CIBTech Journal of Pharmaceutical Sciences ISSN: 2319–3891 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/cjps.htm
2015 Vol.4 (3) July-September, pp.12-25/Debnath et al.
Research Article

FORMULATION, DEVELOPMENT AND *IN-VITRO* RELEASE KINETICS OF LINAGLIPTIN TABLET USING DIFFERENT SUPER DISINTEGRATING AGENTS

***Manidipa Debnath, Ashutosh Kumar S. and Madugula Dharmaraju**
Department of Pharmaceutics, A.K.R.G College of Pharmacy, Nallajerla, West Godavari, A.P, 534112
**Author for Correspondence*

ABSTRACT
Linagliptin is an anti-diabetic drug used for the treatment of type 2 diabetes, it is belongs to the class of dpp-4 inhibitor. It has long half-life of about 8.6-23.9 hours and hence to achieve immediate therapeutic action it needs immediate release tablet formulation. Among the various techniques using superdisintegrants is a simple approach to formulate immediate release tablets. The objective of the present work is to formulate and evaluate a better formulation and to provide a tablet dosage form with satisfying parameters for the linagliptin immediate release tablets including pre-formulation studies. The prepared tablets were evaluated for physical properties and *in-vitro* dissolution studies. Compatibility studies of linagliptin and excipient has been done by FTIR. Pre formulation and pre compression parameters were evaluated the formulation blends showed good flow properties. FTIR spectra's indicated no interaction between linagliptin and excipients used in the formulation. The prepared tablets fulfilled the official specifications of tablets with regarded to drug content, hardness, friability, weight variation and disintegration time. The dissolution of linagliptin from the tablets obeyed first order kinetics. Based on the dissolution studies formulation F3 contains (6% crospovidone) gave rapid and highest dissolution rate and dissolution efficiency among all the formulations.

Keywords: *FTIR, Linagliptin, In-vitro Study, Kinetics*

INTRODUCTION
Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Various dosage forms administered orally, the tablet is one of the most preferred dosage forms amongst them because of its ease of manufacturing, convenience in administration, accurate dosing, and stability compared with oral liquids and because it is more tamperproof than capsules. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors (Mukesh *et al.*, 2007). Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. The emphasis on the availability of drug highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behavior (Bhowmik *et al.*, 2009). Disintegrants are agents added to tablet (and some encapsulated) formulations to promote the breakup of the tablet (and capsule "slugs") into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. A disintegrant used in granulated formulation processes can be more effective if used both "intragranularly" and "extragranularly" thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. Most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of such tablets (Mohanachandran *et al.*, 2011).
In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth. The task of developing rapidly disintegrating tablets is accomplished by using a suitable superdisintegrants (Deshmkh *et al.*, 2012). In recent years several newer

agents have been developed known as "Superdisintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Water penetration rate and rate of disintegration force development are generally positively related to disintegrant efficiency in non soluble matrices. However, such a positive correlation is not always observed between tablet disintegration time and drug dissolution rate (Kaur *et al.*, 2010).

Superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution (Kumar and Nirmala, 2012).

Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. Number of factors affects the disintegration behaviour of tablets. The optimum concentration of the super disintegrant can be selected according to critical concentration of disintegrant. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrant action. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet (Bikashapathi *et al.*, 2011; Formulation).

Linagliptin (Somsuvra *et al.*, 2013; Ryuichi and Sho-ichi, 2013; Ritesh *et al.*, 2013; Angelo and Guntram, 2013; Julienne and Elizabeth, 2008; Somsuvra *et al.*, 2013; Elena *et al.*, 2013; Nasser and Dennis, 2013; Nancy and Ann, 2013; RxList 19, 20, 21) is an anti diabetic drug used for the treatment of type 2 diabetes, it is belongs to the class of DPP-4 inhibitor.

The Linagliptin is a moisture sensitive drug and it has long biological half-life about 8.6-23.9 hours and this drug need immediate therapeutic action in the treatment hence direct compression method chosen for immediate release tablet preparation. The formulation is to be prepared in such a way that the tablets will disintegrate very fast and make the drug present in the formulation to be ready for the dissolution. The faster dissolution can be achieved by using different superdisintegrants in different concentrations and a comparative study of different superdisintegrants has been carried out.

MATERIALS AND METHODS

The following materials were obtained from commercial sources and used for the formulation. The drug Linagliptin was received as gift sample from Dr. Reddy's Labs. Other excipients were received from different manufacturer sodium starch glycolate, crospovidone, Mannitol, magnesium stearate and talc from S.D fine chemicals Limited, Hyderabad, Telagana, India; cross carmellose sodium from Essel Fine Chemicals, Mumbai, India; and opadry white from Colorcon chemical limited, India.

Equipments Used

The following equipments were used for the formulation were M/S Cad mach machinery Co. Pvt. Ltd., digital weigh balance from Shimadzu, Japan; Fluidized bed dryer, double cone blender from Cadmach, Ahmadabad, Gujarat. Rapid mixture granulator from Remi, Mumbai; Monsanto Hardness tester from Pharma lab, Ahmedabad; Roche Friabilator from Tab-Machines, Mumbai, Disintegration tester from Electrolab, Chennai; Dissolution apparatus from Electrolab TDT 08L; UV-VIS Spectrophotometer from Labindia, Mumbai. The hot air oven from Tempo Instruments, Mumbai; and glass wares from Borosil and Anumbra.

Preformulation Studies (Gopinath and Naidu, 2011; Kailash et al., 2013)

The first step in any formulation activity is careful consideration of a complete physicochemical profile of the active ingredients available, prior to initiating a formulation development activity. The basic purpose of the preformulation activity are to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product, and to ultimately provide a basis for optimizing drug product quality and performance. Drug-excipient stability study forms heart of such data. Following receipt of the preformulation information, the formulator may prepare a general summary

statement concerning the drug and its properties relative formulation. Before embarking actual experimental run preformulation considerations become important.

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailable. Further the use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substances to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, bulk density, tapped density, compressibility and melting point.

Micromeritical Properties: The following micromeritical properties of all the formulations were determined like Densities, Compressibility index, Angle of repose and Hausner ratio. They were calculated and all estimated parameters were found within the limits.

Drug Excipients Compatibility Studies: The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added to the formulation. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious and safe. Fourier-transform infrared (FTIR) spectra of the Drug and polymer were obtained on Alpha Brooker FTIR (Tokyo, Japan). The spectra were scanned over the wave number range of 4200 to 500 cm^{-1}.

