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Original Article

Dissolution enhancement of glimepiride via refined liquisolid system for bioequivalent tablet

[Mejora de la disolución de glimepirida mediante un sistema liquisólido refinado para comprimidos bioequivalentes]

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Abstract

Context: Glimepiride is a widely used treatment for type II diabetes mellitus and is classified as a Class II drug in the Biopharmaceutical Classification System. Class II drugs are characterized by high gastrointestinal permeability but low solubility, which can limit their bioavailability. To overcome solubility challenges and achieve bioequivalence with the innovator brand, various methods, including the liquisolid system, have been recommended.

Aims: To evaluate the characteristics of refined liquisolid system-formulated tablets of glimepiride and compare their drug release profiles to the innovator brand.

Methods: A total of twelve formulations were prepared by dispersing glimepiride in a non-volatile solvent, followed by adsorption onto Avicel PH 102 or Neusilin as suitable adsorbents for direct compression. The tablets were assessed for weight uniformity, drug content, hardness, friability, and disintegration time. The dissolution profiles were compared to those of the innovator brand and pure drug. The drug particles in the liquisolid system were further characterized using X-ray diffraction, differential thermal analysis, Fourier-transform infrared spectroscopy, and scanning electron microscopy.

Results: All formulations demonstrated average drug content within the range of 90.0–110.0%, with *in vitro* dissolution rates exceeding 80% within 30 minutes, a rate notably faster than that of the pure drugs. Additionally, some formulations exhibited dissolution profiles similar to those of the innovator brand. The analyses revealed that drug particles were effectively solubilized or dispersed within the adsorbent matrix.

Conclusions: The liquisolid system offers a promising alternative for developing bioequivalent generic glimepiride tablets in the pharmaceutical industry.

Keywords: antidiabetic; direct compression; particle characterization; tablet formulation.

Resumen

Contexto: La glimepirida es un tratamiento ampliamente utilizado para la diabetes mellitus tipo II y está clasificada como un fármaco de Clase II en el Sistema de Clasificación Biofarmacéutica. Los fármacos de Clase II se caracterizan por una alta permeabilidad gastrointestinal pero una baja solubilidad, lo que puede limitar su biodisponibilidad. Para superar los desafíos de solubilidad y lograr la bioequivalencia con la marca innovadora, se han recomendado varios métodos, incluido el sistema liquisolido.

Objetivos: Evaluar las características de los comprimidos de glimepirida formulados con un sistema liquisolido refinado y comparar sus perfiles de liberación del fármaco con los de la marca innovadora.

Métodos: Se prepararon un total de doce formulaciones dispersando glimepirida en un disolvente no volátil, seguido de adsorción en Avicel PH 102 o Neusilin como adsorbentes adecuados para la compresión directa. Se evaluó la uniformidad del peso, el contenido de fármaco, la dureza, la friabilidad y el tiempo de desintegración de los comprimidos. Los perfiles de disolución se compararon con los de la marca innovadora y el fármaco puro. Las partículas del fármaco en el sistema liquisolid se caracterizaron aún más mediante difracción de rayos X, análisis térmico diferencial, espectroscopia infrarroja por transformada de Fourier y microscopía electrónica de barrido.

Resultados: Todas las formulaciones demostraron un contenido de fármaco promedio dentro del rango de 90,0-110,0%, con tasas de disolución *in vitro* superiores al 80% en 30 minutos, una tasa notablemente más rápida que la de los fármacos puros. Además, algunas formulaciones exhibieron perfiles de disolución similares a la marca innovadora. Los análisis revelaron que las partículas del fármaco se solubilizaron o dispersaron de manera efectiva dentro de la matriz adsorbente.

Conclusiones: El sistema liquisolid ofrece una alternativa prometedora para desarrollar comprimidos de glimepirida genéricos bioequivalentes en la industria farmacéutica.

Palabras Clave: antidiabético; compresión directa; caracterización de partículas; formulación de comprimidos.

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INTRODUCTION

Glimepiride, chemically named 1-(p-(2-(3-ethylene-4-methyl-2-oxo-3-pyrroline-1-carboxamide) ethyl) phenyl) sulfonyl)-3-(trans-4-methyl cyclohexyl) urea, is a third-generation sulfonylurea widely used for the treatment of type II diabetes mellitus (Basit et al., 2012). Classified as a Class II drug in the Biopharmaceutical Classification System (BCS), it has a molecular formula of $C_4H_{34}N_4O_5S$ (Fig. 1) and a molecular weight of approximately 490.617 g/mol (Tiwari et al., 2016). Studies indicate that glimepiride is insoluble in water and acidic media but is soluble in dimethyl sulfoxide (DMSO), with slight solubility in various buffers and organic solvents (e.g., dichloromethane) and very limited solubility in methanol. In the gastrointestinal tract, glimepiride exhibits low solubility but high permeability (Abou-Taleb et al., 2020). Research shows its solubility is pH-dependent, with solubility below 0.004 mg/mL at low pH, increasing to 0.02 mg/mL in media with pH above 7 at 37°C (Kinani and Taghi, 2022). Although the daily dose ranges from 1 to 8 mg (Abou-Taleb et al., 2020), its low solubility in the gastrointestinal environment challenges its dissolution and can lead to variable bioavailability.

