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Solubility Enhancement of Poorly Water Soluble Drug

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Abstract
The Biopharmaceutical Classification System includes solubility as one of its core criteria, and dissolution rate is the most crucial variable affecting a drug's bioavailability. A weakly water-soluble medication is defined as a substance with a solubility of less than 1 part per 10,000 parts of water. The medicine with poor solubility exhibits numerous issues with in-vitro formulation. Therefore, it is crucial to increase these medications' solubility by using various solubility improvement procedures. As A BCS class II medication that is essentially insoluble is glimepiride. There was very little information available for the manufacture of solid dispersion by a solvent evaporation approach for glimepiride-urea, however it was discovered that this technique is promising for improving solubility. In the current study, the similar approach was prepared employing the carriers urea and PEG 6000 to increase the solubility of glimepiride. In-vitro dissolution rates are greater for the robust formulation. In phosphate buffer pH 6.8, the in vitro dissolving ability of glimepiride and its equivalent solid dispersions was assessed. When compared to the pure medication, the solid dispersion GUS3 (glimepiride: urea; 1:3) showed the greatest increase in solubility. The tablets were put through a number of tests, and the outcomes were compared to industry standards. Comparing the GUS3 formulation to the commercial form, a greater drug release was observed. This demonstrates how the solid dispersion approach can improve the dissolution of medications that are not very water soluble.
Keywords: Glimepiride, solid dispersion, solubility, solubility enhancement, urea.

Introduction

Nowadays, the majority of new chemical entities (NCE) being developed are meant to be administered orally in a solid dosage form that results in an efficient and repeatable in-vivo plasma concentration. However, the creation of solid dosage forms can be an ineffective means of administration for many medications since up to 40% or more of the NCE produced by drug development programmes have issues with water solubility. Dissolution is the rate-limiting step for the bioavailability of medications with low water solubility. A poorly water-soluble problems with many recently synthesised compounds are frequently the cause of these kinds of problems medicine is one that takes longer to dissolve in gastrointestinal fluid than it does to be absorbed in the gastrointestinal system, according to a more modern definition. The oral administration of the medications as well as the oral delivery of many currently available drugs may be hampered by solubility problems. Drugs with low solubility show a variety of formulation-related issues in in vitro forms, including limited options for drug administration and very complicated dissolution tests with poor connection to in vivo absorption Solubility

with in-vivo and in-vitro features as well as the difficulties in achieving predicted and repeatable in-

vivo/in-vitro correlations (IVIVC). Therefore, it is crucial to increase these medications' solubility by using various solubility improvement procedures[1]. The concentration of the undissolved solid in a solvent under a certain set of circumstances is referred to as solubility. When the solution is saturated, the surplus undissolved solute and the dissolved solute are in balance. The ability of a chemical compound known as a solute to dissolve in a solid, liquid, or gaseous solvent and create a homogenous solution of the solute in the solvent is known as solubility. Fundamentally, the solubility of a chemical relies on the solvent employed along with temperature and pressure. The saturation concentration, at which adding more solute has no further effect on the concentration of the solution, represents the extent of a substance's solubility in a certain solvent. Drugs that are poorly water-soluble are increasingly making it difficult to achieve the sufficient gastrointestinal tract dissolving required for optimal bioavailability[2].

BCS[3]

Table No. 1: BCS Classification

Class	Solubility	Permeability	Absorption pattern	Rate limiting step in the absorption
I	High	High	Well absorbed	Gastric emptying
II	Low	High	Variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorbed	Case by case

Methods of solubility enhancement

Physical alterations

Particle size reduction: Both micronization and nanosuspension can reduce particle size. Each method uses a distinct set of tools to reduce the particle size.

Homogenization: The pharmaceutical and biotechnology sectors frequently utilise traditional homogenizers, Sonicator, and high shear fluid processors for particle size reduction. The suspension is pushed under pressure via a nanoparticle-filled valve. Water bubbles start to develop as a result, but they burst as they exit valves. This process breaks apart the particles.

Wet milling: In another method, a drug solution in a volatile organic solvent is sprayed into a heated aqueous solution. Drug precipitation occurs when a solvent evaporates quickly in the presence of surfactants. For medications including tarazepide, atovaquone, amphotericin B, paclitaxel, and bupravaquone, the nanosuspension method has been used. Every formulation is still in the research phase[4]

Other methods for decreasing particle size

Sonocrystallisation

Reducing particle size has also been accomplished by the effective use of liquid solvents and Antisolvent during the recrystallization of poorly soluble materials. Sonocrystallisation is a revolutionary method for reducing particle size based on crystallisation utilising ultrasound. Sonocrystallisation uses ultrasonic energy with a 20–100 kHz frequency range to cause crystallisation. It not only increases the nucleation rate but also controls the size distribution of the active medicinal components and reduces their size (API). Ultrasound is typically used in applications between 20 kHz and 5 MHz.

Spray drying

A typical technique for drying a liquid feed using a hot gas is spray drying. Normally, this heated gas is air; however, for the oxygen-free drying of delicate items like medicines and solvents like ethanol, nitrogen gas is employed.

