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SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUG GLIMEPRIDE

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ABSTRACT

The present study owed to enhance the dissolution and potential bioavailability of poorly water-soluble glimepiride (GP) through the formulation of solid dispersions using suitable hydrophilic carriers. Solid dispersions and physical mixtures of glimepiride were prepared employing poloxamer 188 and crospovidone as carriers. Glimepiride–poloxamer 188 solid dispersions were developed by melting and solvent evaporation methods, whereas glimepiride–crospovidone systems were prepared by adsorption onto an insoluble carrier. The prepared formulations were evaluated for percentage yield, drug content, solubility in pH 6.8 phosphate buffer, X-ray diffraction (XRD), scanning electron microscopy (SEM), in vitro dissolution, and dissolution efficiency. Among the developed formulations, the glimepiride–poloxamer 188 solid dispersion prepared by the melting method in a 1: 4 drug-to-carrier ratio (GP4)] demonstrated the highest dissolution rate and dissolution efficiency. Based on these findings, GP4 was selected for tablet formulation. Solid dispersion tablets were prepared by direct compression using varying concentrations (2–5%) of the super-disintegrant Ac-Di-Sol. The formulated tablets were further evaluated for physical

appearance, thickness, hardness, friability, disintegration time, drug content, and in vitro drug release. Tablets containing 5% Ac-Di-Sol (T5) exhibited the shortest disintegration time and the highest dissolution efficiency among all formulations. The study suggested that solid dispersion technology is an effective e and economical approach for improving the dissolution characteristics of poorly soluble drugs. Enhancement in dissolution was mainly attributed to improved wettability, reduction in particle size, decreased crystallinity, reduced agglomeration, and conversion of the drug into an amorphous state.

KEYWORDS: Glimepiride, Solid dispersion, Poloxamer 188, Crospovidone, Dissolution enhancement, Bioavailability.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. The disease has emerged as a major global health burden due to its rapidly increasing prevalence and its association with serious complications such as cardiovascular diseases, nephropathy, neuropathy, and retinopathy.[1] Oral hypoglycemic agents remain the cornerstone in the management of type 2 diabetes mellitus because of their effectiveness, patient compliance, and ease of administration. Several classes of oral antidiabetic agents are currently available, including sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors.[2] Despite their therapeutic importance, many oral hypoglycemic drugs suffer from poor aqueous solubility, which leads to low dissolution rates and variable oral bioavailability.[3] Oral drug delivery is the most preferred route of administration owing to its convenience, cost-effectiveness, and patient acceptability. However, the oral absorption of many therapeutic agents is significantly influenced by their aqueous solubility and dissolution behavior in gastrointestinal fluids.[4] With the advancement of combinatorial chemistry and high-throughput screening techniques, a large number of newly developed drug candidates exhibit poor aqueous solubility, thereby creating substantial formulation challenges for the pharmaceutical industry.[5] Drugs with poor water solubility generally show slow dissolution in gastrointestinal fluids, resulting in inadequate absorption and reduced therapeutic efficacy.[6] The Biopharmaceutical Classification System (BCS) classifies drugs into four categories based on their aqueous solubility and intestinal permeability.[7]

- **BCS Class I:** High solubility and high permeability

- **BCS Class II:** Low solubility and high permeability
- **BCS Class III:** High solubility and low permeability
- **BCS Class IV:** Low solubility and low permeability

Among these, BCS Class II drugs present the greatest formulation challenge because their absorption is primarily dissolution rate limited.[8] Therefore, enhancing the dissolution rate and apparent solubility of such drugs is essential to improve oral bioavailability. Glimepiride, a third-generation sulfonylurea derivative widely used in the treatment of type 2 diabetes mellitus, belongs to BCS Class II due to its poor aqueous solubility and high permeability.[9] Glimepiride acts by stimulating insulin secretion from pancreatic β-cells and improving peripheral insulin sensitivity. Although the drug possesses excellent pharmacodynamic activity, its poor solubility in aqueous media results in delayed dissolution and variable gastrointestinal absorption, thereby limiting its bioavailability and onset of action.[10] The dissolution behavior of poorly soluble drugs can be explained by the Noyes–Whitney equation, which describes the relationship between dissolution rate and factors such as surface area, saturation solubility, diffusion coefficient, and thickness of the diffusion layer.[11] Enhancement of dissolution can be achieved by increasing the available surface area, improving wettability, reducing particle size, or increasing saturation solubility.[12] Since modification of hydrodynamic conditions and diffusion coefficients *invivo* is difficult, pharmaceutical formulation approaches mainly focus on increasing drug solubility and surface area. Several techniques have been employed to improve the solubility and dissolution characteristics of poorly water-soluble drugs. These approaches include micronization, nanosuspensions, salt formation, complexation, crystal modification, use of surfactants, lipid-based systems, self-emulsifying drug delivery systems, co-crystallization, prodrug formation, and solid dispersion technology.[13] Particle size reduction techniques such as micronization and nanonization increase surface area but may lead to aggregation and poor flow properties.[14] Salt formation is effective only for ionizable drugs and cannot be applied universally.[15] Complexation techniques using cyclodextrins improve solubility but are associated with high production cost and possible stability issues.[16] Lipid-based systems enhance dissolution but may suffer from formulation instability and manufacturing difficulties.[17] Among the various solubility enhancement techniques, solid dispersion technology has gained significant importance because of its simplicity, effectiveness, and ability to improve both dissolution rate and bioavailability.[18] Solid dispersions are defined as dispersions of one or more active pharmaceutical ingredients in an inert carrier matrix in the

solid state, prepared by melting, solvent evaporation, or combined methods.[19] In solid dispersions, the drug may exist in amorphous, molecularly dispersed, or microcrystalline forms within a hydrophilic carrier matrix, thereby enhancing dissolution properties.[20]

The mechanisms responsible for enhanced dissolution from solid dispersions include reduction in particle size, improved wettability, increased porosity, conversion of crystalline drug into amorphous form, and prevention of aggregation and agglomeration of hydrophobic particles.[21] The amorphous state possesses higher free energy and lower lattice energy than the crystalline form, which contributes to faster dissolution and improved solubility.[22] Solid dispersions are broadly classified into three generations based on the nature of carriers used.[23] First-generation solid dispersions utilize crystalline carriers such as urea, sugars, and organic acids. These systems mainly form eutectic mixtures and crystalline solid solutions.[24] Although they improve dissolution compared to pure drugs, their crystalline nature limits drug release and solubility enhancement. Second-generation solid dispersions employ amorphous polymeric carriers such as polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and ethyl cellulose.[25] In these systems, drugs are molecularly dispersed in amorphous carriers, leading to significant enhancement in dissolution and bioavailability. Third-generation solid dispersions incorporate surfactants or self-emulsifying carriers along with polymers to improve dissolution and prevent recrystallization.[26] Commonly used carriers include poloxamers, Gelucire®, Inutec SP1, and surfactant-polymer combinations. These systems provide improved wettability, enhanced solubilization, and greater physical stability compared to earlier generations.[27] Carriers used in solid dispersion systems can also be classified based on their physicochemical properties and functional roles.[28]

1. **Crystalline carriers:** Urea, mannitol, sugars.
2. **Polymeric carriers:** PEG, PVP, HPMC, ethyl cellulose.
3. **Surface-active carriers:** Poloxamers, Gelucire®, Tweens, Spans.
4. **Superdisintegrant carriers:** Crospovidone, croscarmellose sodium.
5. **Amphiphilic carriers:** Soluplus®, poloxamers, TPGS.

Hydrophilic and surface-active carriers play a vital role in improving dissolution characteristics. Among these carriers, poloxamer 188 has received considerable attention due to its amphiphilic nature, low toxicity, and excellent surfactant properties.[29] Poloxamer 188 is a nonionic triblock copolymer composed of polyethylene oxide and polypropylene oxide

units. It improves drug dissolution by enhancing wettability, reducing interfacial tension, increasing solubilization, and stabilizing amorphous drug particles.[30] Furthermore, its self-emulsifying properties contribute to improved dispersion of hydrophobic drugs in aqueous media.

Crospovidone, a cross-linked polyvinyl pyrrolidone derivative, is another important carrier used to improve dissolution behavior.[31] It possesses excellent swelling and water absorption capacity, resulting in rapid penetration of dissolution medium into the dosage form. Crospovidone also acts as an adsorbent carrier that improves surface area exposure and reduces particle aggregation, thereby facilitating rapid drug release.[32] Various methods are employed for the preparation of solid dispersions, including fusion (melting) method, solvent evaporation method, hot-melt extrusion, spray drying, freeze drying, supercritical fluid techniques, and melt agglomeration.[33] Among these methods, the melting and solvent evaporation techniques are widely preferred due to their simplicity and effectiveness. The melting method offers better molecular dispersion and smaller particle size, whereas the solvent evaporation method is suitable for thermolabile drugs.[34]

Despite their numerous advantages, solid dispersions also exhibit certain limitations such as physical instability, recrystallization during storage, scale-up difficulties, and challenges in dosage form development.[35] Nevertheless, continuous advancements in carrier selection and manufacturing technologies have significantly improved the commercial applicability of solid dispersion systems. Considering the poor aqueous solubility and dissolution-limited absorption of glimepiride, the present study was undertaken to formulate and evaluate solid dispersions of glimepiride using poloxamer 188 and crospovidone as hydrophilic carriers. The objective of the study was to improve the dissolution behavior and potential oral bioavailability of glimepiride through suitable solid dispersion approaches and to evaluate the prepared formulations using physicochemical characterization and in vitro dissolution studies.

