RESEARCH ARTICLE

Design, Development and Characterization of Immediate Release Matrix Tablet of Vildagliptin

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ABSTRACT

In the present study, an immediate-release tablet of vildagliptin is prepared by wet granulation using superdisintegrants. Optimization of the formulation was done in three steps. In the first step, the amount of pregelatinized starch was optimized by preparing four trial batches. A prepared blend of granules and formulations pre and post-compression parameters were evaluated. The amount of pregelatinized starch was optimized to 24 mg. In the next step, the amount of Sjogren-Larsson syndrome (SLS) was optimized in the same way to 1%. Finally, the amount of superdisintegrant-croscarmellose was optimized by preparing four batches and evaluating them for pre and post-compression parameters. The formulation was evaluated for drug release study in comparison with the marketed formulation. It was observed that drug release from batch I10 and I11 batches was comparable with the marketed product. Tablet formulation I11 showed higher disintegration time as compared to I10. Formulation I10 was selected as optimum formulation and evaluated for stability. Croscarmellose sodium was found effective superdisintegrant to formulate immediate release matrix tablets.

Keywords: Croscarmellose, Immediate release tablet, Superdisintegrant.

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INTRODUCTION

The oral route is the preferred route for the administration of therapeutic agents. The rate of absorption is controlled by dissolution rate and the rate of dissolution is increased by various methods.[1] Tablet is defined as solid pharmaceutical dosage forms containing medicament with or without suitable diluents and prepared by either compression or molding methods. Tablets remain popular because of the advantages afforded both to the manufacturer (eg: simplicity and economy of preparation, stability, and convenience in packaging, shipping and dispensing) and the patient.[2] Immediate release are the tablets that disintegrate rapidly and get dissolved to release the medicament.[3,4]

Diabetes mellitus is a major public health issue and affects more than 400 million people worldwide. Diabetes mellitus is caused either by deficiency of insulin secretion, damage of pancreatic β-cell, or insulin resistance related to the non-use of insulin. Type-II diabetes mellitus results from the impairment of pancreatic β-cells that obstruct the individual's ability to use insulin.[5-7]

For effective clinical management of diabetes, it is important to maintain post-prandial blood sugar level. In the present study, immediate-release matrix tablets are formulated using a super disintegrating agent to increase the dissolution rate. Antidiabetic drug Vildagliptin in the immediate release will help to reduce post-prandial blood sugar level.

MATERIALS AND METHODS

Vildagliptin was received as a gift sample, and all other analytical grade chemicals were procured from the market.

Preformulation Studies

Drug Identification and Characterization[8-11]

- Melting Point Determination
- Fourier Transform Infra-Red (FTIR) analysis
- Differential Scanning Calorimetry (DSC)
- UV Spectrophotometric Analysis
- Solubility determination

Drug: Excipient Compatibility Study

Drug-excipient compatibility was performed to assess the suitability of excipients being used in the formulation using FTIR spectroscopy.

Preparation of Granules and Optimization of formulation

Preparation of Granules

Weighed quantity of drug pharmatose 200, pregelatinized starch, and croscarmellose sodium (half quantity) was passed

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through # 40 mesh and mixed cage blender for 10 minutes at 20 rpm. Accurately weighed PVP K-30 and sodium lauryl sulfate was dissolved in purified water to prepare a binder solution. Granules were prepared from the blend, dried and size reduced. Accurately weighed croscarmellose sodium (remaining half quantity), avicel PH 102 and Aerosil were passed through a sieve. Iron oxide red was weighed, passed through a sieve, and mixed with extra granular material. Finally prepared granules were lubricated by sodium stearyl fumarate (SSF). After evaluation of pre-compression parameters, compression was done on 8 stations D- Tooling machine using 12/32" FFBE punch set.

As per Table 1 trial formulations I1 to I4 were prepared by varying amounts of pregelatinized starch, Formulation I5 to I7 were prepared by varying amount of SLS and I8 to I11 were prepared by varying amount of croscarmellose sodium. Formulations were evaluated for pre compression and post-compression parameters.

