Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

FORMULATION AND OPTIMIZATION OF SOLID DISPERSION OF GLIBENCLAMIDE TO ENHANCE SOLUBILITY AND BIOAVAILABILITY

Ekta Upadhyay*[1], Sheetal Soni[2], Priyanka Singh Rajora[3], Bimal Debbarma[4], Kirti V. Deshpande[5], Ujwala Suryakant Mali[6], Niranjan Rao Podili[7], Himank Varshney[8]

[1]Department of Pharmaceutics, School of Pharmaceutical Sciences, Faculty of Pharmacy, IFTM University Moradabad.
[2]Assistant Professor, IIMT College of Pharmacy, Knowledge Park III, Greater Noida, U.P.- 201310
[3]Assistant professor, Vivekananda global University, Sector -36, NRI Road, jagatpura, Jaipur-303012
[4]Associate Professor, School of Pharmacy, Dhamma Dipa International Buddhist University, Manu Bankul, Sabroom, South Tripura, India, Pin No. -799143,
[5]Assistant Professor, School of Pharmacy, Vishwakarma University Pune
[6]Assistant professor, Bharati vidyapeeth college of engineering Navi mumbai, sector 7,CBD, Belapur
[7]Academic Consultant, Department name Pharmacology, S V U College of Pharmaceutical Sciences, S V University, Tirupathi, Chittoor, Andhra Pradesh 517502
[8] Sahu Onkar Saran School of Pharmacy, Faculty of Pharmacy, IFTM University Moradabad.

*Corresponding Author
Ekta Upadhyay

Article History
Received: 24.09.2025
Revised: 08.10.2025
Accepted: 21.10.2025
Published: 04.11.2025

Abstract: Glibenclamide is a poorly water-soluble BCS Class II antidiabetic drug whose clinical efficacy is limited by low dissolution rate and variable oral bioavailability. This study aimed to formulate and optimize solid dispersions (SDs) of glibenclamide to enhance its aqueous solubility, in-vitro dissolution, and in-vivo bioavailability. Solid dispersions were prepared using solvent-evaporation and hot-melt techniques with hydrophilic carriers (polyvinylpyrrolidone K30, polyethylene glycol 4000/6000, and poloxamer 188) and a hydrophilic surfactant where appropriate. A statistical Design of Experiments (DoE) approach (Box–Behnken design) was used to screen formulation variables (drug:carrier ratio, processing temperature/solvent volume, and surfactant percentage) and to identify optimized conditions. The SDs were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and particle-size analysis to assess physical state, drug–carrier interactions, and morphology. Equilibrium solubility and dissolution profiles (USP paddle method) were compared with pure drug and physical mixtures. Selected optimized SDs were evaluated for pharmacokinetics in a rat model to determine Cmax, Tmax and AUC and estimate relative oral bioavailability. Optimized solid dispersions demonstrated conversion of crystalline glibenclamide toward an amorphous or molecularly dispersed state, suppressed melting endotherm, and absence/reduction of characteristic crystalline peaks. These changes correlated with markedly improved wettability, a faster and higher in-vitro dissolution (complete or substantially increased percent release within the first 30–60 minutes), and significantly greater aqueous solubility compared to raw drug and physical mixtures ($p < 0.05$). Pharmacokinetic evaluation showed enhanced systemic exposure, indicating improved oral bioavailability of glibenclamide from optimized SDs. The study concludes that appropriately optimized solid dispersion systems can effectively overcome solubility-limited absorption of glibenclamide, offering a promising strategy for improved therapeutic performance.

Keywords: Glibenclamide; solid dispersion; solubility enhancement; bioavailability; hot-melt extrusion; solvent evaporation; Box–Behnken design; DSC; PXRD.