MATERIALS AND METHODS

Materials

Glimepiride (GMP) was obtained as a gift sample from Shree Chem Products, India. Poloxamer 188 was purchased from BASF Chemicals India Pvt. Ltd., India, while Crospovidone was procured from HiMedia Laboratories Pvt. Ltd., India. Ac-Di-Sol (Croscarmellose Sodium), Microcrystalline Cellulose (MCC), Lactose Monohydrate,

Magnesium Stearate, and Talc were used as pharmaceutical excipients for tablet formulation. Methanol and Potassium Dihydrogen Phosphate were procured from Loba Chemie Pvt. Ltd., India. Ethanol and Sodium Hydroxide were obtained from Merck Specialities Pvt. Ltd., India, whereas Chloroform was purchased from S.D. Fine Chemicals Ltd., India. Acetone, Dichloromethane, Dimethylformamide (DMF), Dimethyl Sulfoxide (DMSO), Hydrochloric Acid, and Potassium Bromide (KBr) used for FTIR studies were of analytical reagent grade and procured from standard commercial suppliers. Distilled water used throughout the study was obtained from the in-house laboratory. All chemicals, solvents, and reagents used in the present investigation were of analytical reagent (AR) grade or laboratory grade and were used without further purification.

METHODS

Preformulation studies

Developing a pharmaceutical dose form requires assessing the physiochemical characteristics of the medication molecule. Pre-formulation research is the initial stage in creating a dosage form. It is essential to investigate the physical and chemical properties of pharmacologically active substances both alone and in combination with excipients. The purpose of the pre-formulation research is to collect information about the drug's ingredients in order to develop a formulation. Determining the physiochemical properties of pharmaceuticals and excipients that could influence the formulation process, formulation design, and pharmacokinetic and biopharmaceutical features of the final product is the aim of pre-formulation research. The following investigations are carried out for the pre-formulation: Pre-formulation studies' primary goal is to generate information that will benefit the environment and improve the development of stable and bioavailable dosage forms.[36]

Organoleptic properties

Color, Odor, and Taste of the drug was recorded using descriptive terminology.[37]

Melting point

Glimepiride's melting point was ascertained using the capillary fusion method and melting point apparatus. The drug powder is placed in a capillary tube with a diameter of 1 mm and a length of 6–7 cm, and the substance is placed in the capillary 3–4 mm from the bottom of the packed capillary tube to determine the melting point of the pure drug sample.[38] The capillary tube is put in an iron stand that is fixed in the thermometer after being moistened with the liquid in the bath. The capillary is so calibrated that the solids in it stand in opposition to the

center of the mercury bulb, and it stays attached to the thermometer by itself. After lowering the thermometer into a beaker filled with paraffin oil, the beaker is gradually heated to a consistent temperature while being continuously stirred. The burner is removed with continuous stirring once the material in the capillary begins to liquefy. The temperature at which the material simply melts and turns transparent is recorded.[39]

λmax determination

GMP's (10 µg/ml) standard stock solution is made by dissolving 10 mg of the medication in a 100 ml volumetric flask with 100 µg/ml of phosphate buffer at pH 6.8. To determine the absorbance, working standard solutions containing 10 µg/ml were scanned in the 200–400 nm UV range by using UV spectroscopy.[40]

FT-IR spectroscopy

FT-IR spectroscopy is most powerful technique for qualitative compound identification. It gives information about the group present in the particular compound. The main application of FT-IR spectrophotometry is determination of the identity of a compound by means of spectral comparison with that of an authentic sample and verification of the presence of functional group in an unknown molecule.[41] The possibility of drug-carrier interaction is investigated by FT-IR. Pure GP, excipients, polymers, and drug and carrier mixtures and optimized formulations are subjected to FTIR studies to investigate the drug, polymer, and excipient interactions. The analysis is performed by using an FT-IR Spectrophotometer (SHIMADZU, Japan), and the IR spectra of the test samples are obtained by the KBr Pellet Technique. The scanning range is 400–4000 cm-1 and the resolution is 4 cm^{-1}.[42]

Solubility Profile

Solubility of Glimepiride in solvents and buffer

GMP is dissolved in methanol, ethanol, acetone, chloroform, dichloromethane, dimethylformamide, dimethyl sulfoxide, distilled water, and different buffer solutions (pH 1.2, 2.2, 6.8, 7.0, and 7.4) in order to assess drug solubility.[43] A mechanical shaker was used to shake the material for eight hours at 37 °C. Whatman filter paper was used to filter the supernatant, and a UV-visible spectrophotometer was used to examine the filtrate.[44]

Drug and carrier compatibility studies

While formulating solid dispersions, it is imperative to give consideration to the compatibility of drug and polymer used within the system. It is therefore necessary to conform that drug is

not interacting with polymer under experimental conditions and shelf life.[45] Desired quantity of drug with specified excipients (Poloxamer188, Crospovidone) in the ratio 1: 1 & 1: 5 was taken and mixed thoroughly, sieved (size no.22) and filled in dried vials. The vials were sealed and kept at 45°C for two weeks. The vials were examined daily at regular interval for discoloration, clump formation and liquefication.[46]

Preparation of Standard Curve

Preparation of 0.1M Hydrochloric Acid: 8.5 ml of hydrochloric acid is transferred into 1000 ml of volumetric flask and made up the volume with distilled water.[39]

Preparation of Phosphate Buffer (pH-6.8): 6.80 g of potassium Dihydrogen orthophosphate and 0.90 g of sodium hydroxide are weighed accurately and dissolved in 1000 ml of distilled water.[39]

Standard Curve of Glimepiride in Methanol

In a 100 ml volumetric flask, 50 mg of Glimepiride is accurately measured, and dissolved in a methanol, and the primary stock solution, containing 250 µg/ml, is prepared. 10 ml of this main stock solution is pipetted into a 100 ml volumetric flask and 100 ml of methanol, containing the drug at a concentration of 10 µg/ml, is used to make up the volume with methanol.[47] Pipette 0.1 ml upto 0.8 ml from the aforementioned secondary stock solution into a 10 ml volumetric flask and then adjust the volume with a methanol. The drug's absorbance was determined using a UV spectrophotometer at 226 nm. The concentration (X-axis) and absorbance (Y-axis) data are used to plot the calibration curve.[48]

Standard Curve of Glimepiride in Distilled water

In a 100 ml volumetric flask, 50 mg of Glimepiride is accurately measured, and dissolved in a distilled water, and the primary stock solution, containing 250 µg/ml, is prepared. 10 ml of this main stock solution is pipetted into a 100 ml volumetric flask and 100 ml of methanol, containing the drug at a concentration of 10 µg/ml, is used to make up the volume with methanol.[47]

Pipette 0.1 ml upto 0.8 ml from the aforementioned secondary stock solution into a 10 ml volumetric flask and then adjust the volume with a methanol.[55] The drug's absorbance was determined using a UV spectrophotometer at 226 nm. The concentration (X-axis) and absorbance (Y-axis) data are used to plot the calibration curve.[49]

Standard Curve of Glimepiride in pH 1.2 buffer

In a 100 ml volumetric flask, 50 mg of Glimepiride is accurately measured, and dissolved in a pH 1.2 acid buffer, and the primary stock solution, containing 250 µg/ml, is prepared.[55] 10 ml of this main stock solution is pipetted into a 100 ml volumetric flask and 100 ml of methanol, containing the drug at a concentration of 10 µg/ml, is used to make up the volume with methanol.[47] Pipette 0.1 ml upto 0.8 ml from the aforementioned secondary stock solution into a 10 ml volumetric flask and then adjust the volume with a methanol. The drug's absorbance was determined using a UV spectrophotometer at 226 nm. The concentration (X-axis) and absorbance (Y-axis) data are used to plot the calibration curve.[50]

Standard Curve of Glimepiride in phosphate buffer pH 6.8

In a 100 ml volumetric flask, 50 mg of Glimepiride is accurately measured, and dissolved in a pH 1.2 acid buffer, and the primary stock solution, containing 250 µg/ml, is prepared. 10 ml of this main stock solution is pipetted into a 100 ml volumetric flask and 100 ml of methanol, containing the drug at a concentration of 10 µg/ml, is used to make up the volume with methanol.[47] Pipette 0.1 ml upto 0.8 ml from the aforementioned secondary stock solution into a 10 ml volumetric flask and then adjust the volume with a methanol. The drug's absorbance was determined using a UV spectrophotometer at 226 nm.[48] The concentration (X-axis) and absorbance (Y-axis) data are used to plot the calibration curve.

Standard Curve of Glimepiride in phosphate buffer pH 7.4.

In a 100 ml volumetric flask, 50 mg of Glimepiride is accurately measured, and dissolved in a pH 1.2 acid buffer, and the primary stock solution, containing 250 µg/ml, is prepared.[55] 10 ml of this main stock solution is pipetted into a 100 ml volumetric flask and 100 ml of methanol, containing the drug at a concentration of 10 µg/ml, is used to make up the volume with methanol.[47] Pipette 0.1 ml upto 0.8 ml from the aforementioned secondary stock solution into a 10 ml volumetric flask and then adjust the volume with a methanol. The drug's absorbance was determined using a UV spectrophotometer at 226 nm.[49] The concentration (X-axis) and absorbance (Y-axis) data are used to plot the calibration curve.