Evaluation of Precompression Parameters[12]

Bulk density: Bulk Density was determined using following formula

$$Bulk\ Density = \frac{M}{Vb}$$

Where M = mass of powder taken (g) and Vb= bulk Volume (cm^3)

Tapped Density: Tapped density was calculated using following formula

$$Tapped\ Density = \frac{M}{Vt}$$

Where M = mass of powder taken (g) and Vt = tapped volume (cm^3)

Carr's Index or Compressibility Index: It was calculated from bulk density and tapped density as per the following formula

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density}$$

Hausner Ratio: Ratio of tapped density to bulk density is also a measure of flow properties and is termed as Hausner ratio.

$$Hausners\ ratio = \frac{Tapped\ Density}{Bulk\ Density}$$

Angle of Repose: Angle of repose is determined by the funnel method using the following formula.

$$\tan\theta = \frac{h}{r}$$

h = height of the pile and r = radius of powder cone

Evaluation of Post Compression Parameters[13,14]

Weight Variation: Twenty tablets were weighed individually, and the average weight was determined. The individual tablet weight was compared with the average tablet weight. For immediate release tablet, the tablet weight is 250.00 mg, and the maximum percent difference allowed is 7.5% i.e. ± 18.75 mg.

Friability Test: Friability for the IR tablets was determined for 100 revolutions at 25 rpm. The Friability of the tablets should be less than 1%.

Hardness: Tablet was selected at random from individual formulations and hardness was measured using Scheluniger digital hardness tester.

Disintegration Test: Disintegration time for both immediate-release tablets was determined using six tablets. Disintegration time for the immediate-release tablets should not be more than 15 minutes.

Dissolution Test: The tablets were evaluated for *in vitro* drug release using USP dissolution apparatus.

The following conditions were applied.

USP Dissolution apparatus	: Type II (Paddle)
Media	: 0.1 N HCL
Volume of dissolution medium	: 900 mL
Speed of paddle rotation	: 75 RPM
Temperature	: 37 ± 0.5°C
Sampling point	: 5, 10, 15, 30, 45, 60 and 90 minutes

The dissolution profiles of test batches were compared with marketed products. Comparison between marketed product and test batches was made using two statistical factors called difference factor (f1) and similarity factor (f2).

Table 1: Vildagliptin immediate-release formulation

	Quantity / Tablet (mg)										
Ingredients	*I1*	*I2*	*I3*	*I4*	*I5*	*I6*	*I7*	*I8*	*I9*	*I10*	*I11*
Vildagliptin	50	50	50	50	50	50	50	50	50	50	50
Pharmatose 200	161	149	137	125	137	136.5	136	146.5	141.5	136.5	131.5
Pregelatinized starch	0	12	24	36	24	24	24	24	24	24	24
Povidone	5	5	5	5	5	5	5	5	5	5	5
Sodium lauryl sulfate	0.5	0.5	0.5	0.5	0.5	1	1.5	1	1	1	1
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Croscarmellose sodium	15	15	15	15	15	15	15	5	10	15	20
Avicel pH 102	15	15	15	15	15	15	15	15	15	15	15
Iron oxide red	1	1	1	1	1	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1	1	1	1	1	1
Sodium stearylfumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total (mg)	250	250	250	250	250	250	250	250	250	250	250

The difference factor (f1) calculates the percentage difference between two profiles, i.e., standard dissolution profile & test sample dissolution profile at each sampling point, and corresponds to a relative error measure between the two profiles.

f1 value should lie between 0 to 15. ideally, it should be as closer as possible to 0.

CDER and FDA defined the similarity factor (f2) as the 'logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products.

It was calculated from the mean dissolution data according to the following equation.

$$F_2 = 50 \text{ X } \log \{[1- (1/n) \Sigma^{n}_{t=1}(R_t - T_t)^2]^{-0.5} \text{ X } 100\}$$

n : No. of time points

R_t : The reference profile at the time point t

T_t : The test profile at the same point.

RESULT AND DISCUSSION:

Drug Identification and Characterization

- *Melting Point Determination:* Melting point of the drugs was found 153-154ºC.
- *DSC Study of Vildagliptin:* The DSC thermogram of pure drug is shown in the Figure 1. The curve showed melting of drug between 153-155°C and endothermic peak at 154.21ºC. The values correspond to the melting point of pure drug and thus confirm the drug's identity and purity.