Analytical Method

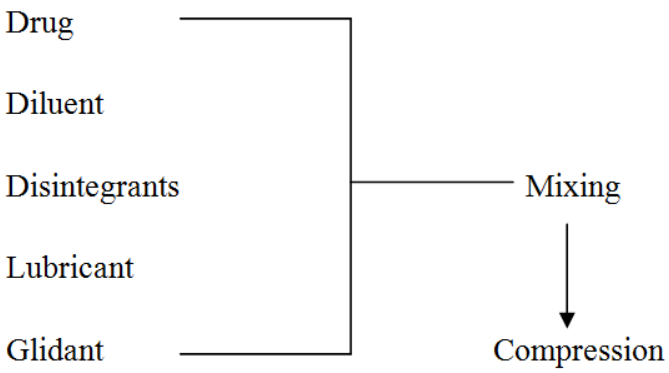
Preparation of standard drug solution: About 25 mg of Linagliptin was dissolved in 25 mL methanol in a 25 mL clean and dry volumetric flask. The standard drug solution containing 1.0 mg of drug per 1.0 mL was suitably diluted with 0.1 HCl to get 10 µg/mL solutions. Further the maximum (λ max) wavelength of drug was determined by using UV spectrophotometer in the wavelength range of 200-400 nm using 0.1 N HCl as a blank.

Construction Calibration Curve of Linagliptin: The standard drug solution containing 1.0 mg of drug per 1.0 mL was suitably diluted with 0.1N HCl to obtain a series of solutions containing 2, 4, 6, 8 and 10µg/mL. The absorbance of these solutions was measured in UV-double beam spectrophotometer (systronics) using 0.1N HCl as a blank.

Preparation of Tablets by Direct Compression Method (Hemanth et al., 2012; Sandeep and Gupta, 2013; Gnana et al., 2012; Ratnaparkhi et al., 2012)

5 mg Linagliptin tablet was prepared by direct compression method as per the formulae given in the table 1. All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine (M/S Cad mach machinery Co.Pvt.Ltd.) to a hardness of 3-5 Kg/wt. using 8 mm flat punches.

Flow Chart for the Direct Compression Method



Film Coating Solution Preparation: Purified water was taken in a stainless steel container equipped with a propeller stirrer. Opadry white was added slowly to the purified water while stirring was continued for 45 minutes or till a smooth homogeneous suspension was obtained. The dispersion was kept under constant agitation, at slow speed, during the entire Coating process. Core tablets were transferred into coating pan and the tablets were warmed while jogging the pan until the tablet bed temperature reaches

approximately 45 ±5°C. The coating pan was started, the film coating suspension was sprayed and the weight gain of the tablets was recorded. The coating was continued till the average tablet weight gained 2.0 ± 0.5 % w/w of core tablet weight.

Table 1: Formulae of Linagliptin Tablets

INGREDIENTS mg/tab	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
API	5	5	5	5	5	5	5	5	5
Crospovidone	5	10	15	_	_	_	_	_	_
Sodium Starch Glycolate	_	_	_	5	10	15	_	_	_
Cross Carmellose Sodium	_	_	_	_	_	_	5	10	15
Mannitol	237.5	232.5	227.5	237.5	232.5	227.5	237.5	232.5	227.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1	1	1	1	1	1	1	1	1
Core Tablet Weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**
COATING MATERIALS*									
Opadry White	20	20	20	20	20	20	20	20	20
Dm Water	100	100	100	100	100	100	100	100	100
Coated Tablet Weight	**255**	**255**	**255**	**255**	**255**	**255**	**255**	**255**	**255**

**NOTE: Weight gain after coating is 20% of total solid contents of coating solution*

Evaluation of Tablets (Pharmainfo.net)

In addition to routine tests for general appearance, Hardness, Friability, Drug content, Weight variation, Uniformity of content and *In-vitro* Drug release must have to be evaluated.

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

$$\% \text{ Deviation} = \frac{\text{Individual weight-Average weight}}{\text{Average weight}} \times 100.$$

Sr. No.	**Average mass**	**Percentage deviation**
1.	130cmg or less	±10
2.	More than 130 mg and less than 324 mg	±7.5
3.	324 mg or more	±5

b. Hardness: For each formulation, the hardness of 6 tablets was determined using the Monsanto Hardness Tester and the average was calculated and presented with standard deviation.

c. Thickness: The thickness of the tablets was determined using a Screw guage.

d. Friability: A sample of 6 tablets was taken and was carefully dedusted prior to testing. The tablets were accurately weighed and placed in the drum of the Roche Friabilator. The drum was rotated for 100 times at 25 rpm and the tablets were removed, dedusted and accurately weighed. Friability of tablets was calculated by using following equation.

$$F = \frac{\text{Initial weight –Final weight}}{\text{Final weight}} \times 100.$$

e. Drug Content: From Each batch of tablets prepared 20 tablets were accurately weighed and powdered. Tablet powder equivalent to 5mg of drug was taken for assay into a 100 ml conical flask and extracted with 3×20 ml quantities of methanol. The methanolic extracts were filtered and collected into a

100 ml volumetric flask and the volume was then made up to 100 ml with methanol. The solution was then suitably diluted with 0.1 N HCl. The absorbance of the solution was measured at 238 nm using UV spectrophotometer.

f. In vitro Dissolution Studies: Dissolution rate of Linagliptin from the tablets prepared was studied in 0.1N HCl (900 mL) employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. One tablet containing 5 mg of Linagliptin was used in each test. A temperature of 37±1°C was maintained throughout the test. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and assayed for Linagliptin at 238 nm. All the dissolution experiments were conducted in triplicate (n=3).

g. Disintegration Test: The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 0.1 N HCl as the immersion liquid and maintained a temperature at 37±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

RESULTS AND DISCUSSION

The physical attributes of the tablet were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The results of various evaluation studies mentioned above are discussed under the following sections:

1. Determination of λ max of Linagliptin: The analysed UV spectrum of Linagliptin is shown in Figure 1. The Linagliptin solution gave maximum absorbance at wavelength of 238 nm. This wavelength is used for analyze the drug solutions.