Modification of the crystal habit

The capacity of an element or compound to crystallise in more than one crystalline form is known as polymorphism. Drugs come in several polymorphs that are chemically similar but varied in terms of solubility, melting point, density, texture, stability, and other physicochemical aspects. According to their thermodynamic characteristics, polymorphs can be broadly divided into enantiotropes and monotropes.

Drug dispersion in carriers

The solid dispersion method was originally discovered in 1961 as a means of reducing particle size and so increasing medication absorption and dissolution rates. The dispersion of one or more active substances in an inert carrier in a solid form is referred to as a "solid dispersions," and it is usually made using the melting (fusion) process, solvent method, or fusion solvent-method. Rapid precipitation by freeze-drying, employing supercritical fluids, and spray-drying—often in the presence of amorphous hydrophilic polymers—are a few novel additional preparation procedures. Melt extrusion is another.The hydrophilic carriers Plasdone-S630, polyvinylpyrrolidone, and polyethylene glycols are most frequently utilised for solid dispersions. Many times, surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68, and Sodium Lauryl Sulphate may also be utilised in the creation of solid dispersion [5]

Complexation

The joining of two or more molecules to create a non-bonded entity with a well defined stochiometry is known as complexation. Hydrophobic contacts, hydrogen bonds, and London forces are examples of relatively weak forces that are used in complexation. Chelates like EDTA and EGTA, polymeric molecular complexes, inclusion complexes, and Cyclodextrin are examples of Complexing agents.

Chemical Modifications

Salt Formation

The most popular and efficient way to speed up the solubility and dissolving rates of acidic and basic medicines is using this technique. Acidic or basic drugs are transformed into salts with greater solubility than the original drugs. Ex. Theophylline, barbiturates, and aspirin.

Co-crystallization

This is a brand-new method that uses co-crystals, also known as molecular complexes, to increase the solubility of drugs. A co-crystal is a crystalline substance held together by non-covalent forces that consists of two or more molecular (and electrically neutral) species. It can be made via sublimation, growth from the melt, or slurry preparation. It can also be made by evaporating a heterogenic solution, combining the components, or grinding them together. It is becoming more and more significant as a salt formation substitute, especially for neutral chemicals.

Co-solvent

It is generally known that the solubility of pharmaceuticals may be significantly altered by the addition of an organic co-solvent to water. By changing the solvent's polarity, weak electrolytes and non-polar compounds' low water solubility can be enhanced. Co-solvent is a kind of solvent used to boost solubility. Blending solvent is another name for it that is frequently used. Small hydrocarbon regions and donor or acceptor groups for hydrogen bonds are present in the majority of co-solvents. Their hydrophobic hydrocarbon regions disrupt the water's hydrogen bonding network, lowering the water's total intermolecular attraction, but their hydrophilic hydrogen bonding groups assure water miscibility [6].

Hydrotropy

It refers to a rise in solubility in water as a result of the presence of several chemicals. It increases solubility by complexation, which involves a minimal contact between the solute with hydrophobic substances including sodium benzoate, sodium alginate, and urea. Ex. Theophylline sublimation with sodium acetate and sodium alginate.

Solubilizing Agents

A variety of solubilizing substances can help increase the solubility of a medicine that is not very soluble. Ex. PEG 400 enhances hydrochlorothiazide's solubility. Recently created excipient modified gum karaya (MGK) was tested as a vehicle for improving

the dispersion of the medication nimodipine, which is weakly soluble [6].

Solid Dispersion Technology

Sekiguchi and Obi were the ones who initially developed the idea of solid dispersion. The dispersion of one or more active substances in an inert carrier in a solid form is referred to as a "solid dispersions," and it is usually made using the melting (fusion) process, solvent method, or fusion solvent method. The medication can be spread molecularly, in crystalline or amorphous particles (clusters)[6].

Advantages of Solid Dispersions

By speeding up the drug's dissolution, solid dispersions are utilised to increase the bioavailability of weakly water soluble drugs.

Solid dispersions are superior to other particle size reduction strategies in terms of increasing solubility since they reduce the size to a maximum of around 2–5 microns, which does not sufficiently increase solubility or drug release in the small intestine and increase bioavailability.

Reduced pre-systemic metabolism may be caused by the carrier, which blocks the enzyme and is in charge of the drug's biotransformation.

The drug's liquid form may be changed into a solid form [7].

Methods of solid dispersion technique

Melting method
Hot stage extrusion
Melt agglomeration
Spray drying
Solvent evaporation method
Freeze drying
Dropping method
Supercritical fluid method
Co-precipitation method

Materials and methods

Materials

The source of glimepiride was Supra chemicals. From Research-Lab Fine Chem Industries, Mumbai, we obtained urea, PEG 6000, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, and other solvents. The other compounds were all classified as analytical reagents.

Phase solubility studies

A stoppered conical flask containing 25 ml of phosphate buffer (pH 6.8), various quantities of the carriers urea and PEG 6000 (1, 2, 4, 6, 8 and 10% w/v), and an excess of glimepiride was added. The mixture was stirred for 24 hours in a rotary flask shaker. After being shaken for 24 hours, the samples were filtered through a 0.45 m membrane filter and put under the UV spectrophotometer's scrutiny.