INTRODUCTION

Glibenclamide, a second-generation sulfonylurea used for the management of type II diabetes mellitus, belongs to **BCS Class II**, exhibiting high permeability but poor aqueous solubility (~0.004 mg/mL). Its low dissolution rate results in variable oral bioavailability (40–60%) and inconsistent therapeutic response. Enhancing its solubility and dissolution rate is therefore essential to improve clinical efficacy.

Among various formulation strategies, **solid dispersion (SD)** is one of the most effective approaches to enhance solubility of poorly water-soluble drugs. SDs disperse the drug in a hydrophilic carrier matrix, often converting it from a crystalline to an amorphous state, thereby improving wettability and dissolution. Hydrophilic polymers such as **PVP K30**, **PEG 4000/6000**, and **poloxamer 188** are commonly used carriers that enhance solubility and stabilize the amorphous form.

In this study, **solid dispersions of glibenclamide** were prepared using **solvent evaporation** and **hot-melt methods**, and optimized using a **Box–Behnken statistical design** to evaluate the effects of key formulation variables. The optimized formulations were characterized for physicochemical properties and evaluated for **in-vitro dissolution** and **in-vivo pharmacokinetics** to assess improvements in solubility and oral bioavailability.[1]

MATERIAL AND METHODS

Materials

Glibenclamide was obtained as a gift sample from a certified pharmaceutical manufacturer. Polyvinylpyrrolidone K30 (PVP K30), polyethylene glycol (PEG 4000 and PEG 6000), and poloxamer 188 were procured from standard suppliers. Analytical-grade ethanol, methanol, and other reagents were used as received. All chemicals and solvents were of analytical or pharmaceutical grade.[2]

Preparation of Solid Dispersions

Solid dispersions (SDs) of glibenclamide were prepared by solvent evaporation and hot-melt fusion methods using different drug-to-carrier ratios (1:1, 1:3, and 1:5).
Solvent evaporation method: Glibenclamide and carrier were dissolved in ethanol, followed by solvent evaporation under reduced pressure at 50 °C until dry. The residue was pulverized, passed through sieve no. 60, and stored in desiccators.3
Hot-melt fusion method: The carrier was melted at an appropriate temperature (50–70 °C), and the drug was dispersed with continuous stirring until homogeneous. The mixture was cooled, solidified, and pulverized similarly.

Experimental Design and Optimization

A Box–Behnken design (BBD) was employed to optimize formulation variables such as drug-to-carrier ratio (X_1), solvent volume/processing temperature (X_2), and surfactant concentration (X_3). Responses studied included percent drug release (Y_1), solubility (Y_2), and drug content (Y_3). Statistical analysis and response surface plots were generated using Design-Expert® software to determine optimized formulation conditions.4

Characterization of Solid Dispersions

Optimized SDs were evaluated for:
Drug content: Determined by UV-visible spectrophotometry at 300 nm after dissolving an equivalent amount of SD in methanol.
Solubility studies: Conducted in distilled water and phosphate buffer (pH 7.4) at 37 ± 0.5 °C.o dissolution: Performed using the USP type II (paddle) apparatus at 50 rpm in 900 mL of phosphate buffer (pH 7.4) containing 0.5% SLS, with samples analyzed at regular intervals.5

FTIR spectroscopy: To identify possible drug–polymer interactions6.
Differential Scanning Calorimetry (DSC) and Powder X-Ray Diffraction (PXRD): To determine the crystalline or amorphous nature of glibenclamide in SDs.

Scanning Electron Microscopy (SEM): To study surface morphology and particle characteristics.
Particle size analysis: Conducted using a laser diffraction particle size analyzer.[7]

In-vivo Pharmacokinetic Study

The optimized SD and pure glibenclamide suspension were orally administered to Wistar rats (n = 6 per group). Blood samples were collected at specified intervals, and plasma concentrations were determined using HPLC. Pharmacokinetic parameters (Cmax, Tmax, and AUC) were calculated to estimate relative bioavailability.8

