JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

ENHANCEMENT OF SOLUBILITY AND FORMULATION OF FAST DISSOLVING TABLETS ANTIDIABETIC DRUG LINAGLIPTIN

[1]Mr. Ajay B. Pole*, [2]Prof. Chhagan R. Doijad, [3] Dr. Sachin B. Dudhe
Department of Pharmaceutics, Maharashtra Institute of Pharmacy (M.Pharm), Bramhapuri, Gondwana University, Gadchiroli, Maharashtra, India

Abstract : This study aimed to enhance the solubility of Linagliptin, an antidiabetic drug, through the formulation of fast dissolving tablets. Solid dispersion complexes of Linagliptin were prepared using polyethylene glycol (PEG) 4000 and PEG 6000 via fusion and solvent evaporation methods. The solubility of these complexes was evaluated, and their potential to enhance drug solubility was assessed. Subsequently, fast dissolving tablets containing Linagliptin were formulated using sodium starch glycolate, crospovidone, and croscarmellose sodium as superdisintegrants, along with other excipients. Pre- and post-compressional parameters of the tablets were determined, including hardness, friability, weight variation, thickness, and drug content. Disintegration time and in-vitro drug release profiles of the tablets were also investigated. The results provide valuable insights into the development of novel formulations for improving the solubility and rapid delivery of Linagliptin, with potential implications for enhancing its therapeutic efficacy in the management of diabetes.

Keywords **- Linagliptin, Solid dispersion, Fast dissolving tablets, Formulation, Evaluation.**

INTRODUCTION :

The US Food and Drug Administration (FDA) created the biopharmaceutics classification system (BCS), which divides drugs into four classifications based on their permeability and solubility. Solubility obstacle occurs in Class II and Class IV of the system, where dissolution is the rate-limiting stage for drug absorption due to its poor solubility.[1] A variety of methods can be employed to improve the solubility and bioavailability of poorly water-soluble medicines. Medication solubilization is commonly achieved by micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, and other processes. Solubilization of poorly soluble medications is a typical challenge in new chemical entity screening studies as well as formulation design and development.[2] The solubility of a medicine can be represented as %, parts, molality, molarity, mole fraction, or volume fraction. Solubility equilibrium is extremely significant in medications. Drugs with low water solubility (BCS class II and IV) exhibit dissolving issues. The BCS is a scientific framework for classifying drugs based on their water solubility and intestinal permeability. When combined with the drug product's in vitro dissolving capabilities, the BCS takes into account three key factors: solubility, intestinal permeability, and dissolution rate, all of which impact the rate and amount of oral drug absorption from sudden release solid oral-dosage forms.[3]

Solubility: - solubility can be defined by 1 gm of solute is dissolved by the number of milliliters of solvent.

Quantitative Solubility: - It can be as defined as the milligram of solute particles that are needed to create a saturated solution.

Qualitative Solubility: Qualitative solubility may be defined as the combination of two phases into a homogenous mixture. According to the introduction of combinatorial chemistry, the characteristics of the newly generated active molecule will shift towards larger molecular weight, and the lipophilicity of the compounds will grow, resulting in a decrease in the drug's water solubility.[4]

A number of approaches can be used to improve the process of solubilizing poorly water-soluble medicines and increasing their bioavailability. The typical approaches for drug solubilization include micronization, chemical modification, pH alteration, solid dispersion, co-solvency, micellar solubilization, complexation, and hydrotropy. The solubilization procedure of poorly water-soluble pharmaceuticals is the most difficult impediment in the research of screening of novel chemical entities as well as formulation creation and design.[5]

Fast dissolving tablet :

Solid dose forms are popular because they are simple to administer, provide accurate dosage, allow for self-medication, reduce discomfort, and, most importantly, improve patient compliance. The most popular solid dose forms are tablets and capsules; nevertheless, one significant drawback of these dosage forms for some individuals is difficulty swallowing. Drinkable has an important part in the ingestion of oral limitless quantities. Individuals typically have difficulty ingesting standard dose forms such as pills when water is not available, when nausea is present, and when coughing occurs unexpectedly during respiratory disorders, allergic conditions, and respiratory illnesses. For these reasons, pills that dissolve or disintegrate fast in the mouth have received a great lot of attention.[6] The issue of gulping might be a common progression in an excessively elderly patient because of the stress of suffocation, hand tremors, dysphasia, and in youngsters because of immature strength and sensory systems, and in schizophrenia patients, this results in poor patient consistency. Close to one-third of the population (mostly children and the elderly) has swallowing difficulties, which leads to poor compliance with oral pill medication medical treatment, resulting in worse overall medical care efficacy.[7] For the past several decades, there has been an increased need in the marketplace for a variety of patient-convenient and compliant dosage forms, which has led to a rise in the demand for innovative technologies.

For many therapeutic drugs used to produce general effects, the oral route is the most popular form of administration due to its numerous benefits and high patient compliance compared to other routes . The United States Food and Drug Administration (USFDA) defines FDT as "a solid dose type containing a medicative substance or active ingredient that disintegrates quickly, sometimes in a matter of seconds once placed upon the tongue". FDTs are also known as mouth dissolving tablets (MDTs), orally disintegrating tablets (ODTs), melt-in-mouth tablets, quick dispersion pills, orodispersible, and fast disintegrating tablets.[9]

Techniques for preparing fast dissolving tablets :

Moulding method:

Tablets are made with hydrophilic components to ensure optimal medication dissolution. The powder bulk is wetted with hydroalcoholic solvent and crushed into a dosage form. The solvent system is then let to evaporate. The taste of medication particles is created by spray congealing a molten combination of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethene glycol, and an active component into lactose-based tablet triturate. The molding procedure is particularly porous since solvents are eliminated during drying, producing a porous aggregate that favors quick disintegration.

