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FORMULATION AND EVALUATION OF MOUTH- DISSOLVING TABLETS OF LINAGLIPTIN PREPARED BY DIRECT COMPRESSION METHOD

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ABSTRACT

Linagliptin belongs to the class of DPP-4 inhibitors. It is mainly used as an anti-diabetic drug for the treatment of type 2 diabetes. But the main drawback of the drug is its longer half-life of about 8.6-23.9 hours. Thereby, the mouth dissolving tablets are introduced to order to achieve the immediate therapeutic action. The main aim of the study is the formulation and evaluation of mouth dissolving tablets of linagliptin by the direct compression method. This technique involves the use of super disintegrants like sodium starch glycolate and croscarmellose. MDTs prepared were evaluated for the pre- and post-compression studies. The *in vitro* dissolution studies explain that the increase in the concentration of super disintegrant in the formulation reduces the disintegration time and improves the dissolution rate of the drug. The formulations with sodium starch glycolate show greater action compared to formulations with croscarmellose. The evaluation studies conclude that the disintegration time is reduced to seconds. The study concludes that the formulation of mouth dissolving tablets using super disintegrants like sodium starch glycolate and croscarmellose is the better technique to ensure faster drug release and patient compliance.

KEYWORDS: Linagliptin, Sodium starch glycolate, Croscarmellose, Mouth-dissolving tablets, Superdisintegrant.

INTRODUCTION

The oral route is considered the most widely used route among all the other routes of administration. though this route of administration has greater advantages, the main limitation of commonly used oral drug delivery forms, such as tablets and capsules, is dysphasia.[1] This is mainly seen in pediatric and geriatric patients due to noncompliance with taking the tablets and capsules. A new novel dosage method has been developed to overcome the problem and make the oral route more convenient for the patients. This new invention is termed a mouth-dissolving drug delivery system.[2]

The mouth dissolving tablets are also called Fast dissolving tablets, melt-in-mouth tablets, and oral dispersible tablets. Fast dissolving tablets are tablets when placed on the tongue, disintegrate instantaneously, releasing the drug, which dissolves or disperses in the saliva.[3] The faster the drug into the solution, the quicker the absorption and onset of clinical effect. These can be prepared by using several methods like: freeze drying, spray drying, tablet molding, sublimation, direct compression, and disintegration addition. However, direct compression is the predominant method for the preparation of mouth dissolving tablets.[4,5]

The mouth dissolving tablets have having best property, which is fast disintegration. This is achieved by the addition of super disintegrants. The super disintegrants like: sodium starch glycolate and croscarmellose. These are the best super disintegrants used in the formulation of mouth dissolving tablets. Hence, tablets get disintegrated in the mouth region. As the tablets have a bitter taste, a Sweetener like mannitol is used to produce a pleasant feel. Due to this phenomenon, it is acceptable to elder people and children. Therefore, Mouth dissolving tablets are widely used in the pharmaceutical industry.[6,7]

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels, necessitating effective and convenient drug delivery systems to enhance patient compliance. Linagliptin, a Dipeptidyl Peptidase-4 (DPP-4) inhibitor, is an effective antidiabetic agent used for the management of Type 2 Diabetes Mellitus (T2DM). Despite of its therapeutic benefits, Linagliptin exhibits poor aqueous solubility, which may lead to slower drug absorption and reduced

bioavailability.[8,9] To overcome this limitation, the formulation of fast-dissolving tablets with suitable super disintegrants is an effective strategy to enhance the dissolution rate and ensure rapid onset of action without the need for water.[10] This approach is particularly beneficial for elderly patients, children, and individuals with dysphagia, who may have difficulty swallowing conventional tablets.

Super disintegrants play a crucial role in FDT formulations by facilitating the rapid breakdown of tablets into smaller particles, thereby enhancing drug release.[11,12] In this study, Sodium Starch Glycolate (SSG) and Croscarmellose Sodium (CCS) were selected as super disintegrants due to their superior swelling and water-wicking properties. These agents promote faster tablet disintegration, ultimately leading to improved drug dissolution and absorption.[13]

The present research aims to formulate and evaluate Linagliptin fast dissolving tablets using direct compression technology with varying concentrations of SSG and CCS. The study further investigates the influence of these super disintegrants on critical tablet properties such as disintegration time, dissolution rate, and overall drug release profile. By optimizing these parameters, the research seeks to develop an effective and patient-friendly dosage form for Linagliptin, enhancing therapeutic efficacy and patient compliance in diabetes management.