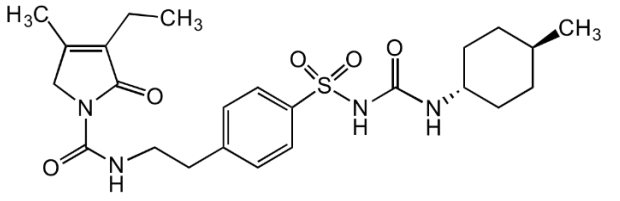

Figure 1. Chemical structure of glimepiride.

Recent studies have identified and explored two polymorphs of glimepiride with documented crystal structures. Form II has shown higher solubility in pH 7.0–7.8 media than form I, and form II tablets released almost twice as many drugs at the same time point in dissolution testing. Both (forms I and II tablets) contain the same excipients as the reference product (Viana et al., 2018). Polymorphism presents challenges for solid dosage forms, especially during storage, because different solid forms can exhibit unique physicochemical properties, affecting in vivo release and therapeutic impact. This phenomenon can complicate the manufacturing and consistency of generic drug formulations.

Dissolution profiles of available generic glimepiride tablets often vary, influencing clinical outcomes. Clinical studies in Egypt, for instance, found that none of the four generic brands matched the efficacy of the innovator product (Abou-Taleb et al., 2020). Similar findings from the Middle East indicate that generics cannot be used interchangeably with the innovator due to these differences. However, recently developed formulations of glimepiride tablets have demonstrated stability and quality comparable to the innovator (Usman et al., 2021), underscoring the need for rigorous screening of market-available products to strengthen healthcare systems. This demand drives the pharmaceutical industry to design tablet formulations that are bioequivalent and interchangeable in clinical practice.

To improve glimepiride's dissolution and bioavailability, various techniques have been employed, including solid dispersions (Joshi et al., 2022; Sakure et al., 2020; Wagh et al., 2012), co-crystals (Jaafar and Radhi, 2020), self-nanoemulsion drug delivery systems (SNEDDS), and other nanosystems (Ahmed et al., 2022a; 2022b; Gaber et al., 2022; Li et al., 2016; Reddy et al., 2019). Additional methods include gel-based tablets (Awadeen et al., 2019), niosomal encapsulation (Mohsen et al., 2017), orodispersible tablets (Kinani and Taghi, 2022), and the liquisolid (LS) system (Singh et al., 2011). Tzankov et al. (2017) demonstrated that glimepiride tablets produced via wet granulation in a fluidized bed exhibited dissolution profiles similar to the reference drug, whereas direct compression or granulation-tableting techniques produced less satisfactory results.

Among the various methods, the LS system shows particular promise for enhancing the dissolution of poorly soluble drugs. This technique involves dissolving or dispersing active pharmaceutical ingredients in non-volatile solvents to form a liquid or suspension, which is then converted into a free-flowing, non-adherent, and easily compressible powder by the addition of carrier and coating or adsorbent materials (Kumar and Sai, 2019). The LS method is a cost-effective approach for large-scale production as it eliminates the need for high-energy heating or volatile organic solvents (Yadav and Yadav, 2009).

Singh et al. (2011) developed a conventional LS system for glimepiride using propylene glycol as the solvent, achieving a glimepiride solubility of 19.46 ± 0.05 µg/mL, higher than with other non-volatile solvents. The formula that successfully enhanced glimepiride dissolution included additional PVP in the liquid medication (at twice the amount of the active substance) and used microcrystalline cellulose and Aerosil as carrier and coating materials. In contrast, Dhall et al. (2019) implemented a refined liquisolid system (RLS) for glimepiride using DMSO as the solvent and Aerosil as the adsorbent. This RLS approach achieved greater dissolution of glimepiride than conventional solid dispersion systems with PVP

or surface solid dispersion systems with Aerosil. The RLS method is an advanced version of the LS system, where the solid drug is dispersed in a non-volatile solvent and adsorbed onto an adsorbent material, followed by thorough blending for uniformity. Unlike the LS system, the RLS method does not require a coating material, making it a simpler and more efficient technique.

In this study, glimepiride form I (the stable form) was used, along with propylene glycol or DMSO as the non-volatile solvent, and microcrystalline cellulose (Avicel PH 102) or Neusilin as alternative adsorbents, without coatings or additional excipients. Neusilin, known for its large surface area and high porosity, offers high adsorption capacity, which has been effective in keeping the drug in a liquid state to enhance dissolution (Vraníková et al., 2015a; 2015b). This research was thus aimed at enhancing the dissolution and bioavailability of glimepiride tablets through the RLS method.

