GREEN CHEMISTRY APPROACH FOR IMPROVEMENT IN PHYSICOCHEMICAL PROPERTIES OF GLIPIZIDE THROUGH COCRYSTAL FORMATION

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KEYWORDS

Green chemistry, Glipizide, Chlorpropamide, Cocrystals, Eutectic mixtures, Physicochemical properties, Solubility enhancement, Mechanochemistry

ABSTRACT

This study aims to improve the physicochemical properties of the poorly water-soluble antidiabetic drug, Glipizide, by forming cocrystals and eutectic mixtures using a green chemistry approach. Enhancing solubility, dissolution rate, and bioavailability is essential for optimizing therapeutic effectiveness. Environmentally sustainable methods, such as solvent-free grinding and mechanochemistry, were utilized to ensure eco-friendliness. Solid-state characterization techniques, including DSC, PXRD, FTIR, and SEM, were employed to confirm the successful formation of cocrystals and eutectic mixtures. This eco-friendly and efficient strategy provides a promising solution to address the solubility challenges of Glipizide.

1. INTRODUCTION

1.1 Background

Green chemistry is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, use, and ultimate disposal (Byrappa K, 2022).

Green Chemistry Perspective

The use of solvent-free grinding and fusion techniques ensured minimal environmental impact while achieving significant improvements in drug properties. This aligns with green chemistry principles by eliminating hazardous solvents and reducing energy consumption.

Glipizide and Chlorpropamide are widely used antidiabetic drugs belonging to the sulfonylurea class. Despite their therapeutic potential, both suffer from poor aqueous solubility and limited bioavailability, which hinders their clinical effectiveness. Enhancing the solubility and dissolution profile of these drugs is imperative for achieving improved therapeutic outcomes(Byrappa K, 2022).

DRUG USED FOR THE STUDY:

Glipizide (GPZ) is an oral hypoglycemic agent classified as a BCS class II drug, characterized by low solubility but high permeability. A search in the Cambridge Structural Database (CSD) revealed only three crystal structures. Two of these structures are of pure glipizide, as reported by (Batisai, 2021) (J. C. Burley, 2005), while the third is a glipizide-piperazineisobutanol methanol solvate hydrate salt (Batisai, 2021). The crystal structure of glipizide features GPZ molecules interacting through N−H···O=S and N−H···O=C dimers, along with amide···amide hydrogen bonds that further stabilize the structure (Figure 1).

(D. Rani, 2018)reported the formation of glipizide co-crystals with picolinic acid (PA), adipic acid (AA), isonicotinic acid (INA), fumaric acid (FA), and sorbic acid (SRA). These co-crystals were characterized and confirmed using differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), and powder X-ray diffraction (PXRD), with the crystal structures solved from PXRD data. In the GPZ-PA co-crystal, O−H···O=C hydrogen bonds connect GPZ and PA molecules, while GPZ molecules interact with one another through N−H···N hydrogen bonds. Additionally, intramolecular N−H···O=S hydrogen bonds are observed within the GPZ molecules.

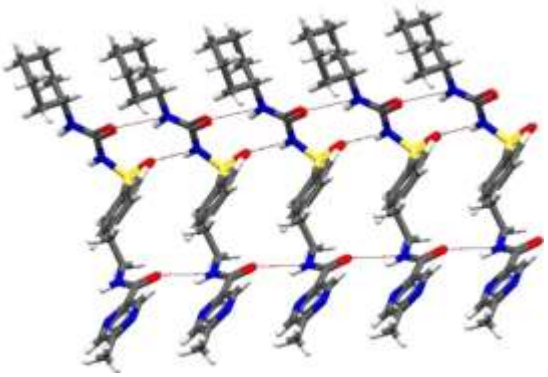

Figure 1:Hydrogen bond interactions in the GPZ crystal structure(CCDC refcode SAXFED01).The GPZ molecules interact via the N-H···O=S and N−H···O=C dimers of the sulfonylurea group.