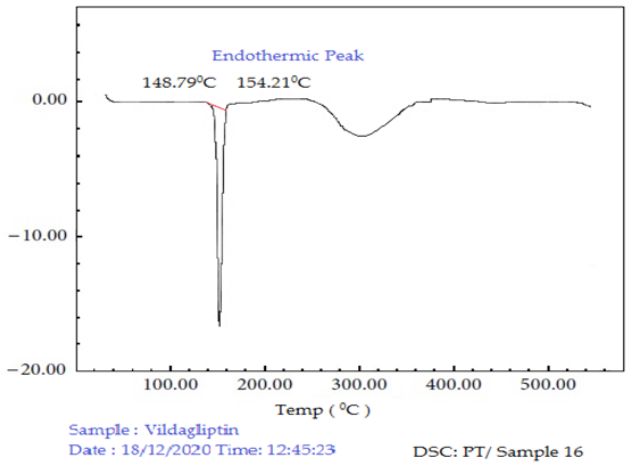

Figure 1: DSC Curve of Pure Vildagliptin

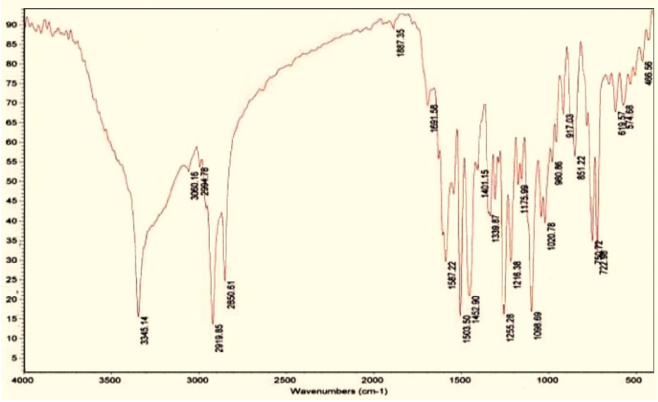

Figure 2: FTIR of Vildagliptin

- *Fourier Transform Infra-Red (FTIR) analysis*

A FTIR spectrum of pure drug was compared with reference spectra for Vildagliptin as shown in Figure 2.

FTIR of Vildagliptin showed characteristic sharp peaks at 3345.14 cm^{-1} due to N-H stretching vibrations, 2919.85 cm^{-1} corresponding to C-H stretching, and 1681.84 cm^{-1} carbonyl group vibrations and 1255.28 cm^{-1} corresponding to C-H (aliphatic) stretching vibrations (Table 2). The peaks observed in the FTIR spectra of pure drug were found to match reported values for Vildagliptin[15,16] thus confirming the identity and purity of drug.

- *UV Spectrophotometric Analysis*
- *Calibration Curve*

The calibration curves of Vildagliptin in 0.1N HCL and Phosphate buffer solution pH 6.8 at 217 nm were developed and absorbance values are given in Tables 2 to 3. It was found to obey Beer's law in the prepared concentration range 5–30 µg/mL (Table 4) (Figures 3 and 4).

- *Determination of Solubility*

The solubility of Vildagliptin in various aqueous media was evaluated by equilibrium solubility method in orbital shaker. The result of solubility study is given in Table 5.

Table 2: Interpretation of FTIR spectra

Wave Number (Cm-1)	*Interpretation*
3345.14	N-H stretching vibrations
2919.85	Methyl Symmetrical Stretching
1681	Aromatic ketone C=O stretching
1255.28	C-H stretching [aliphatic],
851	CH3 symmetrical

Table 3: Standard calibration curve of Vildagliptin in 0.1 NHCl

Sr. No.	*Concentration (µg/mL)*	*Abs ± SD*
1.	5	0.188 ± 0.015
2.	10	0.351 ± 0.018
3.	15	0.529 ± 0.028
4.	20	0.671 ± 0.013
5.	25	0.877 ± 0.048
6.	30	1.021± 0.072