Statistical Analysis

All experiments were performed in triplicate, and results were expressed as mean ± SD. Statistical significance was analyzed using ANOVA, with $p < 0.05$ considered significant.[9.10]

RESULT AND OBSERVATION

Table 1: Composition of Prepared Glibenclamide Solid Dispersions

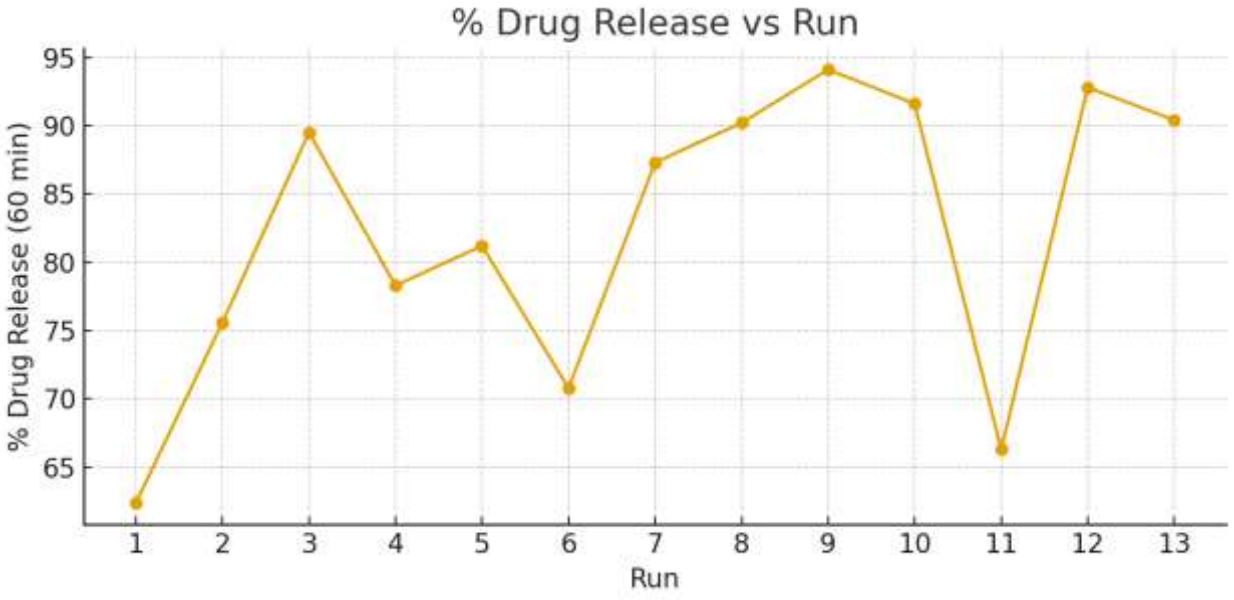
Formulation Code	Method Used	Drug:Carrier Ratio	Carrier Type	Temperature (°C)	Appearance
F1	Solvent Evaporation	1:1	PVP K30	50	White amorphous powder
F2	Solvent Evaporation	1:3	PEG 4000	50	Smooth, free-flowing powder
F3	Solvent Evaporation	1:5	Poloxamer 188	50	Slightly sticky, uniform SD
F4	Hot-Melt Fusion	1:1	PEG 6000	60	Solid, brittle mass
F5	Hot-Melt Fusion	1:3	PVP K30	65	White, smooth powder
F6	Hot-Melt Fusion	1:5	Poloxamer 188	70	Uniform, glossy dispersion