MATERIAL AND METHODS

Materials and chemicals

The active pharmaceutical ingredient, micronized glimepiride, was provided by PT. Phapros Tbk., Indonesia. The glimepiride working standard (from Sigma Aldrich) was sourced locally, along with other materials such as propylene glycol, dimethyl sulfoxide (DMSO), microcrystalline cellulose (Avicel PH 102), sodium starch glycolate, and magnesium stearate (supplied by Bratachem, Indonesia). Neusilin US2 was sourced from Fuji Chemical Co., Japan, through a local supplier. The reference brand for glimepiride, Amaryl 4 mg, was purchased from a local pharmacy. Analytical-grade reagents and solvents, including NaOH and KH_2PO_4, were obtained from Merck.

Preparation of liquisolid tablets

The LS method developed by Spireas and Bolton (2002) was used to determine the adsorbent and solvent quantities needed for formulations containing 4 mg of glimepiride (as shown in Table 1). Each formulation included 5% (w/w) of sodium starch glycolate as a disintegrant and 1% (w/w) magnesium stearate as a lubricant (Windriyati et al., 2020). Glimepiride was dispersed in a non-volatile solvent, adsorbed onto a carrier to form a dry powder, sieved across #60, and then stored in a desiccator for further processing (Dhall et al., 2019).

Prior to compression, the flow properties of the powder were assessed, including the angle of repose, bulk density, and tapped density, which were used to calculate the Hausner ratio and compressibility index. The disintegrant and lubricant were then added and mixed thoroughly for 10 minutes. Finally, the prepared mixture was compressed using a single-punch tablet press to achieve tablets with a hardness of 40–60 N (Singh et al., 2011).

Table 1. Design formula for preparing glimepiride tablet by refined liquisolid system.

Code	Drug-adsorbent ratio	GMP (mg)	Adsorbent (mg)		Lf[*a]	Solvent (mg)		SSG[*b] (mg)	Mg stearate[*c] (mg)	Tablet Weight (mg)
			Avicel PH 102	Neusilin US2		PG	DMSO			
F1	1:30	4	120		0.425	51		8.75	1.75	185.50
F2	1:40	4	160		0.425	68		11.6	2.32	245.92
F3	1:50	4	200		0.425	85		14.45	2.89	306.34
F4	1:30	4		120	0.25	30		7.7	1.54	163.24
F5	1:40	4		160	0.25	40		10.2	2.04	216.24
F6	1:50	4		200	0.25	50		12.7	2.54	269.24
F7	1:30	4	120		0.425		51	8.75	1.75	185.50
F8	1:40	4	160		0.425		68	11.6	2.32	245.92
F9	1:50	4	200		0.425		85	14.45	2.89	306.34
F10	1:30	4		120	0.25		30	7.7	1.54	163.24
F11	1:40	4		160	0.25		40	10.2	2.04	216.24
F12	1:50	4		200	0.25		50	12.7	2.54	269.24

[*a] Liquid load factor, flowable liquid retention potential of adsorbent at 33°. [*b] 5% w/w of the sodium starch glycolate (SSG) as disintegrant. [*c] 1% w/w of the magnesium stearate as lubricant.

Tablets evaluation

Weight variation

Twenty tablets from each formula were randomly selected and weighed individually on an analytical balance, and the average weight and standard deviation were calculated. USP guidelines specify that no more than two tablets should deviate beyond the allowed limits, with none exceedingly twice those limits (USP, 2018).

Drugs content

The test was carried out using a spectrophotometric method, with validation performed in accordance with ICH guidelines. A phosphate buffer solution at pH 7.8, prepared as per USP (2018) guidelines and commonly used as a dissolution medium, was utilized as the solvent for the assay. The maximum absorbance was observed at a wavelength of 228.5 nm. The method demonstrated a linear concentration range of 4–16 µg/mL, a drug recovery rate of 99.78 ± 0.82%, and a relative standard deviation (RSD%) within acceptable limits (<2%). The limits of detection and quantification were determined to be 0.897 µg/mL and 2.72 µg/mL, respectively.

Ten tablets from each formulation were crushed and dissolved in 10 mL of methanol, then diluted with phosphate buffer (pH 7.8) and filtered through a 0.45 µm membrane to a final volume of 100 mL. The solution was sonicated for 15 minutes, and the drug concentration was measured using a Shimadzu UV-1800 spectrophotometer at a wavelength of 228.5 nm (Dhall et al., 2019; USP, 2018). The percent content uniformity of each tablet was calculated and compared to the mean value for each formulation, as specified by USP guidelines (USP, 2018).

Hardness and friability

The hardness of the formulated tablets was evaluated using a YD-1 hardness tester. The mean hardness of six tablets ± standard deviation (SD) was recorded, with hardness expressed as the force (kg/cm²) required to crush the tablets.

Friability testing was performed using a CS-2 friabilator. Twenty tablets from each formulation were accurately weighed (initial weight) and then rotated in the friabilator for 4 minutes at 25 rpm. Afterward, the tablets were re-weighed (final weight). Friability was calculated as the percentage of weight loss, with an acceptable value of up to 1%, as specified by USP guidelines (USP, 2018).

