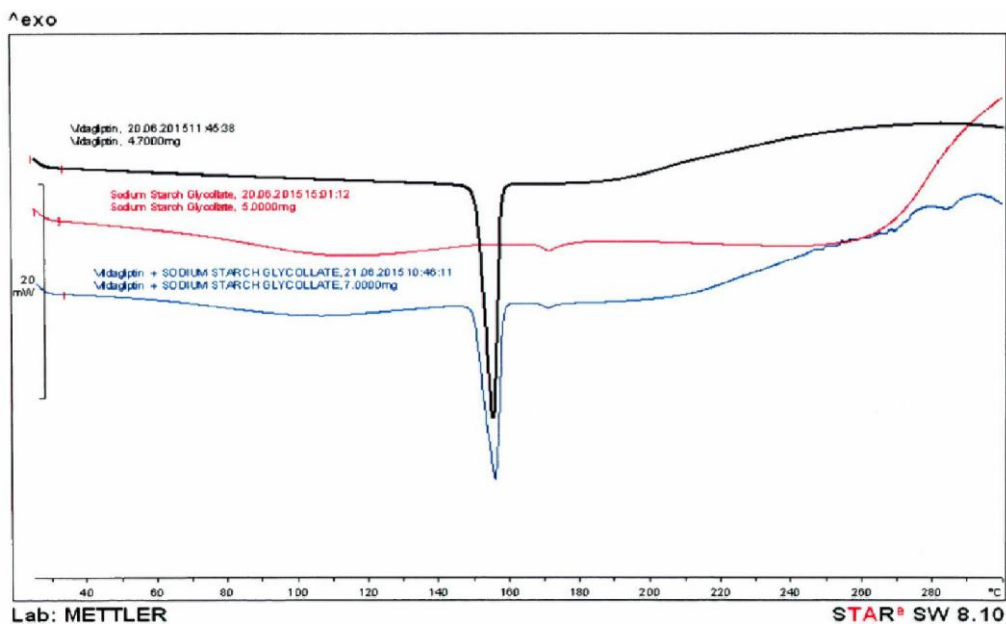


Figure 3: DSC Graph of Vildagliptin and Sodium Starch Glycolate.

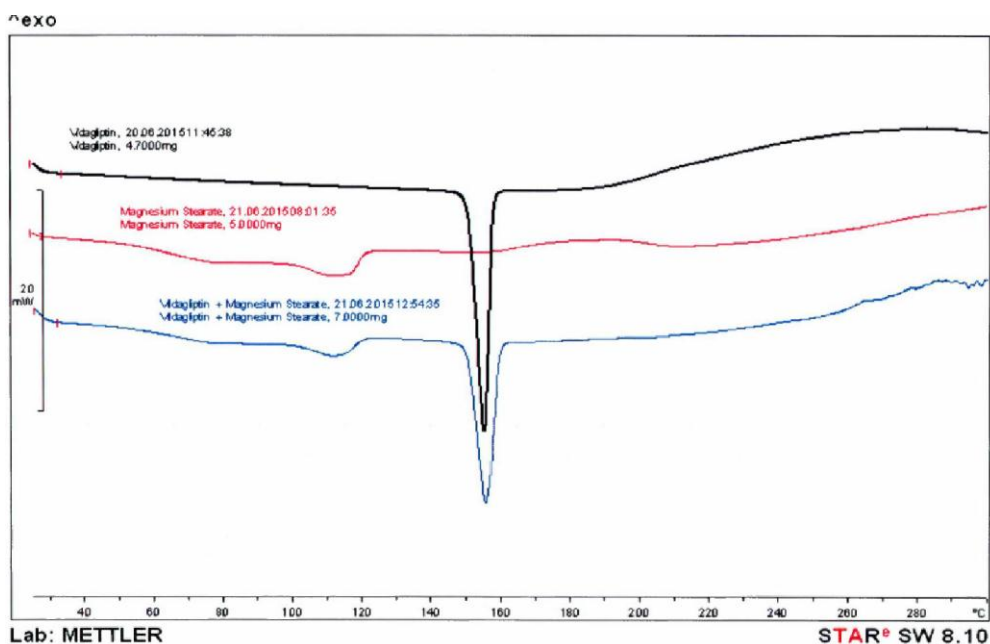


Figure 4: DSC Graph of Vildagliptin and Magnesium Stearate.

