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Development of Formulation and Assessment of First III Generation Glimepiride Sulphonyl Urea Drug

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Abstract
Glimepiride, an oral anti-diabetic medication, is classified as a class II pharmaceutical in the Biopharmaceutics Classification System (BCS) due to its low solubility. The main purpose of it is to cure Type 2 diabetes. Since the wet granulation process was employed in the formulation of the tablets, the solubility enhancement achieved through technique advancement is quite advantageous. The F5 formulation yielded good results using Polyvinylpyrrolidone (PVP) K-30/Povidone K-30 as the wet granulation process and purified water as the binder. Among other medicinal characteristics, the generated tablet formulations were evaluated for friability (%), thickness, hardness, and disintegration time. It was discovered that the solubility in vitro was 0.357 mg/ml,% Drug release in vitro was reported to be 99.96%, and drug content was found to be 99.91%. The USP II equipment was used for the dissolution investigations. The findings demonstrated that using purified water and Polyvinylpyrrolidone (PVP) K-30/Povidone K-30 as a binder in the wet granulation process significantly improved the solubility of glimepiride. The five formulations were finished after the dry mixing excipient, binder material, blending material, and lubricating ingredient were adjusted. The disintegration profile will be diminished in the medication release from the dosage form during a certain time interval. The chosen formula F5 works perfectly in the disintegration time of 3 minutes and 42 seconds.

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Keywords: Glimepiride**,** wet granulation**,** Dissolution, % Drug content

1. Introduction

Figure 1. shows glimepiride's chemical composition as 3-ethyl-4-methyl-N-[2-[4-[(4-methylcyclohexyl)carbamoylsulfamoyl] phenyl] ethyl]-2-oxo-5H-pyrrole-1-carboxamide. Bears the molecular weight of 490.62 g/mol and the chemical formula $C_{24}H_{34}N_4O_5S$. It is a third-generation derivative of sulfonylurea that is mostly used to treat Type 2 diabetes mellitus that is not insulin dependent (1).

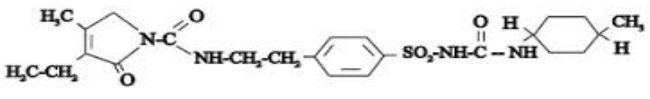

Fig 1: Glimepride's structure

The Biopharmaceutical Classification System (BCS) places glimepiride in class II, which is characterized by high permeability and poor solubility (9). The drug's pH-dependent solubility is not very good. The melting point of glimepiride is 207°C (1). Poor aqueous solubility is known to have a substantial impact on oral bioavaibility, which includes therapeutic efficacy. This is because it results in a low dissolution rate, which in turn leads to reduced absorption in the gastrointestinal system after oral administration (2). Glimepiride acts on the ATP-sensitive potassium channels (KATP) of pancreatic N-cells, which in turn promotes the release of insulin. It seems to be a part of the same sulphonyl urea receptor that, when attaching to 65kD protein on β-cells, binds Glibenclamide. Glimepiride lowers blood glucose 3.5 times more efficiently than glibeenclamide when taken orally. Glimepiride exhibits very low solubility in both acidic and neutral water solutions at 370C (<0.004 mg/mL). The

