Research Article

DESIGN AND EVALUATION OF RAPID RELEASE LINAGLIPTIN TABLET FOR DIABETES TREATMENT

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ABSTRACT

The main purpose of linagliptin is to treat diabetes. Linagliptin instant-release tablets were created to increase the medication's bioavailability and suitability for therapeutic use. The quick-release tablet was formulated employing several polymers through the application of the direct compression technique. Compressibility index, Hausner ratio, weight of tablet, bulk density, taped density, hardness, friability, disintegration time, and in vitro dissolution study. According to preliminary research, formulations with F8 had better drug release properties and were quicker to release. Experimental confirmation of the results was obtained. According to the study's findings, the Linagliptin instant release pill that was produced showed improved cumulative drug release, which in turn improved bioavailability.

KEYWORDS: Linagliptin, Immediate Release Tablet, Anti-Diabetic, Direct Compression Method, Bioavailability.

INTRODUCTION

Characterised by persistently high blood sugar levels, Because of its increasing incidence and associated health risks, diabetes mellitus is a serious global health problem. Antidiabetic drugs are essential in order to control diabetes and reduce its effects. Immediately-release tablets are one of the medication delivery technologies that improve patient compliance and therapeutic results because they have a quick start to action and an exact dosage. This study is developing and evaluating an immediate-release tablet containing [insert name of antidiabetic medicine], a commonly used medication when managing diabetes mellitus type 2. As such, kind of formulation was created because it was needed to provide quick glycaemic control by enabling a dose form to quickly reach therapeutic medication levels in the circulation[1,2]. The most prevalent endocrine condition, diabetes mellitus (DM), affects about 100 million individuals globally (6% of the population). It is brought on by the pancreas' inability or lack of ability to produce enough insulin, which causes variations in blood glucose levels. Numerous bodily systems, including the blood vessels, eyes, kidneys, heart, and nerves, have been discovered to be harmed by it. Type I insulin-dependent diabetes (IDDM) and Type II non-insulin-dependent diabetes (NIDDM) are the two distinct forms of diabetes mellitus. In contrast to Type II diabetes, which is characterised by peripheral insulin resistance and reduced insulin production, Type I diabetes is an autoimmune illness that causes a localised inflammatory response in and around islets that is followed by the selective death of insulin-secreting cells.

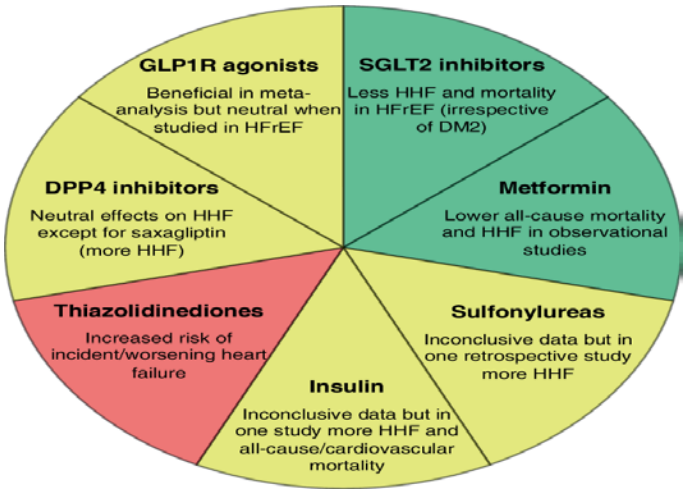


Figure 1: Antidiabetic Agent

Novel drug delivery methods are being created in the current study and research to increase markets and indications, prolong product life cycles, and create possibilities. The most common method for achieving systemic effects is oral administration since it is simple to use, causes little discomfort, may be avoided, is versatile, and most importantly, patient compliance. These solid formulations are less expensive to produce since they don't need to be kept under sterile conditions. Tablets are the preferred solid dose form because to its high precision dosing, patient compliance, and efficient production processes. Should solid dosage form technologies evolve in response to the tremendous advances in drug discovery, such as genomics, excipients and equipment selections would be profoundly impacted. The administration of highly molecular weight protein and

peptide, as well as poorly soluble pharmaceuticals, appears to be greatly encouraged by the development of improved oral protein delivery technology through the use of quick release tablets, which may release the medications at an accelerated pace. Because oral treatment is easy to administer, inexpensive to manufacture, and results in high patient compliance, it continues to be the ideal method for administering therapeutic substances. Given the specific therapeutic situation, many patients demand a rapid commencement of action, necessitating the prompt release of the medication. This issue affects an estimated 50% of the population, which leads to a high rate of therapy that is unsuccessful.