MATERIAL AND METHODS

Materials used and the source

Different chemical materials were used during the formulation of linagliptin mouth dissolving tablets. They are linagliptin, sodium starch glycolate, croscarmellose, lactose, mannitol, microcrystalline cellulose, magnesium stearate, and talc. The super disintegrants like croscarmellose and sodium starch glycolate were from companies like Yarrow Chem Products and Sd Fine-Chem. Limited respectively. Lactose, which is used as a binder, and Mannitol, which is used as a sweetener, were from Thermo Fischer Scientific India Pvt Limited. Microcrystalline cellulose that is used in formulation was obtained from LOBA chemie pvt limited. Magnesium stearate and talc were produced by Otto chemie pvt limited. All these materials were obtained or sponsored by the college management. The drug, linagliptin, used in the formulation of mouth dissolving tablets, was from Pleiades Therapeutics Pvt limited.

Determination of Absorption maxima

5 mg of linagliptin was dissolved in 10 ml 0.1N HCl to get a stock solution of 1mg/ml. From this 10 ml solution was transferred into a 100 ml volumetric flask, and the volume was made up to 100 ml with 0.1N HCl, which was considered as the second stock solution. From this, 0.4 ml of solution was transferred into a 10 ml volumetric flask. The volume was made up to 10 ml with 0.1N HCl and subjected to scanning at the UV range using a Labindia UV 3200 UV/VIS spectrophotometer. From the spectral data, the absorption maxima obtained was 233 nm with a characteristic peak.

Preparation of calibration curve

For the preparation of the calibration curve, 0.2, 0.4, 0.6, 0.8, and 1.0 ml of the second stock solution was transferred into a series of 10 ml volumetric flasks, and volume was made up to 10 ml with 0.1N HCl to get 2,4,6,8, and 10 µg/ml solutions. The optical density values of the resulting solutions were measured at 233nm by using a Labindia UV 3200 UV/VIS spectrophotometer. The optical density values are recorded with statistical data. Concentration versus optical density values are plotted. The method obeyed Beer-Lambert's law, and the solution was stable for 48 h.

Table 1: Calibration curve data.

Concentration (µg/ml)	Absorbance
0	0
2	0.195
4	0.3956
6	0.5762
8	0.7915
10	0.9587

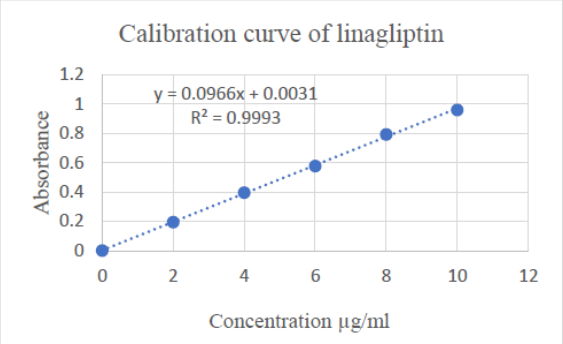

Figure1: Calibration curve of linagliptin in 0.1N HCl.

Pre-formulation studies

It is the first step in the rational development of the dosage form of the drug. It can be defined as an investigation of various physical and chemical properties of a drug substance and its compatibility with the excipients. It is a phase of the research and development process, carried out to develop a safe and effective dosage form.

Evaluation of organoleptic properties

It includes the evaluation of the physical appearance, colour, and odour of the drug substance, which make up the primary characteristics for the identification of a specific material.

Determination of melting point

The melting point of the drug was determined by the Melting Point Apparatus using the Capillary method. In

this method, the fine powder of the drug was taken and placed in the capillary tube whose one end was previously sealed. The capillary tube was placed in the apparatus, and the temperature at which the solid was converted into liquid was noted. This noted temperature is compared with the standard melting point of the drug from the monograph.

FTIR Studies

A small sample of the drug was subjected to IR radiation of 4000 cm^{-1} to 400 cm^{-1} using a Diamond ATR Spectrophotometer, and the characteristic peaks of the sample were obtained, and these are compared to the standard spectra of the drug.

Solubility of the drug

Solubility of Linagliptin was determined in pH 1.2, pH 6.8, and pH 7.4 phosphate buffers. Solubility studies were performed by taking an excess amount of Linagliptin in different beakers containing the solvents. The mixtures were shaken for 24 hours at regular intervals. The solutions were filtered by using whattmann's filter paper. The filtered solutions were analyzed spectrophotometrically at 236 nm.

