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# Formulation and Evaluation of Effects of Superdisintegrants on Immediate Release Tablet of Linagliptin, a DPP-4 Inhibitor

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**Abstract**

The study aimed to develop and evaluate an immediate-release tablet dosage form of Linagliptin. Different concentrations (ranges 5-10%) of super-disintegrants, Croscarmellose sodium (CCS), and Sodium starch glycolate (SSG) were used to prepare nine tablet dosage forms (F1 to F9) through the direct compression method. The compatibility of the formulations was evaluated by FTIR to reveal any possible drug-excipient interactions and it was proved to be compatible with all formulations. Precompression (bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose) and post-compression parameters (weight variation, hardness, thickness, and friability) were analyzed for all tablets and the results were found satisfactory as well as within limits as per USP guidelines. All the formulated batches (F1 to F9) exhibited disintegration of tablets within 2 minutes, where formulation F9 represented the lowest disintegration time (51±3 sec) which was also found significantly better than the marketed product (310±5 sec). In terms of drug dissolution, 90% of drug release was observed for all nine formulations within 45 minutes and formulation F9 (5% CCS and 5% SSG) illustrated the rapid and highest dissolution rate compared to the marketed one's, 100% drug release at 20 minutes and 91.77 % drug release at 30 minutes successively. The respective data sets of drug release were mathematically fitted to several kinetic models and for all formulations, drug release pattern obeyed first-order kinetics amongst those, formulation F2 (r2= 0.98), F4 (r2= 0.99), F5 (r2= 0.98), and F9 (r2= 0.97) were found to be best fitted in this kinetic norm. Based on disintegration time and dissolution data comparison to a brand leader market product, F9 was experienced as the best formulation. Furthermore, it was observed that if SSG and CCS were combined, then these two parameters were more improved compared to their separate uses. Thus, incorporation of the optimum amount of super-disintegrants in a formulation showed rapid swelling, faster disintegration as well as ease of dissolution of tablet dosage forms.

**Keywords:** Linagliptin, Immediate release tablet dosage form, Superdisintegrants, Croscarmellose sodium, Sodium starch glycolate.

## Introduction

Diabetes mellitus is a chronic disease that involves the metabolic and endocrine system of the body and careful considerations of both pharmacological and non-pharmacological interventions are inevitable, because a failure of proper dose and dosage form can lead to critical situations such as hypoglycemic coma and hyperglycemia (Inzucchi *et al.*, 2012).

Linagliptin, chemically named as (R)-8-(3-Aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione with a molecular formula $C_{25}H_{28}N_8O_2$ and molecular weight 472.553 g/mol is one of the prominent anti-hyperglycemic agents of selective DPP-4 (Dipeptidyl peptidase-4) enzyme inhibitor to prevent post-prandial hyperglycemia (Drug bank., 2018 and Pub Chem., 2018). With a prolonged

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terminal half-life of approximately 12 hours, inhibition of DPP-4 activity by Linagliptin is sustained, which indicates the appropriateness of once-daily dosing (Vella, 2012) and immediate-release tablet dosage form with its rapid drug release performance serves the purpose of quick entry of this drug molecule into the systemic circulation since, most of the anti-glycemic drugs are taken just before the meal (Hohl *et al*., 2014).

Drug release from tablets depends on the release profile of the disintegrant and starch is the most commonly used one in tablet formulation which does not exhibit superior performance in terms of faster drug release (Bhuyian *et al*., 2013).

In this experiment, an attempt was made to improve Linagliptin immediate-release tablet formulation by implementing varying concentrations of super-disintegrants (CCS and SSG) to aid faster disintegration, dissolution, and absorption of the drug to achieve prompt hypoglycemic action.

## Materials and Methods

### Materials

From Incepta Pharmaceuticals Limited, Bangladesh as a kind gesture Linagliptin was donated and throughout the study, this drug substance was employed as a working standard to perform quantitative analysis and to manufacture experimented formulations. Sodium Starch Glycolate (SSG), Croscarmellose sodium (CCS), and Lactose were purchased from Colorcon Asia Pvt. Ltd, India whereas, from Wilfrid Smith Ltd. UK Magnesium Stearate and Talc were procured. Moreover, Methanol and Hydrochloric acid (HCl) were collected from Scharlab S.L., Spain, and Merck K Ga A, Germany respectively. Furthermore, a supply of deionized water was obtained by a water purifier system of Millipore Milli-Q from Bedford, MA, USA.

### Methods

*Formulation design:* Immediate release formulation of tablets requires certain excipients namely diluent, disintegrant, binder, glidant, and lubricant (Dave, 2008). In this certain instance, formulations were designed using a genre of disintegrants known as super-disintegrants due to their ability to cause immediate disintegration of the compressed tablets. Lactose was used as diluent due to its very good compressibility and performance as a binder as well. Glidants and lubricants are required in all tablet formulations and in this particular experiment talc and magnesium stearate were used to serve the purpose. In this study, two different super-disintegrants at different concentrations (from 2.5% to 10% of tablet weight) were used for the development of a Linagliptin immediate-release tablet by direct compression method. According to the trial, formulations F1 to F9 were developed, and the impact of formulation of super-disintegrants on drug release profile was evaluated (Carter, 2002). SSG at 5% - 10% of tablet weight was used in F1 to F3 as the sole super-disintegrant. Whereas, in F4 to F6 CCS from 5% - 10% of tablet weight was used but in F7 to F9 combination of SSG and CCS at different concentrations (2.5% - 5% of each) was used as superdisintegrating agents (Table 1).

