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Original Article 1

Development, characterization and pharmacodynamic evaluation of refined liquisolid system of glimepiride for bioequivalent tablet

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Background
Glimepiride, a third-generation sulfonylurea, is a weakly acidic hypoglycemic drug that falls under Class II in the Biopharmaceutical Classification System (BCS). Despite its effectiveness, glimepiride exhibits low solubility and high permeability, leading to inconsistent therapeutic outcomes.

Objective
This study explores the potential of a refined liquisolid system (RLS) for formulating glimepiride tablets, evaluating its drug release profile and pharmacodynamic effects in mice compared to the reference brand, Amaryl®.

Materials and methods
The RLS formulations of glimepiride tablets were developed using 12 different combinations, incorporating Avicel PH 102 or Neusilin as adsorbents, propylene glycol or dimethyl sulfoxide as solvents, and croscarmellose sodium as a disintegrant. Various ratios of excipients to the active ingredient were evaluated, and the tablets were produced through direct compression. The formulations underwent dissolution testing in three simulated gastrointestinal fluids (pH 1.2, 4.5, and 6.8), two biorelevant media, and pharmacodynamic evaluation in normoglycemic mice. The similarity factor (*f2*) was employed to compare the dissolution profiles of the formulations with the innovator brand. Additionally, the area under the curve (AUC_{0-11} hours) and the mean maximum percentage reduction in blood glucose levels (%RBGL) of the RLS formulations were statistically compared to those of the reference.

Results and conclusion
The optimal glimepiride tablets were formulated using dimethyl sulfoxide as the solvent and either Avicel PH 102 or Neusilin as adsorbents. These RLS tablets demonstrated dissolution profiles closely matching those of the reference product, with similarity factor (*f2*) values exceeding 50. Furthermore, there was no statistically significant variation in %RBGL between the RLS tablets and the reference product ($p > 0.05$). Importantly, the glimepiride in the RLS formulation transitioned into an amorphous state. The RLS formulations offer a viable alternative for the industrial production of glimepiride tablets, providing a comparable therapeutic performance to the reference brand while potentially addressing solubility challenges.

Keywords: comparative dissolution study, dimethyl sulfoxide, glimepiride, pharmacodynamic, refined liquisolid system.

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Introduction

Glimepiride ($C_{24}H_{34}N_4O_5S$) is a widely used oral hypoglycemic agent from the sulfonylurea class, primarily prescribed for the treatment of non-insulin-dependent diabetes mellitus. As a Biopharmaceutical Classification System (BCS) Class II drug, glimepiride (Figure 1) has a molecular weight of approximately 490.617 g/mol [1]. Its solubility is highly pH-dependent, with a solubility of less than 0.004 mg/mL at low pH (e.g., gastric conditions) and increasing to 0.02 mg/mL in media with a pH above 7 at 37°C [1-2]. Within the gastrointestinal tract, glimepiride's poor solubility contributes to erratic and variable therapeutic outcomes [1]. These characteristics make it challenging to develop tablets with an adequate

dissolution rate, which directly impacts the drug's systemic bioavailability.

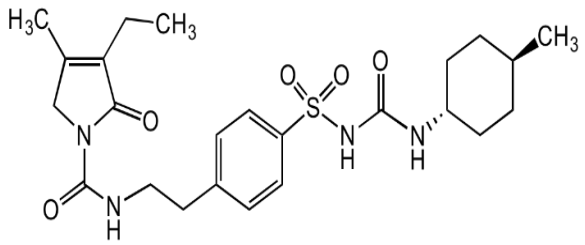


Fig. 1. Chemical structure of glimepiride.