Freeze-drying or lyophilization:

It is a pharmaceutical procedure that enables for the drying of heat-sensitive pharmaceuticals and biologicals at low temperatures using vacuum to remove water by sublimation. Drugs are dissolved or dispersed in a carrier's aqueous solution, transported to prefabricated blister packs, then frozen using a nitrogen flush before being put in the refrigerator. Lyophilization procedures are distinguished by their high porosity and specific surface area, as well as their quick dissolution in the mouth, resulting in excellent drug bioavailability.

Nanoionization:

A recently developed nanomelt technology reduces the particle size of the medicine to nano size by milling it using a patented wet-milling method. The drug's nanocrystals are stabilized against agglomeration by surface adsorption on chosen stabilizers, which are subsequently integrated into MDT. This approach is especially useful for medications that are poorly soluble in water.

Other benefits of this technology include rapid disintegration/dissolution of nanoparticles, which leads to increased absorption and thus higher bioavailability and dose reduction, a cost-effective manufacturing process, conventional packaging due to exceptional durability, and a wide range of doses (up to 200 mg drug per unit).[10,11]

DRUG PROFILE :

Linagliptin:

Linagliptin is a DPP-4 inhibitor developed by Boehringer Ingelheim for the treatment of type II diabetes 5. Linagliptin differs from other DPP-4 inhibitors in that it has a non-linear pharmacokinetic profile, is not primarily eliminated by the renal system, and obeys concentration dependant protein binding. Linagliptin was approved by the FDA on May 2,2011.

Generic names:

Glyxambi, Jentadueto, Tradjenta, Trajenta, Trijardy.

IUPAC Name: 8-[(3R)-3-Aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7dihydro-1H-purine-2,6-dione

Chemical formula: $C_{25}H_{28}N_8O_2$

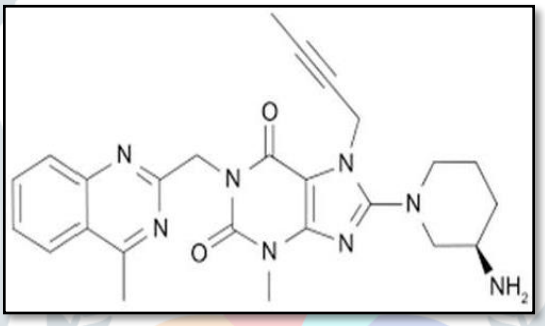

Figure 1: Structure of Linagliptine

Indication:

Linagliptin is indicated for the treatment of type II diabetes in addition to diet and exercise.It should not be used to treat type I diabetes or in diabetic ketoacidosis. An extended-release combination product containing empagliflozin, linagliptin, and metformin was approved bythe FDA in January 2020 for the improvement of glycemic control in adults with type 2 diabetes mellitus when used adjunctively with diet and exercise.

Pharmacodynamics:

A 5mg oral dose of linagliptin results in >80% inhibition of dipeptidyl peptidase 4 (DPP-4)for ≥24 hours. Inhibition of DPP-4 increases the concentration of glucagon-like peptide 1 (GLP-1), leading to decreas d glycosylated hemoglobin and fasting plasma glucose.

Mechanism of action :

Linagliptin is a competitive, reversible DPP-4 inhibitor. Inhibition of this enzyme slows thebreakdown of GLP-1 and glucose-dependant insulinotropic polypeptide (GIP). GLP-1 andGIP stimulate the release of insulin from beta cells in the pancreas while inhibiting releaseof glucagon from pancreatic beta cells. These effects together reduce the breakdown of glycogen in the liver and increase insulin release in response to glucose

Absorption :

Oral bioavailability of linagliptin is 30%

Half life :

The terminal half life of linagliptin is 155 hours.

Uses :

Linagliptin is a medicine used to treat type 2 diabetes. Type 2 diabetes is a condition wherethe body does not makeenough insulin, or the insulin that it makes does not work properly.This can cause high blood sugar levels (hyperglycaemia).

Side effects :

Bloating, hives, welts, itching, or skin rash, large, hard skin blisters, large, hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or sex organs, pains in the stomach, side, or abdomen, possibly radiating to the back, severe joint pain.

RESEARCH METHODOLOGY :

Formulation development of solid dispersions :

A solid dosage form is a comfortable and familiar means of taking medication. Hence, a patient compliance and drug treatment are usually more effective with orally administered medications than other routes of administration. At least 40% of the new chemical molecules tested are drugs having poor aqueous solubility. Many methods are available to improve dissolution rate, solubility characteristics, Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs.

Evaluation of prepared solid dispersion :

Percentage drug content :

For the determination of Linagliptin content, dispersion equivalent to 10 mg of Linagliptin, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernatant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for Linagliptin at 282nm using a validated UV spectrophotometric method.