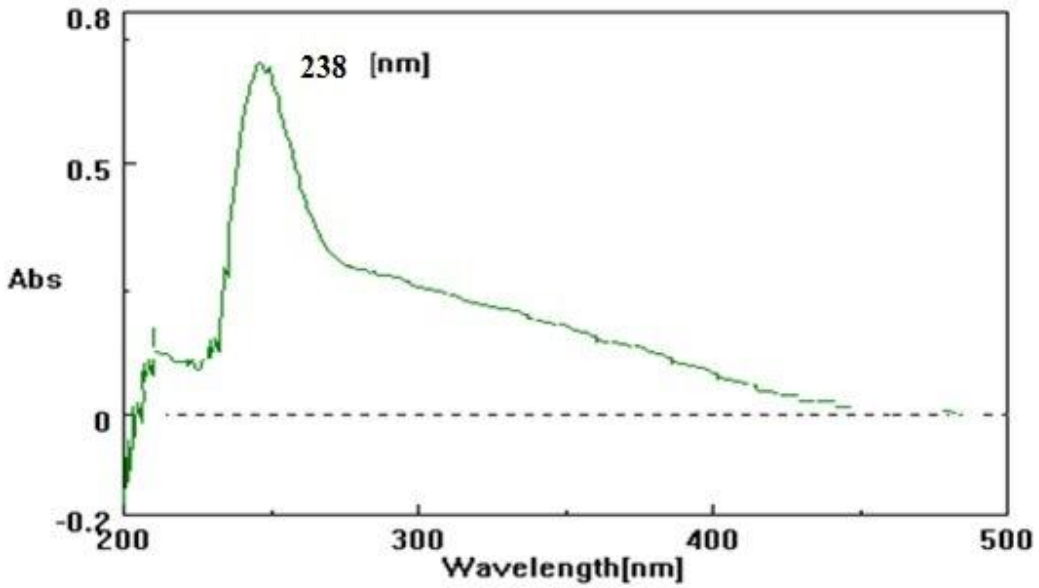


Figure 1: UV Spectrum of Linagliptin

2. Calibration Curve of Linagliptin: The standard calibration curve of Linagliptin was obtained by plotting absorbance vs. concentration. The analysed absorbance values are given in table 2. The standard curve is shown in Figure 2. The standard calibration curve shows the correlation coefficient value of 0.999. The curve was found to be linear in the concentration range of 2-10 µg/mL (Beer's lamberts law range) at 238 nm. The calculations of drug content, in vitro dissolution and stability studies are based on this calibration curve.

Table 2: Standard calibration curve data of Linagliptin

Concentration (µg/mL)	Absorbance
2	0.182
4	0.392
6	0.592
8	0.796
10	0.989

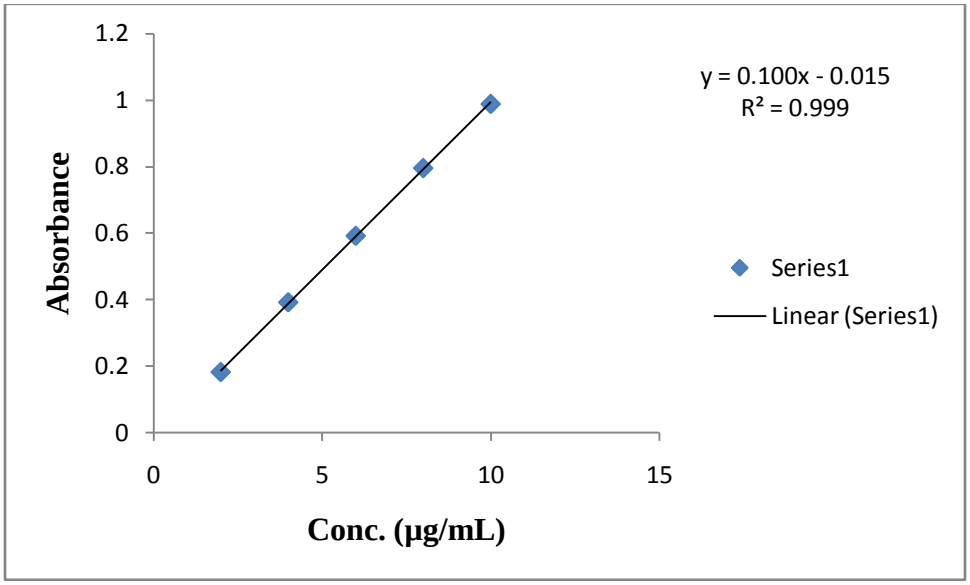


Figure 2: Standard calibaration curve of Linagliptin

3. Pre-Formulation Studies: The Pre-formulation characteristics were evaluated for Linagliptin. The results of Pre-formulation studies are given in Table 3. Melting point of Linagliptin was found to be 203^{o}C. It is within the melting range of Linagliptin (202 – 209°C). The evaluated powder flow characters indicated that pure drug has poor flow properties.

Table 3: Pre-Formulation results for Linagliptin

Parameters	Result
Melting Point	203°C
Bulk density	0.64 g/cc
Tapped density	0.79 g/cc
Hausner's ratio	1.23
Angle of repose	33.2°
Carr's index	18.98

4. Drug-excipients Compatibility Studies: The FTIR spectra of the Linagliptin and excipients (crospovidone, cross carmellose sodium, sodium starch glycolate) used in formulation is shown in Figures 3, 4, 5 and 6. The peak values of FTIR spectra are given in Table 4.