Preparation of solid dispersion by a solvent evaporation method

The drug was individually combined in three different ratios 1:1, 1:2, and 1:3 with the carriers urea and PEG 6000. A precisely measured 100 mg dose of the medication was administered and individually combined with 100, 200, and 300 mg of the carrier urea and PEG 6000 in methanol. A transparent, solvent-free film was created by evaporating this combination. To obtain the solid dispersion, the film was then further dried to constant weight in an oven at 40°C for 24 hours. For further research, the produced solid dispersions were collected and stored at room temperature and 60% relative humidity over silica in a desiccator.[8]

Table No. 2: Composition of formulation and effect of percentage of recovery, drug content.

Sr. No.	Batch Code	Drug: Carrier Ratio	Drug Content (mg)	Carrier Content (mg)
1	F1	1:3	100	100
2	F2	1:2	100	200

3	F3	1:3	100	300

Solubility studies

Glimepiride solubility in water, HCl pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4 was assessed.

Flow properties of solid dispersion

6 grams of the solid dispersion (W) from each formula were added to a measuring cylinder with a capacity of 50 millilitres, and the initial volume was noted to calculate the solid dispersion's bulk density and tapped density. At 2-second intervals, the cylinder was permitted to drop from a height of 2.5 cm onto a hard surface. The tapping continued until there was no longer any loudness change.

Hausner's Ratio

Hausner's Ratio The ratio of tapped density to bulk density, reflects the flow characteristics of the solid dispersion.

Compressibility Index (Carr's Index)

An essential measurement that may be derived from the bulk and tapped densities is the compressibility index. Theoretically, a material is more flowable if it is less compressible. A material with values under 20% has good flow characteristics.

Angle of repose

Bulk density and Tapped density, Hausner's Ratio, Compressibility Index (Carr's Index), and angle of repose were used to determine the flow properties of solid dispersion.

Bulk density and Tapped density

Angle of repose is an indication of the frictional forces existing between the blend particles. It is the maximum angle possible between the surface of the pile of blend and the horizontal plane

Preparation of tablets

The tablet formulations of Glimepiride were prepared by combining the solid dispersions and excipients in different proportions. Glimepiride-Urea solid dispersion (1:3) (GUS3) showed the maximum drug release in 1 hr. Therefore, GUS3 was selected in the tablet formulation. GUS3 equivalent to 2 mg of Glimepiride was used as a drug component of the tablets. The tablets weighing about 200 mg were prepared by direct compression technique. The excipients used were lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, talc and ferric oxide red. All the components of the tablet.

Table No. 3 Formulation Table

Sr.No.	Ingredients	Formulation (mg)	
		GMP	GUS3
1.	Glimepiride	2	-
2.	Glimepiride-Urea solid dispersion	-	8
3.	Microcrystalline cellulose	99	96
4.	Lactose monohydrate	82.8	79.8
5.	Sodium starch glycolate	10	10
6.	Magnesium stearate	4	4
7.	Talc	2	2
8.	Ferric oxide red	0.2	0.2

Characterization of tablet

The tablet was evaluated for weight fluctuation, friability, hardness, disintegration, wetting time, and drug content, among other characteristics.

In vitro dissolution studies

Using USP Dissolution Apparatus II (Paddle type) in 900 ml of phosphate buffer pH 6.8 and stirring at a speed of 50 rpm at 37 0.5 4C, the in-vitro dissolution of the medication from GMP solid dispersion and tablets was calculated. To keep the sink condition, the 5 ml aliquots were removed from the dissolving device at various periodic intervals and replaced with new dissolution media. With the use of a UV-visible spectrophotometer, the absorbance of these solutions was determined at 228 nm. Each study was carried out in triplicate, and the percentage of drug release was computed.

Drug carrier compatibility study

The drug carrier compatibility studies were performed using an FTIR spectrophotometer[9]. The carriers used for the study were Urea and PEG 6000. The drug and the carrier were mixed in a ratio of 1:1. The observed spectrum of the mixture of drug and carrier was compared with the reported FTIR spectrum of individual drug and carrier spectrum[10].

Stability Study

The formulation of the solid dispersion tablet underwent stability experiments in accordance with ICH recommendations. The stability testing was carried out to examine the completed product's physicochemical composition. In accordance with ICH recommendations, the ready tablets were put in the stability test chamber and submitted to stability studies under accelerated testing settings (40 2°C/75 5% RH) for three months. The following assessment criteria for GUS3 tablets were examined as part of a stability study: appearance, hardness, weight change, drug content, disintegration time, and in vitro dissolution investigations at intervals of a month.

Result and discussion

UV Spectroscopy

A standard solution of Glimepiride in methanol and Glimepiride in phosphate buffer pH 6.8 was prepared separately and was scanned over a range of 400 nm to 200 nm. Maximum absorption was observed at 228 nm which was found to be in accordance with UV spectrum of reference.