Phase solubility studies of drug with different carriers

An excess amount of GMP is added to a volumetric flask containing 10 ml of aqueous carrier solutions (pH 1.2 and 6.8 buffers) of Poloxamer 188 and crospovidone at a specified concentrations and placed in a Mechanical shaker and agitated at room temperature for 8 h.[51] The solutions are filtered and analysed at 226 nm using a UV-visible

spectrophotometer.[52] The study was performed in triplicates.

PREPARATION OF SOLID DISPERSIONS OF GLIMEPIRIDE

Preparation of Solid Dispersions of GMP Using Poloxamer 188 as carrier: Both melt and solvent evaporation methods were used to prepare solid dispersions of GMP.[53]

Preparation of Solid Dispersion: Preparation of Solid Dispersion by Melting Method

GMP and poloxamer 188 were weighed according to these weighed ratios. Poloxamer 188 was melted and to the melted poloxamer 188, GMP was added. It was mixed well and flashed cooled in an ice bath and then stored overnight in a desiccator containing $CaCl_2$ and stored until completely dry.[55] The solid mass that results is then pulverized in a mortar to produce a dry, free-flowing powder. The powder is made to pass through a sieve no. 60.[54]

Preparation of Solid Dispersion by Solvent Evaporation Method

The carrier (Crospovidone) is dissolved in different ratios as shown in Table 1 in 10 ml of distilled water, to which the drug is added and stirred well to dissolve the drug 5 ml of ethanol is added to it, and tried to get clear a solution. The substance is heated to evaporate the solvents. The resulting mass is transferred to desiccators containing $CaCl_2$ and stored until completely dry.[55]

Table 1: Formulation Chart of Solid Dispersion.

s.no	Method Used	Formulations	Composition (Drug: Carrier)	Ratio (Drug: Carrier) (mg)
1	Hot Melting Method	GP 1	Glimepiride + Poloxamer	1: 0.5
2		GP 2	Glimepiride + Poloxamer	1: 1
3		GP 3	Glimepiride + Poloxamer	1: 2
4		GP 4	Glimepiride + Poloxamer	1: 4
5	Solvent Evaporation	GC 1	Glimepiride + Corspovidone	1: 0.5
6		GC 2	Glimepiride + Corspovidone	1: 1
7		GC 3	Glimepiride + Corspovidone	1: 2
8		GC 4	Glimepiride + Corspovidone	1: 4

PREPARATION OF PHYSICAL MIXTURES OF GLIMEPIRIDE

Physical mixtures of glimepiride were prepared using various carriers in a particular ratio. First drug and carrier were passed through a 60-mesh screen and then weighed and mixed physically.[55]

Table 2: Depicts the Composition Used for Preparing Physical Mixtures of Glimepiride.

Formulation Number	Drug	Polymer	Drug: polymer ratio
PM1	Glimepiride	Poloxamer 188	1: 1
PM2	Glimepiride	Crospovidone	1: 1

Characterization of Solid Dispersion

Drug Content: A solid dispersion (each formulation) containing 50 mg is weighed accurately and dissolved in 50 ml of phosphate buffer at pH 6.8.[55] The solution was filtered, and the GMP content was analysed by observing absorbance in a UV spectrometer at 226 nm.[47]

Saturation Solubility: GMP and solid dispersions in exorbitant quantities are placed in volumetric flasks containing 10 ml of pH 6.8 phosphate buffer. The samples are placed in a mechanical shaker at 37 °C and 50 rpm for 8 h. A UV spectrophotometer is used to analyze the solutions.[56]

FTIR Spectroscopy: The FTIR spectra of the drug and its formulations are carried out using an FT-IR spectrophotometer (SHIMADZU, Japan). Each formula (5 mg) is mixed with about 100 mg. Potassium bromide was compressed into discs under a pressure of 10, 000 to 15, 000 pounds per square inch. The IR spectra were recorded using an infrared spectrometer.[45]

Electron Microscopy

The external morphology of solid dispersions was analyzed by Scanning Electron Microscope (SEM).[45] The samples were examined under a scanning electron microscope JSM 6100 JEOL JAPAN. XRD patterns were recorded using Philips PW 1729 X-ray generator (computer 1710). Powder X-ray diffraction patterns were traced for glimepiride, various carriers and solid dispersions.[47]

***Invitro* Drug Release**

Accurately weighed preparations equivalent to 10 mg of glimepiride were added to 900 ml of dissolution media (6.8 phosphate buffer) contained in USP dissolution apparatus II (Paddle type) and stirred at speed of 50 rpm at 37±0.5˚C. Five milliliter aliquots were withdrawn at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and replaced by 5 ml of fresh dissolution media (37 ˚C).[55] The collected samples were analyzed after suitable dilution at 226 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The

dissolution of pure glimepiride was done similarly. The release profile data was analyzed for cumulative % dissolved at different time intervals & for dissolution efficiency at 6 min and 10 min.[47]

Formulation Chart of Core Tablet: The composition of RST core tablets is depicted in Table 3. All of the powders used are passed through Sieve No. 45 separately. GMP, Ac-Di-Sol, Avicel PH 101, Talc, Magnesium Stereate are mixed by the geometric addition technique.[55-57] Finally, the direct compression of 80 mg of the blend was weighed and compressed by a tablet punching machine equipped with 10 mm flat-faced punches.[56-57]

Table 3: Formulation Chart of Core Tablet.

Ingredients	T1	T2	T3	T4	T5
GP4	25	25	25	25	25
Ac-Di-Sol	_	1.6	2.4	3.2	4
Avicel PH 101	51	49.4	48.6	47.8	47
Talc	2.4	2.4	2.4	2.4	2.4
Magnesium Stereate	1.6	1.6	1.6	1.6	1.6

*** All weights are expressed in milligrams.**

EVALUATION OF BLENDS

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The various characteristics of blends tested are given below.

Bulk Density

The weight of the powder divided by the bulk volume it takes up is termed the bulk density. It is expressed as gm/ml. The finely weighed amount of powder mixture that had earlier been agitated to break up any agglomerates that had formed was introduced into the measuring cylinder, and the volume was recorded.[58] The following equation is employed to estimate bulk density.

Bulk Density = (mass of the powder) / (Bulk volume)

Tapped Density

The tapped density of a powder is its weight-to-tapped-volume ratio. The powder is transferred into the measuring cylinder using a funnel. The measuring cylinder was tapped on a wooden surface at intervals of two seconds, and the volume acquired is the tapped

volume.[56-58] The unit of measurement is g/ml.

Tapped Density = (mass of the powder) / (Tapped volume)

Angle of Repose

The funnel method is used to determine the powder blend's angle of repose. The funnel is filled with the precisely weighed powder combination. To determine the angle of repose and calculate the diameter of the powder cone, let the powder mixture pass freely through the funnel and onto the surface.[59]

Tan θ = height / radius

Compressibility Index (CI)

Bulk density and tapped density values are used to calculate the compressibility index. The compressibility index can be calculated using the following formula.[58]

Compressibility index = (Tapped density-Bulk density) / (Tapped density) ×100.

Hausner's Ratio

Hausner's ratio, which is calculated by dividing the tapped density by the bulk density, is a crucial factor in determining the flow characteristics of powders and granules.[58] The following formula can be used to determine this.

Hausner's ratio = (Tapped density) / (Bulk density)

Post-compression Parameters

After compression of powder, the tablets were evaluated for physical organoleptic characteristics like color, odor, taste, diameter, thickness, Hardness, Friability, and, Disintegration time.[58]

Thickness

The Vernier calliper scale is used to measure the thickness of the tablets. The average readings are computed after five pills are taken.[61]

General Appearance

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance, which includes in tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws.[37]

Hardness

A tablet us resistance to chipping, abrasion, or fracture under storage transition and handling before to consumption is determined by its hardness, which is defined as the force given across the tablet us diameter to break the tablet. The Pfizer Hardness Tester was used to measure the hardness of each formulation's tablet.[58]

Friability

Ten pre-weighed tablets can be added to the Roche friabilator to test for friability. After then, the machine is programmed to spin at 25 rpm for four minutes, falling six inches every time. After that, the tablets were weighed again. The weight difference is recorded and given as a percentage. Less than 1% weight loss is considered acceptable and falls inside the 10% threshold.[58]

Friability = (W1-W2) / W1 X 100

Where,

W1= weight of tablets before the test.

W2= weight of tablets after test.

Disintegration Time

The *in-vitro* disintegration time is measured using a disintegration test device. Each of the apparatus's six test tubes held one tablet and one disc. The amount of time, expressed in minutes or seconds, needed for the pill to totally dissolve in distilled water and leave no visible bulk in the disintegration device.[58]

Weight Variation Test

Twenty randomly chosen tablets are weighed individually and recorded. Determine the average weight and compare it to the weight of each individual pill.[58] The average weight was determined by.