Several generic formulations available on the market have demonstrated dissolution profiles that deviate from those of the reference product, Amaryl®[3, 4] which may lead to variability in therapeutic efficacy, particularly when patients switch between different brands. An Approach to enhance the dissolution of glimepiride is necessary to ensure its equivalence to the innovator product. This is essential to support therapeutic interchangeability without compromising clinical outcomes. Therefore, it is essential to assess these formulations for chemical and biopharmaceutical equivalence, including their potency, quality, purity, and release profiles of the active ingredient in comparison to the innovator drug.

One promising approach to enhance the dissolution rate of glimepiride is the refined liquisolid system (RLS). Previous studies have shown that the RLS of glimepiride exhibits superior dissolution properties compared to surface solid dispersion, conventional solid dispersion, and marketed formulations [5]. The liquisolid system (LS) is a manufacturing technique in which active pharmaceutical ingredients are dissolved or dispersed in non-volatile solvents to form a liquid or suspension. This liquid is then converted into a free-flowing, non-adherent, and compressible powder by adding carriers and adsorbents [6]. The LS technique is cost-effective and suitable for industrial-scale production as it requires no volatile organic solvents or energy-intensive heating processes [7]. The RLS method represents an advancement over conventional LS techniques. It disperses the solid drug in a non-volatile and non-viscous solvent, which is then adsorbed onto the surface of diluent with high adsorption capacity or high liquid retention potential and blended to achieve homogeneity. Unlike the conventional LS method, the RLS approach eliminates the need for a coating material, simplifying the process [5], and enables the maintainance uniformity in thickness and continuity of single-layer/multi-layered particles in the adsorbate. By minimizing the number of excipients and processing steps, this formulation strategy not only facilitates scalability and manufacturing efficiency but also reduces production costs. Collectively, these attributes highlight the potential applicability of this RLS method in the development of cost-effective, high-quality generic glimepiride products.

In this study, an RLS system was developed using magnesium aluminum metasilicate (Neusilin®) as the adsorbent in the refined liquisolid (RLS) system, offering a viable alternative to the commonly used silicon dioxide, as previously reported by Dhall (2019) [5]. In addition, this work explores the use of a moderately viscous nonvolatile solvent, propylene glycol, in combination with microcrystalline cellulose as an alternative carrier material, thereby broadening the formulation possibilities within the RLS platform. In earlier studies, RLS tablets of glimepiride were successfully developed using propylene glycol or dimethyl sulfoxide (DMSO) as non-volatile solvents and Avicel PH 102 or Neusilin as adsorbents. Dissolution testing in USP-recommended media [8] demonstrated improved drug release compared to pure glimepiride [9], similar to findings for other drugs such as atorvastatin calcium [10]. To ensure the quality and equivalence of generic products to the reference, a comparative in vitro dissolution study is an essential initial step before conducting bioequivalence studies. In Indonesia, bioequivalence testing for generic drugs like glimepiride is mandated by the Indonesian Food and Drug Authority [11-12]. This study aimed to assess the similarity factor (f_2) of RLS-formulated glimepiride tablets compared to the reference brand Amaryl®. A comparative dissolution study was conducted using simulated gastrointestinal fluids and biorelevant media, complemented by pharmacodynamic evaluation in normoglycemic rats as a preliminary step toward human bioequivalence studies.

Materials and methods

Materials

Micronized glimepiride, used as the active pharmaceutical ingredient, and croscarmellose sodium were generously provided by PT. Phapros Tbk., Indonesia. The glimepiride working standard (Sigma Aldrich) was procured from a local supplier. Additional materials included propylene glycol, dimethyl sulfoxide (DMSO), microcrystalline cellulose (Avicel PH 102), and magnesium stearate, all purchased from Bratachem, Indonesia. Neusilin US2 was sourced from Fuji Chemical Co., Japan, via a local supplier. The innovator brand of glimepiride (Amaryl® 4 mg, by Sanofi) was obtained from a local pharmacy. Other reagents and solvents utilized were of analytical

grade quality, including HCl, glacial acetic acid, sodium acetate dihydrate, NaOH, NaH_2PO_4, NaCl, and KH_2PO_4, all supplied by Merck. A biorelevant medium was prepared using 3F® powder, which contained bile salts and lecithin, and was purchased from Biorelevant.com Ltd., London, UK.