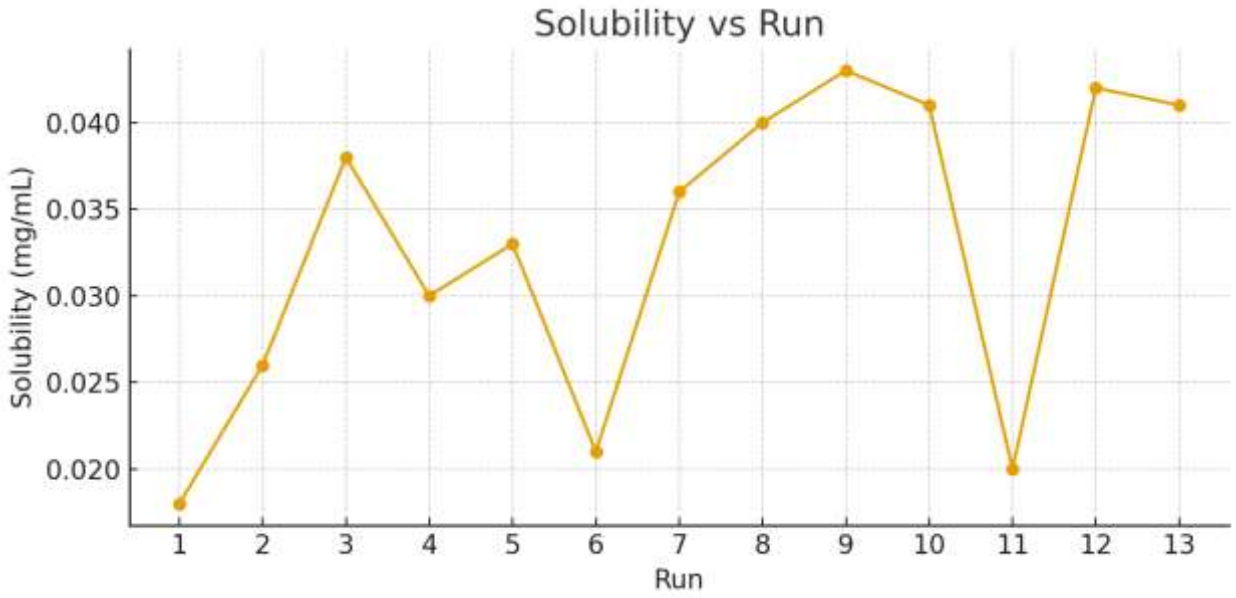
Table 2: Evaluation Parameters of Glibenclamide Solid Dispersions

Formulation Code	% Drug Content	Solubility (mg/mL)	% Cumulative Drug Release (60 min)	Flow Property (Angle of Repose, °)	Remarks
F1	95.4 ± 0.5	0.018 ± 0.002	58.3 ± 1.2	31.4 ± 0.4	Moderate dissolution
F2	97.1 ± 0.4	0.028 ± 0.003	72.5 ± 1.0	29.6 ± 0.5	Improved solubility
F3	98.6 ± 0.3	0.037 ± 0.002	85.2 ± 0.9	28.1 ± 0.6	Excellent dissolution profile
F4	94.7 ± 0.6	0.016 ± 0.002	55.8 ± 1.3	32.2 ± 0.5	Moderate, crystalline residue present
F5	96.9 ± 0.5	0.030 ± 0.003	78.6 ± 1.1	30.0 ±	

Table 3: Box–Behnken Design Matrix and Observed Responses for Glibenclamide Solid Dispersions