medication's solubility is slightly increased to 0.02 mg/mL in liquids that have a pH higher than 7. (3). A person with diabetes mellitus has high blood sugar because of either inadequate insulin synthesis by the body or inappropriate insulin absorption by body cells. The hormone insulin, which is secreted by the pancreas, enables body cells to absorb glucose and transform it into energy. Glucose can cause issues with veins, nerves, and other organs if it is not absorbed by the body's cells and accumulates in the blood. The oral mode of administration is thought to be the most widely used because of its simplicity in self-administration, small size, and convenience of manufacture. Diabetes mellitus is mostly seen in four kinds. Type I, Type II, and other variations of the illness are among them, as is gestational diabetes. Glimepiride is the first III generation sulphonyl urea; it is extremely potent and has a long half-life of action (4) (12). Patients with type 2 diabetes mellitus (T2DM) are more likely to develop macrovascular complications like coronary artery disease (CAD), peripheral arterial disease (PAD), stroke, and transient ischemic attack (TIA) as well as microvascular complications like diabetic retinopathy, neuropathy, and diabetic nephropathy as a result of inadequate glycemic control (5). If diet and exercise alone are not enough to restore and sustain normal glycemic control, then pharmacologic treatment is necessary to bring people with type 2 diabetes' blood glucose levels and glycated haemoglobin (HbA1c) readings to nearly normal levels. Sulfonylureas (SUs) are oral antidiabetic medications that can be used by people with type 2 diabetes because they increase the release of insulin from pancreatic beta-cells and have a variety of extrapancreatic effects, such as increased insulin-mediated absorption of glucose in peripheral tissues. Extrapancreatic effects have also been reported with glimepiride. Furthermore, glimepiride increases the number of glucose transporter molecules in the plasma membranes of peripheral muscle and adipose tissue, which enhances glucose absorption. Glimepiride is rapidly and completely absorbed when taken orally13; the impact of meals on this process is minimal. The complete metabolic pathway of glimepiride is carried out by hepatic oxidative biotransformation. Glimepiride is metabolised by the hepatic cytochrome P450 2C9 isoenzyme to the cyclohexyl hydroxymethyl derivative (M1), which is further hydrolyzed by cytosolic enzymes to the carboxyl derivative (M2). The half-life of glimepiride elimination is five hours after a single dose and nine hours after several doses. The usual starting dose for new therapy is one to two milligrammes of glimepiride administered once day with breakfast or the first big meal. Depending on the metabolic condition, the daily dose can be raised to glimepiride 3 or 4 mg once day over the course of one to two weeks. The highest recommended dosage is eight milligrammes once day (6). This study looks at the solubility and bioavailability of glimepiride, an anti-diabetic drug (10).

The aim of this study was to formulate glimepiride into uncoated tablets for oral administration using the wet granulation process to prevent hyperglycemia.

2. Materials and Methods

Materials

Glimepiride was obtained as kind gift Sample from Swiss Garnier Genexia Ltd., Sikkim. Lactose monohydrate, Maize starch, Microcrystalline cellulose, Sodium starch glycolate, Polyvinylpyrrolidone (PVP) K-30 were obtained as kind gift Sample from SBL Pvt Ltd, Sikkim., Polyvinylpyrrolidone (PVP) K-90, Colloidal silicon dioxide, Magnesium stearate, Purified Talc, Croscarmellose sodium and yellow oxide of iron were obtained as kind Gift Sample from Sangrila Industries Pvt Ltd, Sikkim. All the materials were used as an analytical grade.

Methods

a) **Glimepiride's Characteristics (6):** The melting point was ascertained by the capillary method, and the temperature at which the compound starts to melt and melts completely was noted.

b) **Glimepiride's Standard Curve (2):** Phosphate buffer pH 7.8 was used to generate a glimepiride standard curve, with values ranging from 1 to 11 µg/mL.

c) **λ max Determination:** An ultraviolet (UV) spectrophotometer is utilised to ascertain the maximum wavelength (λmax) at which the medicine exhibits the highest absorbance in various solvents. The values for λmax in ethanol, water, and Phosphate buffer solution are listed in Table 3.

Glimepiride Uncoated Tablet Formulation and Assessment (2)

d) **Blends Assessment:** The different attributes of the studied mixes include loss on drying.

e) **Estimating the Blend before Compression:** The characterization research involves determining the parameters of the blend before compression by measuring the angle of repose, bulk and tapped densities, Carr's index, and Hausner ratio.

Making Uncoated Tablets Containing 4mg of Glimepiride (2)

Tablets containing 4 mg of glimepiride uncoated were made by wet granulation (F5).

Table 1: Preparation of Tablet Content

S. No.	Ingredients	Formulation (mg) F1	Formulation (mg) F2	Formulation (mg) F3	Formulation (mg) F4	Formulation (mg) F5
1.0	Glimepiride	4.00	4.00	4.00	4.00	4.00
2.0	Lactose monohydrate (add in dry- mixing)	101.00	131.00	151.00	171.00	181.00
3.0	Maize starch (add in dry- mixing)	10.00	10.00	10.00	14.00	15.00
4.0	Microcrystalline cellulose (add in dry- mixing)	10.00	15.00	20.00	25.00	30.00
5.0	Sodium starch glycolate (add in dry- mixing)	7.00	3.00	6.00	4.00	6.00
6.0	Polyvinylpyrrolidone (PVP) K-30/Povidone K-30 (as binder)	0.00	6.00	6.00	0.00	4.00
7.0	Polyvinylpyrrolidone (PVP) K-90 / Povidone K-90 (as binder)	4.00	0.00	0.00	3.00	0.00
8.0	Purified Water (as binder) *	40.00	40.00	40.00	40.00	44.00
9.0	Maize starch (as binder)	2.00	0.00	2.00	0.00	0.00
10.0	Colloidal silicon dioxide (add in blending stage)	1.00	1.00	1.00	1.00	1.00
11.0	Purified Talc (add in blending stage)	1.00	0.50	1.00	0.00	0.50