In-Vitro Drug Release Study^[18-20]

In-vitro drug dissolution studies of the prepared formulations were carried out by using 900 ml of 0.01N HCl standard dissolution medium maintained at temperature of 37°C ± 0.5 °C. The % drug release were calculated by with-drawing the samples from the experimental medium and running the sample on HPLC at definite time interval such as after 5, 10, 20, 30 and 45 minutes interval. The observed result were reported below in the Table 4.

Systematically for comparisons of % drug release and it was observed after 45 minutes that all the batches shows release profile as per the reported specification.

As formulation F08C shows consistent release of the drug after 45 minutes so it may be considered as an important criteria to be chosen it as optimized batch.

The dissolution pattern was compared with the marketed reference sample and the release pattern was similar to the reference sample from market.

Table 4: Results for *in-vitro* drug release of immediate release tablet of vildagliptin

Time(min)	REF	F01	F02	F03	F04	F07	F08
0	0	0	0	0	0	0	0
5	81	65	59	81	49	67	85
10	91	78	79	87	58	78	93
20	96	86	85	90	64	86	98
30	97	93	94	95	77	93	101
45	98	95	98	97	86	97	102

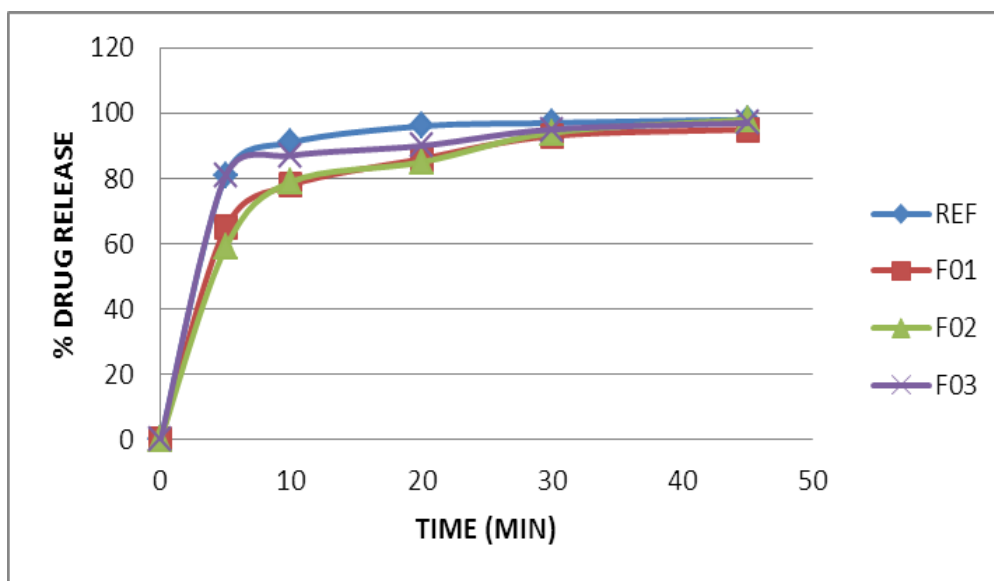


Figure 5: comparison of % drug release of various formulations with the marketed preparation.

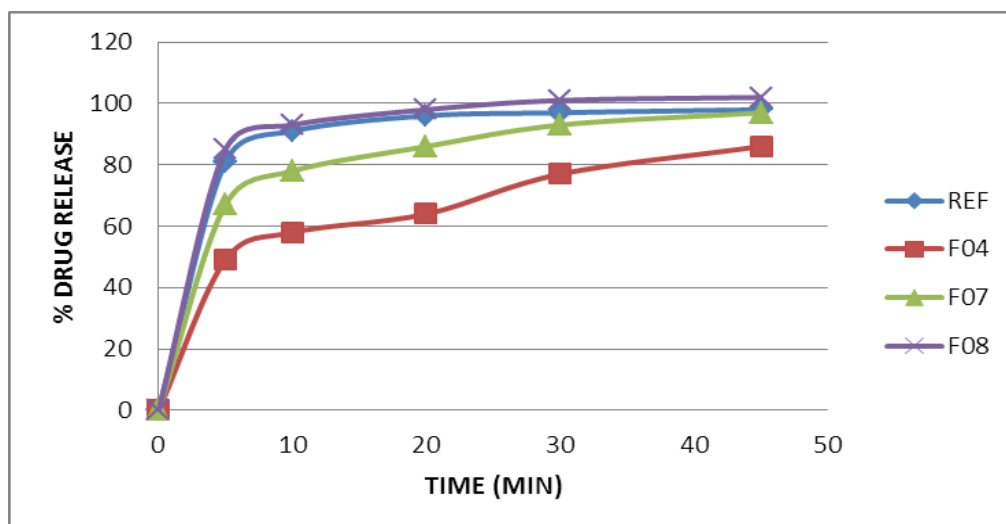


Figure 6: % Drug Release for Formulation F04, F07, F08 and reference product.