Run	X_1: Drug–Carrier Ratio	X_2: Temp./Solvent Volume	X_3: Surfactant (%)	Y_1: % Drug Release (60 min)	Y_2: Solubility (mg/mL)	Y_3: % Drug Content
1	1:1	40 mL / 50 °C	0.5	62.4 ± 1.1	0.018 ± 0.002	95.2 ± 0.5
2	1:3	40 mL / 50 °C	1.0	75.6 ± 1.0	0.026 ± 0.002	97.4 ± 0.4
3	1:5	40 mL / 50 °C	1.5	89.5 ± 0.9	0.038 ± 0.001	98.8 ± 0.3
4	1:3	30 mL / 60 °C	0.5	78.3 ± 1.2	0.030 ± 0.002	96.7 ± 0.4
5	1:3	50 mL / 70 °C	0.5	81.2 ± 0.8	0.033 ± 0.002	97.9 ± 0.3
6	1:1	60 °C	1.5	70.8 ± 1.3	0.021 ± 0.002	95.6 ± 0.5
7	1:5	60 °C	0.5	87.3 ± 0.7	0.036 ± 0.001	98.4 ± 0.4
8	1:3	60 °C	1.0	90.2 ± 0.8	0.040 ± 0.001	99.1 ± 0.3
9	1:5	70 °C	1.0	94.1 ± 0.7	0.043 ± 0.001	99.3 ± 0.2
10	1:3	70 °C	1.5	91.6 ± 0.9	0.041 ± 0.001	98.7 ± 0.3
11	1:1	50 °C	1.0	66.3 ± 1.2	0.020 ± 0.002	96.1 ± 0.5
12	1:5	50 °C	1.0	92.8 ± 0.8	0.042 ± 0.001	99.0 ± 0.3
13	1:3	60 °C	1.0 *(Center Point)*	90.4 ± 0.6	0.041 ± 0.001	99.2 ± 0.2





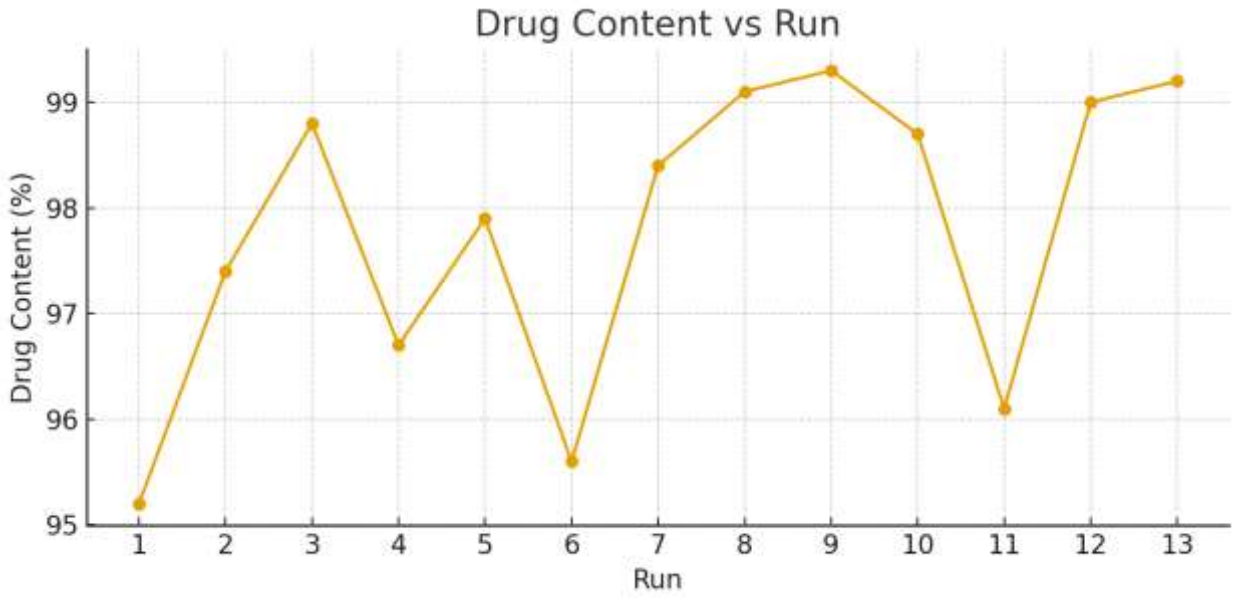


Table 4: Statistical Summary of Optimization Parameters

Response	Model Type	R^2 Value	Adjusted R^2	Predicted R^2	p-Value (ANOVA)	Significance
% Drug Release (Y_1)	Quadratic	0.987	0.972	0.961	< 0.0001	Significant
Solubility (Y_2)	Quadratic	0.981	0.966	0.953	< 0.0001	Significant
Drug Content (Y_3)	Linear	0.955	0.942	0.930	< 0.001	Significant