Tablets and capsules are the most commonly used medication delivery mechanisms available. They are immediate-release oral dose forms. These items work by breaking down in the stomach and then dissolving in gastrointestinal fluids. Drug absorption from the GIT and release from the traditional tablet dose form rely on two primary mechanisms. The pill will first dissolve, and the particles will disintegrate before entering the bloodstream through the GIT. When it comes to pharmaceuticals that are highly soluble, disintegration is the rate-limiting process, and when it comes to drugs that are poorly soluble, dissolution[3].

MATERIAL AND METHOD

Linagliptin was retrieved from Laurus lab. HPMC, Lactose monohydrate, Polyvinylpyrrolidone, Sodium starch glycolate, Magnesium Stearate, Sodium Stearyl Fumarate, Opadry White collected from DEF pharma and FMC biopharma.

Method

Direct Compression Method

The creation of the 5 mg linagliptin instant release tablet was done using a direct compression technique. A development lab-scale trial was carried out to determine the parameters of the manufacturing process, including blending, compression, and coating, based on the target product profile, an assessment of the physiochemical properties of the drug substances and other ingredients, a review of the literature, and the scientific procedure carried out prior to the manufacturing process. As ultimate objective of the research was to produce a product with a suitable in vitro dissolving profile[4].

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
	Quantity of mg per Tablet							
Linagliptin	5	5	5	5	5	5	5	5
Hydroxy propyl methyl cellulose	-	-	5	15	20	10	15	15
Lactose monohydrate	69	60	60	60	60	57	57	57
Polyvinylpyrrolidone	18	25	20	10	5	13	13	13
Sodium Starch Glycolate	-	-	-	-	-	3	-	-
Sodium stearyl fumarate	-	2	2	2	2	4	2.5	2.5
Magnesium stearate	4	4	2	2	2	2	1.5	1.5
Total wt.	98	98	94	94	94	98	98	98

Opadry range	2	2	6	6	6	2	2	2
Total wt.	100	100	100	100	100	100	100	100

Table 1: Formulation Table Of Immediate Release Tablet Of Anti-Diabetic Linagliptin

EVALUATION OF IMMEDIATE RELEASE TABLET

Pre-Compression Parameter

Organoleptic Properties

The colour, odour, taste, and appearance of the API were all noted as organoleptic properties.

Melting Point Determination

By placing a small quantity Within a capillary tube with a closed end for API, melting point ascertained. The temperature at which the medication melts was measured using electrically powered melting point equipment with the capillary tube within. After completing this three times, the average value was determined[5].

Solubility

It was investigated in what solvents the received API sample was soluble in.

Calibration Curve

In order to create the stock solution, 25 mg of linagliptin were weighed, transferred, and sonicated for 10 minutes in a 50-ml clear, dry volumetric flask to dissolve the drug. The remaining 50 ml was then made up with diluent. Eight µg/ml (the working standard) was obtained by further diluting the 1.6 ml of stock standard solution in 100 ml with diluent. Then, to make 4, 6, 8, 10, and 12 µg/ml of solution, put 0.8, 1.2, 1.6, 2, and 2.4 ml of diluent to dilute the volume after adding standard to a 100 ml volumetric flask. Next, using diluent as a blank, the absorbance was measured at 276 nm[6].

Bulk Density

The mass to volume ratio of an untapped powder sample is known as the bulk density. A bulk density of g/ml is used to express it. The organisation and density of the powder particles affect bulk density, respectively. The sample's processing and storage are influenced by the bulk density. The following is a mathematical representation[7,8].

Bulk density = Weight of the drug / Bulk volume

Taped Density

Using graduated cylinder, bulk powder is mechanically tapped until a difference in volume is noticed in tapped density. By dividing the mass by powder's ultimate volume, tapped density is computed here.

Tapped density = Weight of the granules / Tapped volume

Hausner Ratio

A Monsanto hardness tester was used to assess the tablets' hardness. Hardness is one of the most critical elements in transportation. A Pfizer hardness tester was used to determine hardness of 10 pills. The unit of measurement is kg/cm2.