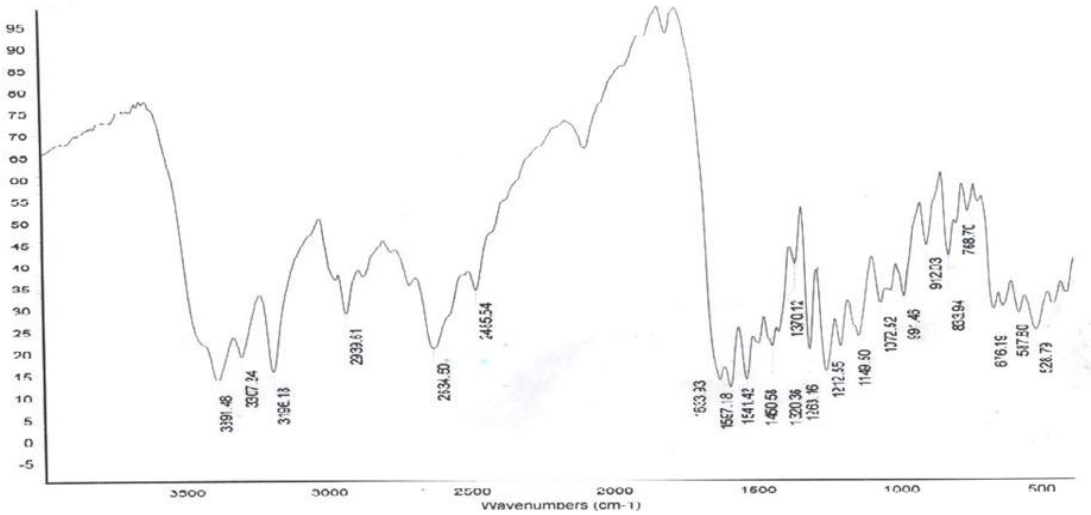


Figure 3: FTIR Spectra of Linagliptin

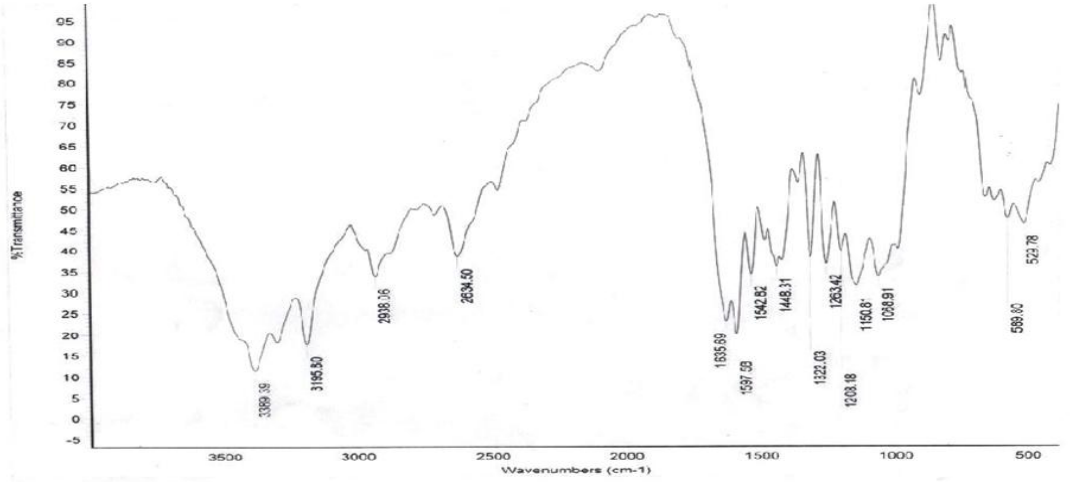


Figure 4: FTIR Spectra of Linagliptin and CP

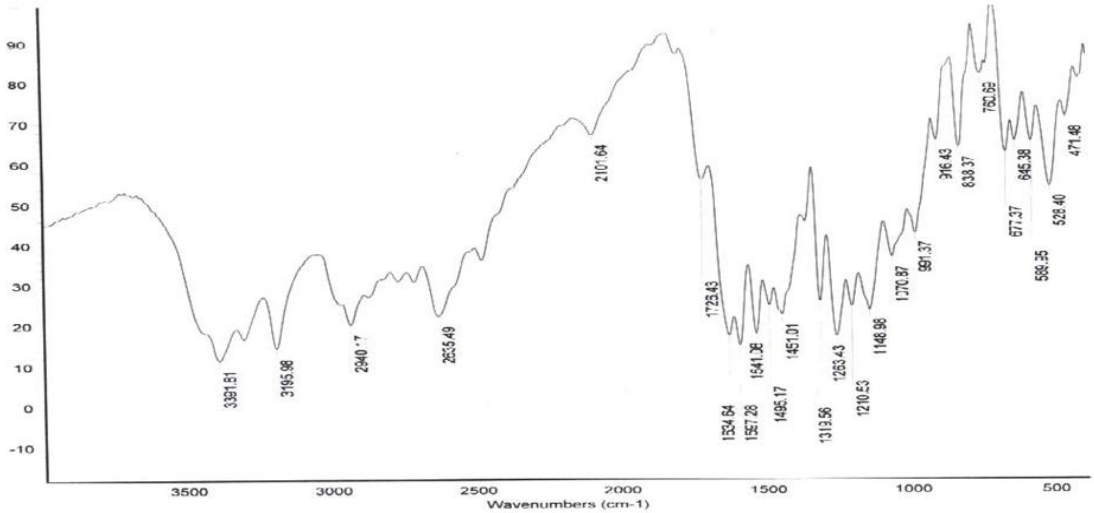


Figure 5: FTIR Spectra of Linagliptin and CCS

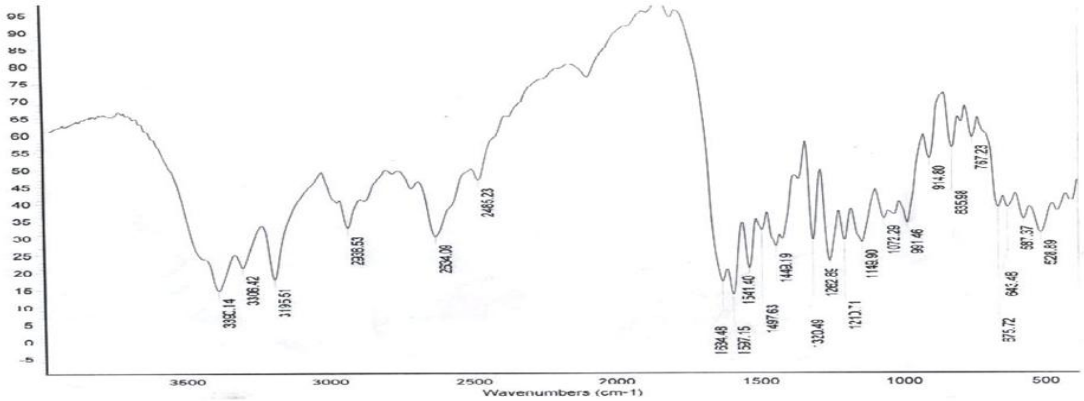


Figure 6: FTIR Spectra of Linagliptin and SSG

Table 4: Wave Numbers of FTIR peaks of Linagliptin + excipients

FTIR Samples	Peak Values (Wave Number) (cm^{-1})
Linagliptin	3391.48, 2634.50, 1597.18, 676.19
Linagliptin and CP	3390.83, 2633.89, 1597.23, 643.85
Linagliptin and CCS	3390.14, 2634.09, 1597.15, 643.48
Linagliptin and SSG	3391.81, 2635.49, 1597.28, 589.95

The characteristics absorption peaks of Linagliptin are obtained at 3391.48, 2634.50, 1597.18, and 676.19. The peaks obtained in the spectra's of each excipient correlate the peaks of drug spectrum. By correlation, it indicates that drug (Linagliptin) is compatible with the components.

5. Pre-compression Parameters: The mixed drug and excipient blends of the ingredients were evaluated for their pre-compression parameters. The prepared blends were subjected to the evaluation of angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The evaluated parameters are given in Table 5.