12.0	Sodium starch glycolate (add in blending stage)	5.00	8.50	3.00	7.00	7.50
13.0	Croscarmellose sodium (add in blending stage)	4.00	0.00	5.00	0.00	0.00
14.0	Magnesium stearate (add in lubrication stage)	1.00	1.00	1.00	1.00	1.00
	Total	150.00	180.00	210.00	230.00	250.00

Note: *Purified water is not consider for average weight.

Wet Granulation Methodology

A maximum relative humidity of 65% and a maximum temperature of 30°C were used during the production process.

Step I: A 40 mesh SS screen was employed for filtering after glimepiride and lactose monohydrate were combined geometrically. Colour and maize starch were blended, and the mixture was sifted through an 80 mesh stainless steel filter. A 40 grit screen composed of microcrystalline cellulose and sodium starch glycolate was used to sift the residual material.

Step II: Formulation F1: Continuous mixing of dissolved Povidone K-90 and Polyvinylpyrrolidone (PVP) K-90 was done with purified water. Make a starch slurry with purified water. Hot purified water was mixed with starch slurry to make a paste. After that, the Povidone K-90 solution was made, added starch paste, and allowed to cool to room temperature (25 ± 3^0C).

Formulation F2: A solution of Polyvinylpyrrolidone (PVP) K-30/Povidone K-30 dissolved in purified water was prepared with continuous stirring.

Formulation F3: A solution was prepared by stirring together dissolved Polyvinylpyrrolidone (PVP) K-30 / Povidone K-30 and purified water. Prepare a starch slurry using purified water. A solution of starch was added to a heated mixture of purified water, forming a paste. Subsequently, a solution of Povidone K-30 was introduced to a starch paste and allowed to cool at room temperature (25 ± 3^0C).

Formulation F4: A solution was prepared by dissolving Polyvinylpyrrolidone (PVP) K-90/Povidone K-90 in purified water while continuously stirring.

Formulation F5: A solution was prepared by dissolving Polyvinylpyrrolidone (PVP) K-30/Povidone K-30 in purified water with constant stirring.

Step III: Transfer all materials to the Rapid Mixture Granulator and mix for 8 minutes with the Agitator set to a slow speed and the chopper turned off. Then, add the binder solution from step II and continue mixing for 1 minute with the Agitator still set to a slow speed and the chopper turned off. Next, operate the Agitator at a low speed and the Chopper at a high speed for 35 seconds in order to achieve a consistent and uniform granule mass. The granular mass was placed in a Fluid bed drier for drying. The entrance air temperature should not exceed 58°C, and the output temperature should be maintained at 26 ±4°C. The drying process continued until the Loss on Drying reached a range of 1.8 to 3.0% at 105°C, as measured by a Halogen moisture analyzer for a duration of 5 minutes. Next, carry out the preparation of required granules by sifting them through a 20 mesh sieve with a stainless steel screen. Retain the granules that pass through a 1.5 mm screen by milling them using a multimill with forward-facing knives and a slow speed.

Step IV: Pass the Colloidal silicon dioxide, Purified Talc, Sodium starch glycolate, Croscarmellose sodium through a 40 mesh sieve using a stainless steel screen. Magnesium stearate was individually sifted using a 60 mesh filter with a stainless steel screen.

Step V: Blending: Step III and step IV are loaded into a blender and mixed for a duration of 14 minutes. The addition of magnesium stearate occurred, followed by a thorough mixing for a duration of 4 minutes.

Step VI: The Granules Were Moved for Compression.

Formulation F1: Utilized was an 8.0 mm, upper punch and lower Punch plain, round standard concave punch was used. The in-process parameter for the standard weight is 150.0 mg. The individual weight variation is 150.0 mg with a tolerance of ±7.5%. The weight variation of 20 tablets is 3.000g with a tolerance of ±5%. The thickness should be 3.0±0.5mm. The hardness should be 5.0±3Kp. The friability should not exceed 1.0%. The disintegration time should not exceed 15 minutes. Description- Plain on both sides, round, biconvex, uncoated tablet with a white to off-white colour.