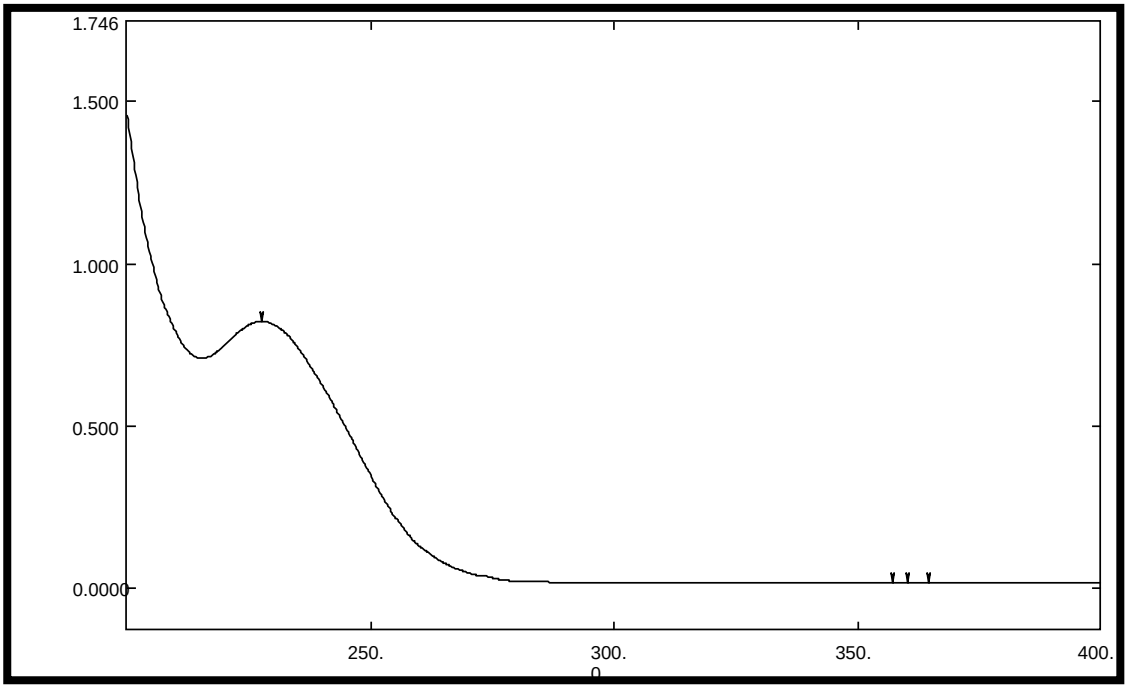


Figure no. 1:UV-Visible spectra of Glimepiride in Phosphate buffer(pH 6.8)

FTIR Spectroscopy

The identity of the drug was confirmed by comparing IR Spectrum of Glimepiride. The reported peaks of pure Glimepiride remained

unaltered in the spectrum obtained for the received drug sample. This confirms that the drug obtained was not degraded and can be used for formulation. The characteristics bands of the drug are reported in the respective table.

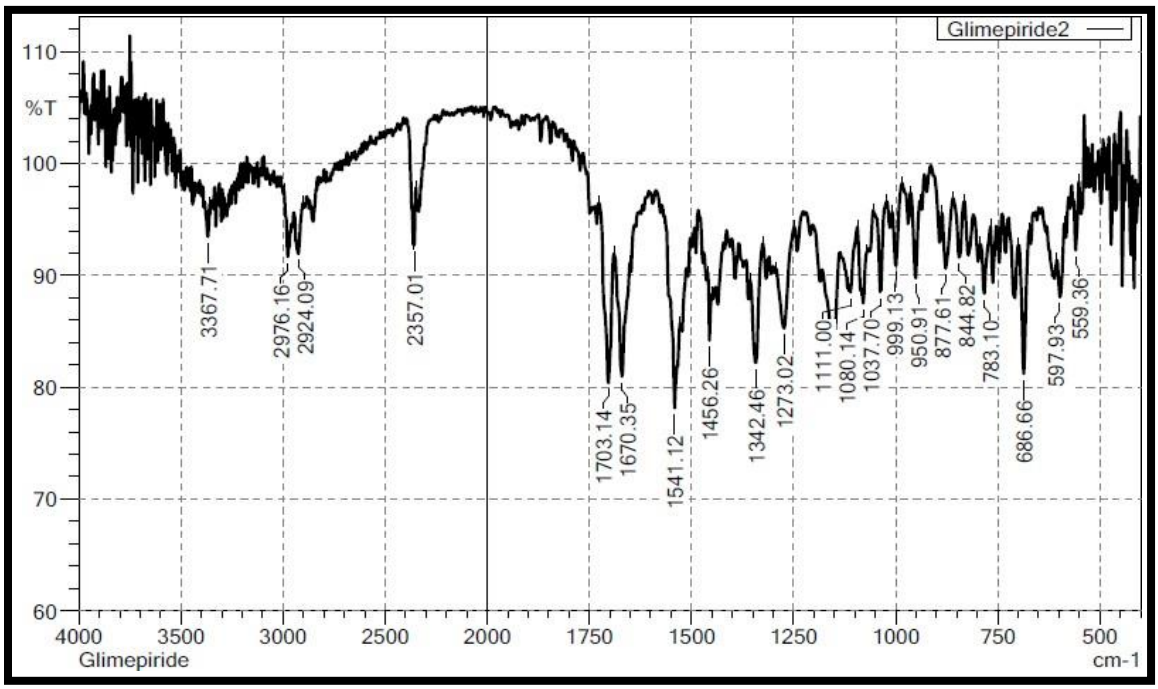


Figure No. 2: IRSpectra of Glimepiride

Melting Point Determination

The capillary tube method was used to assess the drug's melting point. Glimepiride's melting point was examined in a lab and was discovered to be between 205°C and 210°C. It matched the melting point that was cited in the literature.