Formulation development of fast dissolving tablets of Linagliptin :

The fast dissolving tablets of Linagliptin were prepared using the sodium starch glycolate, Crospovidone and croscarmellose sodium as superdisintegrant, mannitol as diluent, aspartame as sweetening agent, and talc as flow promoter and magnesium stearate as lubricant, the composition of each batch is shown in Table no. 7.3. The raw materials were passed through a 100-mesh screen prior to mixing. The drug and other ingredients weremixed together and a sufficient quantity of alcoholic solution of PVP K-30 (10%w/v) was added and mixed to form a coherent mass (Suryadevara *et al.*, 2016). The wet mass was granulated using sieve no. 12 and regranulated after drying through sieve no. 16. Granulesof the all formulations were then dried in a vacuum oven (Vertex, VT4810) at 60°C for 12 h resulting in localized drying. The final moisture content of the granules was found to be between 1- 2%, which was determined using an IR moisture balance. During drying, the menthol sublimed with the formation of a porous structure on the surface of the tablet. The dried granules were then blended with talc, magnesium stearate and compressed into tablets using flat face round machine on a Rimek-I rotary tablet machine.

Evaluation of post compression parameter :

Shape and colour of tablets:

Uncoated tablets were examined under a lens for the shape of the tablet and colour wasobserved by keeping the tablets in light

Thickness test :

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper.

Weight variation test :

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The followingpercentage deviation in weight variation is allowed (6.8).

Hardness test :

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

Friability test :

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

% Friability = (Loss In Weight/ Initial Weight)×100

The test complies if tablets not loss more than 1% of their weight.

Uniformity of drug content :

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer (pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted upto 100 ml with phosphate buffer (pH 6.8) and the drug content was determinedspectrophotometrically at 282nm.

Dissolution rate studies :

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at 37±0.2□C. The scheme of using the simulated fluids at different timing was as follows: A tablet placed in dissolution media (900 ml, phosphate buffer, pH 6.8) at 37±0.2 C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml phosphate buffer(pH 6.8). The samples withdrawn were assayed spectrophotometrically at 282 nm using UV visible spectrophotometer. The release of drug was calculated with the help of Standard curve of Linagliptin.

RESULT AND DISCUSSION :

Results of physical evaluation :

1.	Color	White powder
2.	Odor	Odorless
3.	Taste	Bitter
4.	Texture	Solid

Table 1: List of sensory characters

Table.1 provides a comprehensive list of sensory characteristics for a substance, presumably a pharmaceutical compound or an ingredient.

Results of solubility :

S. No.	Solvent used	Solubility
1.	Water	Slightly Soluble
2.	0.1 N HCl	Freely soluble
3.	Ethanol	Sparingly soluble
4.	Methanol	Soluble
5.	Chloroform	Soluble
7.	0.1 N NaOH	Soluble
8.	6.8 pH phosphate buffer	Soluble

Table 2 : Solubility of Linagliptin

Table 2 presents the solubility characteristics of Linagliptin, a medication commonly used to treat type 2 diabetes. The solubility of Linagliptin varies across different solvents, whichis crucial for understanding its pharmacokinetic behavior and formulation development. In water, Linagliptin exhibits slight solubility, implying that it may not readily dissolve inaqueous solutions, which could impact its absorption and bioavailability upon oral administration. However, the solubility increases significantly in 0.1 N HCl, where it becomes freely soluble. The solubility of Linagliptin in ethanol is sparing, indicating limited dissolution in this organic solvent. Similarly, it shows solubility in methanol and chloroform, suggesting that these solvents might be useful for certain pharmaceutical applications where Linagliptin needs to be dissolved. Linagliptin demonstrates solubility in 0.1 N NaOH and 6.8 pH phosphate buffer, further expanding its potential utility in different formulation strategies.

Results of melting point :

Result: The melting point of Linagliptin was found to be 201-203°C

Results of identification Test using FTIR Spectroscopy :

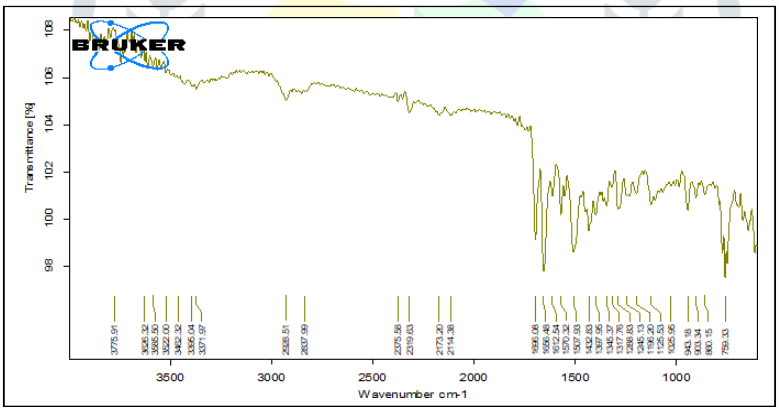

Figure 2 : FT-IR Spectrum of pure drug (Linagliptin)

S. No.	Peak Position (cm^{-1})	Remark
1.	3371.97	O-H stretching
2.	2928.51	C=O stretching
3.	1666.43	C=C stretching
4.	1245.13	C-N stretching

Table 3 : Interpretation of FT-IR spectra

Results of loss on drying:

Result: The percentage of loss on drying of Linagliptin was found 0.276±0.002.