Table 4: Standard calibration curve of Vildaglitpin in 6.8 phosphate buffer

Sr. No.	*Concentration (µg/mL)*	*Abs ± SD*
1.	5	0.181 ± 0.010
2.	10	0.359 ± 0.013
3.	15	0.513 ± 0.034
4.	20	0.681 ± 0.054
5.	25	0.873 ± 0.053
6.	30	1.023 ± 0.072

Drug-Excipient Compatibility Study

Physical Observation of Mixture

Physical mixtures of drug and excipients were observed physically after 1 month. Vildagliptin was found to be compatible with all the excipients used in our formulation. There was no change in color or physical appearance was seen. The observations are shown in Table 6.

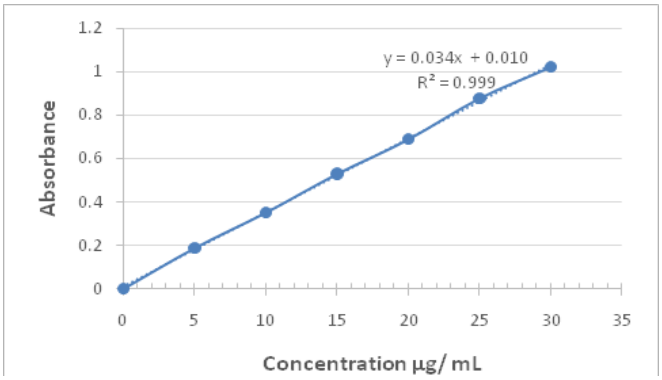

Figure 3: Standard calibration curve of vildagliptin in 0.1 N HCl

Table 5: Solubility Studies Data

S. No.	*Media*	*Solubility (mg/mL)*
1	Purified Water	11.05+ 0.07
2	pH 1.2 HCl buffer	10.61+ 0.03
3	pH 6.8 phosphate buffer	10. 34+ 0.03

FT-Infrared Spectroscopic Analysis:

FTIR of Vildagliptin showed characteristic sharp peaks at 3345.14 cm^{-1} due to N-H stretching vibrations, 2919.85 cm^{-1} corresponding to C-H stretching, and 1681.84 cm-1 carbonyl group vibrations and 1255.28 cm^{-1} corresponding to C-H (aliphatic) stretching vibrations. The FTIR spectra of drugs with excipients showed no change in the FTIR pattern of all the functional groups of Vildagliptin. The peaks observed in

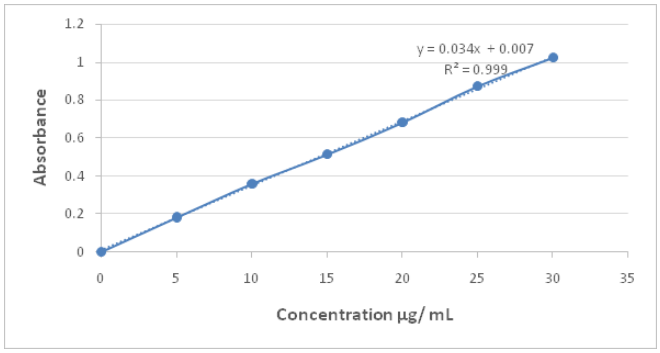

Figure 4: Calibration curve of vildagliptin in 6.8 phosphate buffer

Table 6: Drug Excipient compatibility study- findings of physical observation study

Drug: Excipient (1:1)	*Observation*		
	Description	*Room temperature*	*40 °C /75% RH*
Vildagliptin IP	White to off white powder	White to off white powder	White to off white powder
Vildagliptin: Pharmatose 200	White to off white powder	White to off white powder	White to off white powder
Vildagliptin: Pregelatinized Starch	White to off white powder	White to off white powder	White to off white powder
Vildagliptin: PVP K-30	White to off white powder	White to off white powder	White to off white powder
Vildagliptin: Croscarmellose Sodium	White to off white powder	White to off white powder	White to off white powder
Vildagliptin: Avicel PH 102	White to off white powder	White to off white powder	White to off white powder
Vildagliptin: Sodium Lauryl Sulfate	White to off white powder	White to off white powder	White to off white powder
Vildagliptin: Aerosil	White to off white powder	White to off white powder	White to off white powder
Vildagliptin: Iron Oxide Red	Brick Red Colored Powder	Brick Red Colored Powder	Brick Red Colored Powder
Vildagliptin: Sodium StearylFumarate	White to off white powder	White to off white powder	White to off white powder