Solubility studies

Glimepiride was found to be soluble in water, HCl pH 1.2, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 at concentrations of 7.35, 6.34, 24.45 and 24.78 g/ml, respectively. Phosphate buffer with a pH of 6.8 was utilised as a dissolving medium in consideration of the physiological circumstances present in the gastrointestinal system.

Table No. 4: Solubility study of Glimepiride in different solvents

Sr. No.	Solution	Solubility(µg/ml)
1.	Water	7.35
2.	HCL pH 1.2	6.34
3.	Phosphate buffer pH 6.8	24.45
4.	Phosphate buffer pH 7.4	24.78

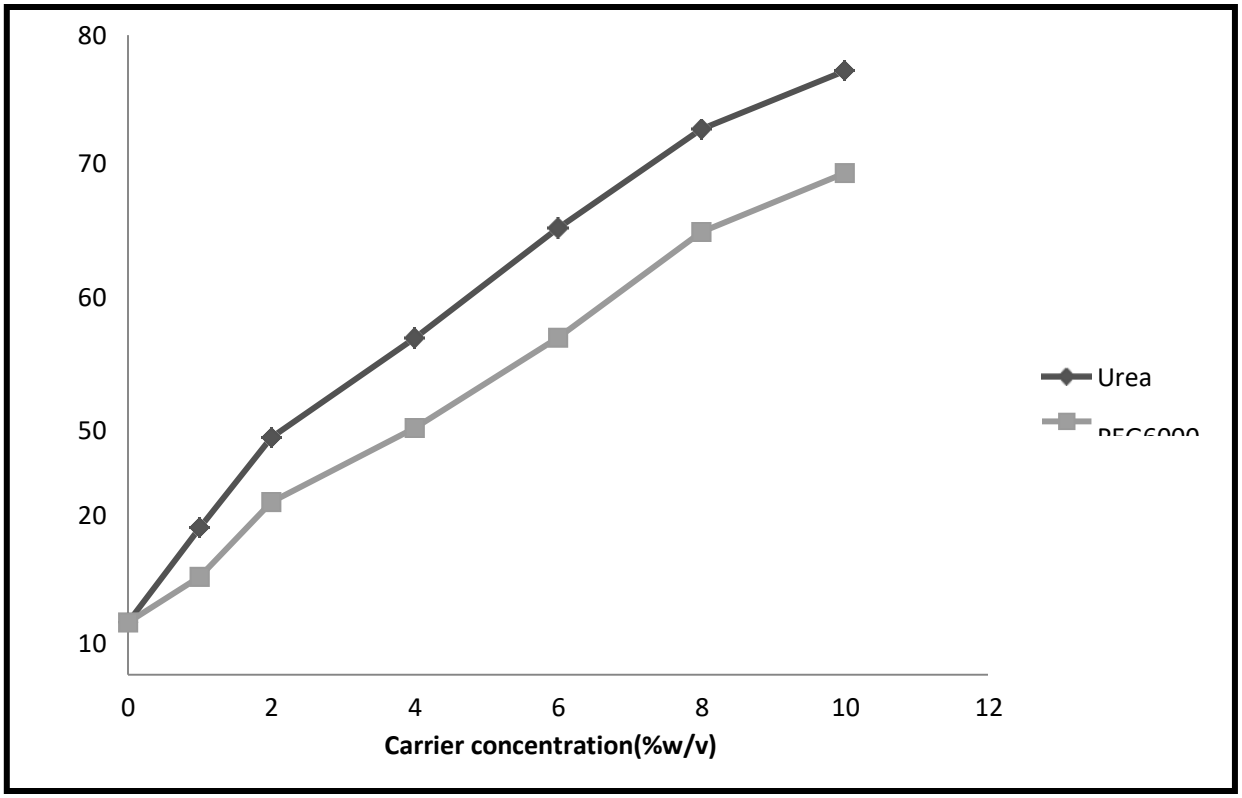
Preparation of solid dispersions

Phase Solubility Studies

The drug's solubility increased linearly in the test concentration employed in the phase solubility experiments of glimepiride in the presence of increasing concentrations of different carriers. Urea was shown to have the greatest effect on solubility when compared to PEG 6000. The solubility curves demonstrated a linear rise with rising carrier concentration.