Formulation F2: Utilized was an 8.0 mm, upper punch and lower Punch plain, round standard concave punch was used. The standard weight was 150.0 mg; the individual weight variation was 180.0 mg ± 7.5%; the weight variation of 20 tabs was 3.600g ± 5%; the thickness was 3.4±0.5mm; the hardness was 5.0±3Kp; the friability was 1.0%; and the maximum disintegration time was 15 minutes. Description- Plain on both sides, round, biconvex, uncoated tablet with a white to off-white colour.

Formulation F3: Utilized was an 9.0 mm, upper punch and lower Punch plain, round standard concave punch was used. Standard weight 210.0 mg, Individual weight variation 210.0 mg ±5%, Weight variation of 20 tabs 4.200g ±3%, Thickness 3.6±0.5mm, Hardness 4.0±3Kp, Friability not to exceed 1.0%, and Disintegration time not to exceed 15 minutes were the inprocess parameters. Description- Plain on both sides, round, biconvex, uncoated tablet with a white to off-white colour.

Formulation F4: Utilized was an 9.0 mm, upper punch and lower Punch plain, round standard concave punch was used. Standard weight 230.0 mg, Individual weight variation 230.0 mg ±5%, Weight variation of 20 tabs 46200g ±3%, Thickness 3.7±0.5mm, Hardness 5.0±3Kp, Friability not to exceed 1.0%, and Disintegration time not to exceed 15 minutes were the inprocess parameters. Description- Plain on both sides, round, biconvex, uncoated tablet with a white to off-white colour.

Formulation F5: Utilized was an 9.0 mm, upper punch and lower Punch plain, round standard concave punch was used. Standard weight of 250.0 mg, Individual weight variation of 250.0 mg ±5%, Weight variation of 20 tabs 5.000g ±3%, Thickness 3.9±0.5mm, Hardness 6.0±3Kp, Friability not to exceed 1.0%, and Disintegration time not to exceed 15 minutes were the inprocess parameters. Description- Plain on both sides, round, biconvex, uncoated tablet with a white to off-white colour.

Step VII: Polyvinyl chloride (PVC) was used in blister packing, and foil was utilized for the stability charge.

Tablet Characteristics after Compression (8) (11)

Thickness and Diameter: The diameter and thickness of the tablets were measured with Vernier callipers..

Uniformity of Weight: The weights of each of the twenty tablets were measured after they were selected at random for weight variance.

Weight Variation. Following the weight of the product's 20 tablets, the upper limit (HL) and lower limit (LL) were calculated using the following formulas:

Average wt = total wt/20
Average wt × 5% = n
HL = Av. wt + n
LL = Av. wt − n

Friability: The tablets' friability was evaluated using the Electrolab Friabilator. Its expression is a percentage (%). Ten tablets were weighed before being placed in the friabilator. The friabilator was ran at 25 rpm for four minutes. Four minutes later, we weighed the tablets again. Next, the following formula was used to calculate the friability:

Friability (%) = initial weight – final weight x100 initial weight

Hardness: The Monsanto hardness tester was used to determine the hardness of 20 randomly selected tablets.

Disintegration Time Test: The disintegration time of a pill is measured with a disintegrator and water as the media, and it can only take up to 15 minutes to disintegrate completely.

f) Measuring Drug Content (2): The drug concentration was determined by dissolving a solid dispersion equivalent to 4.0 mg of glimepiride in at least 100 ml of methanol using a UV double beam spectrophotometer set at 228 nm. Phosphate buffer (pH 7.4) was then added to the volume to make 100 ml, and the mixture was filtered using membrane filter paper with a mesh size of 0.45 µm.

g) Determining Solubility (2): Phase solubility analysis was performed in accordance with Higuchi and Connors' guidelines. Twenty-five millilitres of phosphate buffer (pH 7.4), filled into stoppered conical flasks, received an excess of solid dispersion. The mixture was shaken for a whole day in a rotary flask shaker. After shaking to achieve equilibrium, two millilitre aliquots were removed at one-hour intervals and filtered through Whatman filter paper. The filtrate was analysed spectrophotometrically at 228 nm. Three consecutive shakes were performed until the readings were consistent.