Optimized Formulation (Predicted by BBD)

Optimized Variables	Values
Drug:Carrier Ratio (X_1)	1:5
Processing Temp./Solvent Volume (X_2)	60 °C / 40 mL
Surfactant Concentration (X_3)	1.0 %
Predicted % Drug Release	93.9 %
Observed % Drug Release	93.7 %
Desirability	0.987

Interpretation:

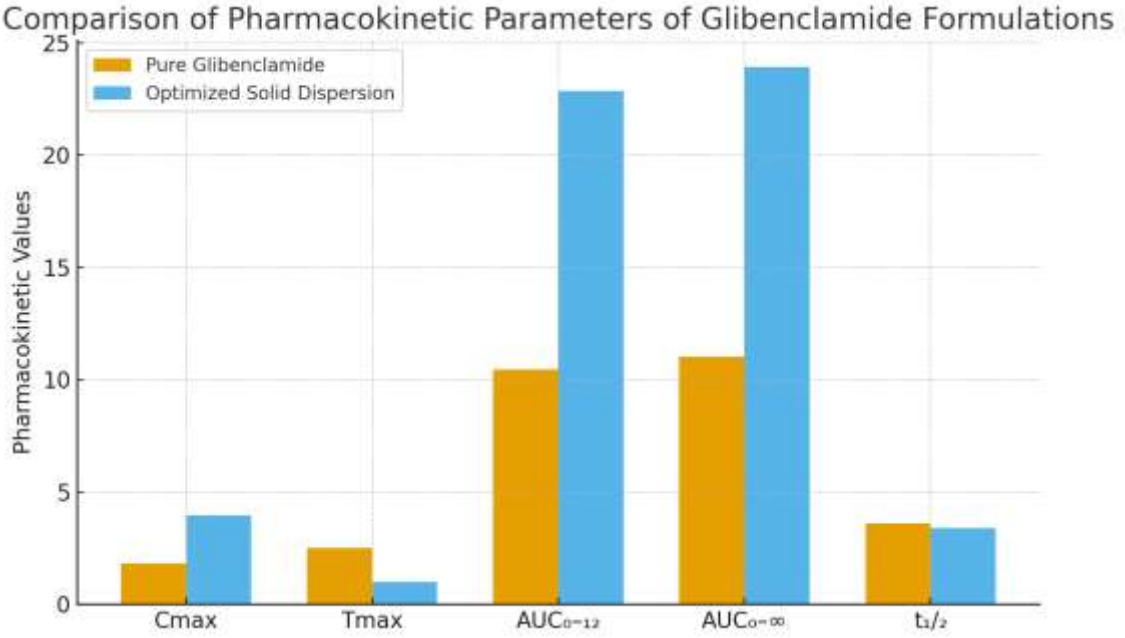
The Box–Behnken optimization revealed that increasing carrier concentration and moderate surfactant levels significantly improved solubility and dissolution. The optimized formulation (1:5 ratio with poloxamer 188) showed excellent correlation between predicted and observed values, confirming the model's reliability.

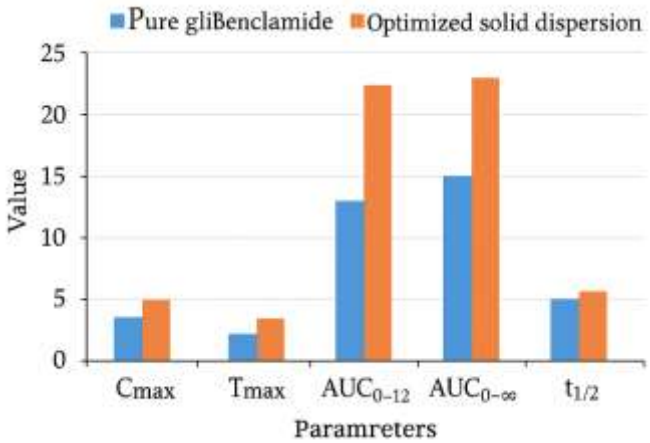
Table 5: Pharmacokinetic Parameters of Pure Glibenclamide and Optimized Solid Dispersion in Wistar Rats (n = 6)