*Evaluation of physical properties of the formulation mix:* Powder blends of the formulations were subjected to pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio to determine physical properties i.e. nature of flow and compressibility. The evaluation was done by using all the strategies as laid out in pharmacopoeia. (World Health Organization, 2012 and Pharmacopoeia, U.S., 2004).

*Angle of repose:* The angle of repose is the maximum slope angle of non-cohesive material. For the determination of the angle of repose of powder a ruler, a petridish, a stand, a funnel, and a tape was used. The powder was allowed to flow through the funnel fixed to a stand at a definite height, usually 10 cm. The angle of repose (φ) was then calculated by measuring the height (h) and radius (r) of the heap of granules formed.

$$\varphi = \tan\text{-}1(h/r)$$

**Table 1. Design of formulations (all measurements are in mg).**

| Formulation | Linagliptin | SSG | CCS | Lactose | Mg- stearate | Talc | Total weight |
|---|---|---|---|---|---|---|---|
| F-1 | 5 | 10 | - | 182.5 | 1.5 | 1 | 200 |
| F-2 | 5 | 15 | - | 177.5 | 1.5 | 1 | 200 |
| F-3 | 5 | 20 | - | 172.5 | 1.5 | 1 | 200 |
| F-4 | 5 | - | 10 | 182.5 | 1.5 | 1 | 200 |
| F-5 | 5 | - | 15 | 177.5 | 1.5 | 1 | 200 |
| F-6 | 5 | - | 20 | 172.5 | 1.5 | 1 | 200 |
| F-7 | 5 | 5 | 5 | 182.5 | 1.5 | 1 | 200 |
| F-8 | 5 | 7.5 | 7.5 | 177.5 | 1.5 | 1 | 200 |
| F-9 | 5 | 10 | 10 | 172.5 | 1.5 | 1 | 200 |

*Loose bulk density and tapped bulk density:* For the measurement of bulk density and tapped density, a graduated cylinder was used. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by measuring a quantity of 4 g of powder blend from each formulation and was introduced into a 10ml measuring cylinder. Afterward, initial volume was observed then the cylinder was allowed to tap until no further change in volume was noted (Aulton, 2002). By using the following formula bulk density and tapped density were calculated-

$$\text{Bulk density, LBD } (\rho_b) = \frac{\text{Bulk volume of the powder}}{\text{Weight of the powder}}$$

$$\text{Tapped density, TBD } (\rho_t) = \frac{\text{Tapped volume of the powder}}{\text{Weight of the powder}}$$

*Carr's Index and Hausner's ratio:* Carr's index or Carr's compressibility index and Hausner's ratio are a sign of compressibility and flowability of powder blend which is important for dose uniformity. These parameters are measured by the following equations.

$$\text{Carr's Index (\%)} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{TBD } (\rho t)}{\text{LBD } (\rho b)}$$

*Evaluation of compatibility:* Physical and chemical interactions between drugs and excipients will affect the chemical, physical, therapeutic properties and stability of the dosage form (Monton *et al.*, 2014). To conduct the compatibility study mortar, pestle, FTIR instrument (UATR Two, PerkinElmer, USA) were used. Peak frequencies of standard Linagliptin were taken followed by 2 mg of formulated crushed tablets powder by placing the samples under sample platform of FTIR machine and raising the pressure to 60psi by pressure tower and compression tip. Then peak frequencies of both Linagliptin standard and formulated tablets were compared (Patel *et al.*, 2015).

*Manufacture of tablets:* Electronic balance (AY220, Shimadzu, Japan), vortex mixer (Biobase, China), mortar, pestle, mesh 40 sifter, and rotary tablet press (Emtech, USA) were used to manufacture nine different batches of tablets by direct compression. Active Pharmaceutical Ingredient (API), super-disintegrants, and other excipients were weighed in milligrams in an electronic balance separately for 30 tablets per formulation according to proposed formulations. API, super-disintegrants (CCS, SSG), lactose, and magnesium stearate were sieved thoroughly by mesh 40 sifter followed by

mixing properly for 15 minutes. After that talc was added and mixed again for another 5 minutes. Then, tablets were compressed by rotary tablet press and stored in an airtight container at room temperature in the laboratory for further study (Tousey, 2015).

*Evaluation of physical characteristics of formulated tablets:* These studies were conducted according to the official method to evaluate if any changes took place in the physical properties of compressed tablets due to the operational variation in rotary tablet press machine (Chandrasekaran, 2011 and Bhowmik *et al.,* 2012).

*Weight variation:* To study weight variation, 20 tablets from each formulation were randomly weighed using an electronic balance, and then the individual weight was compared with the average weight for determining weight variation.