Results of determination of λ_{max} of Linagliptin :

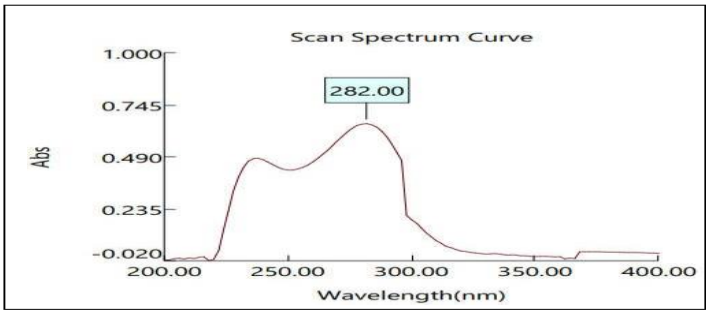

Figure 3 : U.V. Spectra of Linagliptin

S. No.	Conc. (µg/ml)	Mean absorbance
1.	1	0.145
2.	2	0.268
3.	3	0.402
4.	4	0.521
5.	5	0.654

Table 4: Calibration curve of Linagliptin in 6.8 pH phosphate buffer

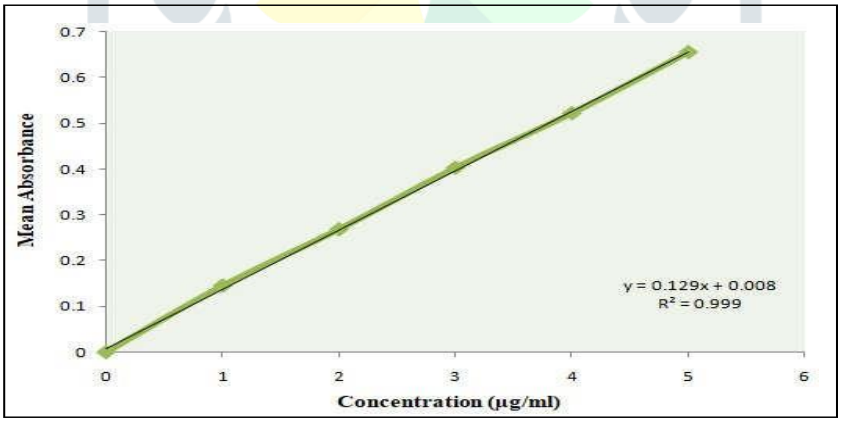

Figure 4: Calibration curve of Linagliptin in 6.8 pH phosphate buffer

S. No.	Parameter	pH 6.8 phosphate buffer
1.	Linearty Range	1-5 µg/ml
2.	Regression Equation	Y = 0.129 x + 0.008
3.	Correlation Cofficient	0.999

Table 5: Stastical data for linearty

The calibration curve of Linagliptin in 6.8 pH phosphate buffer was constructed to determine the relationship between the concentration of Linagliptin and its corresponding absorbance values at a specific wavelength, typically measured using UV-Vis spectroscopy. This calibration curve provides a means to quantify the concentration of Linagliptin in unknown samples based on their absorbance readings. The statistical data for linearity, as presented in Table 5, includes the linearity range, regression equation, and correlation coefficient for the calibration curve in 6.8 pH phosphate buffer. The linearity range indicates the concentration range over which the response of the detector (UV-Vis spectrophotometer) is linearly related to the concentration of Linagliptin in the sample. In this case, the linearity range is reported as 1-5 µg/ml, suggesting that the calibration curve is valid within this concentration range.

The regression equation represents the mathematical relationship between the concentration of Linagliptin (x) and its corresponding absorbance (y) values. The equation provided is in the form of y = mx + c, where 'm' is the slope of the line (0.129) and 'c' is the y-intercept (0.008). This equation allows for the calculation of Linagliptin concentration in unknown samples based on their absorbance values within the linearity range. The correlation coefficient (R^2) is a measure of the strength and direction of the linear relationship between the concentration of Linagliptin and the absorbance readings obtained from the calibration curve. A correlation coefficient close to 1 indicates a high degree of linearity and a strong correlation between concentration and absorbance. In this case, the correlation coefficient is reported as 0.999, suggesting an excellent linear relationship between Linagliptin concentration and absorbance values in 6.8 pH phosphate buffer.

Results of solubility study of different solid dispersion :

F. Code	Complex	Solubility (mg/ml)
Fusion method		
	Pure drug	0.65
F1	Drug: PEG 4000 (1:1)	1.25
F2	Drug: PEG 4000 (1:5)	1.36
F3	Drug: PEG 4000 (1:10)	1.48
F4	Drug: PEG 6000 (1:1)	1.32
F5	Drug: PEG 6000 (1:5)	1.56
F6	Drug: PEG 6000 (1:10)	1.68
Solvent evaporation method		
F7	Drug: PEG 4000 (1:1)	1.55
F8	Drug: PEG 4000 (1:5)	1.85
F9	Drug: PEG 4000 (1:10)	1.92
F10	Drug: PEG 6000 (1:1)	1.74
F11	Drug: PEG 6000 (1:5)	2.36
F12	Drug: PEG 6000 (1:10)	2.05

Table 6: Solubility of different solid dispersion complexes

Results of % solubility Enhancement :

Parameter	% Solubility enhancement			
	Drug: PEG 4000			
	1:1	1:5	1:10	Pure Drug
% Solubility Enhancement	192.30	209.23	227.69	0.65
	Drug: PEG 6000			
	1:1	1:5	1:10	
% Solubility Enhancement	203.076	240.00	258.46	

Table 7: Percentage cumulative drug release of Fusion method

Parameter	% Solubility enhancement			
	Drug: PEG 4000			
	1:1	1:5	1:10	Pure Drug
% Solubility Enhancement	238.46	284.61	295.38	0.98
	Drug: PEG 6000			
	1:1	1:5	1:10	
% Solubility Enhancement	267.69	363.07	315.38	

Table 8 : Percentage cumulative drug release of solvent evaporation method.