Compressibility Index

To describe the nature of powders and granules, this is one of the most crucial factors.

Carr's index (%) = Tapped density - Bulk density / Tapped density × 100 Hausner's ratio

Post Compression Parameter

Weight Of Tablet

From each batch, twenty pills were chosen at random and weighed separately. Twenty pill weights were averaged, and their standard deviation was computed. The batch passed the weight variation test if the difference between the weights of no more than two individual tablets and the average was larger than the % indicated by the authorities and if none of the tablets' weights varied by a greater amount than twice the percentage indicated by the tablet.

Hardness

A tablet's hardness level reveals how well it can tolerate handling-related mechanical stress. The tablet's hardness was assessed for each formulation using this method. It's stated in N. The pills' hardness was assessed after ten were chosen.

Friability

For tablets, take ten whole pills and set them aside. Weighing more than 650 mg, and a sample of whole tablets equating to around 6.5 mg. Carefully remove the pills, making sure to weigh the exact amount required. In the Roche friabilator, place the tablet. After removing any loose dust from them and correctly weighing them, the friability was run at 25 rpm for 100 revaluations. Tablet users may experience weight loss of up to 1.0% of their body weight. Using the following formula, the percentage friability was determined[9].

$$\% F = [1-(W/W0)] \times 100$$

Disintegration Time

Using the disintegration device USP (Electrolab), All of the tablet formulations' in vitro disintegration times were measured. An in vitro disintegration test employing disintegration medium was conducted in 900 ml at 37 ± 2^{o} C Each formulation's six pills were ingested and put in tubes with a disintegration device. The duration of total disintegration was recorded[10].

In Vitro Dissolution Study

An in vitro dissolving research using a pH 6.8 phosphate buffer was conducted improve formulation of linagliptin tablets and a reference standard. The drug concentration was ascertained using the HPLC technique, with the dissolving media maintained at 37 ± 0.5°C[11].

RESULT AND DISCUSSION

Pre-Compression Parameter

Organoleptic Properties

Properties	Observation
Colour	White to off white powder
Taste	Bitter
Odour	Odourless
Appearance	Off white Powder

Table 2: Organoleptic Properties of Immediate Release Tablet Of Anti-Diabetic Linagliptin

Melting Point Determination

The literature's stated range of 197–200ºC is where the melting point of API was discovered to be 198^{0}C. The medication is therefore considered pure.

Solubility

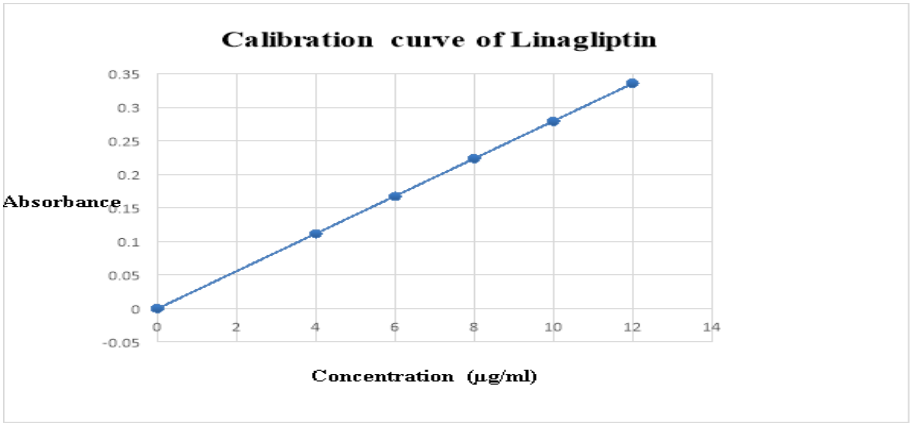
Different solvents (aqueous and organic) were used to test the API sample's solubility. The analysis is limited to a qualitative level. As a consequence, the following outcomes were reached:

Sr.No.	Solvent	Solubility
1	Alcohol and Water	Freely soluble
2	Methylene chloride	Very slightly soluble

Table 3: Solubility Immediate Release Tablet Of Anti-Diabetic Linagliptin

Calibration Curve

A UV spectrophotometer was used to produce a solution with varying concentrations of linagliptin and scan it at 276 nm. Plotting the graph of absorbance vs concentration, it was discovered to be linear between 4 and 12 µg/ml, demonstrating conformity with Lambert and Beer's law.