Preparation of refined liquisolid system tablet

The modified (refined) liquisolid system described by Spireas and Bolton (2002) [13] was utilized to determine the appropriate amounts of adsorbent and solvent for the formulation, each containing 4 mg of glimepiride as shown in Table 1. In all formulations, 5% disintegrant and 1% lubricant were included in the process [10].

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

Code	Drug-adsorbent ratio	Glimepiride (mg)	Adsorbent (mg)		Lf adsorbent*[a]	Solvent (mg)		CCS*[b] (mg)	Mg stearate*[c] (mg)	Tablet weight (mg)
			Avicel PH 102	Neusilin US2		PG	DMSO			
F1	1:30	4	120		0.25	30		7.7	1.54	163.24
F2	1:40	4	160		0.25	40		10.2	2.04	216.24
F3	1:50	4	200		0.25	50		12.7	2.54	269.24
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		0.25		30	7.7	1.54	163.24
F8	1:40	4	160		0.25		40	10.2	2.04	216.24
F9	1:50	4	200		0.25		50	12.7	2.54	269.24
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 : Flowable liquid retention potential at 33°.
*b : 5% w/w of the disintegrant CCS.
*c : 1% w/w of the lubricant Mg stearate.

Glimepiride was first dispersed in a non-volatile solvent to ensure solubilization. The resulting mixture was gradually added to the adsorbent material until a dry, free-flowing powder was obtained. The prepared powder was stored in a desiccator before proceeding to the next step [5]. Subsequently, croscarmellose sodium (disintegrant) and magnesium stearate (lubricant) were incorporated into the blend. Ensuring good flowability of the liquisolid powder was a critical prerequisite before tablet compression. Pre-compression analysis included tests for flowability, such as the angle of repose, bulk and tap density for determined Carr's index and Hausner ratio. Finally, the blend was compressed into tablets using a rotary tablet press machine equipped with a 10 mm punch to achieve tablets with a hardness of 40-60 N [10].

Tablet evaluation

The evaluation of tablet characteristics encompassed weight variation, hardness, friability, and disintegration time, all performed in compliance with USP guidelines. The assay method for determining drug content was validated spectrophotometrically using a Shimadzu UV-1800 in accordance with ICH guidelines. The method demonstrated maximum absorbance at 227 nm (in pH 7.8), with a linear range of 4–16 µg/mL and a high correlation coefficient (r^2 = 0.99995). Drug recovery was calculated at 99.78 ± 0.82%, and the relative standard deviation (RSD%) was within acceptable limits (<2%), ensuring the method's accuracy and precision. The detection and quantification limit (LOD and LOQ) were identified as 0.897 µg/mL and 2.72 µg/mL, respectively. For drug content analysis, ten tablets

from each formulation were evaluated. Each tablet was individually crushed and transferred to a beaker containing 10 mL of methanol. The solution was then diluted with phosphate buffer (pH 7.8) and filtered through a 0.45 µm membrane filter into a 100 mL volumetric flask. The resulting mixture was subjected to sonication for 15 minutes to ensure complete dissolution, and the glimepiride content was measured spectrophotometrically at 227 nm. The glimepiride concentration was measured using a standard calibration curve. The drug content for each tablet was expressed as a percentage of the theoretical content 4 mg per tablet [5].