*Friability:* The Friability of tablets was determined by using a Friability tester (EF-2, Electrolab, India). Initially, 10 tablets were weighed and machine rotated at 25 rpm for 4 min. After removal of fines, the tablets were again weighed and the percentage of weight loss was calculated.

$$\text{Friability} = \frac{\text{Weight of the tablet before testing(W1)} - \text{Weight of tablet after testing(W2)}}{\text{Weight of tablet before testing (W1)}} \times 100$$

*Thickness uniformity:* Five tablets from each batch were considered for thickness measurement by Vernier calipers and average values were calculated.

*Hardness measurement:* The compression force of immediate-release tablets was kept low for better disintegration. Five tablets from each batch were measured by using the YD-1 tablet hardness tester (Saintyco, China) and the average was calculated.

*Evaluation of disintegration time:* Disintegration time is measured for evaluating the tablet's quality and also for determining batch consistency and uniformity. In this experiment, 6 tablets from each batch with a disc were placed in 6 tubes of the basket of USP tablet disintegration test apparatus (ED-2L, Electrolab, India) filled with 900 ml 0.1 N HCl as disintegration medium maintained at 37±2º C. After measuring the disintegration time of formulated tablets marketed product's disintegration time was also measured. The time was taken in seconds and complete disintegration of tablets was measured and recorded.

*Preparation of standard curve:* A standard curve was prepared for determining the concentration of drug release by comparing the unknown concentration of samples to a set of standard samples of known concentration during the dissolution study. Test tubes, volumetric flask, 5 ml pipette, cuvettes, methanol, 0.1 N HCl, Linagliptin, and UV spectrophotometer (UVD-3200, Labomed, USA) were used during the preparation of the standard curve. Precisely weighed 10 mg of Linagliptin was dissolved in 100 ml of methanol into a 100 ml dried and clean volumetric flask leaving a stock solution of 100 µg/ml. Next, the stock solution was further diluted 10 times by 0.1 N HCl to a concentration of 10 µg/ml solution. The wavelength of maximum absorbance (λ max) of the drug was determined by using UV spectrophotometer in the wavelength range of 200-500 nm using 0.1N HCl as a blank sample (Debnath *et al.,* 2015).

*Evaluation of drug dissolution:* Distilled water, 0.1N HCl, USP Dissolution Apparatus II of Electrolab, India, 5ml pipettes, test tubes, beaker, cuvettes, and UV spectrophotometer were used to evaluate drug dissolution. The dissolution rate of the prepared tablets, as well as the marketed product, were studied in 900 ml 0.1N HCl using USP Dissolution Apparatus II 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 during the test. Samples of dissolution medium (5 ml) were pulled out and filtered through a filter of 0.45µm pore size at specific time intervals and assayed for the presence of Linagliptin by measuring the absorbance at 296 nm.

*In vitro release kinetics models:* In-vitro release kinetics were determined to measure the release of API from a dosage form with time. To study Zero-order drug release kinetics data obtained from in-vitro drug release were plotted as the cumulative amount of drug released versus time in an hour and for First-order drug release kinetics, it was plotted as log cumulative percentage of drug remaining versus time in an hour. Cumulative percentage drug release versus square root of time was employed to study Higuchi release kinetics model and to study Korsmeyer-Peppas drug release model log cumulative percentage drug release versus log time was plotted. Finally, to study the Hixson-Crowell drug release kinetics, data obtained from the in-vitro release were plotted as the cube root of percentage drug remaining versus time in an hour (Ramteke *et al*., 2014).

*Statistical analysis:* Disintegration time and percent drug release of formulated products and reference marketed product obtained after 30 minutes were compared by performing unpaired t-test through Graph pad prism (version 7) and Microsoft excel 2013 to estimate the difference between two products.

## Results and Discussion

*Physical characteristics of pre-compression powder mix:* In this experiment, all 9 formulations indicated good flow properties as the Carr's index was within the range of 14.22±1.551 - 20.60±2.802, Hausner's ratio 1.21±0.079 - 1.34±0.180 and Angle of Repose 25.1±0.022 - 29.5±0.022 (Table 2) since, Carr's index up to 20, Hausner's ratio less than 1.25 and Angle of Repose less than 40 indicate fair to excellent flow properties of granule (Pharmacopoeia, U.S., 2004).