Disintegration time

In vitro disintegration studies were conducted using a tablet disintegration test apparatus (BJ 2, China). One tablet was placed in each of the six tubes of the basket assembly, with a disk added to each tube. The assembly was then submerged in a one-liter beaker containing 0.1N HCl (pH 1.2), maintained at a temperature of 37 ± 2°C. The basket was moved up and down through a distance of 5–6 cm at a frequency of 32 cycles per minute. The time required for the complete disintegration of each tablet was recorded. Disintegration time testing for uncoated tablets was performed in triplicate, with a target time of less than 15 minutes, as per USP guidelines (USP, 2018).

In vitro dissolution

Dissolution tests on six RLS tablets and the reference brand followed USP immediate-release standards (USP, 2018) in a type II apparatus (Electrolab TDT-08L) at 75 rpm in 500 mL phosphate buffer (pH 7.8) maintained at 37 ± 0.5°C. Aliquots of 5 mL samples were collected at 5, 10, 15, 20, and 30 minutes, filtered (0.45 µm), and analyzed spectrophotometrically at 228.5 nm. Dissolution outcomes were expressed as Q_{30} for comparison with the pure drug. The dissolution profiles of RLS tablets and the reference brand were compared using the similarity factor (f_2), calculated with the following equation [1].

$$f_2 = 50 \cdot log\left\{100 \cdot \left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}\right\} \quad [1]$$

Where *n*: the number of time points at which the percentage of drug dissolved was measured; *Rt*: the percentage of drug dissolved from reference formulation at a given time point; and *Tt*: the percentage dissolved from the test formulation at the same time point.

The similarity factor ranges from 0 to 100, with a value of 100 indicating identical dissolution profiles between the test and reference products, while lower values reflect increasing dissimilarity. A similarity factor (f_2) above 50 suggests that the two profiles are comparable (FDA, 2023; Muselik et al., 2021).

Particle characterization

Scanning electron microscopy (SEM)

Surface morphology was observed with SEM. Samples were mounted on aluminum stubs with double-sided carbon adhesive and platinum-coated (JEOL JEC-3000FC Auto Fine Coater). Imaging was done using a JEOL JSM-6510LA at 10 kV (Ahmed et al., 2020a).

X-ray powder diffraction (XRD)

RLS tablets were characterized with XRD by crushing them, loading them into a sample holder, and scanning them with a Bruker AXS D8 Advance Eco over a 2θ range of 10–80° (Jaafar and Radhi, 2020).

Fourier Transform Infra-red (FTIR) spectroscopy

FTIR spectra for RLS tablets, adsorbents, and pure glimepiride were obtained with a Perkin Elmer UATR Spectrum two across 4000–400 cm^{-1} using the KBr pellet technique (Dhall et al., 2019).

Differential Thermal Analysis (DTA)

DTA thermograms were recorded with a TG-DTA-DSC instrument (NEXTA STA Hitachi STA200RV), heated at 10°C/min from 30 to 400°C under nitrogen at 100 mL/min (Jaafar and Radhi, 2020; Singh et al., 2011).

Statistical analysis

All data were presented as mean ± standard deviation across at least three independent experiments. Statistical analysis was conducted on dissolution data, Q_{30} using ANOVA or Tukey's multiple comparison test, with significance set at $p<0.05$.

RESULTS AND DISCUSSION

Liquisolid compact

The flow properties of glimepiride RLS powder, including flow rate, angle of repose, and compressibility index, were within acceptable limits, indicating satisfactory flowability (data not shown). The RLS formulation was prepared using non-volatile solvents—propylene glycol or DMSO—due to the solubility of glimepiride in both. Avicel PH 102 and Neusilin were selected as adsorbents for their capacity to absorb the solvent while maintaining good flowability. According to mathematical models developed by Spireas and Bolton (2002); both adsorbents could effectively form liquisolid powder, facilitating conversion into a liquisolid dosage form.

The glimepiride RLS tablet characteristics, including weight uniformity, hardness, friability, disintegration time, and drug content, are summarized in Table 2. The tablet weight remained consistent, owing to a uniform powder blend in the RLS tablet formulation. All tablets displayed hardness within the 4-5 kg/cm^2 range with no broken or deformed samples; however, some formulations exhibited friability exceeding 1%. Based on standard hardness and friability metrics, the formulations are expected to demonstrate sufficient toughness to withstand handling, packaging, and transport. Additionally, the disintegration time of these formulations was below 15 min (6-15 min), which supported a rapid release rate, meeting the disintegration requirements for uncoated tablets. All RLS tablets produced contained glimepiride within 99–101%, adhering to the USP compendial specifications of 90.0–110.0% for 4 mg tablets, thus ensuring uniform drug content across tablets. This weight and content uniformity confirmed that the preparation process was consistent and reliable.

Table 2. Characteristic of glimepiride liquisolid tablet.