Glipizide (1-cyclohexyl-3-[[4-[2-[[(5-methylpyrazine-2-yl) carbonyl]amino] ethyl] phenyl] sulphonyl] urea), (Pharmacopoeia, 2017)is a second-generationsulfonylurea derivative that is widely used as oralantihyperglycemic drug for the treatment non-insulin dependent diabetes mellitus (VV, 2013)(Jena BR, 2017)(TT, 2011)(Rathod DR, 2012)(KK, 2017).

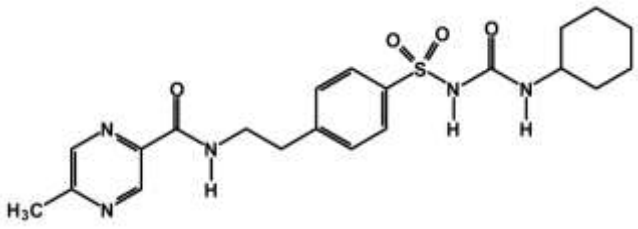

Fig. 2: Structure of Glipizide

1.2 The Need for Green Chemistry

Traditional solubility enhancement methods, such as solvent-based crystallization, often involve the use of hazardous organic solvents, leading to environmental concerns and toxicity risks. Green chemistry principles prioritize sustainability, safety, and efficiency, making it an ideal approach for drug formulation. Techniques such as solvent-free grinding and mechanochemistry are eco-friendly alternatives for cocrystal and eutectic mixture formation (Byrappa K, 2022).

1.3 Cocrystals and Eutectic Mixtures

Cocrystals are crystalline materials composed of the active pharmaceutical ingredient (API) and a pharmaceutically acceptable coformer, which can enhance solubility without altering the drug's therapeutic activity. Eutectic mixtures involve the intimate mixing of two components at a specific composition to achieve a lower melting point, which can improve solubility and dissolution behaviour (Thakuria R, 2023).

Thisarticle presents a comprehensive overview of pharmaceutical co-crystals, including preparation methods, physicochemical properties, and applications.Like salts, co-crystals provide various benefits such as improved drug solubility, dissolution rate, bioavailability, physical and chemical stability, and process ability. They may also enable improvement of the API purity, crystallinity, particle size, and flow ability. Poor solubility is a significant and growing issue for the small molecule pharma pipeline. Active pharmaceutical ingredient (API) processing can address API solubility early in drug development. Salt and co-crystal formation are two options that present different benefits and challenges. Pharmaceutical co-crystals can be employed to improve vital physicochemical characteristics of a drug, including solubility, dissolution, bioavailability and stability of pharmaceutical compounds while maintaining its therapeutic activity(Thakuria R, 2023).

The prominent reason of which is its ability to modify physicochemical properties of active pharmaceutical ingredients. During the development of the pharmaceutical product, formulators must optimize the physicochemical properties of active pharmaceutical ingredients. Pharmaceutical co-crystals can be employed to improve vital physicochemical characteristics.

Co-crystals can be used as an alternative approach based on crystal engineering to enhance specific physicochemical and biopharmaceutical properties of active pharmaceutical ingredients (APIs. In comparison, any API (irrespective of acidic, basic or non-ionized forms) can form co-crystals with a suitable co-former.

Over the last two decades, pharmaceutical co-crystals have attracted significant attention from academia and pharmaceutical industries due to the potential to improve the physicochemical properties of APIs by modifying the crystal structure without altering the pharmacological nature. We will summarize the recent advances of pharmaceutical co-crystals, including preparation methods and modulations of physicochemical properties and applications of co-crystals.

The solution-based method (including solvent evaporation, anti-solvent method, cooling crystallization, reaction co-crystallization and slurry conversion) and the solid-based

method (neat grinding, liquid-assisted grinding and melting crystallization) will be introduced. Co-crystallization through various methodologies leads to improved physicochemical properties of active pharmaceutical ingredients. Different solution based and solid based techniques can be used for preparing co-crystals. This process will most likely result in enhanced bioavailability, flow ability, solubility, and tablet ability (Lu J, 2023).