Table 5: Angle of Repose, Bulk Density, Tapped Density, Carr's Compressibility Index and Hausner's ratio

Formulation Code	Angle of Repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility (%)	Hausner's ratio
F1	28.23	0.58	0.71	15.492	1.22
F2	27.31	0.57	0.70	14.285	1.23
F3	25.22	0.56	0.67	13.432	1.19
F4	29.37	0.61	0.72	16.666	1.18
F5	28.22	0.60	0.70	15.289	1.16
F6	27.37	0.59	0.69	14.285	1.17
F7	30.17	0.62	0.73	17.808	1.18
F8	29.19	0.61	0.71	15.492	1.16
F9	28.88	0.60	0.70	14.676	1.16

6. Evaluation of Tablets: The Linagliptin immediate release tablets prepared by direct compression method contain three superdisintegrants namely crospovidone, sodium starch glycolate, crosscarmellose sodium with each superdisintegrants used in three different concentrations as per formulae given in Table 6. The prepared tablets were evaluated for physical properties.

Table 6: Evaluations of Tablet Parameters

Formulation Code	Uniformity of Thickness (mm)	Weight Variation (mg)	Drug Content (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)
F1	3.13±0.05	256.0±2.013	4.79±0.148	3.87±0.29	0.36	11
F2	3.17±0.06	255.5±2.153	4.82±0.113	3.76±0.29	0.21	09
F3	3.18±0.05	255.5±2.652	4.92±0.067	3.70±0.29	0.13	08
F4	2.97±0.03	256.6±2.88	4.89±0.176	3.76±0.29	0.34	23
F5	3.13±0.05	255.0±1.032	4.90±0.031	3.24±0.29	0.30	19
F6	3.15±0.13	255.1±1.272	4.92±0.021	3.66±0.29	0.21	17
F7	2.90±0.05	255.1±2.171	4.70±0.148	3.24±0.29	0.47	59
F8	2.97±0.03	255.4±3.045	4.83±0.113	2.96±0.29	0.42	48
F9	2.98±0.03	255.6±2.197	4.88±0.054	2.90±0.29	0.41	43

7. In vitro Dissolution Studies: The dissolution of Linagliptin from the prepared tablets was studied in 0.1 N HCl as a dissolution medium. The dissolution data are given in Tables 7, 8 and 9. The dissolution profiles are shown in fig 7, 8, 9, 10, 11 and 12. The dissolution data were analysed as per zero order and first order models. The dissolution parameters like dissolution efficiency (DE_{15}%), dissolution rate constant (K_1), Percent drug dissolved in 10 mins (PD_{10}%) and Time for 50%, 90% drug dissolved (T_{50}%, T_{90}%) were estimated and the results are given in Table 13.

Table 7: Dissolution Data of Linagliptin Tablets F1, F2 and F3 (with crospovidone 2, 4, 6% concentrations respectively)

Time (mins)	Percentage Drug Dissolved ($\bar{X}$ ± SD) (n=3)		
	F1	F2	F3
0	0.00	0.00	0.00
5	85.87±2.58	91.56±1.8	96.33±1.14
10	89.72± 1.11	94.31±2.63	100
15	93.58±1.54	97.06±1.17	-
20	95.60±1.07	99.45±1.13	-
25	97.43±2.63	100.00	-
30	99.08±1.8	-	-

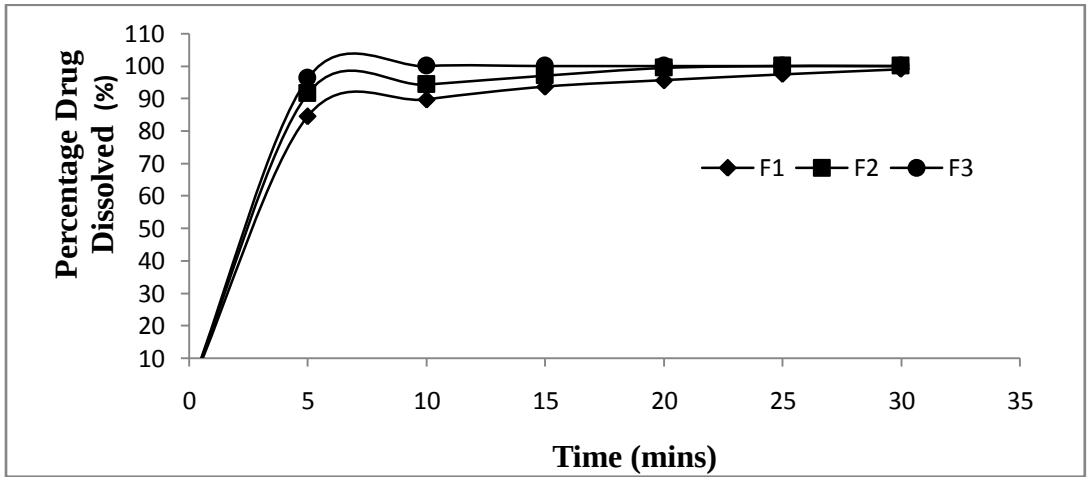


Figure 7: Dissolution Profiles of Linaglitpin Tablets F1, F2 and F3 (with crospovidone 2, 4, 6% concentrations respectively)

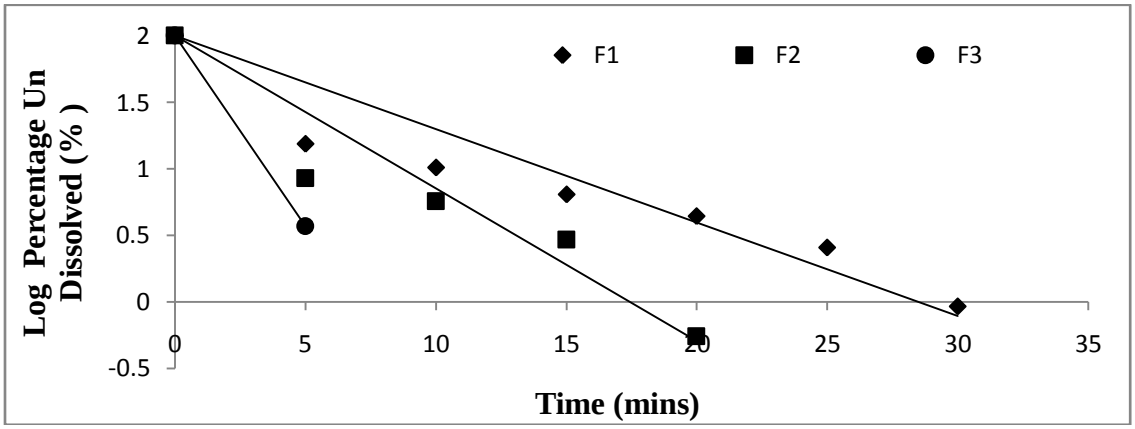


Figure 8: First Order Plots of Linagliptin Tablets F1, F2 and F3 (with crospovidone 2, 4, 6% concentrations respectively)

The dissolution of Linagliptin from the tablet formulations F1, F2 and F3 (2, 4 and 6% crospovidone used) was higher and rapid. Among the three formulations F3 (crospovidone 6%) gave highest dissolution rate (0.66 min^{-1}). The Linagliptin tablets containing crospovidone achieved more than 90% of the drug dissolved in 15 mins may be due to the crospovidone rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. CP is dens cross-linked homopolymers of N-vinyl 2-pyrrolidones. Their porous particle morphology enables them to rapidly absorb liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration.