Code	Weight variation (mg)	Hardness (kgf)	Friability (%)	Disintegration time (min)	Drug content (%)
F1	180.38 ± 6.83	5.80 ± 0.37	0.31 ± 0.12	6.66 ± 0.05	100.69 ± 1.07
F2	245.91 ± 5.39	4.95 ± 0.83	0.55 ± 0.22	6.33 ± 0.07	99.76 ± 1.61
F3	305.25 ± 9.64	4.01 ± 1.45	0.77 ± 0.19	6.73 ± 0.03	100.95 ± 0.84
F4	163.57 ± 7.28	5.40 ± 0.61	0.99 ± 0.16	15.58 ± 0.31	100.61 ± 1.08
F5	214.51 ± 6.28	5.51 ± 0.76	0.91 ± 0.16	14.04 ± 0.04	100.58 ± 0.51
F6	270.81 ± 3.83	5.31 ± 1.10	0.96 ± 0.11	12.85 ± 0.29	100.14 ± 0.31
F7	182.18 ± 5.25	4.71 ± 0.46	0.62 ± 0.06	5.66 ± 0.47	101.52 ± 2.82
F8	248.21 ± 6.13	5.64 ± 0.55	1.81 ± 0.45	6.96 ± 0.23	100.51 ± 1.34
F9	306.15 ± 8.19	5.70 ± 1.23	1.75 ± 0.26	7.88 ± 0.25	101.69 ± 1.56
F10	162.37 ± 7.81	5.18 ± 0.90	1.87 ± 0.13	15.59 ± 0.43	101.19 ± 1.03
F11	212.71 ± 6.21	6.31 ± 0.54	2.71 ± 0.11	14.67 ± 0.30	101.95 ± 0.62
F12	268.51 ± 4.92	5.75 ± 1.28	2.93 ± 0.36	8.99 ± 0.38	101.39 ± 0.92

Data represent mean ± standard deviation, n = 20 for weight, n=6 for hardness, n = 3 for friability, n = 3 for disintegration time, n = 10 for assay of drug content. No statistical analysis was performed, as the value analysis was based on the criteria outlined in the USP (2018).

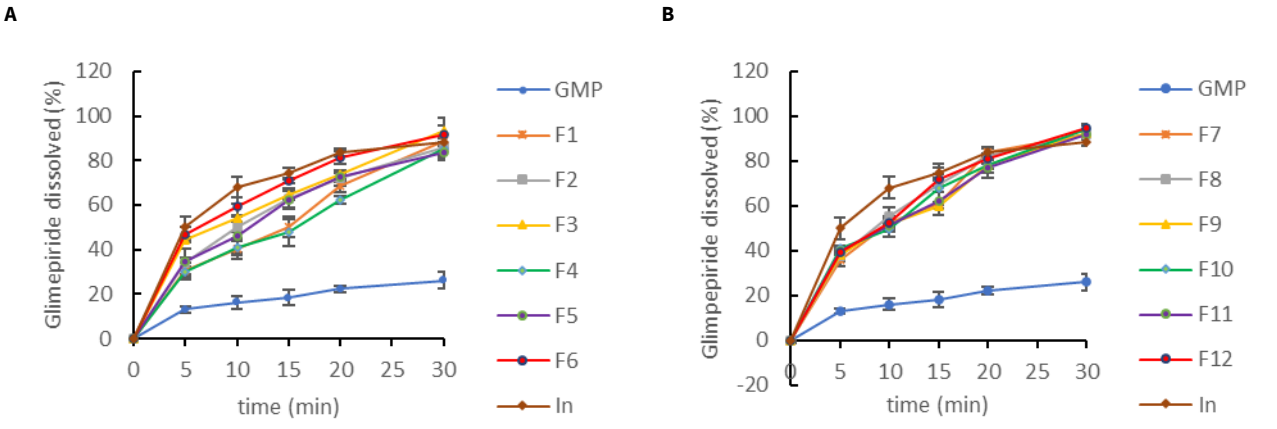

Figure 2. Dissolution profile of glimepiride in phosphate buffer pH 7.8.

(A) RLS tablets F1-F6, innovator brand Amaryl (In), and pure drug (GMP); **(B)** RLS tablets F7-F12, innovator brand Amaryl (In), and pure drug (GMP). Data points are the mean percentage of the amount dissolved at each sampling time with corresponding standard deviation (n = 3).

The tablet characterization data indicated that all parameters fell within acceptable limits. This outcome resulted from the optimized direct compression method and the use of materials with suitable compressibility and compatibility. The adsorbents, which are the main ingredients in the formulation of RLS tablets, namely Avicel PH 102 and Neusilin, are recognized for their favorable tablet-forming properties. Additionally, the inclusion of sodium starch glycolate as a disintegrant facilitated the rapid disintegration of the liquisolid tablets. Magnesium stearate, serving as a glidant and lubricant, contributed to the tablets' relatively low friability. However, RLS tablets with Neusilin adsorbent exhibited higher friability and longer disintegration times, likely due to its lower water absorption capacity and limited compatibility with starch-based disintegrants. When Neusilin is used as an adsorbent in the liquisolid technique, croscarmellose sodium is recommended as a more effective disintegrant for rapid disintegration (Anoname, 2023; Shete et al., 2019). Beyond adsorbent properties, such as surface area and liquid absorption capacity, compatibility with the disintegrant proved to be a critical factor in the successful formulation of liquisolid tablets (Kumar and Sai, 2019).