The results of the percentage solubility enhancement demonstrate the efficacy of different formulations in improving the solubility of the drug, both with the fusion method and the solvent evaporation method.

Table 7 presents the percentage solubility enhancement achieved with the fusion method for both PEG 4000 and PEG 6000. For the formulations with PEG 4000, the percentage solubility enhancement increased with higher ratios of the polymer. For example, the 1:10 ratio exhibited the highest enhancement, with a 227.69% increase compared to the puredrug. Similarly, formulations with PEG 6000 showed increased solubility enhancement with higher ratios, reaching a maximum of 258.46% for the 1:10 ratio.

Results of drug content :

Formulation	Label claim	Amount found*	Label claim (%)
Physical mixture	10mg	9.98	99.80±0.25

Table 9: Results of drug content (Drug: PEG 6000, 1:5)
* Average of three determination

*****Average of three determination

The label claim for the formulation was 10 mg of the drug. Upon analysis, the amount ofdrug found in the formulation was determined to be 9.98 mg. This indicates that the actual drug content in the formulation is very close to the labeled amount, with

only a minor deviation observed.The percentage of label claim calculated based on the amount found in the formulation is 99.80%. This suggests that the formulation contains nearly the expected amount of drug as per the label claim, with a high level of accuracy and consistency. The results of the drug content analysis indicate that the formulation with a drug-to-polymer ratio of 1:5 (Drug: PEG 6000) meets the label claim specifications effectively. The minor deviation observed between the labeled amount and the amount found in the formulation is within acceptable limits, suggesting good formulation uniformity and accuracy in drug content. The high percentage of label claim (99.80%) reflects the reliability and precision of the manufacturing process in delivering the intended drug content in the formulation. This ensures that patients receive the correct dosage of the drug, which is crucial for achieving desired therapeutic outcomes and ensuring safety.

Results of disintegration time of all formulations :

The disintegration time was performed using an USP disintegration test apparatus with distilled water at 37 ± 0.5°C, Table 8.12. The disintegration time was taken to be the time when no granules of any tablets were left on the mesh of the apparatus. The time reported to obtain complete disintegration of six tablets were recorded. The mean disintegration time and standard deviations were calculated.

N=3 mean±S.D

S. No.	Formulation code	Disintegration Time* (Sec.)
1.	F1	98±3
2.	F2	75±2
3.	F3	65±4
4.	F4	102±5
5.	F5	95±6
6.	F6	88±3
7.	F7	63±4
8.	F8	73±2
9.	F9	70±4

Table 10: Results of disintegration time of all formulations

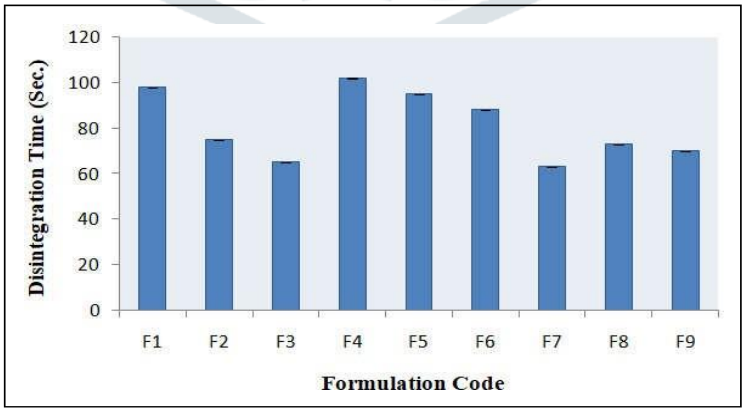

Figure 5: Graph of in vitro disintegration time of all formulations

The disintegration time, a pivotal parameter in tablet formulation, signifies the tablet's ability to swiftly break down into smaller particles when exposed to bodily fluids, thus facilitating drug release and absorption. Across the formulations tested, significant variations in disintegration time were observed, reflecting differences in dissolution behavior and disintegration properties.

Notably, formulation F3 demonstrated the shortest disintegration time, clocking in at 65±4 seconds, indicating rapid breakdown and dissolution of the tablet matrix upon exposure to physiological fluids. Conversely, formulations F1, F4, and F5 exhibited relatively longer disintegration times, hinting at slower dissolution rates or potential challenges in tablet disintegration. These discrepancies in disintegration times may stem from several factors, including variations in formulation composition, properties of excipients used, and nuances in tablet manufacturing processes.