Preparation of mouth-dissolving tablets of linagliptin

Accurately weigh the quantity of Linagliptin, lactose, mannitol, magnesium stearate, and talc. 6 formulations are prepared using super disintegrants like sodium starch glycolate and croscarmellose. 5mg, 10 mg, and 15 mg of sodium starch glycolate are added in formulations 1,2, and 3, respectively. Whereas in formulations 4,5, and 6, croscarmellose of 5 mg, 10 mg, and 15 mg is added, respectively. Firstly, the drug and super disintegrant are mixed using a mortar and pestle, following the addition of excipients like lactose, mannitol, magnesium stearate, and talc in their increasing orders. The required amount of carboxy methyl cellulose is added to make up the mixture of 300 mg. Mouth-dissolving tablets of linagliptin were prepared by direct compression of the mixture.

Table 2: Formulation of Mouth-dissolving tablets of linagliptin.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
linagliptin	5	5	5	5	5	5
Sodium starch glycolate	5	10	15	_	_	_
Croscarmellose	_	_	_	5	10	15
Lactose	25	25	25	25	25	25
Mannitol	30	30	30	30	30	30
Microcrystalline cellulose	223	218	213	223	218	213
Magnesium stearate	6	6	6	6	6	6
Talc	6	6	6	6	6	6
Total	300	300	300	300	300	300

Post formulation studies

Tablet's hardness

The hardness of the tablet is defined as the force applied across the diameter of the tablet to break the tablet. The resistance of a tablet to chipping, abrasion, or breakage under the conditions of storage, transformation, and handling before usage depends on its hardness.

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, and disintegration, and determined in Kg/cm^2 by the Monsanto hardness tester.

Tablet's friability

The friability of the tablet was checked by using the Roche Laboratory friabilator. This device subjects several tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inches with each revolution. A pre-weighted sample of 6 tablets was placed in a friabilator, then operated for 100 revolutions. Tablets were dusted and re-weighed; the loss in weight of the tablet is the measure of friability and is expressed in percentage as.

% friability = [(Initial Weight-Final Weight)/Initial Weight] X100

Weight variation

10 tablets of each batch were selected randomly and weighed. After that, a single tablet was weighed and calculated % deviation concerning the average weight of 10 tablets by using this formula.

% deviation = [(Individual Weight -Average. Weight)/Avg. Weight.] X 100

***In vitro* dispersion time**

The tablet was added to 10.0 ml 0.1 N HCl at 37+0.5 °C. The time required for the complete dispersion of a tablet was observed.

Wetting time

Five circular tissue papers of 10 cm diameter were placed in a Petri dish with a 10 cm diameter. Ten milliliters of water-soluble dye (eosin) solution was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time.

***In vitro* disintegration time**

The *in vitro* disintegration time was determined by using the USP disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus, and one

disc was added to each tube. The time taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Drug-content

Five tablets were weighed individually and powdered. The powder equivalent to the average weight of tablets was weighed and extracted, and concentration was determined by measuring absorbance at 233 nm with a UV-visible spectrophotometer.

Dissolution test

The dissolution studies were carried out using a USP 2 paddle apparatus. Paddles were allowed to rotate at 50 rpm, and 900 ml of 0.1N HCl was used as a dissolution medium. The temperature of the dissolution medium was 37±0.5 °C. The duration of dissolution studies was 24 min, and samples (10 ml) were withdrawn at 2 min time intervals (subsequently, 10 ml dissolution medium was replaced) and filtered through 0.45 µm Whatmann membrane filter paper. The concentration of dissolved drug from tablets was determined spectrophotometrically at a wavelength of 233 nm. The dissolution study for each batch was carried out with three randomly selected tablets.

RESULTS AND DISCUSSION

In the present study, an attempt has been made to formulate and evaluate mouth-dissolving tablets of Linagliptin by the direct compression method using sodium starch glycolate and croscarmellose as super disintegrants. Six formulations were prepared, and the complete composition of all batches is shown in Table 2. The tablets were then characterized for various physicochemical parameters.

Pre-formulation studies

Organoleptic properties

Linagliptin is a white to yellow colored solid/crystalline powder. Linagliptin is usually odourless, but it has a bitter taste.