1.4 Objective of the Study

The aim of this study is to improve the physicochemical properties of Glipizide through cocrystal and eutectic mixture formation using green chemistry-based approaches. This study also explores the role of coformers and sustainable processing techniques in achieving solubility enhancement.The present study is aimed to develop a simple, rapid, selective andeconomical UV spectrometric method for quantitative determinationof Glipizide in bulk and pharmaceutical dosage form. The method was demonstrated as per ICH Q2 (R1) guidelines (drugbank) (Sarangi RR, 2011).

2. Methodology

2.1 Approaches in Computer-Based Screening (Gadekar A, 2023)

Computer-based screening methods have emerged as powerful tools in the field of pharmaceutical cocrystallization. These techniques facilitate the identification of suitable coformers for active pharmaceutical ingredients (APIs) and help predict the stability, solubility, and physicochemical properties of the resulting cocrystals. By reducing the need for extensive trial-and-error experiments, computational approaches save significant time and resources during the early stages of cocrystal development.

1. **Crystal Structure Prediction (CSP)**(Gadekar A, 2023)**:**
    - CSP algorithms predict the most stable crystal structures that a compound can form based on molecular geometry, intermolecular interactions, and thermodynamic stability.
    - The approach helps identify possible cocrystal structures and polymorphs for APIs when combined with specific coformers.
    - Example: Tools such as *GRACE*, *Polymorph Predictor*, and *CrystalPredictor* are widely used for this purpose.
2. **Molecular Docking and Modelling:**
    - Molecular docking predicts the likelihood of hydrogen bonding, π-π stacking, or van der Waals interactions between the API and coformer molecules.
    - Computational models simulate the molecular arrangement to determine if the pair will form a stable cocrystal structure.

- Software like *AutoDock*, *Materials Studio*, and *Gaussian* are used to model these interactions.

3. **Quantum Mechanical Calculations:**
   - These calculations predict the energy of molecular systems, hydrogen bonding strengths, and interaction energies between API and coformers.
   - Techniques such as Density Functional Theory (DFT) provide highly accurate predictions of intermolecular interactions.
4. **Artificial Intelligence and Machine Learning:**
   - Machine learning algorithms are trained on large datasets of known cocrystals to predict new API-coformer combinations.
   - AI tools can identify patterns, predict solubility enhancements, and assess cocrystal stability based on molecular descriptors.
   - **Example:** Applications like *COSMO-RS* (Conductor-like Screening Model for Real Solvents) and AI-assisted tools are increasingly adopted in the pharmaceutical industry.
5. **Molecular Simulations:**
   - Molecular dynamics (MD) simulations predict the behaviour of molecular interactions over time, assessing the stability of cocrystals under specific temperature and pressure conditions.
   - These simulations help evaluate cocrystal formation under realistic conditions.

Benefits of Computer-Based Screening

1. **Efficiency:**
   - Reduces the need for extensive experimental trials by narrowing down potential API-coformer combinations.
2. **Cost-Effectiveness:**
   - Minimizes resource usage and accelerates the early stages of cocrystal development.
3. **Enhanced Predictability:**
   - Provides insights into the thermodynamic stability, solubility, and bioavailability of the predicted cocrystals.
4. **Systematic Screening:**
   - Allows screening of large libraries of coformers to identify the most suitable candidates for a given API.

Limitations

1. **Accuracy Issues:**
    - The accuracy of computational models depends heavily on the input parameters and the quality of algorithms used.
2. **Computational Demand:**
    - Some methods, such as quantum mechanical calculations or large-scale simulations, require significant computational power.
3. **Experimental Validation:**
    - Computational predictions must be validated through experimental methods such as grinding, solvent evaporation, and characterization techniques (e.g., XRD, FTIR).

Computer-based screening has transformed the field of pharmaceutical cocrystal development by offering a faster, cost-effective, and systematic approach to identify suitable coformers. By integrating methods such as crystal structure prediction, molecular docking, and machine learning, computational tools enhance the likelihood of identifying stable and functional cocrystals. Despite its limitations, the synergy between computational and experimental approaches holds great promise for accelerating cocrystal design and development.