Table No.5: Phase solubility studies of Glimepiride in presence of different carriers

Sr. No.	Concentration of carrier (%w/v)	Solubility(µg/ml)	
		Urea	PEG6000
1.	0	-	-
2.	1	16.35	12.21
3.	2	27.67	21.59
4.	4	39.11	29.86
5.	6	48.85	40.14
6.	8	65.24	53.37
7.	10	74.52	59.75



FigureNo.3:Phase solubility curve of Glimepiride in presence of different carriers

Drug-Carrier Compatibility Studies

The interaction between the medication and carriers was investigated using infrared spectral analysis. It was discovered that the FTIR spectra of pure glimepiride and solid dispersion formulations at a 1:1 ratio were similar. The functional groups found in glimepiride, urea, PEG 6000, and other excipients had an absorption peak that was within the acceptable range. Peaks within the range of functional groups were visible in the IR spectra of both the formulations' solid dispersion and pure glimepiride. This proves that there was no chemical connection, contact, or breakdown of the glimepiride used in the formulations with the medication and carriers. Thus, it was determined that there was no change between the functional group peaks of glimepiride in solid dispersion by comparing the FTIR spectra of pure glimepiride and solid dispersions of glimepiride since they were found to be unmodified, showing that they were chemically compatible.

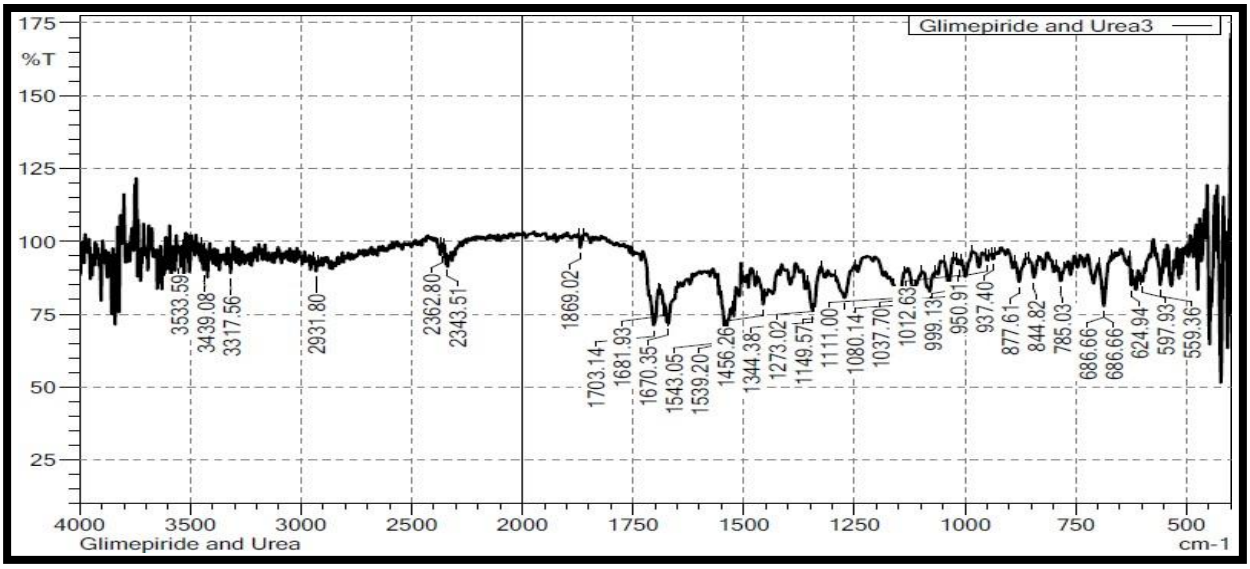


Figure No. 4:IR Spectra of Glimepiride-Urea solid dispersion

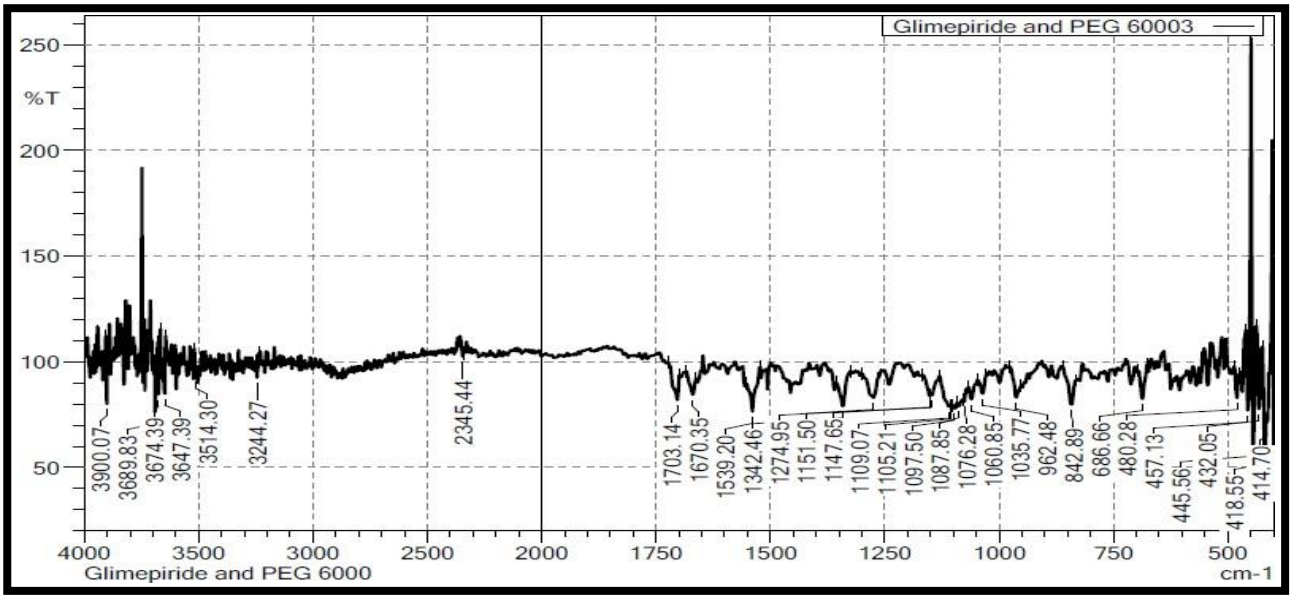


Figure No. 5:IR Spectra of Glimepiride-PEG6000 solid dispersion

Table No.6:IR spectra l peaks in $cm^{-1}$of Glimepiride-PEG6000 solid dispersion

Sr. No.	Wavelength(cm^{-1})	Inference
1.	3514.30	N-Hstretch
2.	3244.27	C-Hstretch
3.	2345.44	O-Hstretch
4.	1539.20	N=Ostretch
5.	1342.46,1274.95	C-Nstretch
6.	1109.07,1151.50	C-Ostretch

Evaluation of solid dispersions

Evaluation of flow properties of solid dispersion. For the various ratios of glimepiride-urea solid dispersions, the flow characteristics were found.

Bulk density

The bulk density and tapped density of the powder blends were found to be in the range of 0.58 g/cc to 0.62 g/cc, indicating that they had satisfactory flow

Carr's Index

The powder's compressibility is represented by the compressibility index, which indicates the friction between particles. Utilizing Carr's index, it was The powder's compressibility, which reflects the friction between particles, is represented by the Hausner's ratio. The Hausner's ratio was determined to be between 1.17 to 1.20, indicating that the mix has good flow properties.

Angle of Repose