Table 8: Dissolution Data of the Formulations F4, F5 and F6 (with sodium starch glycolate 2, 4, 6% concentrations respectively)

Time (mins)	Percentage Drug Dissolved ($\bar{X}$ ± SD) (n=3)		
	F4	F5	F6
0	0.00	0.00	0.00
5	83.67±3.56	89.36±3.64	95.05±2.46
10	86.97±1.38	91.93±1.35	99.45±1.13
15	89.17±2.39	95.05±2.3	100.00
20	92.11±2.42	98.35±1.43	-
25	96.33±1.43	100.00	-
30	99.45±0.92	-	-

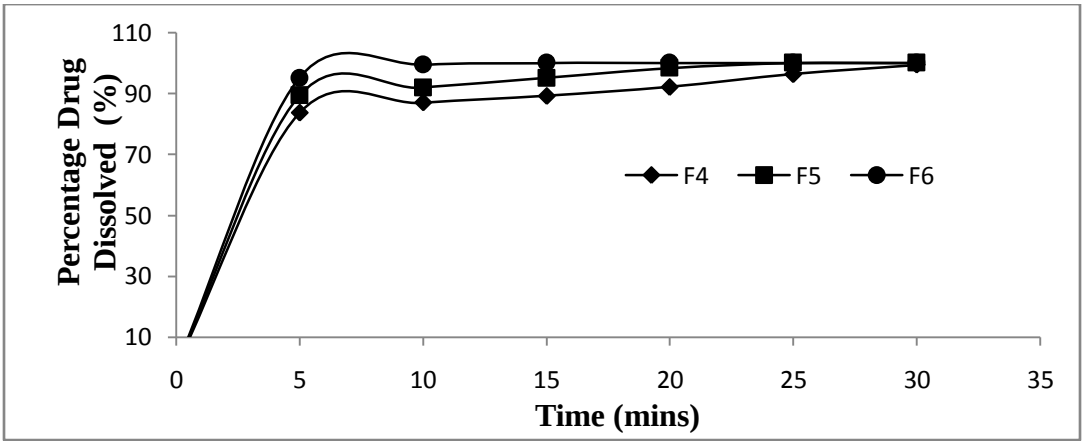


Figure 9: Dissolution Profiles of Linaglitpin Tablets F4, F5 and F6 (with sodium starch glycolate 2, 4, 6% concentrations respectively)

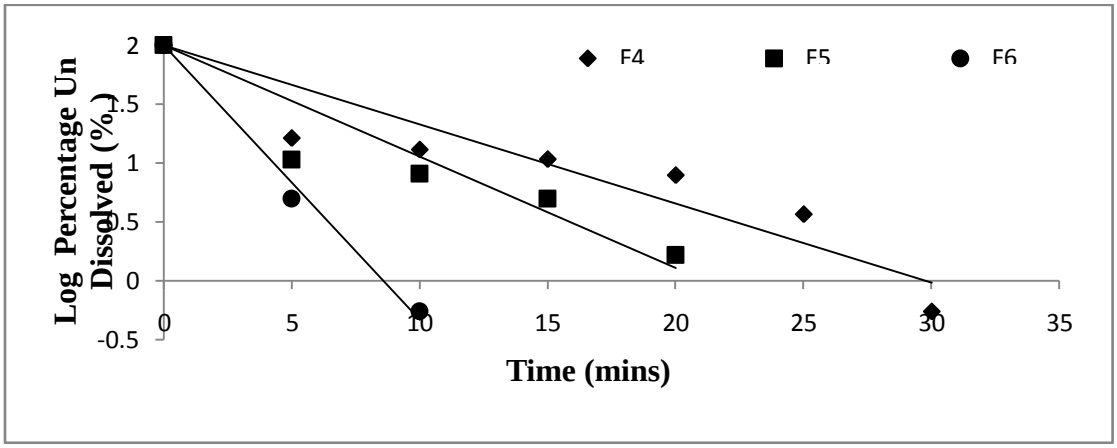


Figure 10: First Order Plots of Linaglitpin Tablets F4, F5 and F6 (with sodium starch glycolate 2, 4, 6% concentrations respectively)

The dissolution of Linagliptin from the tablet formulations F4, F5 and F6 (2, 4, 6% sodium starch glycolate used) was faster. Among the three formulations F6 (sodium starch glycolate 6%) gave highest dissolution rate (0.52 min^{-1}). The Linagliptin tablets containing sodium starch glycolate achieved more than 85% of the drug dissolved in 15 mins may be due to the sodium starch glycolate exhibits disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Table 9: Dissolution Data of the Formulations F7, F8 and F9 (with cross carmellose sodium 2, 4, 6% concentrations respectively)

Time (mins)	Percentage Drug Dissolved ($\bar{X}$ ± SD) (n=3)		
	F7	F8	F9
0	0.00	0.00	0.00
5	81.28±2.39	84.04±2.39	88.99±2.39
10	84.59±3.71	87.16±2.68	93.39±3.51
15	88.99±2.68	91.93±3.29	97.80±1.14
20	91.38±2.89	93.76±1.68	100.00
25	93.21±1.29	96.88±2.39	-
30	95.78±2.48	100.00	-