**Table 2. Physical parameters of Linagliptin granules.**

| Formulation | Bulk Density (g/ml) | Tapped Density (g/ml) | Angle of Repose (ºC) | Hausner's Ratio | Carr's Index (%) |
|---|---|---|---|---|---|
| F1 | 0.642 ±0.021 | 0.785 ±0.010 | 29.5 ±0.022 | 1.22 ±0.051 | 18.217±2.351 |
| F2 | 0.659 ±0.011 | 0.798 ±0.007 | 26.7 ±0.016 | 1.21 ±0.079 | 17.42 ±1.105 |
| F3 | 0.631 ±0.028 | 0.792 ±0.016 | 25.1 ±0.022 | 1.26 ±0.020 | 20.33 ±1.021 |
| F4 | 0.697 ±0.005 | 0.801 ±0.004 | 27.8 ±0.014 | 1.32 ±0.047 | 14.92 ±2.108 |
| F5 | 0.681 ±0.001 | 0.782 ±0.026 | 26.3 ±0.001 | 1.34 ±0.180 | 14.83 ±2.719 |
| F6 | 0.674 ±0.032 | 0.785 ±0.013 | 25.2 ±0.033 | 1.29 ±0.010 | 16.47 ±0.985 |
| F7 | 0.646 ±0.020 | 0.809 ±0.037 | 27.7 ±0.027 | 1.25 ±0.033 | 20.15 ±1.630 |
| F8 | 0.665 ±0.013 | 0.802 ±0.011 | 27.2 ±0.019 | 1.28±0.0112 | 20.60 ±2.802 |
| F9 | 0.682 ±0.018 | 0.779 ±0.008 | 25.9 ±0.002 | 1.30 ±0.050 | 14.22 ±1.551 |

*Compatibility evaluation:* Excipients used in the formulation were analyzed with Linagliptin using FTIR to evaluate any chemical interactions between drug and excipients. Figure 1 (A to D) depicts the FTIR spectrum of Linagliptin as well as various combinations tested in this work. As we can see there were no major variations in the spectrum that might indicate degradation of the drug or any type of chemical bonding so, compatibility of the excipients used in this experiment to Linagliptin is evident.

*Physical properties of formulated tablets:* Uniform thickness was found in the range of 4.82±0.03 - 4.89±0.04 in manufactured tablets of 9 formulations. In terms of weight variation average percentage of deviation of formulated tablets was found within the limit. Also, below 1% friability was observed in experimented formulations that comply with the compendial specifications. Moreover, uniformity in the hardness of the tablets was also observed (Table 3).

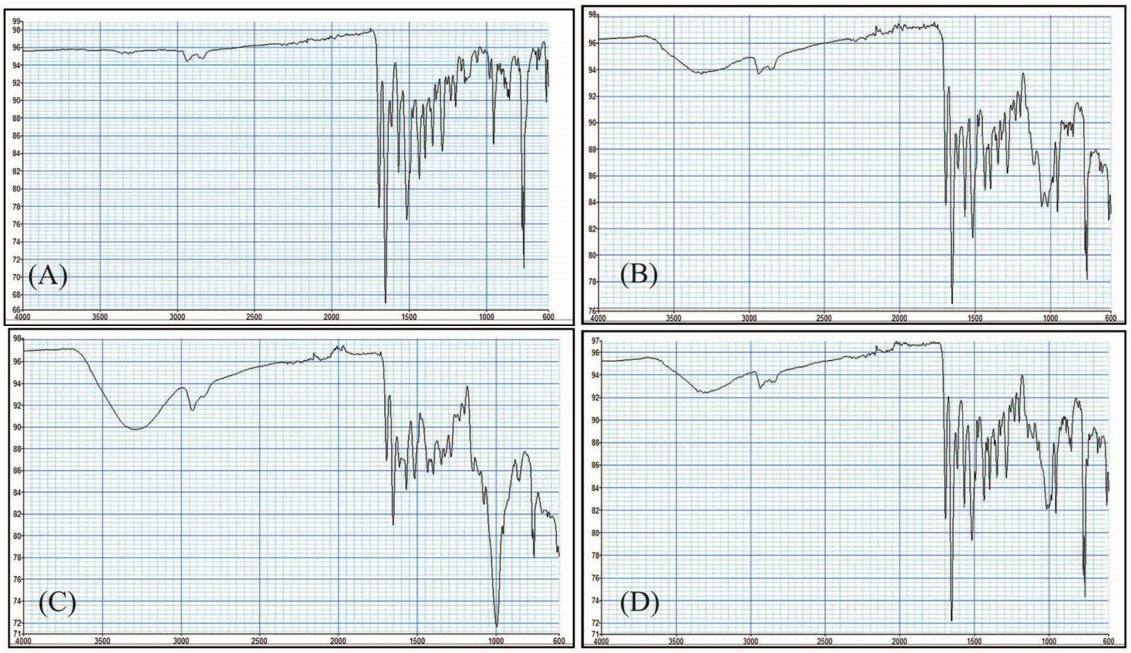


Figure 1. FTIR spectrum of (A) Linagliptin, (B) Linagliptin and CCS mix, (C) Linagliptin and SSG mix, and (D) Physical mixer of the powder blend.