Comparative dissolution study

Comparative dissolution tests were performed on six tablets from both the RLS formulation and the innovator brand, Amaryl®. The tests were performed using a USP type II apparatus (Electrolab TDT-08L) operating at a rotation speed of 75 rpm with 500 mL of media, including phosphate buffer, acetate buffer, and simulated gastric fluid each with a pH of 6.8, 4.5 and 1.2. Biorelevant media were also utilized in this test, specifically Fasted State Simulated Intestinal Fluid (FaSSIF) with a pH of 6.5 and Fasted State Simulated Gastric Fluid (FaSSGF) with a pH of 1.6. FaSSIF contains bile salts (such as sodium taurocholate) and lecithin in a buffer solution, while FaSSGF contains acid (HCl), pepsin, bile salts, lecithin, and sodium chloride at a low pH to simulate gastric fluids. The temperature was consistently maintained at 37 ± 0.5°C throughout the tests. At predetermined time points (10, 15, 30, 45, and 60 minutes), 5 mL aliquots were taken from the dissolution media and promptly replaced with an equivalent volume of fresh buffer to preserve sink conditions. The obtained samples were passed through a 0.45 µm membrane and analyzed spectrophotometrically at the respective maximum wavelength for each medium.

Pharmacodynamic evaluation

The in vivo study was conducted using *Rattus norvegicus (male Wistar rats)*, in accordance with the protocol approved by the Health Research Ethics Committee of the Faculty of Health, Dian Nuswantoro University (Number 636/EA/KEPK-FKes-UDINUS/VII/2024). This protocol complies with the principles established in the Declaration of Helsinki and the ICH-GCP. The selection criteria for the rats included an age range of 6–8 weeks, a minimum body weight of 120 g, and a normal level of blood glucose 70–140 mg/dL. Exclusion criteria encompassed a body weight above 200 g or below 120 g, signs of poor health (e.g., reduced reactivity), and blood glucose levels exceeding or falling below the normal range. Additionally, rats that experienced health complications resulting in death during the sampling period were included in the dropout criteria [14-15].

The in vivo pharmacodynamic study was performed simultaneously administered as a single dose under fasting conditions. A total of 13 groups were included in the study, corresponding to the number of formulations evaluated, comprising 12 RLS formulations and one innovator product. Each group consisted of six test animals. The rats were acclimatized for one week before the experiment [14]. Powdered RLS tablets were suspended in 1% carboxymethyl cellulose (CMC) to facilitate oral administration via gavage. The dosage of glimepiride administered was 0.018 mg per 200 g of body weight (BW), determined from a human dose of 1 mg for a 70 kg individual and adjusted using an interspecies conversion factor [16]. The rats were fasted overnight (10 hours) before the experiment while having unrestricted access to water. Blood glucose levels were measured using the glucose oxidase-peroxidase (GOD/POD) method with a diagnostic kit. Blood samples were obtained by making a small incision on the tail, with a droplet placed on a glucometer strip for glucose measurement. The pre-administration blood glucose level (t_0, BG_0) was recorded as the baseline. Following this measurement, the rats were administered a suspension of glimepiride (dose: 0.018 mg per 200 g of BW). Food was withheld for 5 hours post-administration, but water was provided. Blood samples were subsequently drawn at 1, 3, 5, 7, 9, and 11hours post-administration (BG□), using the same procedure [15]. The percentage reduction in blood glucose levels (%RBGL) was calculated using the formula:

$$\%\ Reduction\ Blood\ Glucose\ Level = \frac{BG\ (0) - BG\ (t)}{BG(0)} \times 100\%$$

Where BG ($_0$) represents the blood glucose level before drug administration, and BG (t) denotes the blood glucose level after drug administration. The %RBGL was used as an indicator of the hypoglycemic response. A relationship curve between mean %RBGL and time was constructed. Additionally, the area under the curve ($AUC_{0-11}h$) was calculated for each formulation [14].

Solid state characterization

The selected RLS formulations, pure drug, and corresponding adsorbent were further characterized for a drug-excipient compatibility study.

Differential scanning calorimetry

Samples (2–5 mg) were placed in aluminum crucibles and analyzed using a DSC-60Plus instrument (Shimadzu, Japan). The temperature

range was set between 30°C and 300°C, with a heating rate of 10°C per minute [5].