Determination of melting point

The melting point of Linagliptin was determined to be 194°C by the capillary method.

Solubility

Solubility of Linagliptin was carried out at 25°C using 0.1 N HCL, 6.8 phosphate buffer, and purified water, This is given in Table 3.

Table 3: Solubility of linagliptin.

Medium	Solubility (mg/ml)
Water	0.156
0.1N HCl	0.205
6.8 Buffer	0.384
7.4 Buffer	0.328

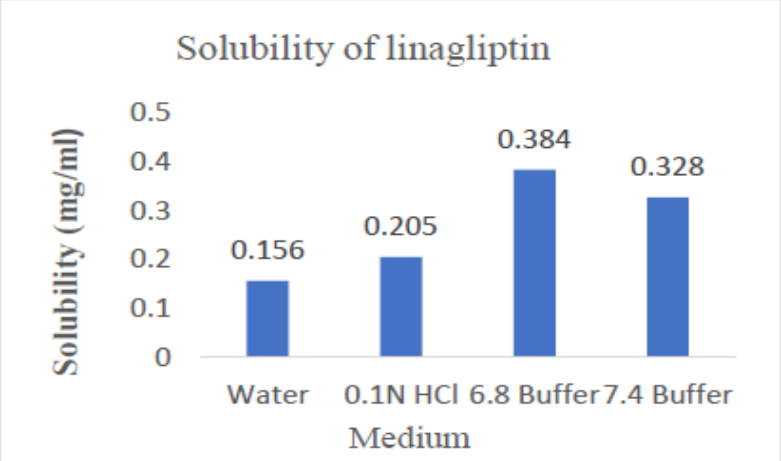

Figure 2: Solubility graph of linagliptin.

FTIR STUDIES

The FTIR studies were performed on mouth-dissolving tablets of Linagliptin prepared using sodium starch glycolate in a ratio of 1:1.

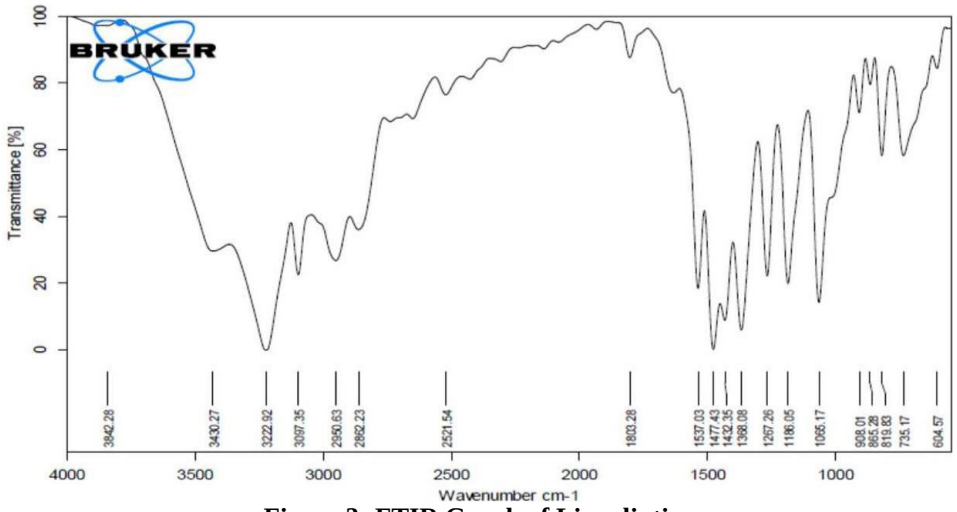

Figure 3: FTIR Graph of Linagliptin.