Average weight = (Weight of 20 tablets) / 20

Uniformity of Drug Content

Ten randomly selected tablets, of each formulation, were weighed and average weight was calculated and the tablets were powdered in a glass mortar pestle. The weight equivalent to 5 mg Glimepiride was weighed.[58] The weighed amount was dissolved in 5 ml of dichloromethane in separate 10ml volumetric flask using magnetic stirrer, the volume was adjusted to 10 ml, with methanol and the solution was filtered. An aliquot of 0.2 ml from this

solution were diluted to 10 ml with methanol in separate volumetric flask. The content in each formulation was determined spectrophotometrically at 226 nm.[48]

In-vitro Dissolution Studies

In-vitro dissolution studies for the pure drug, the core tablet without solid dispersion, the formulation of solid dispersion, Physical mixture, and the marketed tablet are carried out in a pH 6.8 phosphate buffer using the dissolution apparatus USP type 2 (Paddle) method 4. The test is performed at a stirring speed of 75 rpm with a temperature maintained at 37±0.5°C in 900 ml of pH 6.8 buffer for 60 min.[58] The dissolution samples of 5 ml are withdrawn at sampling intervals and the dissolution medium is replaced with 5 ml of pH 6.8 phosphate buffer after each sample withdrawal. The concentration of the drug was estimated in the aliquots withdrawn by measuring the absorbance at 226 nm using a UV spectrophotometer after filtering the solution through the Whatman filter paper. The concentration was determined from the standard plot and finally, the results are plotted as cumulative % drug release versus time.[47]

RESULT AND DISCUSSION

Pre-formulation Studies of Drug

Organoleptic property of drug

Physical observation of the drug revealed that GMP is a whiteto yellowish white, odorless, crystalline powder.

Solubility Study

The drug is highly soluble in dimethyl sulfoxide, dichloromethane and dimethylformamide, soluble in methanol, slightly soluble in chloroform and ethanol, and practically insoluble in acetone and water. The solubility of drug in buffers increases as the pH of the buffers was increased from acidic to basic. The solubility of drug in different solvents and buffers are shown in Table 4 and 5 respectively.

Table 4: Solubility of Glimepiride in Various Organic Solvents.

S.No	Solvents	Solubility
1	Methanol	++
2	Ethanol	+
3	Acetone	-
4	Chloroform	+
5	Dichloromethane	+++
6	Dimethylformamide	+++

7	Dimethylsulfoxide	+++
8	Water	-

+++ Freely soluble, ++ Soluble, + Slight soluble, - Practically Insoluble

Table 5: Solubility of Glimepiride in Various Buffer Solutions.

S.No	Buffers(pH)	Solubility(µg/ml)
1	1.2	6.79 ± 0.18
2	6.8	14.31 ± 0.28
3	7.4	16.38 ± 0.16

Mean ± S.D. (n = 3)

Melting Point

The melting point of GMP is seen to be at 208.67 ± 4.16˚C the reported melting point of the drug was found at the at 207 ˚C, hence the experimental values were in good agreement with the official values.

λmax Determination

The maximum absorption of GMP was found to be 226 nm represented in the figure 1.

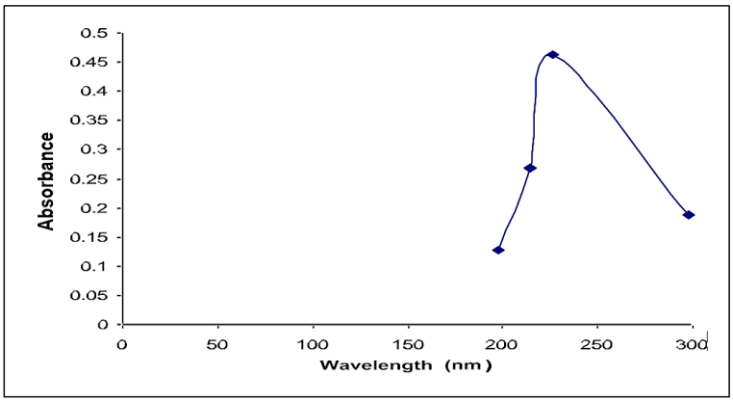

Figure 1: λmax of Glimepiride.

Incompatibility Study

GMP pure drug

The IR spectrum was measured in the solid state as KBr dispersion. For these peaks are similar to the reported peaks of GMP as in the figure 2.

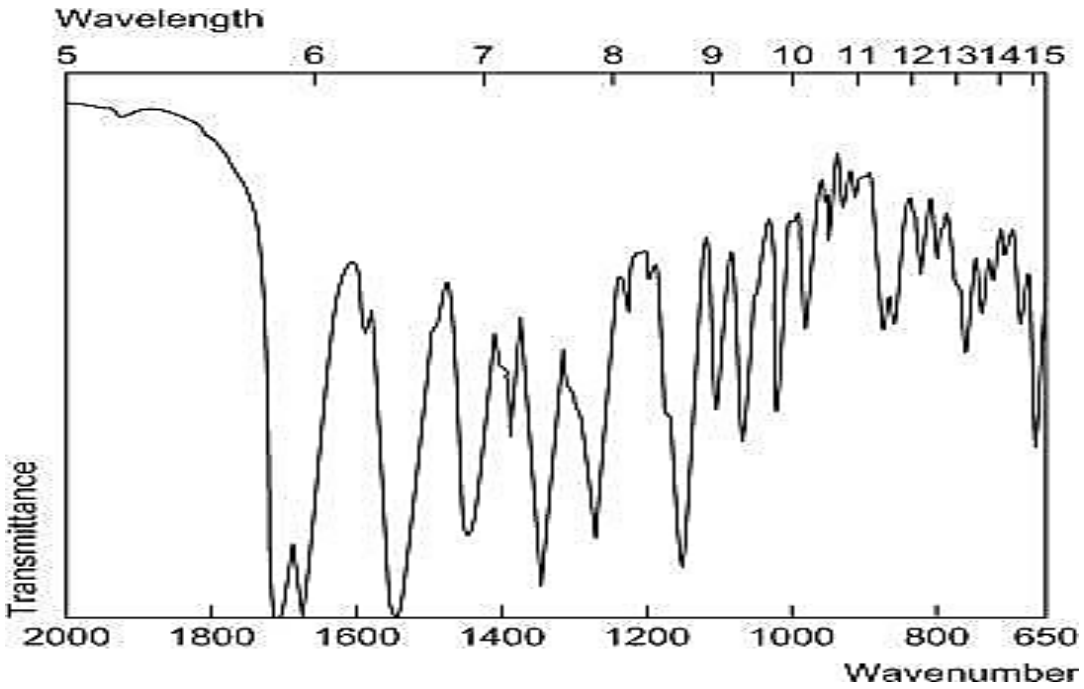

Figure 2: IR Spectra of Glimepiride.

Drug-Carrier Interaction Study

The major peaks obtained in the pure drug were in the same characteristic bands without any significant spectral changes. The FT-IR peak of spectra for solid dispersion showed no shift and No Disappearance of the characteristic peaks suggesting that there is No Interaction between the drug and indicating that they were chemically compatible.

DETERMINATION OD STANDARD CALIBIRATION CURVE

Calibration Curve and Linearity Study of Glimepiride

The linearity of glimepiride was evaluated by constructing calibration curves of absorbance versus concentration in the concentration range of 1–20 µg/mL. The absorbance values increased proportionally with increasing drug concentration, demonstrating good adherence to Beer–Lambert's law throughout the studied range. The calibration plots exhibited excellent linearity with regression coefficients (R^2) ranging from 0.9986 to 0.9999, indicating a strong correlation between concentration and absorbance. The regression equations obtained for the calibration curves were, Figure 3: $Y = 0.0464x + 0.0073$ (R^2 = 0.9995), Figure 4: $Y = 0.0553x + 0.0150$ (R^2 = 0.9986), Figure 5: $Y = 0.0456x - 0.0055$ (R^2 = 0.9995), Figure 6: Linear relationship observed over the tested concentration range, and Figure 7: $Y = 0.0512x - 0.0172$ (R^2 = 0.9990). The high regression coefficients and near-zero intercept values confirm the reliability and accuracy of the analytical method for quantitative estimation of glimepiride. The obtained results demonstrate that the absorbance response is directly

proportional to concentration within the studied range, thereby validating the method's linearity and suitability for subsequent preformulation and formulation studies. The calibration curves showed minimal deviation from linearity, further indicating the precision of the spectrophotometric method employed for glimepiride analysis.

Overall, Beer–Lambert's law was obeyed in the concentration range of 1–20 µg/mL, and the developed analytical method exhibited excellent linearity, making it appropriate for routine quantitative determination of glimepiride during preformulation investigations.

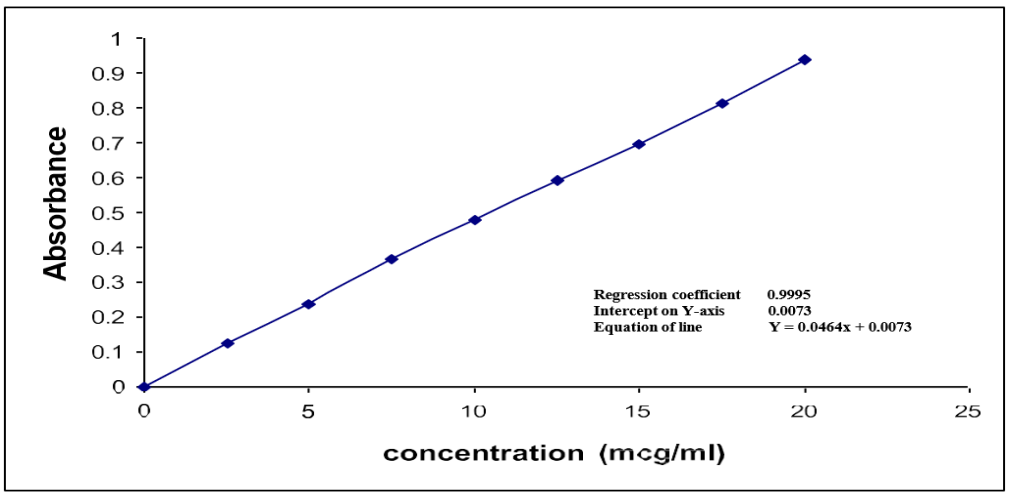

Figure 3: Standard Calibration Curve of Glimepiride in Distilled Water.