h) In vitro Drug Distribution (2): The USP Dissolution apparatus II included 900 ml of 7.4 phosphate buffer dissolution medium, which was combined with precisely weighed preparations equal to 4 mg of glimepiride at a speed of 50 rpm and 37±0.5˚C. Five millilitre aliquots were taken at 10, 20, 30, 40, 50, and 60 minutes and replaced with five millilitres of fresh dissolving media (37˚C). The collected samples were tested using a UV-visible spectrophotometer against a blank after being properly diluted at 228 nm. Pure glimepiride was dissolved in a similar way.

i) Accelerated Stability Investigations [4]: As part of an accelerated stability research, the chosen formulation (F5) was stored for three months at 40°± 2°C and 75±5% relative humidity in sealed high density polyethylene bottles to monitor the effects of temperature and relative humidity. Each month, a physical evaluation was conducted.

3. Result and Discusion

Glimepiride's Characteristics

Table 2: Glimepiride's characteristics

Examinations	Outcomes
Appearance	'White to yellowish'
Melting point	187-193°C
Nature	'Crystalline powder'
Solubility	In acid media at 25°C (<0.004 mg/ml)

Table 3: Characterization of pure glimepiride peaks

Group functioning	Reference wave number in cm^{-1}	Obtained wave number in cm^{-1}
OH	3251-3401	3370.219
C-H Stretch	2751-3103	2921.877
C=O (carbonyl)	1655-1714	17163.658
-C=C-Aromatic	1449-1651	1591.023
Para substituted	823-938	821.114

Glimepiride's Standard Curve

The glimepiride standard curve in the concentration range of 1–11 µg/mL (Fig. 2) was nearly linear, with an R^2 value of 0.996.

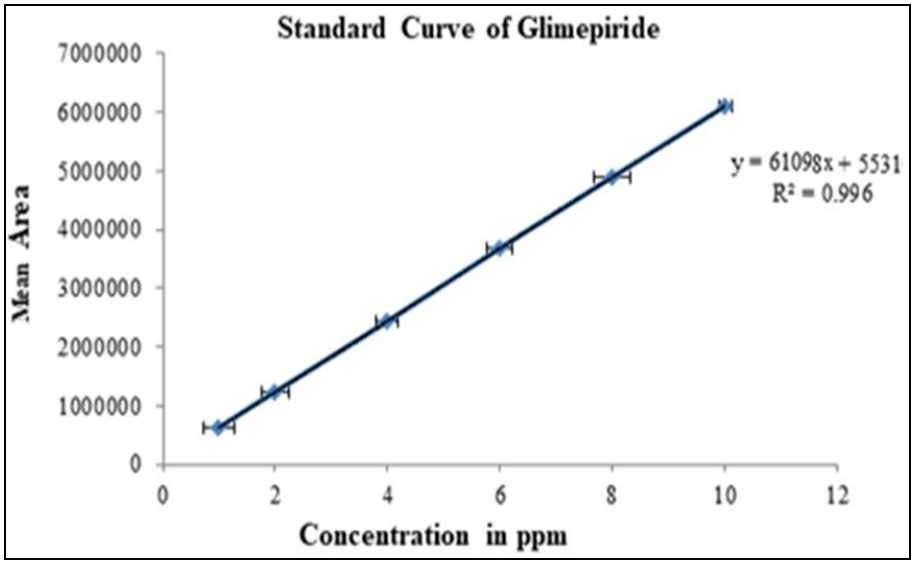

Fig 2: Glimepiride's standard curve

Table 4: The highest absorbance at λmax in various solvents

Solvent	λmax in nm
'Phosphate buffer solution'	220
'Water'	219
'Ethanol'	218

Table 5: Blends Assessment

Formulations	Loss on drying
F1	2.1
F2	2.4
F3	2.3
F4	2.7
F5	2.5

Table 6: Assessment of Pre-compression Blend

Formulations	'Angle of repose' (degree± SD)	'Bulk Density' (g/mL± SD)	'Tapped Density' (g/mL± SD)	'Carr's Index' (%± SD)	'Hausner's ratio' (%± SD)
F1	21º.20±0.05	0.225±0.05	0.261±0.03	14.74±0.06	1.16±0.09
F2	22º.22±0.08	0.224±0.03	0.263±0.03	14.65±0.04	1.18±0.05
F3	26º.18±0.05	0.253±0.07	0.288±0.06	13.17±0.09	1.15±0.08
F4	25.26±0.01	0.228±0.03	0.262±0.05	11.95±0.06	1.15±0.06
F5	26º.28±0.06	0.231±0.05	0.263±0.06	11.96±0.05	1.14±0.08