Optimization of Formulation

Precompression Parameter Evaluation

Table 7: Evaluation of precompression parameter

Batch No.	*Angle of Repose*	*Bulk Density(g/ml)*	*Tapped Density(g/ml)*	*Carr'sIndex(%)*	*Hausner Ratio*
I1	33.50	0.55	0.65	15.38462	1.18
I2	31.67	0.53	0.61	13.11475	1.15
I3	29.35	0.52	0.59	11.86441	1.13
I4	31.23	0.53	0.63	15.87302	1.19
I5	29.50	0.53	0.60	11.66	1.13
I6	29.67	0.52	0.59	11.86	1.13
I7	29.35	0.52	0.59	11.86	1.13
I8	29.66	0.53	0.60	11.66	1.13
I9	29.61	0.53	0.59	10.16	1.11
I10	29.51	0.53	0.60	11.66	1.13
I11	29.87	0.62	0.70	11.42	1.12

Post compression parameter evaluation:

Table 8: Evaluation of post compression parameter

Batch No.	*Avg. Tab Wt. (mg)*	*Thickness (mm)*	*Hardness (Kg/cm2)*	*Avg Disintegration Time(min)*	*Friability (%)*
I1	250 ± 2.1	2.72 ±0.01	5.1	5 min 27 Sec	0.31
I2	250 ± 1.9	2.72 ±0.01	5.2	4min 02 Sec	0.23
I3	250 ± 1.8	2.72 ±0.01	5.4	3 min 19 sec	0.19
I4	250 ± 2.0	2.72 ±0.01	5.7	3 min 23 sec	0.16
I5	250 ± 1.9	2.72 ±0.01	5.4	3 min 21 Sec	0.18
I6	250 ± 1.9	2.72 ±0.01	5.4	3min 15 Sec	0.18
I7	250 ± 1.9	2.72 ±0.01	5.4	3 min 14 sec	0.17
I8	250 ± 1.8	2.72 ±0.02	5.5	3 min 58 Sec	0.17
I9	250 ± 1.9	2.72 ±0.01	5.5	3 min 29 Sec	0.18
I10	250 ± 1.9	2.72 ±0.01	5.4	3 min 13 sec	0.19
I11	250 ± 1.7	2.72 ±0.01	5.4	3 min 16 sec	0.19