Dissolution studies

Glimepiride tablets were dissolved in a phosphate buffer at pH 7.8, following the USP monograph (USP, 2018). This medium was chosen due to the higher solubility of glimepiride at this pH compared to lower pH levels. The dissolution profiles of the pure drug, the RLS tablets, and the innovator brand are shown in Fig. 2. At 30 min (Q_{30}), the drug release exceeded 80% for all RLS formulations and the innovator brand, meeting USP monograph standards, whereas the pure drug showed only 26% release. No significant difference was observed in the Q_{30} parameters ($p>0.05$) between the RLS formulations and the innovator tablet. While all RLS tablets met the target dissolution criteria, their dissolution profiles at each sampling time differed from those of the innovator brand. Notably, only two RLS formulations containing propylene glycol (F3 and F6) exhibited dissolution profiles comparable to the innovator tablet, with similarity factor (f_2) values exceeding 50. In contrast, all formulations containing DMSO demonstrated dissolution profiles comparable to the innovator tablet. The dissolution of glimepiride from RLS tablets using propylene glycol as a non-volatile solvent was less effective in achieving the same dissolution level as the innovator tablet compared to formulations using DMSO. This difference can be attributed to the significantly higher solubility of glimepiride in DMSO (11 mg/mL) compared to propylene glycol (19 µg/mL) (Reddy et al., 2019; Singh et al., 2011). Achieving a dissolution comparable to that of the innovator with propylene glycol required a considerably higher amount of solvent, as seen in formulations F3 and F6.

However, dissolution testing at pH 7.8, as outlined in the USP monograph, did not fully demonstrate product equivalence with the innovator. Therefore, a comparative dissolution study using FDA-recommended gastrointestinal media at pH values of 1.2, 4.5, and 6.8 is needed to establish equivalence. The dissolution test results in this study served as a preliminary screening to select candidate formulations for further comparative dissolution testing and *in vivo* bioequivalence assessments aimed at developing bioequivalent tablets.

These findings are consistent with those of Dhall et al. (2019), who developed an RLS of glimepiride using DMSO as a solvent and Aerosil as an adsorbent. In RLS tablets, the character of the drug particles available for dissolution is influenced by dispersion in a

non-volatile solvent, a central feature of this technique. The use of propylene glycol or DMSO facilitated the wetting and dispersion of the drug into finer, more soluble particles. Upon tablet disintegration, the drug particles were dispersed at a molecular level, effectively increasing the surface area for dissolution.

SEM

Microphotographs of pure glimepiride, the selected RLS formulation (F3), and the adsorbent are shown in Fig. 3. The pure glimepiride particles exhibited an irregular crystal structure, as noted by Datir et al. (2022), while Avicel PH 102 consisted of porous particles. Within the RLS system, the drug particles were entrapped within the excipients, indicating that the drug was solubilized in the non-volatile solvent before being adsorbed onto the adsorbent. These results align with findings for clopidogrel (Mohammed and Akkam, 2018) and fexofenadine (Yehia et al., 2015) in similar liquisolid compacts.

XRD

Polymorphic changes in the active pharmaceutical ingredient are critical, as they can impact dissolution and bioavailability. In this study, XRD analysis was used to assess polymorphic changes in glimepiride within RLS tablets, aiming to identify any structural alterations compared to the initial powder. The XRD diffractogram results are presented in Fig. (4A). Glimepiride displayed characteristic diffraction peaks at 2θ values of 13.44°, 16.69°, 18.14°, 19.19°, and 21.05°, confirming its crystalline state with a crystallinity index of 68.3%. These diffraction patterns for initial glimepiride were consistent with those reported by Viana et al. (2018) and Jaafar and Radhi (2020). Fig. 4A also shows a prominent peak at a 2θ angle of 22.4 for Avicel PH 102. This major peak, characteristic of Avicel PH 102, was present in the F3 formulation, with no distinct peaks for glimepiride powder, indicating that only Avicel PH 102 retained its crystalline state. This suggests that the drug was solubilized in the liquisolid formulation or fused within the adsorbent. The absence of a crystalline state in the RLS formulation likely results from solubilization and near-molecular dispersion of the drug in the non-volatile solvent, which acts as a vehicle potentially adsorbed onto the adsorbent. This solubilization of glimepiride was found to enhance dissolution. These findings are consistent with the studies by Singh et al. (2011) and Dhall et al. (2019), who formulated LS and RLS of glimepiride to enhance dissolution.