**Table 3. Physical properties of Linagliptin immediate-release tablets (F1 to F9).**

| Formulation | Average Weight Variation mg (n=20) Mean ± SEM | Hardness Kg/cm2 (n=5) Mean ± SEM | Thickness mm(n=5) Mean ± SEM | Friability% (n=20) Mean ± SEM |
|---|---|---|---|---|
| F1 | 199.4±0.5 | 3.07±0.05 | 4.88±0.01 | 0.76±0.012 |
| F2 | 198.5±0.8 | 3.01±0.02 | 4.82±0.03 | 0.32±0.127 |
| F3 | 200.2±0.3 | 3.09±0.07 | 4.87±0.01 | 0.82±0.061 |
| F4 | 199.7±0.7 | 3.07±0.05 | 4.89±0.04 | 0.72±0.018 |
| F5 | 201±0.5 | 3.05±0.04 | 4.88±0.03 | 0.37±0.122 |
| F6 | 197.9±0.6 | 3.04±0.02 | 4.86±0.02 | 0.78±0.138 |
| F7 | 202.4±0.8 | 3.07±0.02 | 4.87±0.01 | 0.27±0.325 |
| F8 | 199.3±0.1 | 3.03±0.05 | 4.88±0.01 | 0.84±0.110 |
| F9 | 200.9±0.2 | 3.09±0.04 | 4.89±0.03 | 0.52±0.090 |

*Evaluation of disintegration time:* Disintegration time evaluation is incredibly vital for immediate release tablets as it assists swallowing and additionally plays an important role in increasing drug absorption, hence promoting bioavailability. The disintegration time of prepared tablets was within the range. All formulated tablets in this study provided better disintegration time compared to the marketed product and in statistical comparison, the results were found significant also (Table 4 & 5). This significant difference in disintegration time can be attributed to the use of super-disintegrants. While it is not specifically known whether the marketed product used any super-disintegrant but the stark difference in disintegration time indicates that the marketed product did not utilize any such ingredient.

**Evaluation of drug release**

*Determination of λ max:* Linagliptin standard solution gave maximum absorbance at the wavelength of 296 nm. For further analysis of this drug substance in solution, this wavelength was employed. Figure 2 shows the analyzed UV spectrum of Linagliptin.

**Table 4. Comparison of disintegration time of formulated products and market product.**

| Tablet | Tablet Disintegration Time (sec) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 | F-9 | Market Product |
| T-1 | 107 | 91 | 78 | 111 | 95 | 80 | 90 | 75 | 53 | 314 |
| T-2 | 102 | 90 | 72 | 110 | 92 | 78 | 92 | 77 | 51 | 306 |
| T-3 | 103 | 92 | 75 | 105 | 90 | 82 | 91 | 80 | 49 | 313 |
| T-4 | 108 | 89 | 77 | 106 | 91 | 77 | 87 | 74 | 49 | 312 |
| T-5 | 106 | 88 | 73 | 109 | 89 | 81 | 86 | 78 | 52 | 309 |
| T-6 | 104 | 90 | 76 | 110 | 94 | 76 | 88 | 79 | 52 | 307 |
| Avg. | 105 | 90 | 75 | 108 | 92 | 79 | 89 | 77 | 51 | 310 |

**Table 1. Comparison of t-test values of disintegration time.**

| Formula | t-Value | Degree of Freedom | p-Value | Inference |
|---|---|---|---|---|
| F-1 | 173.3 | 5 | <0.0001 | Significant |
| F-2 | 164.0 | 5 | <0.0001 | Significant |
| F-3 | 243.2 | 5 | <0.0001 | Significant |
| F-4 | 83.4 | 5 | <0.0001 | Significant |
| F-5 | 127.3 | 5 | <0.0001 | Significant |
| F-6 | 178.9 | 5 | <0.0001 | Significant |
| F-7 | 122.3 | 5 | <0.0001 | Significant |
| F-8 | 118.5 | 5 | <0.0001 | Significant |
| F-9 | 149.5 | 5 | <0.0001 | Significant |

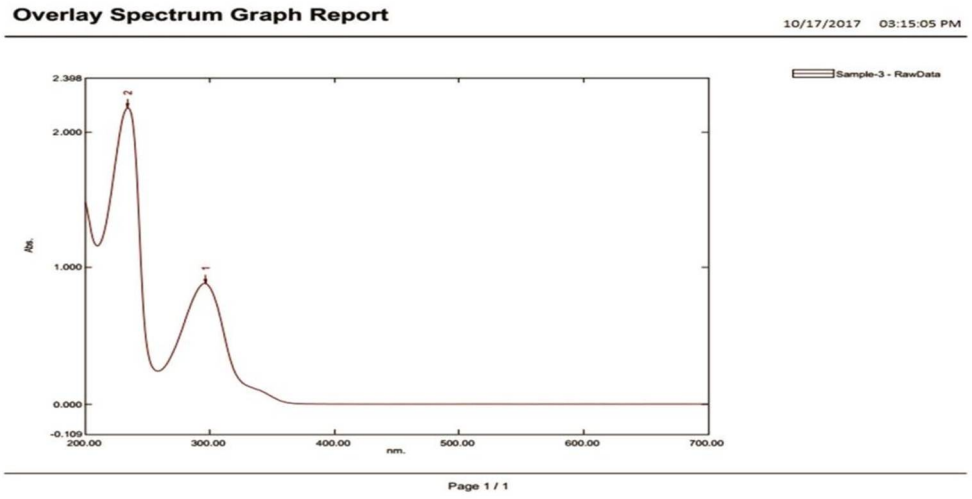


Figure 2. UV spectrum of Linagliptin**.**

*Calibration curve preparation:* Stock solution of Linagliptin (1000 µg/ml) was appropriately diluted with 0.1N HCl to get solutions containing 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 µg/ml of drug concentration. The absorbance of those solutions was determined at 296 nm and with a regression coefficient ($R^2$) of 0.9985 calibration curve of Linagliptin was prepared (Figure 3).