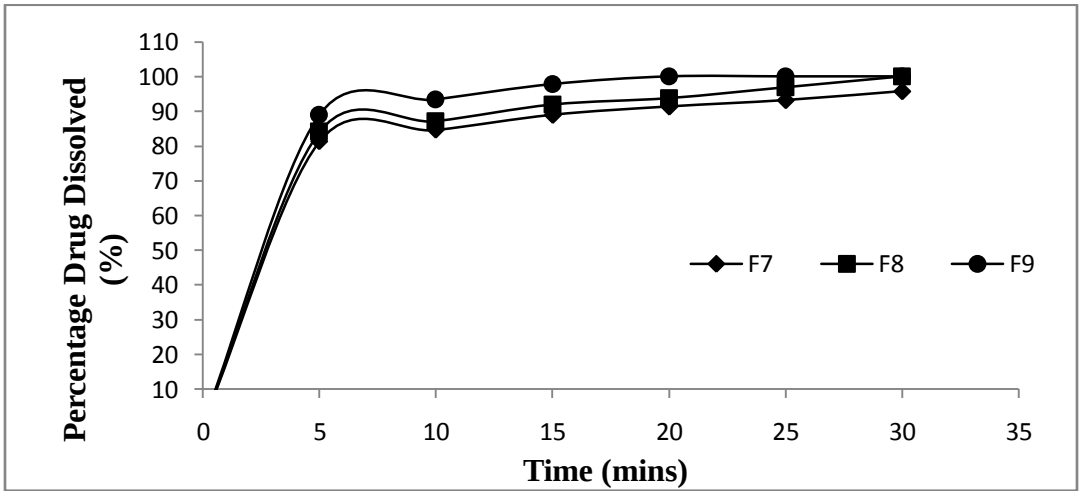


Figure 11: Dissolution Profiles of Linaglitpin Tablets F7,F8 and F9 (with cross carmellose sodium 2, 4, 6% concentrations respectively)

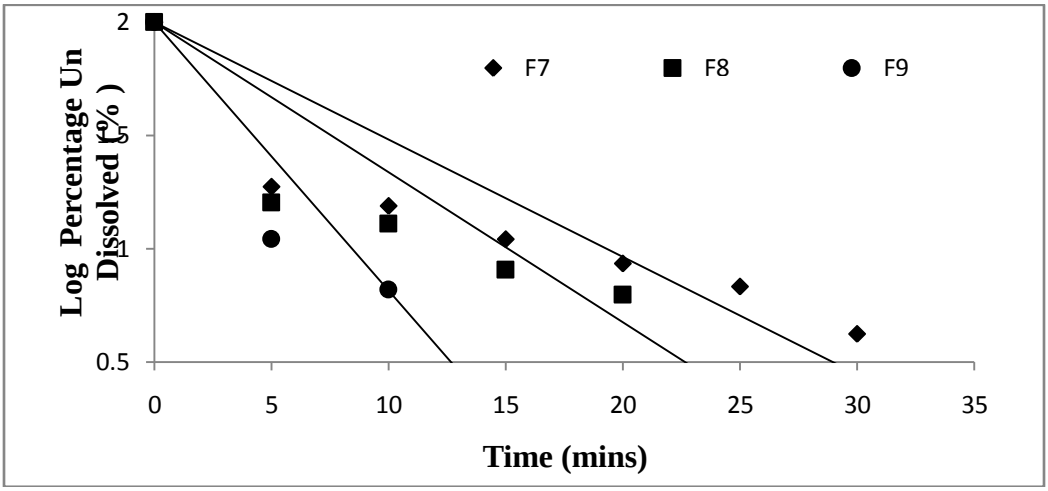


Figure 12: First Order Plots of Linaglitpin Tablets F7, F8 and F9 (with cross carmellose sodium 2, 4, 6% concentrations respectively)

The dissolution of linagliptin from the tablet formulations F7, F8 and F9 (2, 4, 6% cross carmellose sodium used) was quicker. Among the three formulations F6 (cross carmellose sodium 6%) gave highest dissolution rate (0.23 min^{-1}). The Linagliptin tablets containing cross carmellose sodium achieved more than 85% of the drug dissolved in 15 mins may be due to the cross carmellose sodium exhibits the wicking and swelling ability of the disintegrant is best utilized.

8. Dissolution Parameters: The dissolution data analysed as per zero order and first order kinetic model. The dissolution profiles and first order plots are shown in figures 7, 8, 9, 10, 11 and 12. The correlation coefficient (r) value are higher in first order model when compared to zero order models indicated the drug dissolution from the tablets followed first order model. From the zero order model the dissolution parameters like dissolution efficiency for 15 min (DE_{15} %), Percent dissolved in 10 min (PD_{10} %), time for 50% of dissolution of drug (T_{50}) from tablets and time for 90 Percent dissolution. From the first order model the dissolution rate constant (K_1) calculated and the results are given in Table 13.

Table 13: Dissolution Parameters of Linagliptin Prepared Tablets

Formulation Code	DE 15%	K_1 ($mins^{-1}$)	PD 10%	T_{50} (mins)	T_{90} (mins)
F1	55.8	0.13	89.72	3	12
F2	59.27	0.24	94.31	2.5	5
F3	62.33	0.66	100	2.5	4
F4	54.35	0.14	86.97	2.5	16.5
F5	57.89	0.18	91.93	3	7.5
F6	61.64	0.52	99.45	2.5	4.5
F7	53.2	0.09	84.59	3	17.5
F8	54.96	0.12	87.16	3	13.5
F9	58.42	0.23	93.39	3	7

Among three sets of formulations the dissolution parameter results indicated Crospovidone contain set of formulations gave highest dissolution rates and dissolution efficiency. In a set of formulation individually among 2, 4, 6% concentration of superdisintegrants contain formulations the super disintegrant 6% contained formulations gave high dissolution rate K_1 (0.66, 0.52, 0.23 for F3, F6, F9 respectively) and dissolution efficiency (62.33, 61.64, 58.42 for F3, F6, F9 respectively).

Based on the in vitro dissolution profiles and dissolution parameters the dissolution of Linagliptin from the prepared tablets were more in the crospovidone contain formulations when compared to other

formulations contain sodium starch glycolate and cross carmellose sodium as superdisintegrants. In crospovidone contain formulations F1 (2%), F2 (4%), F3 (6%). The formulation F3 gave highest dissolution rate K_1 (0.66 min^{-1}) and dissolution efficiency (62.33%), percentage dissolved in 10 min ($PD_{10\%}$) 100% and achieve T_{50} in 2.5 min, T_{90} in 4 min. Hence Crospovidone 6% contain formulation F3 concluded as an optimized formulation.

Conclusion

Linagliptin is an anti-diabetic drug used for the treatment of type 2 diabetes, it is belongs to the class of dpp-4 inhibitor. It has long half-life of about 8.6-23.9 hours and hence to achieve immediate therapeutic action it needs immediate release tablet formulation. Among the various techniques using superdisintegrants is a simple approach to formulate immediate release tablets. The objective of the present work is to formulate and evaluate a better formulation and to provide a tablet dosage form with satisfying parameters for the Linagliptin immediate release tablets including pre-formulation studies. The prepared tablets were evaluated for physical properties and *in-vitro* dissolution studies. Compatibility studies of Linagliptin and excipient has been done by FTIR.