In vitro dissolution rate studies :

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	35.65	1.552	64.35	1.809
5	2.23607	0.69897	69.98	1.845	30.02	1.477
10	3.16228	1	88.85	1.949	11.15	1.047
15	3.87298	1.17609	98.74	1.994	1.26	0.100

Table 11 : In-vitro drug release data for optimized formulation F7

Zero order release kinetics of formulation F7

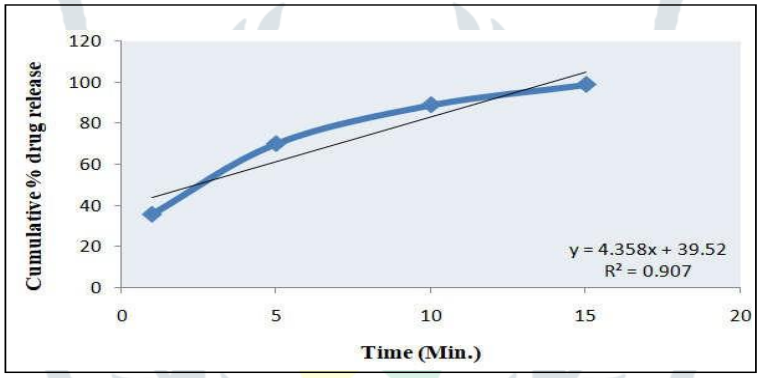

Figure 6 : Graph of zero order release Kinetics of formulation F7First order release Kinetics of formulation F7

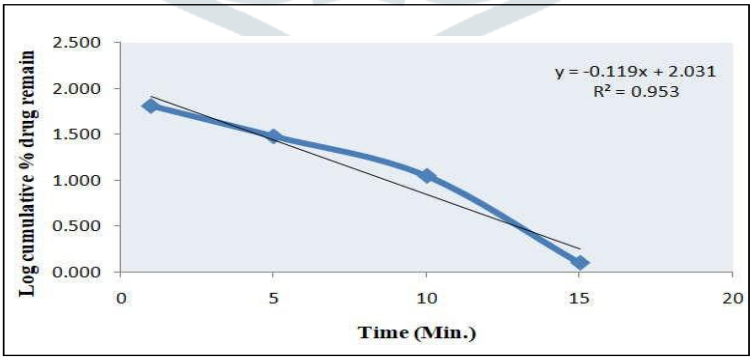

Figure 7 : Graph of first order release kinetics of formulation F7

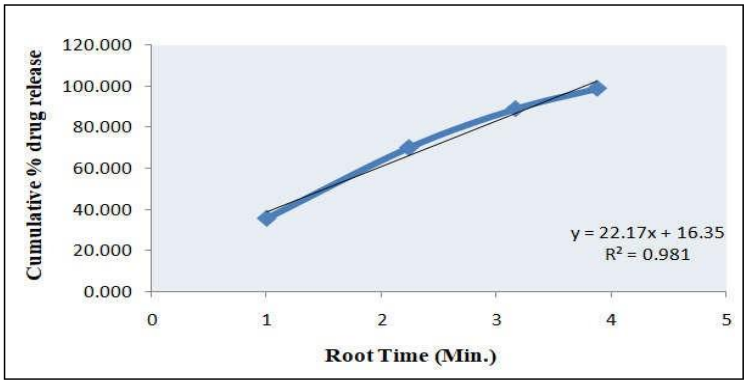

Figure 8 : Graph of Higuchi release kinetics of formulation F7

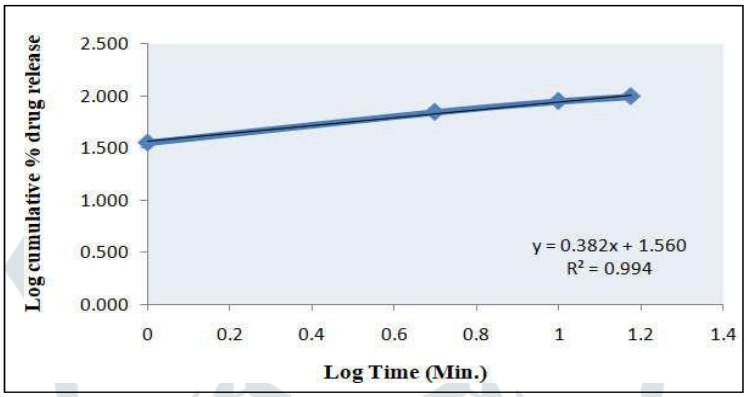

Figure 9 : Graph of Peppas release kinetics of formulation F7

Batch	Zero Order	First Order	Higuchi Kinetics	Peppas model
	r^2			
F7	0.907	0.953	0.981	0.994

Table 12 : Regression analysis data

The in-vitro drug release data for the optimized formulation F7 provides valuable insights into the release kinetics and performance of the formulation over time. The cumulative percentage of drug release increased progressively with time, reaching 35.65% at 1 minute and steadily escalating to 98.74% at 15 minutes. This release profile suggests that the drugis released in a sustained manner over the test duration. The observed drug release kinetics indicates a sustained-release behavior, where the drug is released gradually from the formulation over an extended period. This sustained release profile is often desirable for medications requiring prolonged therapeutic action and reduced dosing frequency, as it can help maintain consistent drug levels in the bloodstream and improve patient compliance. The formulation's sustained-release characteristics can be attributed to its composition and design, which likely incorporate polymers or excipients that control the rate of drug release. These components may form a matrix or barrier around the drug particles, regulating their diffusion and dissolution in the dissolution medium.