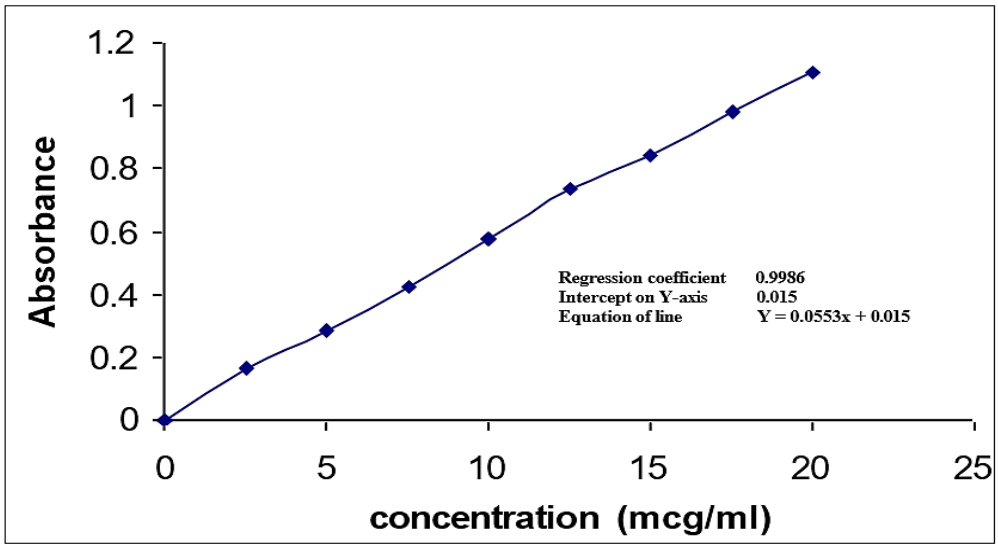

Figure 4: Standard Calibration Curve of Glimepiride in Distilled Water.

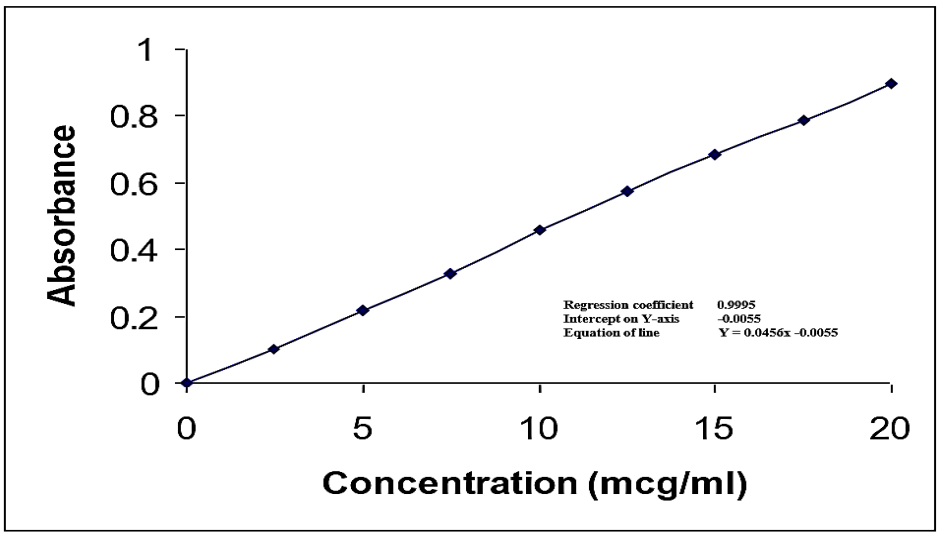

Figure 5: Standard Calibration curve in phosphate buffer 1.2 buffer.

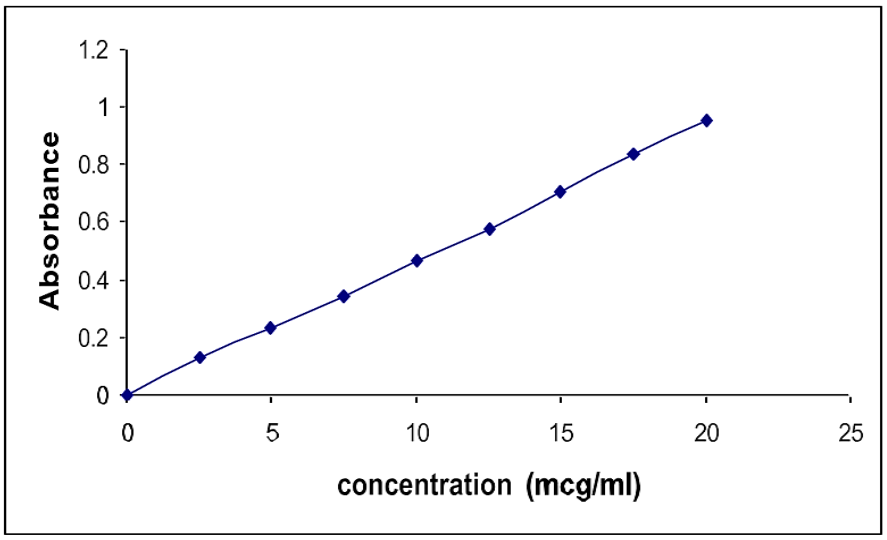

Figure 6: Standard Calibration curve in pH 6.8 buffer.

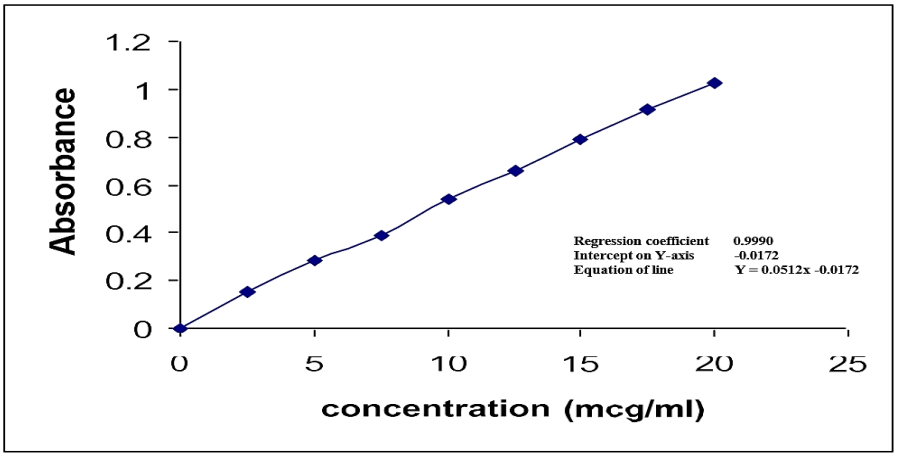

Figure 7: Standard Calibration curve in pH 7.4 buffer.

Drug Content

The drug content of the prepared glimepiride solid dispersions was determined to assess the uniformity of drug distribution within the carrier matrix. The percentage drug content of all formulations was found to be within the acceptable range of 98.42 ± 0.179% to 99.80 ± 0.374%, indicating efficient incorporation of glimepiride into the carrier systems and minimal drug loss during the preparation process and the values are represented in the table 5. Among the formulations prepared using different carrier concentrations, formulation GP4 (99.56 ± 1.978%). The results indicate that increasing the carrier concentration improved the dispersion of glimepiride within the carrier matrix, leading to enhanced drug entrapment and content uniformity. Formulations containing higher carrier ratios generally exhibited superior drug content values, suggesting improved molecular dispersion and reduced drug aggregation. This observation may be attributed to the increased availability of carrier molecules that facilitate the uniform distribution of the drug throughout the solid dispersion system. Overall, the drug content analysis confirmed the successful incorporation of glimepiride into the solid dispersion formulations with excellent content uniformity. The high drug content values and low standard deviation observed among the formulations indicate the reliability of the preparation method and support the suitability of the developed solid dispersions for further evaluation. Based on the drug content results, formulations GP4 were identified as the optimized formulations due to their high drug loading efficiency and uniform drug distribution.

Table 5: Percentage Yield and Drug Content of Solid Dispersion of Glimepiride.