2.2 Characterization Techniques

To confirm the formation of cocrystals and eutectic mixtures, the following solid-state characterization techniques were employed (Shekhawat PB, 2022):

1. **Differential Scanning Calorimetry (DSC)**: To study melting behaviour and thermal transitions.
2. **Powder X-ray Diffraction (PXRD)**: To identify changes in crystalline patterns.
3. **Fourier Transform Infrared Spectroscopy (FTIR)**: To analyse molecular interactions between drug and conformers.
4. **Scanning Electron Microscopy (SEM)**: To observe surface morphology and particle size.
5. **Solubility and dissolution studies:** Solubility and dissolution are critical parameters that directly influence the bioavailability of poorly water-soluble drugs. Cocrystallization has emerged as an effective strategy to enhance these properties without altering the pharmacological activity of the active pharmaceutical ingredient (API). Solubility refers to the concentration of a substance that dissolves in a solvent at equilibrium, while dissolution is the process by which a substance goes into solution over time. Cocrystal formulations aim to improve both solubility and dissolution rates by optimizing the solid-state properties of the API (Shekhawat PB, 2022).

Mechanism of Solubility and Dissolution Enhancement

1. **Hydrogen Bonding and Molecular Interactions:**
   - Cocrystals are formed by non-covalent interactions, such as hydrogen bonding and π-π stacking, between the API and a coformer. These interactions modify the crystal lattice energy and intermolecular forces, often leading to enhanced solubility.
2. **Modification of Crystal Packing:**
   - Cocrystals typically possess a more favourable packing arrangement compared to the pure API, reducing the lattice energy and improving solubility.
3. **Improved Surface Area and Wettability:**
   - Some cocrystals exhibit enhanced wettability due to the addition of hydrophilic coformers, leading to improved dissolution rates.
4. **Reduced Hydrophobic Interactions:**
   - Incorporating coformers that are hydrophilic in nature can help overcome the hydrophobicity of poorly soluble APIs, increasing solubility in aqueous environments.

Techniques for Solubility and Dissolution Testing of Cocrystals

1. **Equilibrium Solubility Studies:**
   - This involves suspending excess cocrystals in a solvent (water or buffer solutions) under constant agitation at a specific temperature until equilibrium is reached. The resulting solution is filtered and analyzed using techniques like UV-Vis spectroscopy or high-performance liquid chromatography (HPLC).
   - **Significance:** Compares the solubility of the cocrystal to that of the pure API and physical mixtures.
2. **Intrinsic Dissolution Rate (IDR):**
   - IDR is determined using a rotating disk method, where a compact of the cocrystal is exposed to a solvent under controlled conditions. The rate of dissolution is measured as the mass of API dissolved per unit time and area.
   - **Significance:** Determines the kinetics of cocrystal dissolution.
3. **Supersaturation Studies:**
   - Cocrystals often create a supersaturated solution due to their metastable nature, which enhances drug absorption. Supersaturation profiles are studied over time to evaluate the ability of cocrystals to maintain solubility levels above equilibrium.

4. **Dissolution Testing in Biorelevant Media:**
    - Dissolution studies are performed in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) to mimic in-vivo conditions. This assesses the performance of cocrystals under physiological conditions.
5. **pH-Dependent Solubility Testing:**
    - Since solubility can vary with pH, cocrystals are tested across a range of pH values (1.2–7.5). This is particularly important for weakly acidic or basic drugs.
6. **Solid-State Characterization Before and After Dissolution:**
    - Techniques like powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR) are used to confirm the stability and integrity of the cocrystal structure during dissolution.