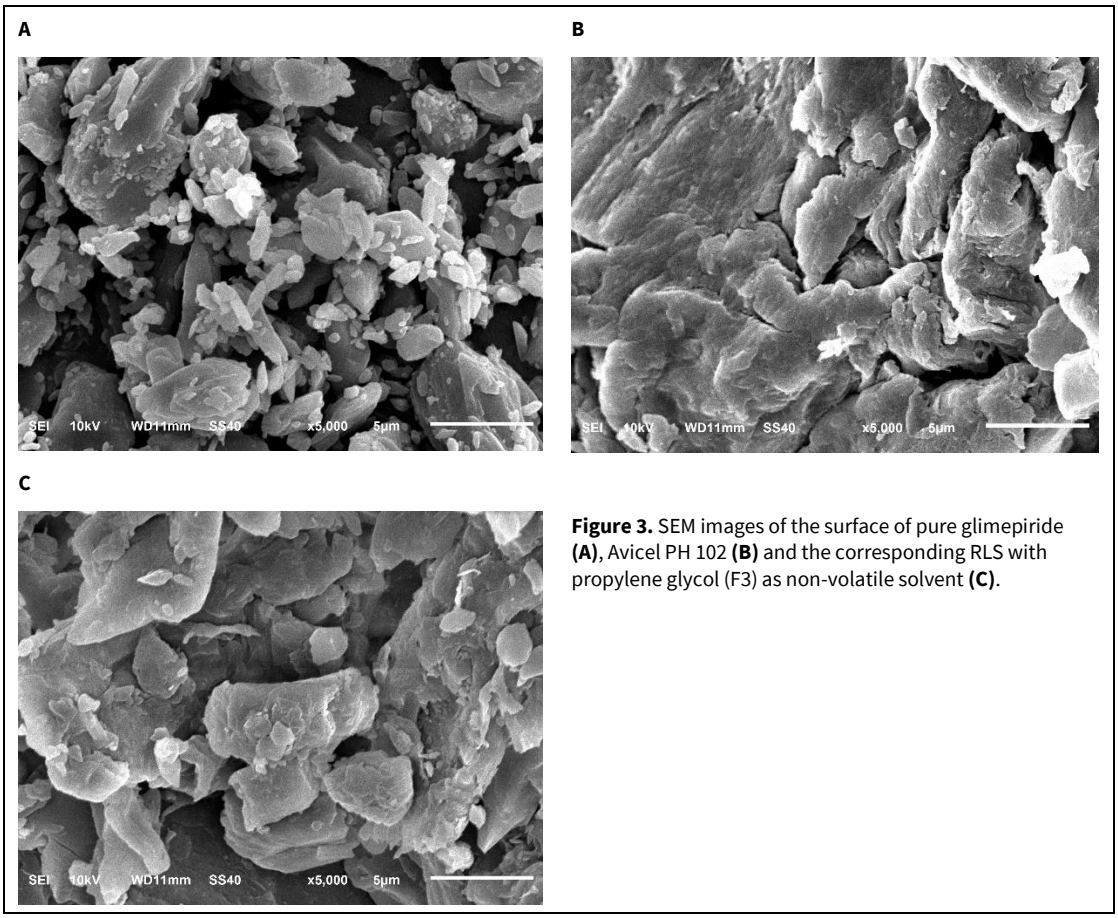

Figure 3. SEM images of the surface of pure glimepiride **(A)**, Avicel PH 102 **(B)** and the corresponding RLS with propylene glycol (F3) as non-volatile solvent **(C)**.