S.No	FORMULATIONS	% YIELD	% DRUG CONTENT
1	GP 1	98.5	98.90±1.02
2	GP 2	98.17	98.84±1.09
3	GP 3	98.43	98.43±1.21
4	GP 4	99.13	99.56±1.978
5	GC 1	98.33	98.42±0.179
6	GC 2	98.0	99.80±0.374
7	GC 3	99.05	99.68±0.647
8	GC 4	99.03	99.14±0.950

Mean ± SD (n=3)

Saturation Solubility Study

The saturation solubility study showed that the solubility of the drug increased significantly after the preparation of solid dispersions. The pure drug exhibited very low solubility (0.014 ± 0.0153 mg/mL) in pH 6.8 phosphate buffer, indicating its poor water solubility. The

physical mixtures (PM1 and PM2) showed only a slight increase in solubility, which may be due to improved wetting of the drug particles by the carrier. However, the enhancement was much lower than that observed with the solid dispersions. Among the solid dispersion formulations, GP1–GP4 showed a gradual increase in solubility with increasing carrier concentration. Formulation GP4 exhibited the highest solubility (0.628 ± 0.0086 mg/mL), followed by GP3, GP2, and GP1 as represented in the table 6. The improved solubility may be attributed to better wetting of the drug, reduced particle size, increased surface area, and uniform dispersion of the drug within the hydrophilic carrier matrix. Similarly, GC1–GC4 formulations also showed improved solubility (as represented in the table 6) compared to the pure drug, with GC4 exhibiting the highest solubility among the GC formulations. However, the solubility enhancement observed in the GP formulations was greater than that of the GC formulations, indicating better solubilizing efficiency of the GP carrier system. The results clearly demonstrate that increasing the concentration of the carrier enhanced the saturation solubility of the drug. The hydrophilic carrier improved drug wettability and maintained the drug in a dispersed state, leading to enhanced solubility. Among all formulations, GP4 was identified as the optimized formulation due to its highest saturation solubility and potential for improved dissolution and bioavailability.

Table 6: Solubility Data of Solid Dispersions in 6.8 Phosphate Buffer at 25 °C.

S.No	FORMULATIONS	Solubility (mg/ml)
1	Pure Drug	0.014 ± 0.0153
2	PM 1	0.127 ± 0.0468
3	PM 2	0.122 ± 0.0468
4	GP 1	0.561 ± 0.0065
5	GP 2	0.594 ± 0.0021
6	GP 3	0.614 ± 0.0065
7	GP 4	0.628 ± 0.0086
8	GC 1	0.198±0.011
9	GC 2	0.268±0.012
10	GC 3	0.346±0.009
11	GC 4	0.376±0.006

Mean ± SD (n=3)

Electron Microscopy

X-ray Diffraction Studies

X-ray diffraction studies were carried out to investigate the crystalline nature of pure glimepiride and the optimized solid dispersion formulation (GP4). The diffraction patterns were recorded using a Philips PW 1729 X-ray diffractometer with Cu-Kα radiation. The

XRD pattern of pure glimepiride exhibited numerous sharp and intense diffraction peaks at various 2θ values, confirming its highly crystalline nature. The presence of these characteristic peaks indicates a well-ordered crystal lattice structure of the drug. The intense peaks observed between 15° and 30° (2θ) are characteristic of crystalline glimepiride and are in agreement with previously reported diffraction patterns. In contrast, the XRD pattern of the optimized formulation GP4 showed a marked reduction in the intensity of the characteristic crystalline peaks of glimepiride. Although some drug peaks were still detectable, their intensities were considerably decreased and several peaks appeared broadened. This reduction in peak intensity suggests a decrease in crystallinity and partial conversion of the drug into an amorphous or molecularly dispersed state within the carrier matrix. The diminished crystallinity observed in GP4 (Figure 8) may be attributed to the successful incorporation of glimepiride into the hydrophilic carrier during the preparation of solid dispersions. The carrier prevents the drug molecules from arranging into a regular crystal lattice, thereby reducing crystal growth and promoting amorphization. The amorphous form possesses higher free energy and greater molecular mobility, resulting in enhanced saturation solubility and dissolution rate. The XRD findings correlate well with the saturation solubility studies, where GP4 exhibited the highest solubility among all formulations. The reduction in crystallinity is one of the major factors responsible for the improved solubility and dissolution behavior of the optimized solid dispersion. Therefore, XRD analysis confirms that the solid dispersion technique effectively altered the physical state of glimepiride, contributing to its enhanced pharmaceutical performance.

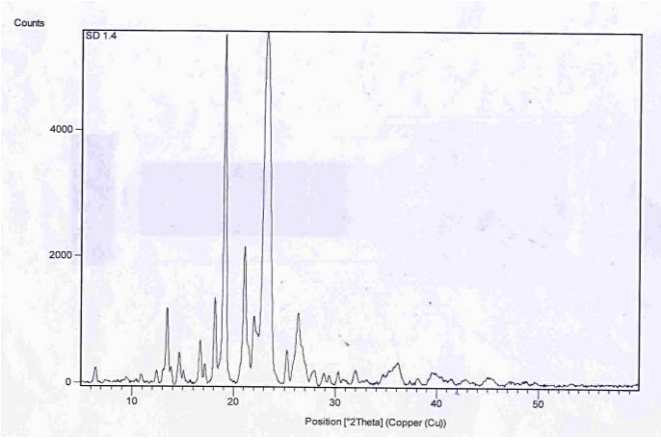

Figure 8: X-ray Diffractogram of GP4 Formulation.

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) was performed to examine the surface morphology of

pure glimepiride and the optimized solid dispersion formulation GP4. The SEM image of pure glimepiride revealed distinct elongated and needle-shaped crystals with smooth surfaces, indicating its crystalline nature. The drug particles were relatively large and exhibited a well-defined geometric structure, which is characteristic of crystalline materials. Such crystalline particles generally possess lower wettability and slower dissolution characteristics. In contrast, the SEM micrograph of the optimized formulation GP4 (Figure 9) showed irregularly shaped, aggregated particles with rough and porous surfaces. The characteristic needle-shaped crystals of glimepiride were no longer clearly visible, suggesting that the drug was dispersed within the carrier matrix. The particles appeared smaller and less ordered compared to those of the pure drug. The marked change in particle morphology indicates strong interaction between glimepiride and the hydrophilic carrier during solid dispersion preparation. The reduction in particle size, increased surface roughness, and loss of crystalline structure contribute to improved wettability and increased surface area available for dissolution. These morphological modifications facilitate faster penetration of the dissolution medium into the particles, thereby enhancing drug solubility and dissolution rate. The SEM observations support the XRD results, which demonstrated a reduction in crystallinity in the GP4 formulation. Thus, the SEM study confirms the successful formation of solid dispersion and explains the improved solubility and dissolution characteristics observed for the optimized formulation.

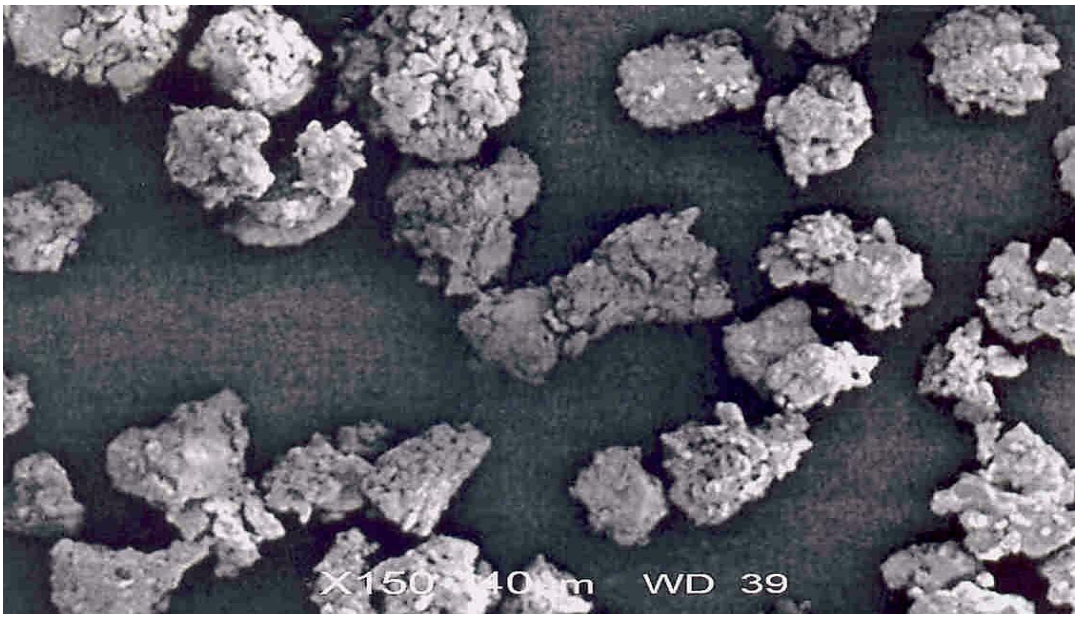

Figure 9: Scanning Electron Photomicrograph of GP4.