*Evaluation of dissolution data:* In-vitro drug release studies of the prepared tablets were done using 0.1N HCl maintained at 37±2°C as dissolution media. Dissolution data present in table 6 shows that, as the concentration of the disintegrant increased, the time required for the complete dissolution of the drug decreased i.e. the amount of drug released at a specific time interval was increased. It was also observed that when two super-disintegrants were combined, drug dissolution was better compared to the same amount of any single super-disintegrant.

The impact of super-disintegrants on the dissolution of drugs has been documented before. Researchers have found that super-disintegrants such as SSG and CCS significantly increase drug dissolution rates (Rojas *et al.*, 2012 and Setty *et al.*, 2008). So, it is not surprising that a similar result was observed here. When compared with the marketed product, the percentage of drug released was significantly higher for the formulated products as inferred from unpaired t-test when considering the percentage of drug release at 30 minutes (Table 7 & 8) which proves the further advantage of experimented formulations over the traditionally formulated market product.

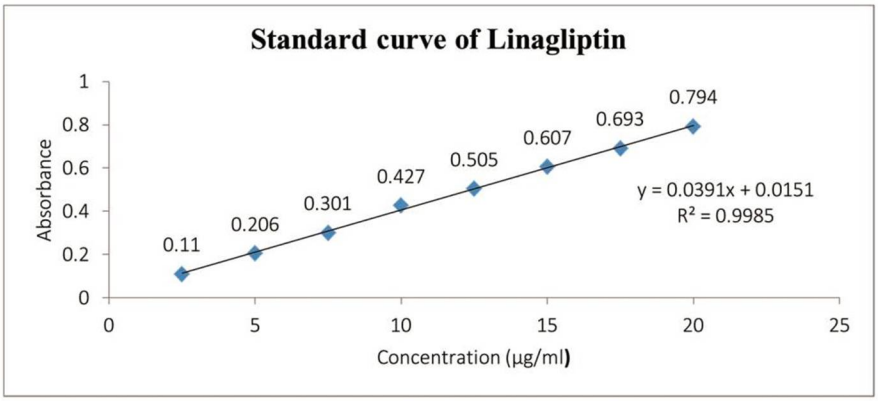


Figure 3. Standard curve of Linagliptin.

**Table 6. Evaluation of percentage of drug release.**

| Time (Min) | Drug Release Percentage | | | | | | | | | Market Product |
|---|---|---|---|---|---|---|---|---|---|---|
| | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 | F-9 | |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 83.39 | 85.41 | 89.71 | 81.09 | 85.04 | 88.17 | 86.19 | 91.55 | 92.71 | 57.53 |
| 10 | 90.73 | 92.39 | 94.64 | 89.21 | 90.25 | 91.29 | 91.27 | 96.84 | 98.35 | 70.94 |
| 15 | 95.19 | 97.39 | 97.95 | 93.18 | 94.99 | 95.31 | 94.08 | 98.43 | 99.96 | 75.04 |
| 20 | 98.12 | 99.26 | 99.33 | 97.83 | 98.97 | 98.54 | 97.81 | 99.67 | 100 | 82.01 |
| 30 | 99.21 | 99.91 | 100 | 99.03 | 99.39 | 100 | 98.85 | 100 | 100 | 91.77 |
| 45 | 100 | 100 | 100 | 99.95 | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 7. Percentage of drug release at 30 minutes.**

| Tablet | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 | F-9 | Market Product |
|---|---|---|---|---|---|---|---|---|---|---|
| T-1 | 99.01 | 99.98 | 99.98 | 98.95 | 99.4 | 100 | 98.9 | 100 | 100 | 91.82 |
| T-2 | 98.97 | 99.93 | 100 | 99.15 | 99.47 | 100 | 98.91 | 99.97 | 100 | 91.56 |
| T-3 | 99.33 | 99.91 | 100 | 99.21 | 99.21 | 100 | 98.89 | 100 | 100 | 91.78 |
| T-4 | 99.08 | 99.87 | 99.99 | 98.89 | 99.1 | 100 | 98.93 | 99.96 | 100 | 91.93 |
| T-5 | 99.51 | 100 | 100 | 99.22 | 99.73 | 99.98 | 98.87 | 100 | 100 | 91.79 |
| T-6 | 99.36 | 99.77 | 100.03 | 98.76 | 99.43 | 100.02 | 98.6 | 100.07 | 100 | 91.74 |
| Avg. | 99.21 | 99.91 | 100 | 99.03 | 99.39 | 100 | 98.85 | 100 | 100 | 91.77 |