Factors Affecting Solubility and Dissolution of Cocrystals

1. **Nature of the Coformer:**
    - The selection of a hydrophilic or hydrophobic coformer influences solubility enhancement. Coformers like *nicotinamide*, *saccharin*, and *maleic acid* are commonly used to improve aqueous solubility.
2. **Cocrystal Stoichiometry:**
    - The ratio of API to coformer affects the crystal structure and, consequently, the solubility behaviour.
3. **Particle Size and Morphology:**
    - Smaller particle sizes provide a larger surface area for dissolution, leading to faster solubility.
4. **Solvent Type and Polarity:**
    - The solubility of cocrystals can vary with the choice of solvent due to differences in polarity and interactions with the solid-state structure.
5. **Polymorphic Transformations:**
    - During dissolution, cocrystals may undergo polymorphic transitions or convert to the parent API, which can affect solubility and dissolution rates.

Applications of Solubility and Dissolution Studies

1. **Formulation Development:**
    - Improved solubility and dissolution profiles enable the development of oral formulations for poorly water-soluble drugs.

2. **Bioavailability Enhancement:**
    - By improving solubility and maintaining supersaturation, cocrystals enhance the in-vivo absorption and therapeutic efficacy of APIs.
3. **Stability Studies:**
    - Solubility testing helps identify conditions under which cocrystals are stable or prone to transformation into less soluble forms.
4. **Drug Screening and Selection:**
    - Solubility and dissolution studies aid in the screening and selection of coformers during the design of pharmaceutical cocrystals.

Solubility and dissolution studies play a critical role in evaluating the performance of cocrystal formulations. By enhancing the solubility and dissolution rates of poorly water-soluble drugs, cocrystals provide a promising approach to improving drug bioavailability. The combination of experimental techniques, such as equilibrium solubility testing, intrinsic dissolution studies, and characterization tools, allows for a comprehensive assessment of cocrystal performance under varying conditions.

6. *In vivo* Studies

In vivo studies play a critical role in evaluating the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of cocrystal formulations. While solubility and dissolution studies assess the performance of cocrystals in vitro, in vivo studies determine how these formulations behave in a biological system. This includes evaluating absorption, bioavailability, therapeutic efficacy, and safety. *In vivo* studies are essential for confirming the advantages of cocrystals over pure APIs or other solid forms, particularly for poorly water-soluble drugs. The time versus plasma concentration profile for many of the crystal forms is to be studied using HPLC (High Performance Liquid Chromatography) and the parameters involved are C_{max}, T_{max}, and AUC.

3. EXPERIMENTAL

Materials used

Pure standard Glipizide was obtained as a gift sample from Ajantapharma Ltd. Mumbai. Commercial tablet of Glipizide formulationwas purchased as research sample from Wockhardt Ltd,Aurangabad. DMF is used as a solvent.

Instrument used

UV-Visible double beam spectrophotometer (Systronics-2201) with1 cm matches quartz cell, electronic balance (SHIMADZU-AY220) and a sonicator (Oscar ultrasonic cleaner Microclean-103) was used in the study.

Preparation of standard stock solution

Standard stock solution of Glipizide (GLP) was prepared bydissolving 10 mg GLP in 10 ml of DMF to obtain concentration of1000µg/ml.

Spectrum measurement of glipizide in DMF

The second stock solution was prepared by diluting 0.5 ml of theabove standard stock solution upto10 ml and scanned between 200-400 nm in UV-Visible double beam spectrophotometer. The UVabsorption spectrum of Glipizide showed peak at 275 nm. Themaximum wavelength of 275 nm was selected for the present study.