Invitro Dissolution Studies

The *invitro* dissolution study was carried out to evaluate the effect of solid dispersion on the dissolution behavior of glimepiride. The cumulative percentage drug release profiles of pure drug, physical mixtures (PM1 and PM2), and optimized solid dispersion formulations (GP3 and GP4) were determined in pH 6.8 phosphate buffer. The pure drug exhibited a slow dissolution rate, releasing only 11.89 ± 0.59% of drug within 2 minutes and 27.72 ± 0.49% after 30 minutes. This poor dissolution behavior can be attributed to the low aqueous solubility and highly crystalline nature of glimepiride. The physical mixtures (PM1 and PM2) showed a slight improvement in drug release compared to the pure drug. PM1 and PM2 released 30.55 ± 0.51% and 29.05 ± 0.01% of drug, respectively, at the end of 30 minutes. The enhanced dissolution observed in physical mixtures may be due to improved wetting of drug particles by the hydrophilic carrier; however, simple mixing was insufficient to produce a substantial increase in dissolution rate. In contrast, the solid dispersion formulations GP3 and GP4 exhibited a remarkable enhancement in dissolution. GP3 showed an initial drug release of 52.46 ± 0.97% within 2 minutes, which increased rapidly to 82.46 ± 0.59% at 6 minutes. Similarly, GP4 exhibited the highest dissolution rate, releasing 55.44 ± 1.33% of drug within 2 minutes and achieving 85.54 ± 0.89% release within 6 minutes. Thereafter, the dissolution profile remained relatively constant, indicating rapid and complete dissolution of the available drug. Among all formulations, GP4 demonstrated the highest dissolution efficiency throughout the study period. The approximately three-fold increase in drug release compared to the pure drug at 30 minutes indicates the effectiveness of the solid dispersion approach in improving the dissolution characteristics of glimepiride as shown in the Figure 10.

The enhanced dissolution behavior of GP3 and GP4 can be attributed to several factors. The hydrophilic carrier improved the wettability of drug particles and facilitated rapid penetration of the dissolution medium. Furthermore, the solid dispersion process reduced particle size and increased the effective surface area available for dissolution. XRD studies revealed a reduction in drug crystallinity, while SEM analysis demonstrated significant changes in particle morphology. The partial conversion of crystalline drug into an amorphous form increased its free energy and molecular mobility, thereby enhancing dissolution. In addition, molecular dispersion of the drug within the carrier matrix prevented particle aggregation and promoted faster drug release. The dissolution results correlate well with the saturation solubility studies, where GP4 exhibited the highest solubility among all formulations. The

increased solubility and reduced crystallinity collectively contributed to the superior dissolution performance of the optimized formulation. Therefore, the solid dispersion technique successfully enhanced the dissolution rate of glimepiride, with GP4 identified as the optimized formulation capable of improving oral bioavailability.

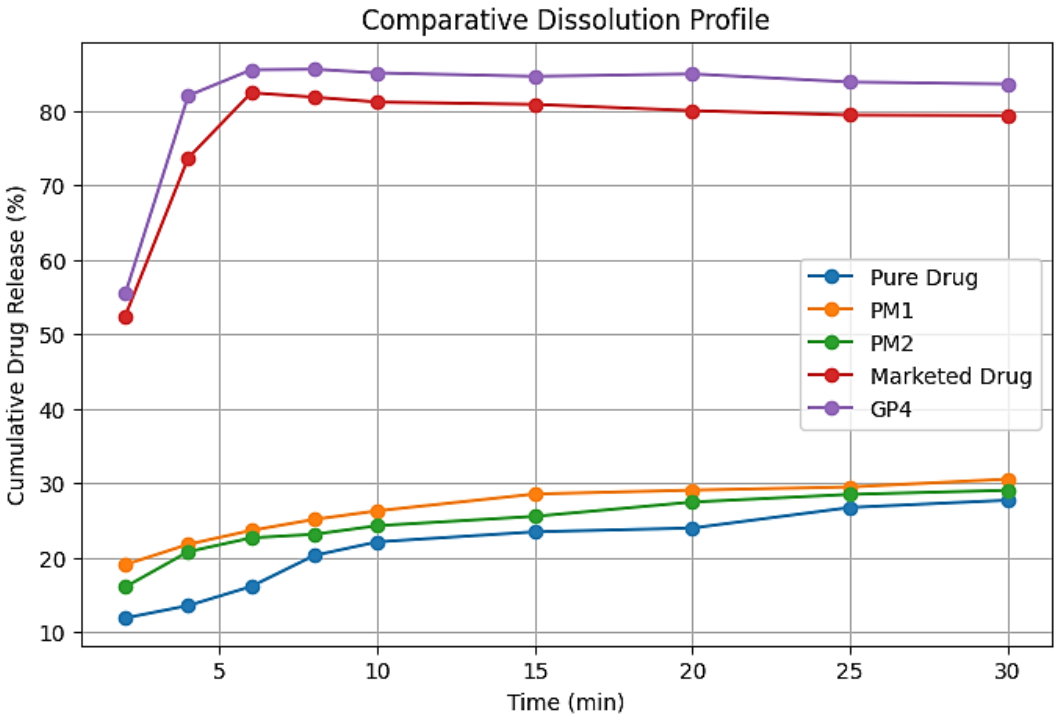

Figure 10: Dissolution Release Profile of pure drug, PM 1, PM 2, Marketed Drug, and GP.

Evaluations for Core Tablet Preparation

Pre-formulation Studies of Drug, Polymer & Excipients

Physical characteristics including the angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio were used to characterize drugs, polymers and excipients. The physical properties of all the materials are within an acceptable range.

Pre- Compression Parameter of Core Granules

Table 7: Pre- Compression Parameter of Core Granules.

Formulation Number	Thickness (mm)	Weight (mg)	Hardness (Kg/Cm^2)	Friability (%)	Disintegration Time (Minutes)
T1	3.14	80.08 ± 2.09	3.6 ± 0.31	0.54 ± 0.10	7
T2	3.14	81.64 ± 2.04	3.2 ± 0.14	0.79 ± 0.09	11
T3	3.14	78.52 ± 1.94	3.4 ± 0.16	0.62 ± 0.13	14
T4	3.14	80.13 ± 1.94	3.9 ± 0.22	0.65 ± 0.13	19
T5	3.14	83.06 ± 1.88	3.7 ± 0.28	0.47 ± 0.19	30

Mean ± SD (n=3)

The post-compression evaluation of formulations T1–T5 demonstrated satisfactory tablet quality within acceptable pharmacopeial limits as shown in the table 7. All formulations exhibited uniform thickness (3.14 mm) and acceptable weight variation, indicating consistent tablet manufacturing. Hardness values ranged from 3.2 to 3.9 kg/cm², providing adequate mechanical strength, while friability values remained below 1%, confirming good resistance to abrasion. The disintegration time increased from 7 minutes (T1) to 30 minutes (T5), suggesting that excipient concentration influenced tablet disintegration behaviour. Formulation T1 showed the fastest disintegration and is suitable for immediate drug release, whereas T5 exhibited greater tablet integrity and prolonged disintegration. Overall, all formulations possessed acceptable physical characteristics and mechanical stability.

Post compression parameter of core tablet

Table 8: Characterization of Glimepiride Solid Dispersion Tablets.

Formulation Number	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Compressibility index (%)	Angle of Repose (°)
T1	0.391	0.405	1.035	3.456	25.32
T2	0.376	0.399	1.061	5.764	26.43
T3	0.398	0.407	1.022	2.211	25.54
T4	0.402	0.419	1.042	4.057	24.43
T5	0.379	0.387	1.021	2.067	26.13

(n=3)

The pre-compression parameters of glimepiride solid dispersion tablet granules were evaluated to determine their suitability for tablet compression. The results indicated that all formulations (T1–T5) possessed good flowability, compressibility, and packing characteristics, which are essential for uniform die filling and consistent tablet production. The bulk density values ranged from 0.376 to 0.402 g/mL, while the tapped density values ranged from 0.387 to 0.419 g/mL (table 8). The relatively small difference between bulk and tapped densities suggests good packing ability of the granules with minimal interparticle void spaces. Hausner's ratio values were found between 1.021 and 1.061 (table 8), which are well below the acceptable limit of 1.25, indicating excellent flow properties and low cohesiveness of the powder blend. The compressibility index (Carr's index) values ranged from 2.067% to 5.764% (table 8), demonstrating excellent compressibility and flow behavior. Lower compressibility index values indicate reduced friction between particles and better flow

characteristics. Formulation T5 exhibited the lowest compressibility index (2.067%) (table 8), suggesting superior flowability and packing efficiency among all formulations. The angle of repose values varied from 24.43° to 26.43° (table 8). Since all values were below 30°, the granules were considered to possess excellent flow properties. Formulation T4 showed the lowest angle of repose (24.43°), indicating the best flow behavior, whereas T2 exhibited the highest value (26.43°) (table 8), although still within the acceptable range for good flowability. Overall, the pre-compression evaluation confirmed that all formulations exhibited excellent flow and compressibility characteristics, making them suitable for direct compression into tablets. The favorable values of Hausner's ratio, compressibility index, and angle of repose suggest that the prepared granules would ensure uniform die filling, consistent tablet weight, and reproducible tablet quality during large-scale manufacturing.