Table 7: Assessment of uncoated tablets

Formulations	'Weight Variation' (mg)	'Hardness' (kg/cm2)	'Thickness' (mm)	'Friability' (%)	'Disintegrating time' (minutes)
F1	150±1.25	3.35±0.12	3.00±0.26	0.17±0.09	9 min 48 Second
F2	180±0.61	4.50±0.59	3.21±0.41	0.25±0.15	5 min 31 Second
F3	210±0.50	3.60±0.50	3.51±1.27	0.18±0.19	11 min 35 Second
F4	230±055	4.80±0.21	3.10±0.27	0.26±0.08	7 min 57 Second
F5	250±055	6.0±0.26	3.90±0.25	0.28±0.07	3 min 42 Second

Estimating the Drug content

The drug concentration of the glimepiride was found to be between 96.21 and 99.91; these values are within the allowed range.

Investigations of Solubility

The solubility profile of glimepiride was found to be 0.0085 mg/ml, indicating an urgent need to improve the drug's dissolution and solubility. Prepared by kneading the dough. That amounts to 0.357 mg/ml. An augmentation of solubility at saturation

Table 8: Estimating of % Drug content and solubility Investigations

Formulation Code	%Drug content	Solubility mg/ml
Pure drug	-	0.0085
F1	96.21	0.128
F2	98.56	0.163
F3	97.47	0.212
F4	98.21	0.239
F5	99.91	0.357

In Vitro Drug Dissolution Investigations

The tablets were put in a pH 7.4 solution to see if they would dissolve. This is the phosphate buffer shown in Figure 3. The drug release in vitro was found to be 99.95%.

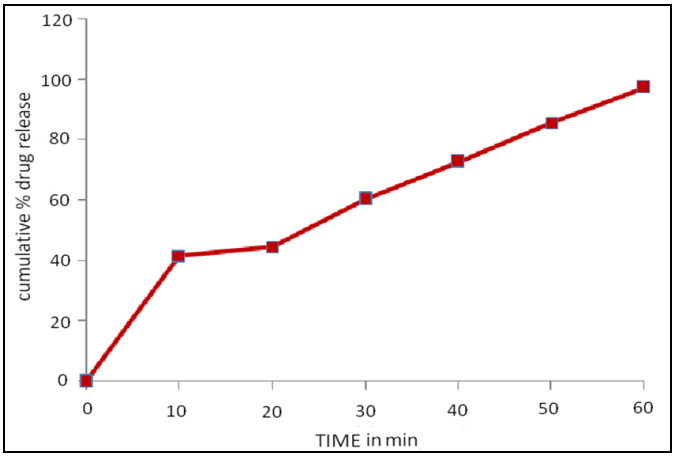

Fig 3: The in vitro drug release profile of a manufactured tablet

Stability Evaluations

Accelerated stability trials yielded the data presented in Table 9, which indicated that the tablets did not display any physical changes (colour change, friability, or hardness), assay, or dissolving qualities during the study period, in accordance with the ICH requirements.

Physical attributes of F-5 both before and after accelerated stability studies

Table 9: An overview of the physical attributes of the F-5 before and after quick stability studies.

Parameter	Prior to initial stability investigations	After stability investigations
Thickness (mm)	3.91±0.25	3.91±0.29
Hardness (kg/cm^2)	6.2±0.25	6.10±0.50
Friability (%)	0.28 ± 0.08	0.21 ± 0.14
Drug content (%)	99.91±1.47	99.87 ± 1.19
In-vitro drug release	99.96	99.88

Conclusion

Using the wet granulation process, 4 MG of glimepiride uncoated tablets were created. Purified water and polyvinylpyrrolidone (PVP) K-30, also known as Povidone K-30, were utilised as the formulation's binder. The parameters of individual weight variation, hardness, thickness, friability, and disintegration time for uncoated glimepiride tablets were assessed and determined to be adequate. Studies on Accelerated Stability were conducted at 40°± 2°C and 75±5% relative humidity. Drug content was found 99.91% and in-vitro dissolution found 99.96% of formulated tablets.

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