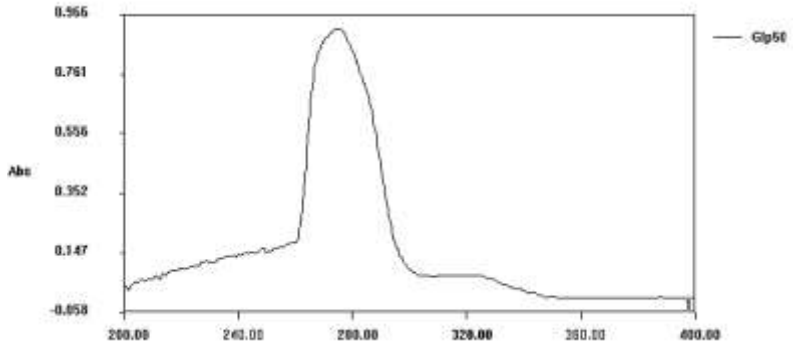

Fig 2: Absorption maxima of Glipizide at 275 nm

Assay

Weigh and powder 20 tablets. Weigh accurately a quantity of thepowder containing 10 mg of glipizide transferred into 10 ml ofvolumetric flask and dissolved in DMF. This solution was sonicated, and the final volume was made up to the mark with DMF. 1 ml ofsolution was transferred into 10 ml volumetric flask and adjust up tothe mark with DMF. The absorbance of this solution measured at275 nm. The result of assay was shown in Table 1.

Method validation

Validation parameter such as Linearity and range, Accuracy,precision, ruggedness, robustness, LOD and LOQ according to ICHQ2(R1) guideline(ICH Guidelines Q2 (R1), 2005).

Linearity

Aliquots of 0.1, 0.2, 0.3, 0.4,0.5 and 0.6 were taken from standardstock solution and the volume made upto10 ml with DMF.Calibration curve was plotted between absorbance versusconcentration (Fig. 3).

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Range

The range of an analytical procedure is an interval between upper andlower concentrations of an analyte in the sample for which it has beenshowed that the analytical procedure has a suitable level of linearity, accuracy, precision. The obtained range of an analyte is 10 to 60 µg/ml.

Accuracy

Accuracy was determined by preparing solution of differentconcentration that is 50%, 100%, 150%. The percentage recoverywas calculated (Table 3).

Table 1: Assay of glipizide tablet

Brand name	Label	claim Assay
Glynase	5 mg	98.5 %

Table 2: Linearity of glipizide

S. No.	Concentration (µg/ml)	Absorbance
1	10	0.144
2	20	0.344
3	30	0.523
4	40	0.693
5	50	0.846
6	60	1.007
Regression equation,y=0.0171x−0.0063		
R^2=09977		

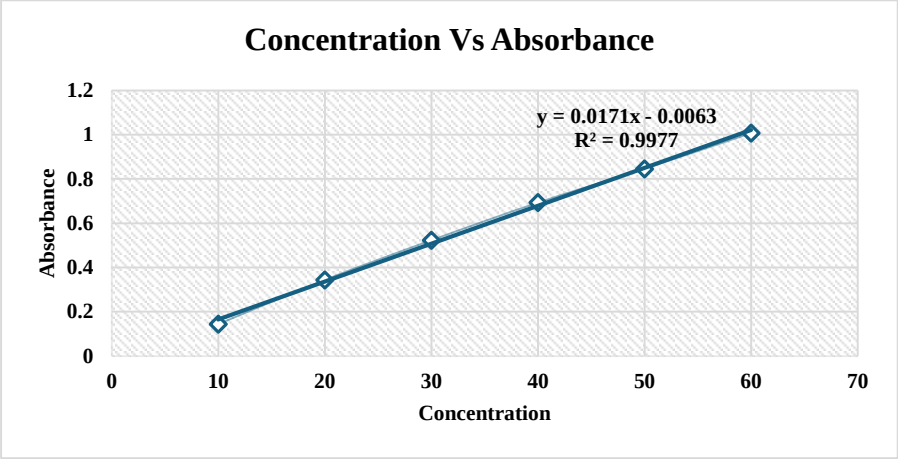

Fig. 3: Calibration curve of glipizide in DMF

Table 3: Result for accuracy

Name of drug	Level of recovery	Concentration (µg/ml)	Amount recovery	Mean % recovery
Glipizide	50%	20	18.73	99.2
	100%	40	38.73	99.6
	150%	60	58.15	98.65

Table 4: Intraday precision data of glipizide

Concentration (µg/ml)	Absorbance
30	0.523
30	0.527
30	0.526
30	0.525
30	0.531
30	0.530
Mean	0.527
SD	0.0030
%RSD	0.58%

This indicates excellent precision since the %RSD is well below 2%.