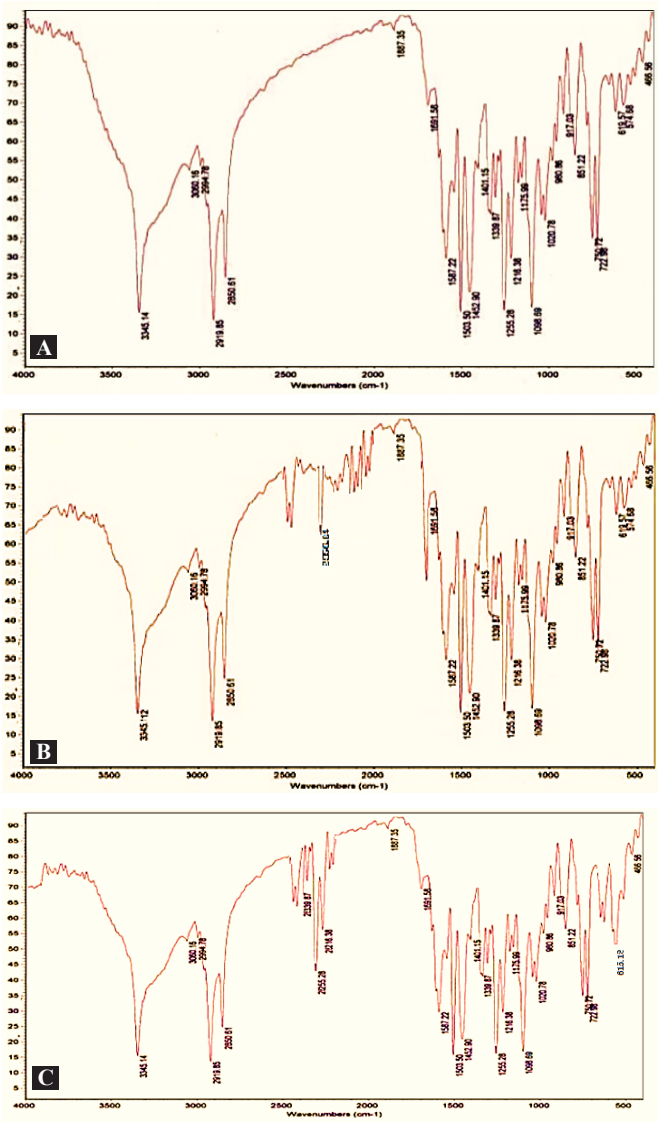

Figure 5: FTIR spectra of (A) Vildagliptin; B) Vildagliptin + Pharmatose 200; C) Vildagliptin + Pregelatinised Starch

Table 9: Dissolution profiles

Time in min	*% Cumulative Drug Release*				
	Reference	*I8*	*I9*	*I10*	*I11*
5	23.81	6.96	10.93	19.32	19.46
10	51.81	21.85	36.87	45.71	46.94
15	69.96	43.2	49.28	67.62	68.63
30	84.68	59.34	64.32	83.49	83.81
45	93.79	70.51	79.53	92.80	92.34
60	99.8	86.8	91.8	98.71	98.12
90	99.83	94.61	97.36	99.78	99.32
F1 similarity factor		18.23	16.25	2.16	2.19
F2 similarity factor		39.65	17.33	89.36	89.25

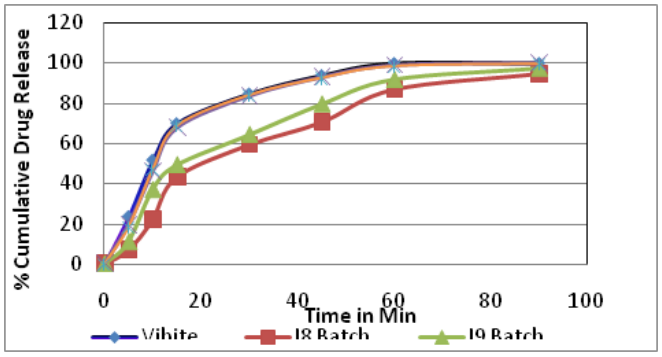

Figure 6: *In-vitro* drug release of Vildagliptin from trial formulations

the FTIR spectra of pure drugs were found in FTIR spectra of a physical mixture of drug and excipients (Figure 5).

In-vitro Drug Release

Percent Cumulative drug release was evaluated for trial batches prepared using varying concentration of Croscarmellose in comparison with marketed immediate-release Vildagliptin. The Drug release for I8 and I9 batch was slow as compared to marketed product. *In-vitro* drug release of Vildagliptin from I10 and I11 batch was comparable to release profile of marketed

formulation (Table 9 and Figure 6). Similarity factor f1 and f2 calculation showed that formulation I10 and I11 were very similar in drug release as compared to reference immediate-release Vildagliptin. However, Tablet formulation batch I11 showed more disintegration time than I10.

CONCLUSION

The drug excipient compatibility study using FTIR revealed no chemical interaction and thus no incompatibility between Vildagliptin and excipients. Immediate-release tablets were prepared by wet granulation technique , tablet were evaluated by precompression (Table 7) and post compression (Table 8) parameters. Amount of pregelatinized starch was optimized to 24 and SLS concentration was optimized to 1%. Formulations I8 to I11 prepared by varying concentrations of superdisintegrant I10 and I11 showed optimum release kinetics. Formulation I10 was selected as optimum formulation for showing faster disintegration and dissolution rate. Croscarmellose sodium was found effective as super-disintegrant to formulate an immediate release matrix tablet of Vildagliptin.