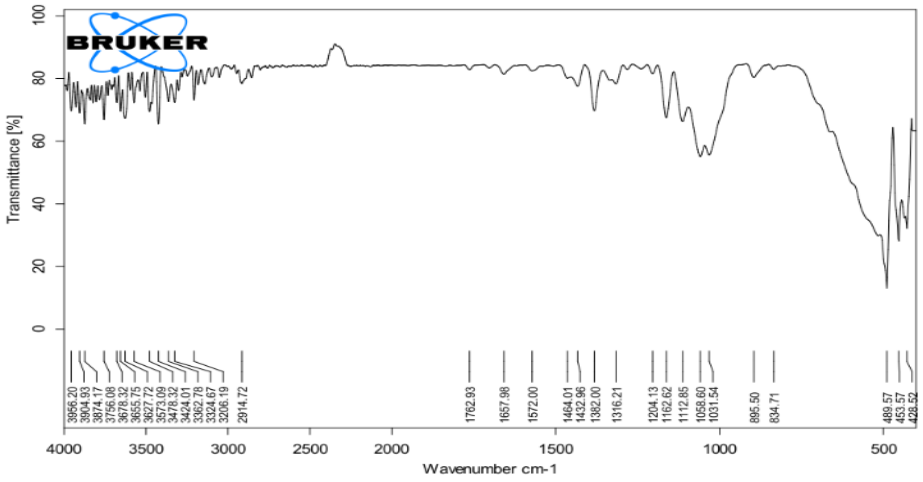

Figure 4: FTIR spectra of Mouth-dissolving tablets of Linagliptin by direct compression method at a 1:1 ratio using sodium starch glycolate.

Pre-Compression parameters

The Pre-Compression parameters like Bulk density, tapped density, Tapped and Bulk volumes, angle of repose, Carr's index (%), and Hausner's ratio of Linagliptin are given in Table 4.

Table 4: Pre-Compression parameters.

Formulation code	Bulk volume (ml)	Bulk density (g/cc)	Tapped volume (ml)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
F1	5.6	0.535	5.1	0.588	26.2	9.013	1.099
F2	5.7	0.526	5.3	0.566	27.85	7.067	1.076
F3	5.8	0.517	5.2	0.576	26.35	10.243	1.114
F4	5.8	0.517	5	0.6	30.41	13.833	1.160
F5	5.8	0.517	5.1	0.588	28.30	12.074	1.137
F6	5.9	0.508	5.3	0.566	29.11	10.247	1.114

- The Angle of repose of different formulations was < 25, which indicates that the material had excellent flow properties. So, it was confirmed that the flow property of blends was free-flowing.
- The Bulk density of the blend is between 0.50 g/cm^3 to 0.53g/cm^3.
- Tapped density was found to be between 0.56 g/cm^3 to 0.6 g/cm^3. These values indicate that the blend has good flow properties.
- Carr's index was found to be between 9.01 and 13.83, and Hausner's ratio was about 1.09-1.16 for all the formulations.
- This concludes that the formulation blends have good flow character.

Post-Compression parameters

The post-compression parameters of linagliptin are given in Table 5.

Table 5: Post Compression Parameters.

Formulation Code	Average weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (s)	Drug Content (%)
F1	293	3.56	15	0.6825	22	84.1853
F2	295	3.67	17	0.6779	20	94.2902
F3	300	3.63	18	0.6557	18	82.7342
F4	300	3.73	18	0.6666	20	87.6328
F5	303	3.65	18	0.6451	15	93.8321
F6	300	3.62	18	0.6666	12	91.3881

Weight variation test

All the formulations (F1-F6) tablets passed the weight variation test as the % weight variation was within the pharmacopeial limits. The weight variation of the tablets was found to be uniform with low standard deviation values.

Hardness test

The measured hardness of tablets of all the formulations ranged between 3-4 kg/cm^2. This ensures good handling characteristics of all the batches.

Disintegration test

It was found between 10-25 seconds, ensuring that all the formulations were rapid disintegrating type.

Friability test: The percentage friability was less than 1% in all the formulations, ensuring that the tablets were mechanically stable.

***In vitro* dissolution test**

In vitro dissolution data of pure drug and different mouth-dissolving tablets of linagliptin prepared by using sodium starch glycolate and croscarmellose. Here, the cumulative percentage of drug release is given in Table 6.

Table 6: The *in vitro* dissolution profile of mouth-dissolving tablets of linagliptin prepared by sodium starch glycolate and croscarmellose in 1:1,1:2, and 1:3 ratios.

Time (Minutes)	F1	F2	F3	F4	F5	F6
2	49.3076	56.2132	58.9860	51.5139	53.4825	57.0804
4	52.0629	64.2657	69.0559	67.4055	67.8076	69.9370
6	72.5804	74.4713	86.9667	72.2132	75.9615	76.0314
8	83.9230	87.5979	90.7202	80.6013	82.5796	87.7693
10	88.7867	91.2657	96.6748	88.3741	88.7972	92.2762
20	95.4440	95.7707	99.1048	94.6042	95.2692	95.5524
30	98.2552	98.6041	100	97.9125	98.4090	98.8916
45	100	100	100	100	100	100
60	100	100	100	100	100	100

The *In vitro* dissolution studies data are given in Table 6. This data concludes that the formulations (F1-F6) are formulated with the help of super disintegrants like Sodium starch glycolate and Croscarmellose. Among all the formulations, F3 has a higher dissolution rate than the other formulations. It dissolute about 99.10% at the end of 20 minutes. This data explains that the formulations are immediate-release types.