The high cumulative percentage of drug release, nearing 99% at 15 minutes, suggests efficient drug delivery and dissolution properties of the formulation. This sustained and controlled release profile may be advantageous for medications targeting chronic conditions or requiring prolonged therapeutic effects. The regression analysis data for batch F7, using different kinetic models, provides valuable insights into the drug release mechanism and kinetics of the formulation. The coefficient of determination (r^2) values obtained from fitting the experimental data to each model indicate the degree of correlation between the predicted and observed drug release profiles. For batch F7, the coefficient of determination for the zero-order model is 0.907, suggestinga

moderate fit of the model to the experimental data. The zero-order model assumes that the rate of drug release is constant over time, independent of the drug concentration. While the correlation is not as strong as desired, the model still provides valuable

information about the release kinetics of the formulation. The coefficient of determination for the first-order model is higher at 0.953, indicating a better fit of the model to the experimental data compared to the zero-order model. The first- order model describes drug release as a linear function of time and assumes that the rate of drug release decreases exponentially over time. The higher r^2 value suggests that the first- order model may more accurately describe the release kinetics of batch F7. The Higuchi kinetics model, with an r^2 value of 0.981, demonstrates a strong fit of the model to the experimental data. The Higuchi model is commonly used to describe drug release from matrix systems where diffusion is the primary mechanism of drug release. The high correlation coefficient suggests that the Higuchi model adequately captures the drug release behavior of batch F7. Finally, the Peppas model shows the highest coefficient of determination at 0.994, indicating an excellent fit of the model to the experimental data. The Peppas model is often used to describe drug release from polymeric systems exhibiting anomalous or non-Fickian transport, where both diffusion and polymer relaxation contribute to drug release. The highr^2 value suggests that the Peppas model accurately describes the complex release kinetics of batch F7.

CONCLUSION :

The solubility of Linagliptin, an antidiabetic drug, was investigated in various solvents, revealing its limited solubility in water but good solubility in 0.1 N HCl, ethanol, methanol, chloroform, 0.1 N NaOH, and 6.8 pH phosphate buffer. Linagliptin exhibited a white powder appearance with an odorless nature and a bitter taste. Its texture was described as solid. Infrared spectroscopy (FT-IR) analysis revealed characteristic peaks corresponding to O-H stretching, C=O stretching, C=C stretching, and C-N stretching at specific wavenumbers. The bitter taste of Linagliptin may necessitate the incorporation of taste-masking agents or flavorants into the tablet formulation to enhance patient acceptability. Additionally, the solid texture of Linagliptin suggests the need for suitable excipients to aid in tablet disintegration and dissolution. Overall, the formulation development process yielded fast dissolving tablets of Linagliptin with desirable pre- and post-compressional parameters and efficient drug release characteristics, demonstrating their potential for rapid drug delivery applications in the treatment of diabetes. In conclusion, the formulation and evaluation of fast dissolving tablets of Linagliptin represent a significant advancement in pharmaceutical technology aimed at enhancing patient compliance and therapeutic outcomes in the treatment of diabetes. Through meticulous formulation development and rigorous evaluation of tablet parameters, including pre- and post-compressional characteristics, the study has successfully demonstrated the feasibility of producing tablets with rapid disintegration properties and consistent drug release profiles. The in-vitro drug release studies further validate the optimized formulation's efficacy indelivering Linagliptin in a timely and efficient manner, suggesting its potential for improved therapeutic outcomes. Moreover, regression analysis results indicate the formulation's stability and predictability, supporting its suitability for clinical application. Overall, the findings of this study underscore the promising prospects of fast dissolving tablets as a patient-friendly dosage form for Linagliptin, offering convenience, efficacy, and potential benefits for diabetes management.

REFERENCE

[1] Abhishek Soni, Raju L. Formulation and Evaluation of Fast Disintegrating Tablet Containing Hydrochlorothizide. Indian Journal of Pharmacy and Pharmacology, 2015;2(2); 119-133.

[2] Aher et al, Review: Fast Dissolving Tablet, International Journal of Current Pharmaceutical Research, Vol 10, Issue 2, 2018.

[3] Aluru Nishitha1, A.Anil Kumar. Formulation and Evaluation of Linagliptin Nanospheres. J. Pharm. Sci. & Res. 2021; Vol. 13(5), 288-293.

[4] Ankur Sharma, Abhishek Jain, Anuj Purohit, Rakesh Jatav and R. V. Sheorey. Formulation and evaluation of aceclofenac fast dissolving tablets. Int. J. of Pharm. & Life Sci. (IJPLS). 2011; Vol. 2, Issue 4: 681-686.

[5] Arijit Gandhi. Mouth Dissolving Tablets: A New Venture in Modern Formulation Technology. The Pharma

Innovation. 2012; Vol. 1: No. 8: 14-31.

[6] CH. Jyothi, K. Akhil Kumar, M. Mamatha, N. Mamatha, G. Soujanya and Dr.K. Hemamalini. Formulation and evaluation of fast dissolving tablets of zidovudine using sublimation technique. World Journal of Pharmaceutical Research. 2018; Vol. 7, Issue13, 912-924.

[7] Ch. Sai Babu. Formulation and evaluation and stability studies of bilayer tablets of metformin and linagliptin. World Journal of Pharmaceutical Research. 2019; Vol 8, Issue 13, 868-880.