REFERENCES

1. Raina B, Shrivastava B, Bhargava A, Sharma S, Sharma AR, Bajwa PS, Design, development and optimization of immediate release tablet of deflazacort, Journal of Drug Delivery and Therapeutics. 2019; 9(2):250-254 http://dx.doi.org/10.22270/jddt.v9i2.2411
2. Sudarshan B. Kakad, and Dr. Punit R. Rachh, A review on Bi-layer tablet: an emerging trend, European Journal of Pharmaceutical and Medical Research, 2019,6(8), 223-229.
3. Setty CM, Prasad DVK, Gupta VRM, and Sa B. Development of fast dispersible aceclofenac tablets: effect of functionality of superdisintegrants. Indian J Pharm Sci. 2008; 70(2):180-184. DOI: 10.4103/0250-474X.41452.
4. Sharma N, Pahuja S and Sharma N: Immediate release tablets: a review. Int J Pharm Sci & Res 2019; 10(8): 3607-18. doi: 10.13040/IJPSR.0975-8232.10(8).3607-18.
5. Khursheed R, Singh SK, Wadhwa S, Kapoor B, Gulati M, Kumar R, Ramanunny AK, Awasthi A, Dua K. Treatment strategies against diabetes: Success so far and challenges ahead. Eur J Pharmacol. 2019, 5;862:172625. doi: 10.1016/j.ejphar.2019.172625.
6. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047-53. doi: 10.2337/diacare.27.5.1047.
7. Wong CY, Al-Salami H, Dass CR. Potential of insulin nanoparticle formulations for oral delivery and diabetes treatment. J Control Release. 2017 Oct 28;264:247-275. doi: 10.1016/j.jconrel.2017.09.003.
8. Carstensen JT. Preformulation, In: Modern Pharmaceutics, Ed Banker GS, Rhodes CT, 4th Ed. Marcel Dekker, Inc. New York. 2002: 167-185.
9. Aulton ME. In: Pharmaceutics: The Science of Dosage Form Design, 2nd ed, Livingstone C. Elsevier Science Ltd., 2002: 136-146.
10. Shrestha P, Bhandari SK, Islam SM, Reza MS, Adhikari S. Design and Development of Immediate and Sustained Release Tablets of Vildagliptin, Research Journal of Pharmaceutical, Biological and Chemical Sciences 2014; 5(4): 811-825
11. Sravani, K., D. Priyanka, R. Sravani, K. S. Reddy, and D. V. Kumar, Formulation and Evaluation of Vildagliptin Immediate Release Tablet, World Journal of Pharmaceutical Research 2018; 7(5): 1214-1226.
12. Cavatur RK, Vemuri NM, Suryanarayanan R. Preformulation Studies for Tablet Formulation Development. In: Augsburger LL, Hoag S, editors. Pharmaceutical Dosage form. 3rd ed. Boca Raton: CRC Publication; 2013. P. 138-59.
13. Mohamed Rahamathulla, MD Naushad Alam, Umme Hani, Qais Ibrahim and Yahya Alhamhoom , Development and in vitro evaluation of effervescent floating matrix tablet of neritinib: An anticancer drug, Pakistan Journal of Pharmaceutical Sciences, 2021, 34(4): 1297-1303. doi.org/10.36721/PJPS.2021.34.4.REG.1297-1303.1
14. Debjit Bhowmik, Rishab Bhanot, Darsh Gautam, Parshuram Rai, K.P. Sampath Kumar. Formulation and Evaluation of Telmisartan Fast Dissolving Tablets by Direct Compression Method. Res. J. Pharm. Dosage Form. & Tech. 2017; 9(3): 131-139. doi: 10.5958/0975-4377.2017.00022.2
15. Dewan I, Islam S, Rana MS. Characterization and Compatibility Studies of Different Rate Retardant Polymer Loaded Microspheres by Solvent Evaporation Technique: In Vitro-In Vivo Study of Vildagliptin as a Model Drug, Journal of Drug Delivery 2015, Article ID 496807, http://dx.doi.org/10.1155/2015/496807.
16. Suroshe RS *et al*, Development and characterization of osmotic drug Delivery system of model drug, World Journal of Pharmaceutical Research 2018; 7 (18): 1158-1171.