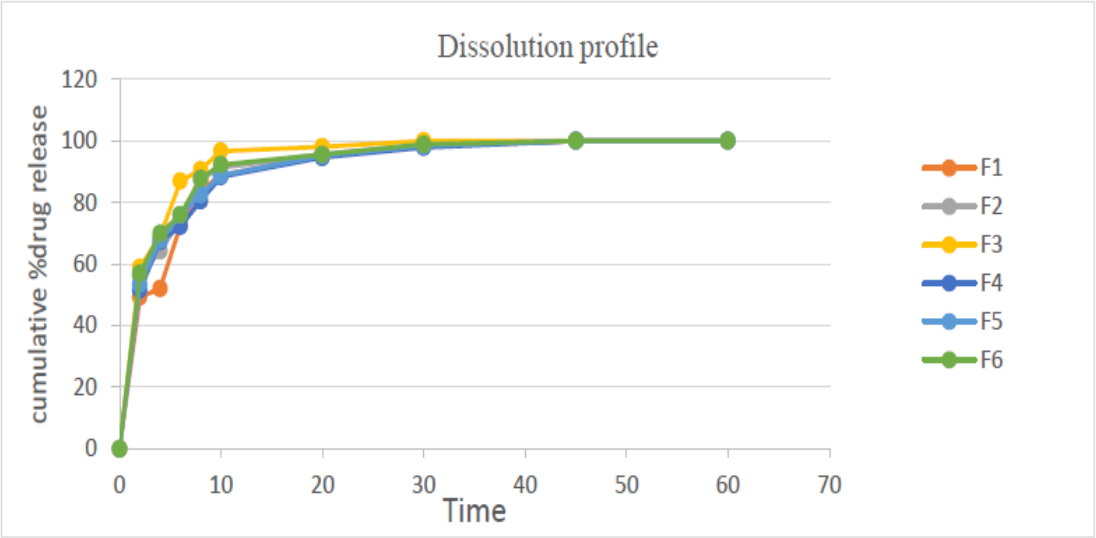

Figure 5: The *in vitro* dissolution profile of mouth-dissolving tablets of linagliptin prepared by sodium starch glycolate and croscarmellose in 1:1,1:2, and 1:3 ratios.

DRUG RELEASE KINETICS OF SODIUM STARCH GLYCOLATE

Table 7: Cumulative % drug released vs Time (Zero order kinetics).

Sl No	Time (Minutes)	Cumulative % drug released		
		F1	F2	F3
1.	0	0	0	0
2.	2	49.307	56.213	58.986
3.	4	52.062	64.265	69.055
4.	6	72.580	74.471	86.966
5.	8	83.923	87.597	90.720
6.	10	88.786	91.265	96.674
7.	20	95.444	95.770	98.104
8.	30	98.255	98.604	100
9.	45	100	100	100
10.	60	100	100	100