Graph 1: Calibration Curve of Immediate Release Tablet Of Anti-Diabetic Linagliptin

Bulk Density, Tapped Density, Compressibility Index, Hausner Ratio:

The features of powder mix ranging from F1 to F8 are listed in the table above. Based on the compressibility index and Hauser's ratio values, the blend of the previously indicated formulation has adequate flow properties and a compressibility index.

Formulation. no	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio
F1	0.574	0.740	21.10	1.16
F2	0.610	0.751	20.23	1.18
F3	0.582	0.752	21.01	1.19
F4	0.612	0.774	22.8	1.22
F5	0.614	0.788	21.98	1.24
F6	0.622	0.768	21.03	1.20
F7	0.598	0.761	20.9	1.25
F8	0.590	0.765	21.01	1.27

Table 4: Bulk Density, Tapped Density, Compressibility Index, Hausner Ratio of Immediate Release Tablet Of Anti-Diabetic Linagliptin

Post Compression Parameter

When compared to other formulations, batch number F8 out of eight comparative batch with variable disintegrant formulations was judged be adequate. This showed that the manufactured tablet's thickness, hardness, and disintegration time were comparable to those of the marketed formulation tablet. The maximum amount of weight lost during the friability test should not exceed 1%. The tablets passed the friability test, according to the outcome.

Sr No	Weight Variation (mg)	Hardness(N)	Thickness(mm)	Disintegration Time	Friability (%)	Assay (%)
F1	101	65	3.70	40 sec	0.5	100.2
F2	102	70	3.72	51sec	0.4	99.5
F3	101	82	3.81	1min 05sec	0.5	98.6
F4	102	80	3.84	1min 30sec	0.6	99.1
F5	98	95	3.68	3min 38sec	0.3	100.2
F6	100	84	3.69	2min 75sec	0.4	99.5

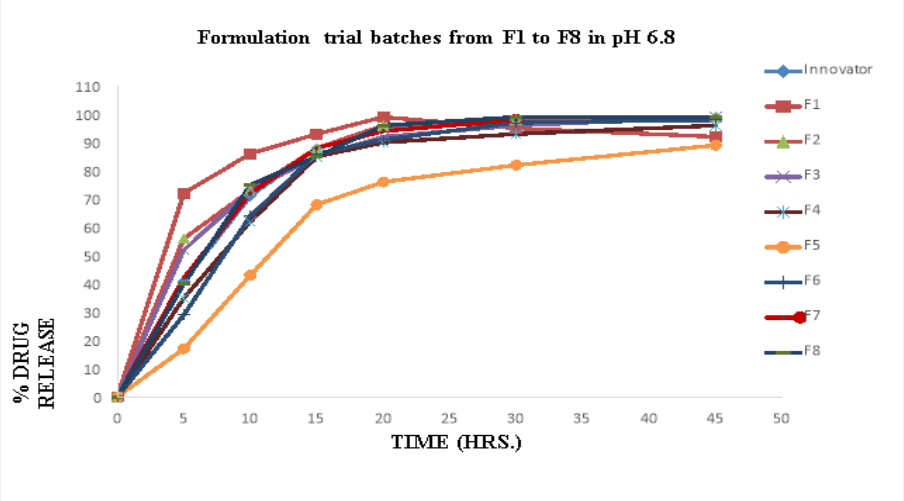
F7	101	85	3.65	2min 15sec	0.5	100.6
F8	100	84	3.68	2 min 12sec	0.4	100.2

Table 4: Post Compression Parameter of Immediate Release Tablet Of Anti-Diabetic Linagliptin

In Vitro Dissolution Study

Time	**% Drug Release**								
	Innovator	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0	0
5	41	72	56	52	35	17	29	42	40
10	71	86	73	73	62	43	64	72	75
15	88	93	88	85	85	68	86	88	85
20	95	99	96	92	90	76	91	94	96
30	98	95	98	96	93	82	97	98	99
45	99	92	99	99	96	89	98	99	99
60	100	89	95	100	97	92	99	100	100

Table 5: In Vitro Dissolution Study of Immediate Release Tablet Of Anti-Diabetic Linagliptin



Graph 2: In Vitro Dissolution Study of Immediate Release Tablet Of Anti-Diabetic Linagliptin