Pre formulation and pre compression parameters were evaluated the formulation blends showed good flow properties. FTIR spectra's indicated no interaction between Linagliptin and excipients used in the formulation. The prepared tablets fulfilled the official specifications of tablets with regarded to drug content, hardness, friability, and weight variation and disintegration time. The dissolution of Linagliptin from the tablets obeyed first order kinetics. Based on the dissolution studies formulation F3 contains (6% crospovidone) gave rapid and highest dissolution rate and dissolution efficiency among all the formulations. As the concentration of superdisintegrants increases the dissolution rate and dissolution efficiency also increases. The results of the present work conclude that Linagliptin immediate release tablets could be employed using crospovidone as a superdisintegrants to achieve faster dissolution of Linagliptin.

RFERENCES

Angelo Avogaro and Guntram Schernthaner (2013). Achieving glycemic control in patients with type 2 diabetes and renal impairment. *Acta Diabetologica* **50**(3) 283-291.

Bhowmik B, Chiranjib B, Krishnakanth K, Pankaj A and Chandira RM (2009). Fast Dissolving Tablet: An Overview. *Journal of Chemical and Pharmaceutical Research* **1**(1) 163-177.

Bikashapathi D, Saikrishna K, Kumar UA and Sabitha G (2011). Fast Dissolving Table: An Update. *International Research Journal of Pharmacy* **2**(3) 45-53.

Deshmkh H, Chandrashekhara Nagesh, Murade A and Usgaunkar S (2012). Superdisintegrants: A Recent Investigation and Current Approach. *Asian Journal of Pharmaceutical Technology and Innovation* **2** 19-25.

Elena Sebokova, Andreas Christ D, Markus Boehringer and Jacques Mizrahi (2013). Dipeptidyl Peptidase IV Inhibitors: The Next Generation of New Promising Therapies for the Management of Type 2 Diabetes. *Current Topics in Medicinal Chemistry* **7**(6) 547-555.

Formulation (No Date). HIV/AIDS Antiretroviral Drugs Classification. Available: http://formulationvinensia.com.

Gnana Chaitanya N, Shailaja D, Subrahmanyam KV and Shiva Sri Krishna (2012). Formulation and evaluation of fast disintegrating tablets of sitagliptin phosphate. *International Journal of Pharma World Research* **3**(3) 1-14.

Gopinath R and Naidu RAS (2011). Pharmaceutical Preformulation Studies – Current Review. *International Journal of Pharmaceutical & Biological Archives* **2**(5) 1391-1400.

Hemanth Kumar G, Jaganathan K, Sambath Kumar R and Perumal P (2012). Formulation and in-vitro evaluation of bilayer floating tablets of metformin hydrochloride and sitagliptin phosphate. *International Journal of Advanced Pharmaceutics* **2**(2) 64-81.

Julienne Kirk K and Elizabeth Oldham C (2008). Sitagliptin and Vildagliptin: Efficacy of Therapy in Type 2 Diabetes. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* **2**(3) 162-171.

Kailash Vilegave, Gali Vidyasagar and Pratibha Chandankar (2013). Preformulation Studies of Pharmaceutical New Drug Molecule and Products: An Overview. *American Journal of Pharmacy and Health Research* **1**(3) 1-20.
Kaur T, Gill B, Kumar S and Gupta GD (2010). Mouth Dissolving Tablets: A Novel Approach to Drug Delivery. *International Journal of Current Pharmaceutical Research* **3** 1-7.
Kumar GP and Nirmala R (2012). Fundamental Aspects of Superdisintegrants: A Concise Review. *Journal of Global Pharma Technology* **4** 1-12.
Mohanachandran PS, Sindhumol PG and Kiran TS (2011). Superdisintegrants: An Overview. *International Journal of Pharmaceutical Sciences Review and Research* **6** 105-109.
Mukesh Gohel C, Rajesh Parikh K, Bansari Brahmbhatt K and Shah AR (2007). Preparation and assessment of novel co-processed superdisintegrants consisting of crospovidone and sodium starch glycolate: A Technical Note. *AAPS PharmSciTech* **8**(1) E1-E6.D.
Nancy Thornberry A and Ann Weber E (2013). Discovery of JANUVIA™ (Sitagliptin): A Selective Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type2 Diabetes. *Current Topics in Medicinal Chemistry* **7**(6) 557-568.
Nasser Mikhail and Dennis Cope (2013). Appraisal of Saxagliptin as Treatment of Type 2 Diabetes. *Current Drug Therapy* **5**(2) 111-117.
Pharmainfo.net (No Date). Evaluation of tablet. http://www.pharmainfo.net/satheeshbabu/blog/evaluation-tablet.
Ratnaparkhi Mukesh, Dhage Kiran, Chaudhari Shilpa and Salvankar Shailendra (2012). Formulation and evaluation of immediate release tablets of metformin HCl and glibenclamide using different superdisintegrants. *PharmTech Medica* Available: www.pharmtechmedica.com **1**(3) 81-86.
Ritesh Agrawal, Pratima Jain and Dikshit SN (2013). Linagliptin: A novel methylxanthin based approved dipeptidyl peptidase-4 inhibitor. *Current Drug Targets* **13**(7) 970-983.
RxList (No Date). Type 2 Diabetes: Causes, Symptoms, Treatments. Available: www.rxlist.com.
Ryuichi Morishita and Sho-ichi Yamagishi (2013). A diabetes treatment strategy to reduce the risk of cardiovascular events: Clinical and Potential benefits of linagliptin. Immune, Endocrine and Metab. *Agents in Medicinal Chemistry* **13**(2) 81-88.
Sandeep Nyol and Gupta MM (2013). Formulation development and evaluation of immediate drug release tablet dosage form of sitagliptin phosphate. *International Journal of Pharmaceutical Research and Development* **5**(3) 101-113.
Somsuvra Ghatak B, Devang Patel S, Neeraj Shanker, Ambrish Srivastava, Shrikalp Deshpande S and Shital Panchal J (2013). Linagliptin: A novel xanthine-based dipeptidyl peptidase-4 inhibitor for treatment of type II diabetes mellitus. *Current Diabetes Reviews* **7**(6) 325-335.
Somsuvra Ghatak B, Devang Patel S, Neeraj Shanker, Ambrish Srivastava, Shrikalp Deshpande S and Shital Panchal (2013). Alogliptin: A Novel Molecule for Improving Glycemic Control in Type II Diabetes Mellitus. *Current Diabetes Reviews* **6**(5) 410-421.
www.drugbank.com
www.medicinenet.com
www.wikipedia.com