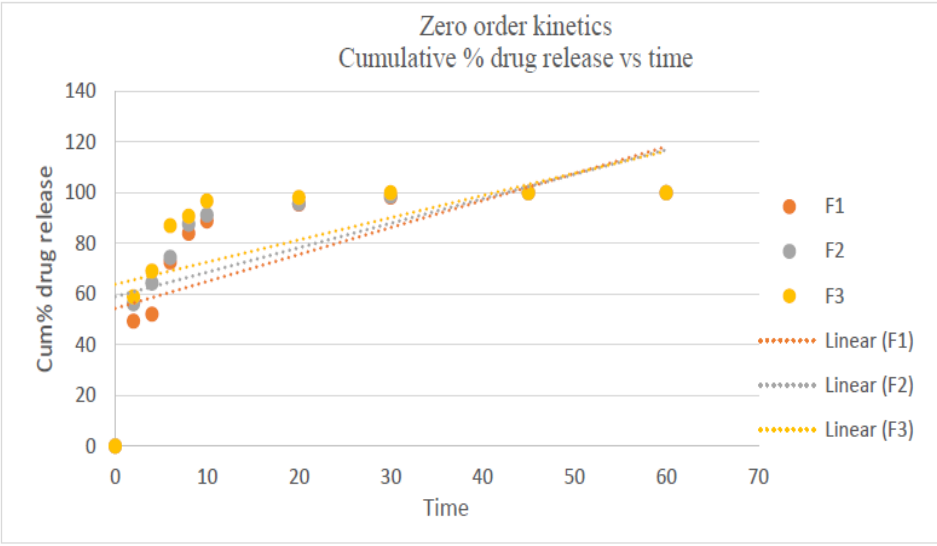

Figure 6: Cumulative % drug release vs Time (Zero order kinetics).

Table 8: Log cumulative % drug remains vs Time (First order kinetics).

Sl. No	Time (Minutes)	Log cumulative % drug remains		
		F1	F2	F3
1.	0	2	2	2
2.	2	1.7049	1.6413	1.6129
3.	4	1.6806	1.5530	1.4905
4.	6	1.4380	1.4070	1.1150
5.	8	1.2062	1.0934	0.9675
6.	10	1.0497	0.9412	0.5218
7.	20	0.6585	0.6262	0.2776
8.	30	0.2417	0.1448	0
9.	45	0	0	0
10.	60	0	0	0

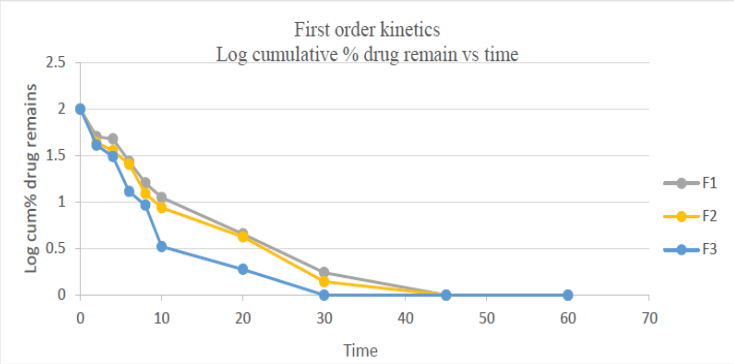

Figure 7: Log cumulative % drug remain vs Time (First order kinetics).

DRUG RELEASE KINETICS OF CROSCARMELLOSE

Table 9: Cumulative % drug release vs Time (Zero order kinetics).

Sl. No	Time (Minutes)	Cumulative % drug release		
		F4	F5	F6
1.	0	0	0	0
2.	2	51.513	53.482	57.080
3.	4	67.405	67.807	69.937
4.	6	72.213	75.961	76.031
5.	8	80.601	82.579	87.769
6.	10	88.374	88.797	92.276
7.	20	94.604	95.269	95.552
8.	30	97.912	98.409	98.891
9.	45	100	100	100
10.	60	100	100	100

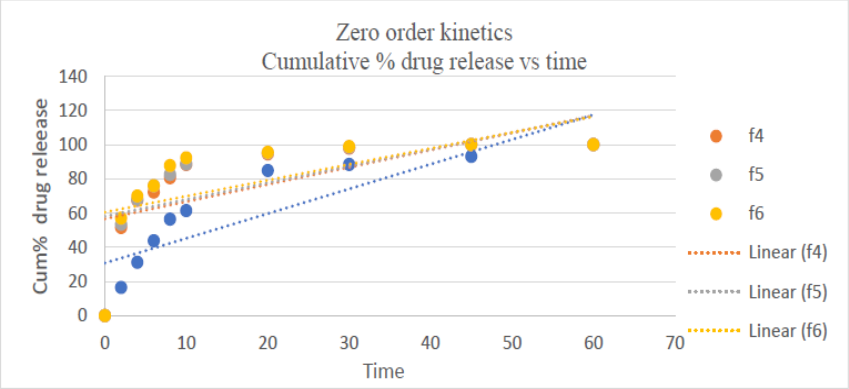

Figure 8: Cumulative % drug release vs Time (Zero order kinetics).

Table 10: Log cumulative % drug remain vs Time (First order kinetics).