Table 5: Interday precision data of glipizide

Concentration (µg/ml)	Absorbance
30	0.523
30	0.527
30	0.528
30	0.526
30	0.529
30	0.530
Mean	0.5272
SD	0.0025
%RSD	0.47%

These values indicate high precision, as the %RSD is well below 2%.

Precision

The precision (measurement of intra-day, inter-day) determined by analysing the six samples of same concentration (30 µg/ml) the absorbance was noted. From the measured absorbance result mean, standard deviation and % RSD was calculated.

Ruggedness

Ruggedness of the method was determined by analysing same sample bydifferent analysts (analyst 1 and 2) at different condition and therespective absorbance were noted and result was indicated as %RSD.

Table 6: Result of ruggedness

Concentration (µg/ml)	Absorbance (analyst 1)	Absorbance (analyst 2)
30	0.523	0.521
30	0.519	0.517
30	0.518	0.520
30	0.520	0.521
30	0.517	0.519
30	0.521	0.524
Mean	0.5197	0.5203
SD	0.0022	0.0026
%RSD	0.42%	0.50%

Robustness

Robustness of the method was determined by carrying out theanalysis at two different wavelength (275 and 277) preparing solution 15 µg/ml.

Table 7: Robustness at wavelength 275 nm and 277 nm (conc.15 µg/ml)

Concentration(µg/ml)	Absorbance (275)	Absorbance (277)
15	0.252	0.251
15	0.254	0.253
15	0.253	0.255
15	0.253	0.254
15	0.250	0.252
15	0.253	0.255
Mean	0.2525	0.2533
SD	0.0015	0.0017
%RSD	0.59%	0.67%

Limit of detection (LOD)

The limit of detection (LOD) was determined by using linearity. LOD was calculated by using equation:

LOD= 3.3 δ/s

Where δ is a standard deviation and s is the slope.

Limit of quantification (LOQ)

The limit of quantification is an individual analytical procedure is thelowest amount of analyte in the sample. LOQ was calculated by usingequation-

LOQ= 10 δ/s

Where δ is a standard deviation and s is the slope.

Table 8: LOD and LOQ determination of Glipizide

Drug	LOD(µg/ml)	LOQ (µg/ml)
Glipizide	3.05	9.26

4.RESULTS AND DISCUSSION

The UV scan of standard stock solution 200-400 nm showed theabsorption maxima at 275 nm. The overlay spectra of differentconcentration range of std Glipizide were recorded (Fig 2). Beers-Lambert's law is applicable in the concentration range between 10to 60 µg/ml. The regression equation was found to be Y=0.0171x-0.0063 and correlation coefficient was found to be 0.9977.The %assay of Glipizide tablet was found to be 98.5%.

Validationparameters are developed as per ICH guideline. Accuracy was foundto be 98.65-100% recovery. Precision for intra-day and inter-day of%RSD was found to be 0.58 and 0.47. LOD and LOQ was foundto be 3.05µg/ml and 9.26 µg/ml by using the formula. Ruggednesswas calculated by two different analysts and two differentlaboratories and the % RSD was found to be 0.42 and 0.50.Robustness was calculated by two different wavelength 275 and277and the %RSD was found to be 0.59 and 0.67.

Hence theproposed method was developed in validation parameters and themethod were found to be simple, rapid, accurate and precise for theroutine analysis of glipizide in bulk pharmaceutical dosage form.

5. CONCLUSION

A simple, rapid, and precise UV-visible spectrophotometric method has been developed for the quantification of glipizide in marketed formulations. The method was validated by evaluating various parameters, including linearity, accuracy, precision (both inter-day and intra-day), robustness, ruggedness, as well as the limits of detection (LOD) and quantitation (LOQ). The results demonstrated that the method is accurate, linear, precise, and reliable. Therefore, it can be effectively applied for the routine analysis of glipizide in bulk and pharmaceutical dosage forms.

ACKNOWLEDGEMENT

The authors express their gratitude to the Principal and management of the Faculty of Pharmaceutical Sciences for providing the necessary research facilities to conduct this work.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declare none

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