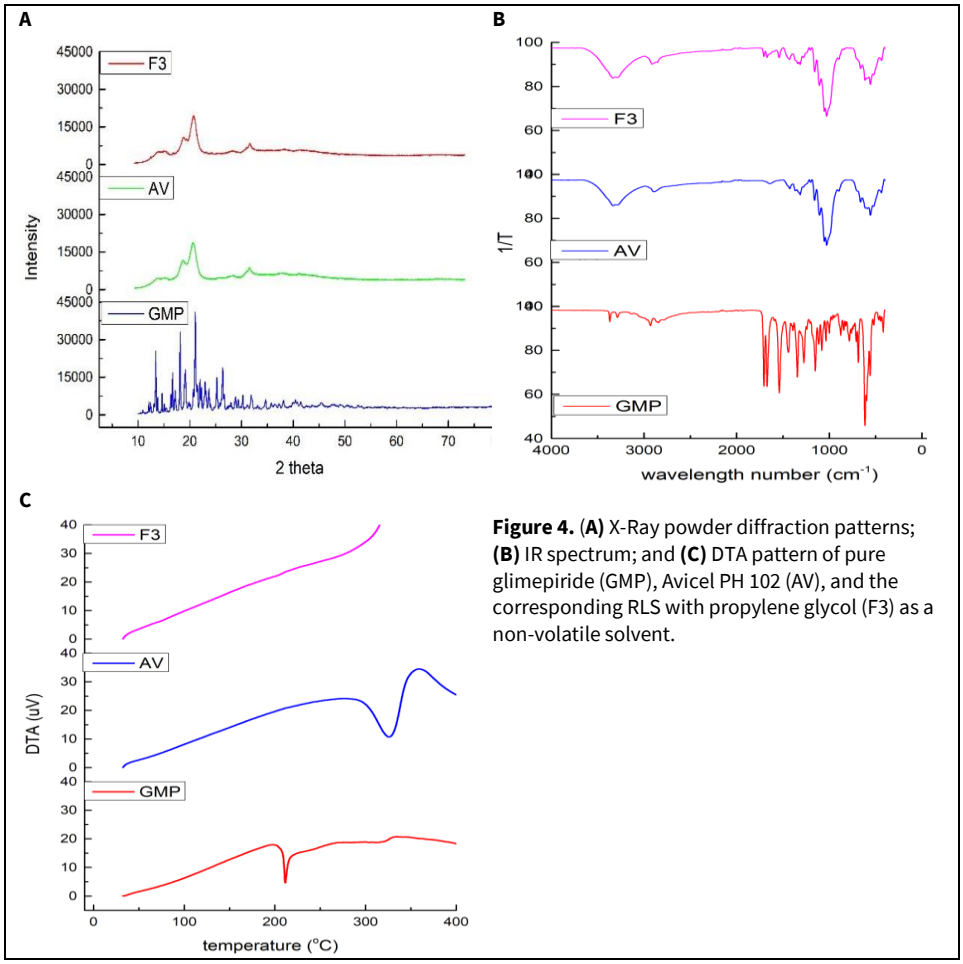

Figure 4. **(A)** X-Ray powder diffraction patterns; **(B)** IR spectrum; and **(C)** DTA pattern of pure glimepiride (GMP), Avicel PH 102 (AV), and the corresponding RLS with propylene glycol (F3) as a non-volatile solvent.

FTIR

Infrared spectroscopy was conducted to evaluate the compatibility of ingredients used in the RLS formulation. The IR spectra of the RLS tablets indicated chemical interactions between the drug and excipients, helping to identify any alterations from the initial powder. FTIR characterization results are shown in Fig. (4B). Glimepiride exhibited two NH stretching bands at 3287 and 3369 cm^{-1}, associated with urea and specific bands for form I (Viana et al., 2018). Other peaks were observed at 1707 and 1674 cm^{-1}, corresponding to the carbonyl group, and at 1348 and 1155 cm^{-1}, related to the sulfonamide group, consistent with literature reports (Ahmed et al., 2022b; Dhall et al., 2019; Jaafar and Radhi, 2020). The characteristic peaks of Avicel PH 102 observed in the F3 formulation demonstrated the absence of glimepiride's distinctive peaks, suggesting the drug was fully internalized within the RLS formulation. This observation implies no significant physical or chemical interactions between the drug and the adsorbent. The FTIR findings align with those of the XRD, indicating that dissolution improvement resulted from glimepiride's solubilization in a non-volatile solvent to increase wettability. These results are in agreement with Ahmed et al. (2022b), who prepared glimepiride in SNEDDS before liquisolid tablet compression, as well as Dhall et al. (2019), who formulated glimepiride RLS to enhance dissolution.

DTA

Differential thermal analysis was employed to assess the compatibility between the drug and excipients, providing precise data on their interactions. The DTA thermogram results are shown in Fig. (4C). The DTA thermogram of initial glimepiride displayed a sharp endothermic peak at 211.46°C, consistent with its melting point. These results align with the findings of Jaafar and Radhi (2020) and Qushawy et al. (2020), who reported a similar endothermic peak for glimepiride at 212.5°C, indicative of its crystalline anhydrous state. Avicel PH 102 exhibited a broad endothermic peak at 324.35°C, likely corresponding to the decomposition of cellulose (Szcześniak et al., 2008). The thermal behavior of the F3 formulation showed a complete disappearance of the characteristic peaks of glimepiride and Avicel PH 102, indicating that the drug was uniformly dispersed within the liquisolid matrix, likely forming an amorphous state. These results align with those of Dhall et al. (2019), who developed glimepiride RLS formulations to improve dissolution.

Limitations of the study

Sodium starch glycolate was used as the disintegrant across all formulations in this study. While compatible with microcrystalline cellulose, sodium starch glycolate proved less compatible when paired with magnesium aluminum metasilicate. Another limitation of the study was that dissolution testing was conducted only under media conditions specified by the USP monograph, without utilizing FDA-recommended media conditions to assess bioequivalence with the innovator formula.

CONCLUSION

The RLS formulation successfully enhanced the dissolution rate of glimepiride, a drug with low solubility. Among the RLS formulas, formulation F3—prepared with propylene glycol as a non-volatile liquid vehicle and microcrystalline cellulose as an adsorbent—demonstrated good flow properties, met USP tablet standards, and showed a dissolution profile comparable to the innovator brand, Amaryl. This improved dissolution was attributed to increased wetting and solubilization of drug particles within the adsorbent. RLS is a straightforward technique that uses a carrier to incorporate the drug without requiring solvent evaporation. These findings underscore the potential of RLS formulation as a viable method for producing glimepiride tablets in the pharmaceutical industry.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Design	x	x					
Definition of intellectual content	x			x			
Literature search	x		x				
Experimental studies		x			x	x	x
Data acquisition		x			x	x	x
Data analysis	x	x		x			
Statistical analysis			x		x	x	x
Manuscript preparation	x	x					
Manuscript editing			x	x			
Manuscript review	x	x	x	x	x	x	x

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