**Table 8. Comparison of unpaired t-test value on drug release percentage at 30 minutes.**

| Formula | t-Value | Degree of Freedom | P-Value | Inference* |
|---|---|---|---|---|
| F-1 | 78.37 | 5 | < 0.0001 | Significant |
| F-2 | 134.2 | 5 | < 0.0001 | Significant |
| F-3 | 157.4 | 5 | < 0.0001 | Significant |
| F-4 | 69.1 | 5 | < 0.0001 | Significant |
| F-5 | 63.53 | 5 | < 0.0001 | Significant |
| F-6 | 163.1 | 5 | < 0.0001 | Significant |
| F-7 | 108.1 | 5 | < 0.0001 | Significant |
| F-8 | 154.3 | 5 | < 0.0001 | Significant |
| F-9 | 166.2 | 5 | < 0.0001 | Significant |

**Table 9. Release rate constants and $R^2$ values for different formulations along with the best-fitted model and drug release mechanism.**

| Formulation No. | Zero-order | | First-order | | Higuchi | | Hixon-Crowell | | Korsmeyer-peppas | | Best fit model | Release mechanism |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | $K_0$ | $R^2$ | $K_1$ | $R^2$ | $K_h$ | $R^2$ | $K_{hc}$ | $R^2$ | n | | |
| F-1 | 0.38 | 86.2 | 0.95 | -4.13 | 0.69 | 106.0 | 0.81 | 5.15 | 0.917 | 0.085 | First-order and Korsmeyer-Peppas | Fickian Release |
| F-2 | 0.36 | 84.8 | 0.98 | -6.97 | 0.67 | 105.6 | 0.77 | 5.34 | 0.865 | 0.074 | First-order | Fickian Release |
| F-3 | 0.33 | 81.7 | 0.95 | -6.06 | 0.64 | 103.7 | 0.72 | 5.25 | 0.953 | 0.064 | First-order and Korsmeyer-Peppas | Fickian Release |
| F-4 | 0.40 | 88.3 | 0.99 | -4.26 | 0.71 | 107.1 | 0.79 | 4.93 | 0.929 | 0.100 | First-order and Korsmeyer-Peppas | Fickian Release |
| F-5 | 0.37 | 85.9 | 0.98 | -5.60 | 0.69 | 105.9 | 0.80 | 5.33 | 0.915 | 0.080 | First-order and Korsmeyer-Peppas | Fickian Release |
| F-6 | 0.35 | 83.9 | 0.92 | -4.88 | 0.66 | 104.5 | 0.78 | 5.44 | 0.970 | 0.075 | Korsmeyer-Peppas and First order | Fickian Release |
| F-7 | 0.37 | 84.6 | 0.93 | -3.85 | 0.68 | 104.7 | 0.80 | 5.04 | 0.955 | 0.071 | Korsmeyer-Peppas and First order | Fickian Release |
| F-8 | 0.31 | 80.0 | 0.95 | -6.83 | 0.62 | 102.7 | 0.68 | 5.09 | 0.914 | 0.050 | First-order and Korsmeyer-Peppas | Fickian Release |
| F-9 | 0.30 | 78.7 | 0.97 | -13.0 | 0.60 | 102.2 | 0.55 | 4.91 | 0.911 | 0.057 | First-order and Korsmeyer-Peppas | Fickian Release |
| Market product | 0.65 | 103.6 | 0.95 | -1.97 | 0.91 | 111.3 | 0.951 | 5.41 | 0.993 | 0.250 | Korsmeyer-Peppas, First-order, Hixson-Crowell and Higuchi | Fickian Release |

*Mathematical modeling of drug release:* From the obtained dissolution data of 9 formulations and market product respective modifications were brought to fit that information in distinct kinetic models and through graphical identification of regression coefficient drug release mechanism was demonstrated (Figure 4). All 9 formulations showed fickian transport which infers diffusion and solvent transport rate controlled drug release from the formulations where the process of polymeric chain relaxation was dominated by diffusion (Bruschi, 2015). In table 9 respective results of the model-dependent kinetic analysis along with the best-fitted model and drug release mechanism are represented.