[8] Ch. Saidulu, M. Jhansirani, R. Aruna, A.M.S. Sudhakar babu. Formulation and evaluation of zolmitriptan fast dissolving tablet using synthetic superdisintegrants. Int JPharm 2014; 4(4):365-370.

[9] Ch.Saibabu, R.Raviteja. Formulation development and stability studies of bilayer tablets of linagliptin and metformin. J. innov.appl. pharm. 2021; Sci, 6(1), 08-14.

[10] Deepak Kumar Panda, Subham Panigrahy, Madhusudan Dash, Suneli Devi, Rajeshree Panigrahi. Formulation and Evaluation of Lisinopril Fast Dissolving Tablets Using Natural Superdisintegrants. Research Journal of Pharmacy and Life Sciences: 2021; Volume 2: Issue 3: Page 95 –101.

[11] Divya Rathore; Dr. Vikas Jain; Narendra Gehalot. Formulation and evaluation of fast dissolving tablets of aceclofenac using natural superdisintegrant. International Journal of Pharmaceutical Sciences & Medicine (IJPSM). 2022; Vol.7, Issue 10, 39-64.

[12] Rakesh Kumar Jat. Formulation and Evaluation of Immediate Release Tablet Dosage Form of Linagliptin and Metformin Hydrochloride. 2021; Vol. 11, Issue 3-S.

[13] Ram Pal, Mohammad Mujahid, Shamim Ahmad. Formulation Development and In- Vitro Evaluation of Linagliptin Transdermal Patch Using Permeability Enhancer. Int. J.Pharm. Sci. Rev. Res.2023; Article No. 04, 19-28.

[14] S.Muralidhar, T.V.Narayana, Ch.S.Phani Kumar, Mahajan Anil Arun. Formulation andEvaluation of Fast Dissolving Tablets by Addition Of Different Concentrations Of Superdisintegrant And By Effervescent Technology. International Journal of Pharmaceutics & Drug Analysis. 2019; VOL.7, ISSUE 1, 1 – 10.

[15] Saha, T., Alam, M.M., Lira, D.N. & Rouf, A.S.S. (2021) Formulation and evaluation ofeffects of superdisintegrants on immediate release tablet of linagliptin, a DDP-4 inhibitor. Bangladesh Pharmaceutical Journal, 24, 168–179

[16] Shah, P., Chavda, K., Vyas, B. & Patel, S. (2021) Formulation development oflinagliptin solid lipid nanoparticles for oral bioavailability enhancement: Role of P-gp inhibition. Drug Delivery and Translational Research, 11, 1166–1185

[17] Sharma R, Rajput M, Pawan P, Sharma S. Review article fast dissolving drug delivery system. Int Res J Pharm 2011; 2:21–9.

[18] Siddiqui MN, Garg G, Sharma PK. Fast dissolving tablets: preparation, characterizationand evaluation: an overview. Int J Pharm Sci 2010; 4:87-96.

[19] Sinko, P.J, Martin's Physical Pharmacy, and pharmaceutical science, Wolters Kluwer, New Delhi 2011.

[20] Sree Giri Prasad. B, Gupta VRM, Yasasvi Narayan. G, K.Vijaya, Tamilselvan A, SivaSubramanian. N. Formulation and evaluation of fast dissolving tablet of Tolvaptan. JGTPS.2015; 6(1): 2403 – 2410.

[21] Vemula VR, Lagishetty V, Lingala S. Solubility Enhancement Techniques. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5(1): 41-51.

[22] Vilas, P. B., Vinayta, R. A., Anirudha, V. M., Arunadevi, S. B., Sanjay, Bais., J. Innov.Pharm. Biol. Sci.2015, 2 (4), 482-494.

[23] Boral A, Sen N, Ghosh LK, Gupta BK. Solid dispersion technology for controlling drug release and absorption. The eastern pharmacist. 1995; 8:141-143.

[24] Tachibana T, Nakamura A. A methode for preparing an aqueous colloidal dispersion oforganic materials by using water-soluble polymers: dispersion of β-carotene by polyvinylpyrrolidone. Kolloid-Zeitschrift und Zeitschrift fur Polymere. 1965; 203(2):130-3.

[25] Suryadevara V, Lankapalli SR, Sunkara S, Sakhamuri V, Danda H. Dissolution rate enhancement of irbesartan and development of fast-dissolving tablets. Egypt Pharmaceut J. 2016; 15:150-7.

[26] Cooper J, Gunn C. Powder flow and compaction. Tutorial Pharmacy. New Delhi, CBS Publishers and Distributors, India. 1986; 10:20-30.

[27] Martin A. Micromeritics. In: Martin A, editor. Physical Pharmacy. Baltimore, MD: Lippincott, Williams and Wilkins; 2001; 423-54.

[28] Carr RL. Evaluating flow properties of solids. Chem. Eng. 1965; 18:163-8.

[29] Lachman L, Lieberman HA. "The theory and practice of industrial pharmacy", In: Gilbert S. Banker and Neil R. Anderson. Tablets. 3rded.Bombay: Varghese publishinghouse; 1990; 297-302.

[30] Willard HH, Merritt Jr LL, Dean JA, Settle Jr FA. Instrumental methods of analysis. 2007; 121-140.

[31] Higuchi T. Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci.1963; 52: 1145–1148

[32] Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm.1983; 15: 25–35.