CONCLUSION

The present study was aimed to develop a formulation of immediate release tablet of Vildagliptin close similar to marketed product by applying a simple manufacturing process such as direct compression. The direct compression process is cost effective and less time consuming. The formulated immediate release tablet was evaluated for different physical and chemical parameters of the immediate release tablet. From the above study it was concluded that the formulation F08 was showing good physical parameters in terms of flow ability and compressibility and the *in vitro* drug release for F08 is higher and dissolution pattern is close similar to marketed product.

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REFERENCES

1. Rohit SK and Amulyaratna LB. Formulation and evaluation of immediate release tablet of valsartan. *International Journal of Pharmaceutical Sciences and Research*, 2015; 6(2): 808-815.
2. Nyol S, Gupta MM. Immediate drug release dosage form: A Review. *Journal of drug delivery and therapeutics*, 2013; 3(2): 155-161.
3. Jaimini M and Rawat S.A Review on Immediate Release Drug Delivery System. *Research Journal of Pharmaceutical Chemical and Biological Sciences*, 2013; 4(2): 1721-1730.

4. Brahmkar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics: A treatise. Absorption of drugs. 2nd ed., Delhi; Vallabh Prakashan, 2009; 24- 27.
5. Swati S, Jyothi N. Formulation and Evaluation of Immediate Release Telmisartan Tablets using Hydrophilic Polymers. Asian Journal of Pharmaceutics, 2017; 11(1): 37.
6. www.drugbank.ca.
7. www.medicines.org.uk/emc.
8. Turkyilmaz A, turp AH. Pharmaceutical formulations of vildagliptin, European Patent Application, EP2915527A1.
9. Lakshmi AP, Kumar MA, Krishna MV, Vijetha KA, Ashwini G. Formulation development of Irbesartan (poorly water-soluble drug) Immediate Release Tablets. International Research Journal of Pharmacy, 2012; 3(2): 117-120.
10. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd edition., Varghese Publishing House, 1991.
11. Atram SC. Formulation and evaluation of immediate release tablet using response surface methodology. Asian J Pharm, 2011; 5: 46-51.
12. Jadhav SB. Formulation and evaluation of immediate release tablets of Imipramine hydrochloride. IJBAR, 2014; 05(11): 560-564.
13. Satish B. Vildagliptin – A New Prospect in Management of Type 2 Diabetes. Indian Journal of Clinical Practice, 2012; 22(8): 377.
14. Mohanachandran PS, Sindhumol PG, Kiran TS. Superdisintegrants: An Overview. International Journal of Pharmaceutical science, 2011; 6(1): 105-109.
15. Chantal M. Vildagliptin: a new oral treatment for type 2 diabetes mellitus. Vasc Health Risk Manag, 2008 D; 4(6): 1349–1360.
16. Zulfiker AH, Islam M, Islam R, Kazi RA, Reza S. Formulation Development Using Maize Starch & Avicel PH101 as Disintegrating Agents And Their Effect On Physical Characteristics & In Vitro Release Profile. International Journal of Pharmaceutical Sciences and Research, 2011; 2(8): 2136-2141.
17. Siddiqui N, Husain A, Chaudhry L, Alam MS, Mitra M and Bhasin PS. Pharmacological and Pharmaceutical Profile of Valsartan: A Review. Journal of Applied Pharmaceutical Science, 2011; 01(04): 12-19.
18. Kumar YG, Sreekanth J. Formulation design and development of SR matrix tablets of vildagliptin by using different grades of carbopol and eudragit. Journal of Chemical and Pharmaceutical Research, 2015; 7(5): 1213-1224.

19. Barden AT, Piccoli B. Simultaneous determination by HPLC method and in vitro dissolution studies for association of vildagliptin and metformin in coated tablets.
20. Shrestha P, Bhandari SK. Design and Development of Immediate and Sustained Release Tablets of Vildagliptin. RJPBCS, 2014; 5(4): 811.