Angle of repose is related to the inter-particle friction or resistance to particle movement. It was determined that the blend's angle of repose ranged from 24°.65 to 25°.12, showing outstanding flow qualities.

Evaluation of Solid Dispersion

Particle size determination of Solid Dispersion

Optical microscopy was used to measure the particle size for the various ratios of Glimepiride-Urea solid dispersions. The particle size was determined to be between 82 and 86 m. The increase in the specific surface area of drug particles accessible for dissolution results from the reduction in particle size. As a result, the reduction in particle size, the rise in surface area, qualities.

Tapped density

The bulk density and tapped density values were determined to be in the range of 0.68 g/cc to 0.74 g/cc, demonstrating the powder blends' favourable flow characteristics.

discovered that the powder's flowability ranged from 16.21% to 17.24%.

Hausner's Ratio

and the change in particle shape increased the pace at which solid dispersion dissolves.

Drug content

A drug content analysis was conducted to ascertain the percentage of the drug in the solid dispersion. The amount of medication was found in various ratios of solid glimepiride-urea dispersions. The findings indicated that between 95% and 98% of the medication was included in the solid dispersions. All ratios' drug content was discovered to be within the 90–110% range.

Determination of % practical yield

The % practical yield was determined for the different ratios of Glimepiride-Urea solid dispersions. The results showed that % practical yield was found in the range of 91%to 93%which was within the limit.

In-vitro Dissolution Studies

In this study, pure Glimepiride and the best release Glimepiride-Urea solid dispersion (GUS3) were both

made into tablets and compared to commercially available tablets of the same dosage of Glimepiride. The outcome showed that only 35.22 percent of the medication was released from the pure Glimepiride tablets after one hour. The Glimepiride-Urea solid dispersion tablets (GUS3) demonstrated 96.84% of drug release after one hour, compared to 82.65% in the commercial tablet. In this way, the solid dispersion formulation demonstrated more drug release and outperformed the commercially available formulation.

Table No.7: Dissolution of Glimepiride from tablet formulations

Sr. no.	Time (min)	Percentage of Glimepiride dissolved		
		GMP tablet	GUS3 tablet	Marketed tablet
1.	0	0	0	0
2.	10	5.68	26.55	22.79
3.	15	11.82	40.17	34.25
4.	20	18.46	52.45	45.53
5.	30	24.37	67.21	58.26
6.	45	29.74	78.68	70.41
7.	60.	35.22	96.84	82.65