Sl. No	Time (Minutes)	Log. Cumulative % Drug Remains		
		F4	F5	F6
1.	0	2	2	2
2.	2	1.6856	1.6676	1.6326
3.	4	1.5131	1.5077	1.4780
4.	6	1.4438	1.3809	1.3796
5.	8	1.2877	1.2410	1.0874
6.	10	1.0654	1.0493	0.8878
7.	20	0.7320	0.6749	0.6481
8.	30	0.3196	0.2016	0.0446
9.	45	0	0	0
10.	60	0	0	0

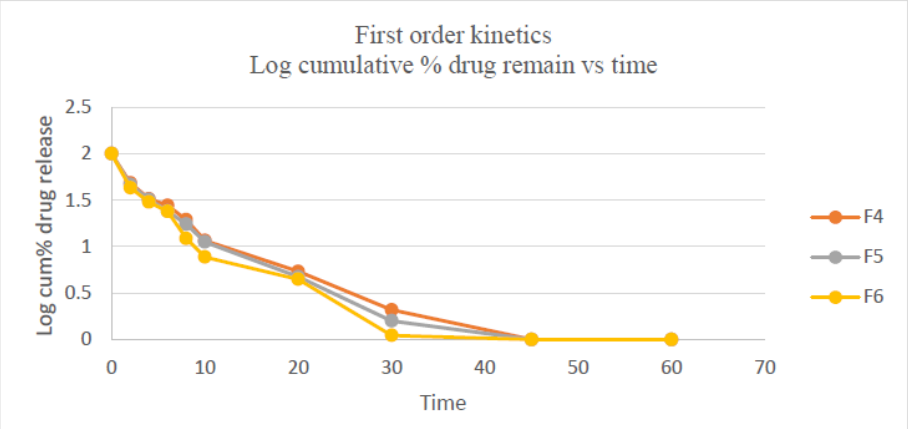

Figure 9: Log cumulative % drug remain vs Time (First order kinetics).

CONCLUSION

Linagliptin is an anti-diabetic drug used for the treatment of type 2 diabetes mellitus; it belongs to the class of DPP-4 inhibitors. It has a long half-life of about 8.6-23.9 hours. Hence, there is a need for immediate therapeutic action. To achieve this property, immediate-release tablet formulations were developed. These mouth-dissolving tablets of linagliptin were prepared by direct compression method using super disintegrants such as sodium starch glycolate and croscarmellose. From the results obtained, it can be concluded that

- The flow properties of the polymer and drug were good.
- The tablets prepared were found to be good without any chipping, capping, or sticking.
- Formulated tablets give satisfactory results for various physicochemical evaluations of tablets like tablet dimensions, hardness, friability, weight variation, in vitro dispersion, and drug content.
- The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
- The percentage drug content was found to be in the range of 82.73 to 94.29.
- The results of the dissolution rate studies indicated a higher dissolution rate of linagliptin mouth-dissolving tablets prepared by using super disintegrants, sodium starch glycolate and croscarmellose, when compared to linagliptin itself
- The *in vitro* dissolution study of linagliptin tablets was tested in 0.1N HCL. From the *in vitro* dissolution data, it was found that the drug release study from formulations containing sodium starch glycolate as a super disintegrant (F1-F3) was faster. The F1 formulation shows maximum drug release at the end of 98.25% at the end of 30mins., whereas the F2 formulation shows the maximum drug release at the end of 98.60% at the end of 30 mins., While the F3 formulation shows the maximum drug release at the end of 99.10% at the end of 20 mins. There is a threefold increase in the rate of dissolution of linagliptin. While the formulations containing croscarmellose as a super disintegrant (F4-F6) show drug release at the end of 30 mins, they are 97.91%, 98.40%, and 98.89%, respectively. From the *in vitro* dissolution studies, it was observed that the increase in the super disintegrant concentration proportionally decreases the time taken for the dissolution. It was observed from the results that formulations containing sodium starch glycolate as a super disintegrant showed a maximum dissolution rate at 99.10% of drug release in F3 in 20 minutes. This shows the effectiveness of super disintegrants in the

order of sodium starch glycolate > croscarmellose. The concentration of super disintegrants in formulations also increased the dissolution rate. It was observed from the results that formulations containing sodium starch glycolate as a super disintegrant showed a maximum dissolution rate of 99.10% drug release in F3 at 20 mins.

- The FTIR studies indicate that there were minor to no interactions at the molecular level.
- Finally, it could be concluded that the mouth-dissolving tablets prepared by using sodium starch glycolate and croscarmellose as super disintegrants would improve the dissolution rate and thereby enhance their systemic availability

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