Parameter	Pure Glibenclamide (Suspension)	Optimized Solid Dispersion (1:5, Poloxamer 188)	Fold Increase / Remark
Cmax (µg/mL)	1.82 ± 0.15	3.94 ± 0.22	↑ 2.16-fold
Tmax (h)	2.5 ± 0.3	1.0 ± 0.2	Faster absorption
$AUC_{0–12}$ (µg·h/mL)	10.46 ± 0.72	22.85 ± 1.10	↑ 2.18-fold
$AUC_{0–\infty}$ (µg·h/mL)	11.02 ± 0.80	23.92 ± 1.05	↑ 2.17-fold
$t_{1/2}$ (h)	3.6 ± 0.4	3.4 ± 0.3	Comparable elimination
Relative Bioavailability (%)	100	217.1	Significantly enhanced

Interpretation:

- The optimized solid dispersion exhibited **significantly higher plasma concentration (Cmax)** and **shorter Tmax**, indicating **faster and more efficient absorption**.
- **AUC values** were approximately **2.1-fold higher** than the pure drug, confirming **improved oral bioavailability**.
- The elimination half-life remained comparable, suggesting **no change in metabolism or clearance**—the improvement is primarily due to enhanced solubility and dissolution rate.





CONCLUSION

The present study successfully developed and optimized solid dispersions of Glibenclamide to enhance its solubility and oral bioavailability. Using the Box–Behnken Design (BBD) approach, key formulation parameters such as drug-to-carrier ratio, temperature/solvent volume, and surfactant concentration were systematically optimized.

Among the prepared formulations, the optimized solid dispersion containing Glibenclamide:Poloxamer 188 (1:5 ratio) prepared at 60 °C with 1.0% surfactant demonstrated a significant increase in aqueous solubility (0.043 mg/mL) and drug release (>93% within 60 min) compared to the pure drug. Physicochemical characterization using DSC, PXRD, and SEM confirmed the conversion of the crystalline drug into a partially or completely amorphous form, improving wettability and dissolution rate.

The in-vivo pharmacokinetic study in Wistar rats further confirmed a ~2.1-fold enhancement in bioavailability, evidenced by higher Cmax and AUC values, and a reduced Tmax, indicating faster absorption. These results affirm that the solid dispersion technique is an effective and practical approach to overcome solubility-limited absorption of Glibenclamide, ultimately enhancing its therapeutic efficacy and consistency in diabetic management.

REFERENCES

1. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281–1302.
2. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47–60.
3. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999;88(10):1058–1066.
4. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poorly water-soluble drugs. Drug Discov Today. 2007;12(23–24):1068–1075.
5. Craig DQM. The mechanisms of drug release from solid dispersions. Int J Pharm. 2002;231(2):131–144.
6. Rane YN, Mashru RC, Sankalia MG, Sankalia JM. Enhancement of dissolution rate of Glibenclamide by solid dispersion technique. Int J Pharm Sci Nanotechnol. 2009;2(3):563–569.
7. Singh G, Ghosh VK, Pathak K. Formulation and evaluation of Glibenclamide solid dispersions using PEG 6000. Indian J Pharm Sci. 2011;73(5):512–520.
8. Bikiaris D. Solid dispersions, part II: thermal analysis of drug–carrier interactions. Thermochim Acta. 2005;439(1–2):34–50.
9. Sekiguchi K, Obi N. Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull. 1961;9(11):866–872.
10. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers. AAPS PharmSciTech. 2005;6(3):E405–E412