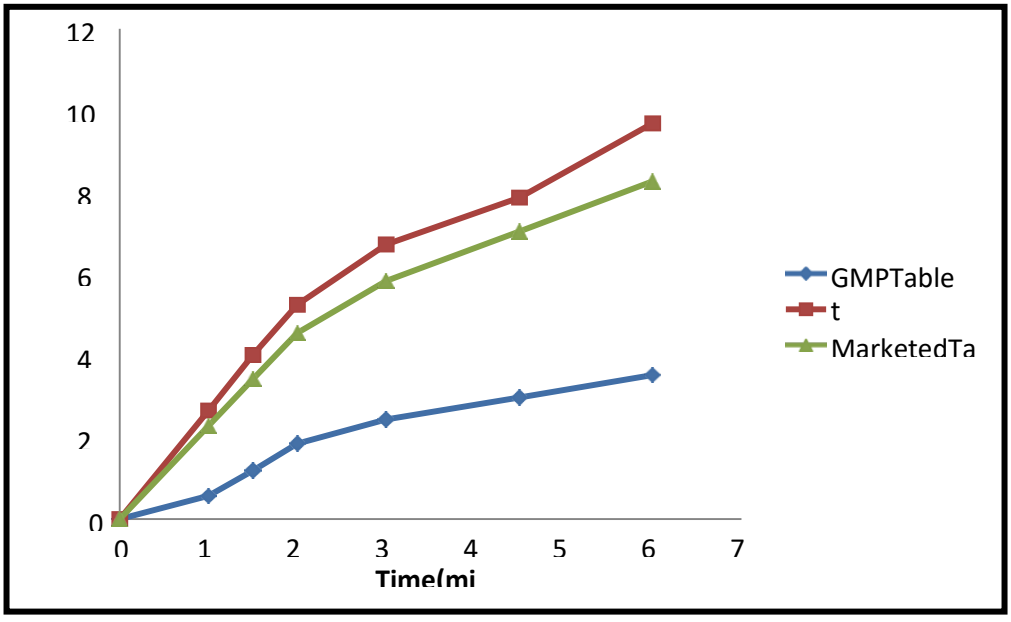


Figure no.6: Cumulative % drug Release vs. time plot of tablet formulation

Stability studies

The GUS3 tablet's stability research, which looked at how ageing affected its physico-chemical characteristics and dissolving rate, was conducted in accordance with ICH recommendations. At one-month intervals, the dissolving rate, medication content, friability, hardness, and average tablet weight of the product were measured. The findings showed that neither the physico-chemical characteristics nor the rate of dissolution differed significantly between the original and stored GUS3 tablet. The GUS3 pills remained stable at 40°C and

75°RH. Hardness, average tablet weight, friability, duration till disintegration, medication content, and dissolving rate did not show any discernible differences. There was also no difference seen in the physical characteristics of GUS3 at the conclusion of the investigation compared to the starting days of the study

TableNo.9: Result and discussion

Sr no.	Parameter	Time plot			
		Initial	1 month	2 month	3 month
1	Appearance	Pink coloured tablets	Pink coloured tablets	Pink coloured tablets	Pink coloured tablets
2	Hardness (kg/cm3)	5.25	5.21	5.19	5.19
3	Average tablet weight (mg)	200.48	200.70	200.62	200.26
4	Drug content (%)	98.52	97.64	97.29	96.88
5	Disintegration time (min)	1.20	1.28	1.39	1.48
6	Cumulative drug release (%)	96.84	96.12	95.70	95.25

Conclusion

According to the findings of current study, the poorly soluble medication glimepiride may be prepared as a solid dispersion using carriers such urea and PEG 6000 to increase the rate of dissolution. Higher in-vitro dissolving rate is demonstrated by the robust formulation of solid dispersion with solvent evaporation by urea. The creation of a solid dispersion using urea and PEG 6000 increased the dissolving properties. The stability research, which lasted three months, was done in accordance with ICH requirements using the best produced solid dispersion formulation. This study shows how making solid dispersions by solvent evaporation improve poorly soluble substances' solubility, dissolution, and bioavailability.

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References

1. *Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor watersoluble drugs. Drug Discovery Today. 2007;12(23–24):1068–75.*
2. *Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:195727.*
3. *Baksh CA, Edelman MJ, Sausville EA, Figg WD, Zhu H, Bauer KS. Population Pharmacokinetics of UCN-01. J Cancer Therapy. 2013;04(10):1513–9.*
4. *Vogt M, Kunath K, Dressman JB. Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. Eur J Pharm Biopharm. 2008;68(2):283–8.*
5. *Chaumeil JC. Micronization: a method of improving the bioavailability of poorly soluble drugs. Methods Find Exp Clin Pharmacology. 1998 20(3):211–5.*
6. *Jagadish B, Yelchuri R, K B, Tangi H, Maroju S, Rao VU. Enhanced dissolution and bioavailability of raloxifene hydrochloride by co-grinding with different superdisintegrants. Chem Pharm Bull. 2010;58(3):293–300.*
7. *Prajapati ST, Gohel MC, Patel LD. Studies to enhance dissolution properties of carbamazepine. Indian J Pharm Sci 2007;69(3):427*
8. *Kaushik S, Pathak K. Solubility enhancement of glimperide: Development of solid dispersion by solvent melt method, characterization and dosage form development. Pharm Biomed Res. 2018.*
9. *Kowalczuk D, Pitucha M. Application of FTIR method for the assessment of immobilization of active substances in the matrix of biomedical materials. Materials (Basel). 2019;12(18):2972.*
10. *Jogala S, Ankathi L, Jarupula RN. Glimepiride fast disintegrating tablets: Formulation, evaluation and in-vivo disintegration and dynamic studies. Int J Pharm Pharm Sci. 2016 ,271–8.*