Content Uniformity

The drug content analysis was performed to evaluate the uniformity of drug distribution within the prepared glimepiride solid dispersion tablets (T1–T5). The results demonstrated that all formulations contained drug content values very close to the theoretical amount of 5 mg per tablet, indicating efficient mixing and uniform distribution of glimepiride throughout the tablet matrix. The drug content ranged from 4.94 ± 0.058 mg to 5.00 ± 0.028 mg per tablet (table 9), corresponding to a percentage drug content of 98.85 ± 1.16% to 100.06 ± 0.55%. Formulation T2 exhibited the highest drug content (100.06 ± 0.55%) (table 9), while T5 showed the lowest value (98.85 ± 1.16%) (table 9). However, all formulations were within the acceptable pharmacopeial limit of 95–105% (table 9), confirming satisfactory content uniformity. The low standard deviation values observed for all formulations indicate minimal batch-to-batch variation and excellent reproducibility of the tablet manufacturing process. The uniform drug content may be attributed to the good flow properties of the granules and effective blending of the solid dispersion with excipients prior to compression. Overall, the drug content results confirm that all formulations achieved excellent content uniformity and complied with pharmacopeial specifications. The findings suggest that the prepared tablets possess consistent drug distribution, which is essential for ensuring dose accuracy, therapeutic efficacy, and product quality.

Table 9: Drug content in the Glimepiride Solid Dispersion Tablets.

Formulation Number	Drug Content (mg per Tablet)	Drug Content (%)
T1	4.97 ± 0.018	99.46 ± 0.36

T2	5.00 ± 0.028	100.06 ± 0.55
T3	4.99 ± 0.036	99.82 ± 0.72
T4	4.96 ± 0.028	99.22 ± 0.55
T5	4.94 ± 0.058	98.85 ± 1.16

Mean±SD (n=3)

***Invitro* dissolution test**

The *invitro* dissolution study was performed to compare the drug release behaviour of pure glimepiride, solid dispersion tablet formulations (T1–T5), optimized solid dispersion (GP4) (Figure 10), and the marketed formulation. The dissolution profiles revealed a substantial enhancement in drug release from the solid dispersion-based formulations compared with the pure drug. The pure drug exhibited poor dissolution throughout the study, releasing only 29.97% of the drug after 60 minutes. This limited dissolution can be attributed to the poor aqueous solubility and highly crystalline nature of glimepiride, as confirmed by saturation solubility and XRD studies.

Among the tablet formulations, T1 showed the slowest release profile, reaching 85.68% drug release at 60 minutes. The slower release may be related to its rapid disintegration but relatively lower efficiency in maintaining the drug in a solubilized state compared to the other formulations. Formulation T2 demonstrated a marked improvement in dissolution, releasing 78.18% drug within 20 minutes and achieving 82.82% release at 60 minutes. The enhanced dissolution may be due to improved wettability and dispersion of the drug within the carrier matrix. T3 exhibited faster drug release than T1 and T2, achieving 82.56% release within 20 minutes and 85.69% release at 30 minutes. The rapid release suggests efficient drug dispersion and increased surface area available for dissolution. T4 showed superior initial dissolution characteristics, releasing 77.58% drug within 10 minutes and reaching 85.99% release at 25 minutes. The faster dissolution may be attributed to improved tablet disintegration and enhanced solubility resulting from the solid dispersion system. Among all tablet formulations, T5 demonstrated the best dissolution performance. It released 51.25% drug within 5 minutes and 82.00% within 10 minutes Figure 10. The formulation achieved 86.72% release at 30 minutes and maintained approximately 86% release throughout the study period. The superior dissolution profile of T5 may be due to optimal excipient composition, improved wettability, reduced particle size, and enhanced drug dispersion within the carrier matrix. The optimized solid dispersion GP4 exhibited the fastest dissolution among all formulations tested. GP4 released 55.44% drug within 2 minutes and 82.06%

within 4 minutes. Maximum release (85.62%) was observed within 8 minutes, indicating extremely rapid dissolution. The enhanced dissolution can be attributed to the conversion of the drug into a partially amorphous state, reduction in crystallinity as observed in XRD studies, and changes in particle morphology confirmed by SEM analysis.

The marketed formulation also showed rapid dissolution, releasing 52.46% drug within 2 minutes and 82.46% within 6 minutes. However, GP4 consistently exhibited slightly higher dissolution values than the marketed formulation during the initial phase of dissolution, demonstrating the effectiveness of the developed solid dispersion approach. The dissolution results correlate well with the saturation solubility study, where GP4 exhibited the highest solubility (0.628 mg/mL), approximately 45-fold greater than the pure drug. XRD studies demonstrated reduced crystallinity, while SEM analysis revealed altered particle morphology and reduced particle size. These physicochemical modifications collectively contributed to enhanced dissolution behavior.Overall, the order of dissolution performance was.

GP4 > T5 > T4 ≈ T3 > T2 > T1 >> Pure Drug

The findings confirm that the solid dispersion technique successfully improved the dissolution characteristics of glimepiride. Among the tablet formulations, T5 was identified as the optimized tablet formulation due to its highest cumulative drug release, while GP4 exhibited dissolution behavior comparable to or better than the marketed product.

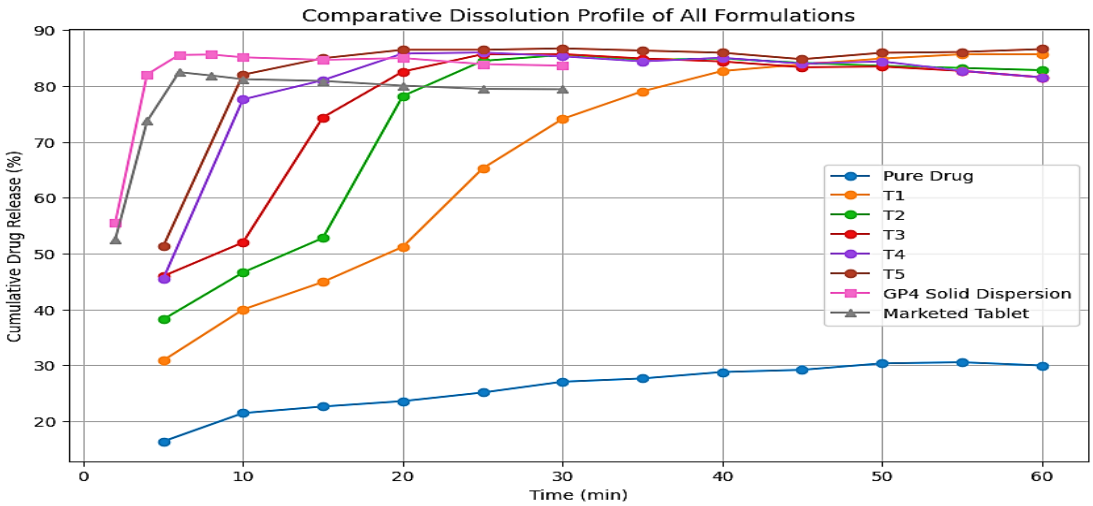

Figure 10: *invitro* dissolution.

CONCLUSION

The present study was undertaken to enhance the solubility and dissolution rate of

glimepiride, a poorly water-soluble antidiabetic drug, through the development of solid dispersion systems and their subsequent formulation into tablets. Preformulation studies confirmed the identity and purity of glimepiride through organoleptic evaluation, melting point determination, FT-IR spectroscopy, and UV spectrophotometric analysis. Drug–carrier compatibility studies revealed the absence of any significant interaction between glimepiride and the selected carriers, confirming their suitability for formulation development. Solid dispersions of glimepiride were successfully prepared using Poloxamer 188 and Crospovidone as carriers. Drug content analysis demonstrated excellent drug incorporation and content uniformity in all formulations. Saturation solubility studies revealed a substantial enhancement in the solubility of glimepiride following solid dispersion formation. Among all formulations, GP4 (Glimepiride: Poloxamer 188, 1: 4 ratio) exhibited the highest solubility (0.628 mg/mL), representing an approximately 45-fold increase compared with the pure drug (0.014 mg/mL).

Characterization studies further confirmed the successful formation of the solid dispersion system. X-ray diffraction analysis demonstrated a significant reduction in the crystallinity of glimepiride in GP4, indicating partial conversion of the drug into an amorphous state. Scanning electron microscopy revealed marked changes in particle morphology, including loss of the characteristic crystalline structure and formation of irregular porous particles. These physicochemical modifications contributed to enhanced wettability, increased surface area, and improved dissolution characteristics. *Invitro* dissolution studies showed a remarkable improvement in the drug release profile of solid dispersion formulations compared with the pure drug and physical mixtures. GP4 exhibited the fastest dissolution rate, releasing more than 85% of the drug within a few minutes, and demonstrated dissolution behavior comparable to or slightly better than the marketed formulation. The enhanced dissolution was attributed to improved wettability, reduced crystallinity, increased surface area, and uniform molecular dispersion of the drug within the carrier matrix. The optimized solid dispersion (GP4) was successfully formulated into tablets and evaluated for pre-compression and post-compression parameters. All tablet formulations exhibited acceptable flow properties, compressibility, hardness, friability, weight variation, drug content uniformity, and mechanical strength within pharmacopeial limits. Dissolution studies of the tablet formulations demonstrated significantly enhanced drug release compared with the pure drug. Among the tablet formulations, T5 exhibited the highest cumulative drug release (86.72%), indicating superior dissolution performance and efficient drug availability.

Overall, the study demonstrated that solid dispersion technology using Poloxamer 188 is an effective strategy for improving the solubility and dissolution behavior of glimepiride. The optimized formulation GP4 and its corresponding tablet formulation T5 showed superior pharmaceutical performance and possess significant potential for enhancing the oral bioavailability of glimepiride. Therefore, the developed solid dispersion-based tablet system represents a promising approach for the formulation of poorly water-soluble drugs and may contribute to improved therapeutic efficacy and patient compliance.

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