CONCLUSION

The goal of the project was to manufacture, produce, and evaluate an immediate-release tablet of an "anti-diabetic drug," such as linagliptin, in a dosage form that would be both stable and robust. The main goal was to create a range of linagliptin antidiabetic pills in accordance with the inventor. In addition to being safe and effective, the IR tablets were designed to have a dissolving profile that was similar to and bioequivalent to that of the reference product. The challenge in creating an IR linagliptin tablet was to employ a powerful disintegrant in order to attain bioavailability quickly. The innovator's disintegration results and the immediate-release tablet

made via direct compression were similar. Based on the results above, it can be said that batch F8 performed comparably to the innovator and that employing super disintegrant improved the dissolving rate, which in turn improved bioavailability. As a result, an immediate-release tablet formulation of the antidiabetic medication linagliptin may be achieved with success.

REFERENCES

(1) Aher, S. S.; Gajare, S. P.; Saudagar, R. B. Linagliptin: A Review on Therapeutic Role in Diabetes Mellitus. *Res. J. Pharm. Technol.* **2017**, *10* (9), 3233–3236. https://doi.org/10.5958/0974-360X.2017.00573.X.

(2) Krishna Veni, D.; Gupta, N. V. Quality by Design Approach in the Development of Solid Lipid Nanoparticles of Linagliptin. *Res. J. Pharm. Technol.* **2019**, *12* (9), 4454–4462. https://doi.org/10.5958/0974-360X.2019.00768.6.

(3) Zalte, A. G.; Saudagar, R. B.; Katkade, P. N. Validated UV- Spectroscopic Estimation of Linagliptin Concentration in Bulk and Dosage Form. *Res. J. Pharm. Technol.* **2016**, *9* (5), 490–492. https://doi.org/10.5958/0974-360X.2016.00090.1.

(4) Wijayanti, E. P.; Pristianty, L.; Faturrohmah, A. Oral Antidiabetic Drug Consumption Adherence in Primary Health Care through PRECEDE Method. *Res. J. Pharm. Technol.* **2020**, *13* (2), 543–546. https://doi.org/10.5958/0974-360X.2020.00102.X.

(5) Rank, M.; Kapupara, P.; Shah, K. Development and Validation of Stability Indicating HPTLC Method for Pioglitazone Hydrochloride and Metformin Hydrochloride. *Res. J. Pharm. Technol.* **2016**, *9* (10), 1555–1561. https://doi.org/10.5958/0974-360X.2016.00305.X.

(6) Jadhav, G. B.; Deshmukh, A. C.; Mundlod, K. N. Effect of Linagliptin and Niclosamide on Streptozotocin Induced Diabetic Neuropathy in Rats. *Res. J. Pharm. Technol.* **2020**, *13* (5), 2101–2106. https://doi.org/10.5958/0974-360X.2020.00378.9.

(7) Sivagami, B.; Purushotham, A.; Sikdar, P.; Chandrasekar, R.; Babu, M. N. A Validated Method for the Simultaneous Estimation of Linagliptin and Metformin in Tablet Dosage Forms by RP-HPLC. *Res. J. Pharm. Technol.* **2020**, *13* (3), 1266–1270. https://doi.org/10.5958/0974-360X.2020.00233.4.

(8) Gaikwad, A. V.; Khulbe, P. A Comprehensive Review on Various HPLC Based Analytical Techniques Used for the Estimation of SGLT2 Inhibitors Type of Antidiabetic Drugs in Various Dosage Forms. *Res. J. Pharm. Technol.* **2020**, *13* (9), 4484–4490. https://doi.org/10.5958/0974-360X.2020.00791.X.

(9) Preeti; Swarupanjali, P. Formulation of Oral Dosage Form of Antidiabetic Drug Glipizide Using Mixed Solvency Method. *Res. J. Pharm. Technol.* **2021**, *14* (1), 427–431. https://doi.org/10.5958/0974-360X.2021.00077.9.

(10) Yadav, P.; Patel, P.; Das, P.; Deshmukh, N.; Pillai, S. Formulation and Evaluation of Pioglitazone HCL Fast Dissolving Tablet Using Solid Dispersion. *Res. J. Pharm. Technol.* **2018**, *11* (12), 5313–5318. https://doi.org/10.5958/0974-360X.2018.00967.8.