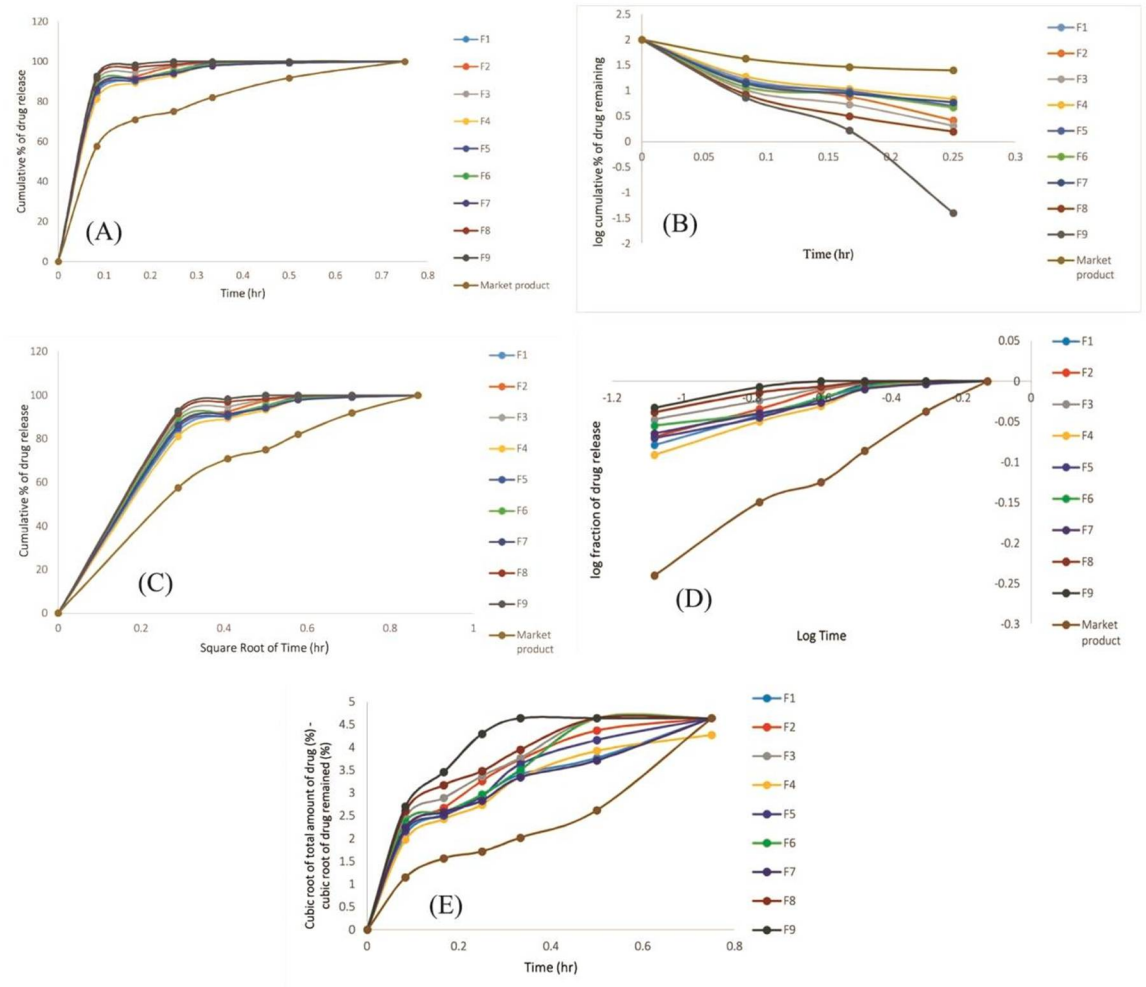


Figure 4. Release kinetic curves for F1 to F9 and market product (A) Zero order (B) First order (C) Higuchi (D) Korsmeyer-Peppas and (E) Hixson-Crowell.

In this study, manufactured immediate release formulations showed a good fit with the Korsmeyer-Peppas model along with fickian transport of drug release. Also, abiding first-order release kinetics in all manufactured formulations indicate the suitability of formulated tablets as immediate-release dosages form. Particularly among the formulations, F9 demonstrated 100 percent of drug release at just 20 minutes while at that time it was only 82.01 percent for the marketed product. Moreover, in terms of disintegration time formulations F1 to F9 and market product represented disintegration time 105±3, 90±2,

75±3, 108±3, 92±3, 79±3, 89±3, 77±3, 51±2, 310±4 sec. respectively, which also proves the uniqueness of formulation F9 over other formulations and brand leader market products considering disintegration time.

## Conclusion

The results of the physical characteristics of the pre-compression powder mix were satisfactory as the angle of repose of the formulations (F1 to F9) were less than 30° which indicates good flow properties of the granules. These results were further supported by lower Carr's index and Hausner's ratio. Most of the formulations (F1 to F9) showed Carr's index between 14.22±1.551 - 20.60±2.802 and it indicates fair flow property which was further backed by the suitable Hausner's ratio 1.21±0.079 - 1.34±0.180. Spectral data from FTIR indicated no interaction between Linagliptin and excipients used in the formulations. The formulated dosage form fulfilled all the official specifications of tablets concerning hardness (3.01 ± 0.02 - 3.09 ± 0.07 kg/cm$^2$), friability (0.27 ± 0.325 to 0.84 ± 0.110%), weight variation (197.9 ± 0.6 to 202.4±0.8 mg) and disintegration time (51 ± 2 to 108 ± 3 min) and there was no change in the physical appearance and color. The dissolution of Linagliptin from the tablets followed first-order kinetics. All 9 formulations showed 90% drug release at 45 minutes. Based on the dissolution studies it was shown that among the formulations, formulation F9 (5% SSG and 5% CCS of the final tablet weight) exhibited rapid and highest dissolution rate (100% drug release at 20 min) compared to other formulations and market product (100% drug release at 45 min). So, it was evident that formulation F9 is superior to a brand leader market product in terms of disintegration time and dissolution rate. From the study we also inferred, a combination of super-disintegrants used at a lower amount compared to the higher percentage of a single disintegrant in a formulation showed a better dissolution rate and dissolution efficiency.

The results of the present work conclude, immediate-release tablets of Linagliptin formulated with super-disintegrants possess better quality compared to regular formulations currently available in the market. It also showed that a combination of two super-disintegrants is better than using a single one to the same extent.

## Conflict of interest

The authors declare no conflict of interest.

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