Fourier transform infrared spectroscopy

Infrared spectra of pure glimepiride, Avicel PH102, Neusilin, and RLS formulations were determined using attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) (α-T; Agilent Cary 630 FTIR spectrometer, USA) in the frequency range of 650–4000 cm^{-1} at 2 cm^{-1} resolution.

X-ray powder diffraction

The XRD patterns of pure ingredients and RLS formulations were recorded using X-ray Diffractometer (Shimadzu XRD-7000, Japan) with Cu as a target. The samples were analyzed in the 2θ angle range of 10-90° with scanning speed 2°/min. The operating voltage and current were 40 kV and 30 mA, respectively.

Scanning electron microscopy

Surface morphology of pure ingredients and RLS formulations was observed using an analytical SEM. The powder samples were mounted on aluminum stubs with double-sided adhesive tape and platinum-coated (JEOL JEC-3000FC Auto Fine Coater). Scanning was done using a JEOL JSM-6510LA at 10 kV.

Statistical analysis

All data were presented as mean ± standard deviation across at least three independent experiments. Statistical analysis of the dissolution data between RLS formulations (F1–F12) and Amaryl® tablet was assessed by similarity factor (*f2*), which quantifies the closeness of the two profiles. The f_2 factor is a logarithmic transformation of the sum-squared error of differences between the reference (innovator) and test (RLS) products across specified time points. In this study, the f_2 value was calculated using the following equation:

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

Rt and *Tt* represent the cumulative percentage of the drug dissolved at time period t for the reference and test products, respectively, where *n* indicates the number of time points. An f_2 value of 50 or higher indicates similar dissolution profiles between the test and reference products [12, 17-18]. Statistical analysis on pharmacodynamic data (AUC) was performed using one-way ANOVA, followed by Tukey's multiple comparison test, with a significance threshold of $p < 0.05$. Products were considered bioequivalent if the significance value was >0.05 and bio-inequivalent if <0.05 [14].

Results and discussions

All tested products complied with the general pharmaceutical standards for weight variation and content uniformity. Additionally, the prepared tablets met the official requirements for hardness, friability, and disintegration time, as summarized in Table 2.

Table 2. Characteristic of refined liquisolid system tablet of glimepiride.

Code	Weight variation (mg)	Hardness (kgf)	Friability (%)	Disintegration time (min)	Drug content (%)
F1	157.6 ± 3.26	5.07 ± 0.76	0.67 ± 0.02	7.05 ± 0,35	99.78 ± 4.46
F2	212.4 ± 7.41	4.78 ± 0.41	0.47 ± 0.48	1..5 ± 0,13	101.58 ± 5.78
F3	268.15 ± 6.01	4.08 ± 0.26	0.48 ± 0.01	1.13 ± 0.02	99.70 ± 3.40
F4	162.9 ± 2.22	6.18 ± 1.01	0.69 ± 0.24	3.18 ± 1.84	97.53 ± 1.53
F5	216.95 ± 3.27	4.53 ± 0.27	0.43 ± 0.01	2.34 ± 0.09	99.07 ± 1.64
F6	265.85 ±5.87	4.88 ± 1.15	0.82 ± 0.06	1.58 ± 0.42	98.20 ± 1.21
F7	154.82 ± 4.79	7.32 ± 0.48	0.67 ± 0.22	3.24 ± 1.11	98.07 ± 1.64
F8	213.13 ± 4.80	4.82 ± 0.38	0.61 ± 0.30	1.40 ± 0.02	99.53 ± 1.53
F9	267.31 ± 10.02	5.44 ± 0.24	0.10 ± 0.08	1.35 ± 0.18	98.20 ± 1.21
F10	156.42 ± 5.34	5.64 ± 1.11	0.46 ± 0.09	2.19 ± 0.14	99.18 ± 2.82
F11	211.13 ± 4.09	5.99 ± 0.93	0.37 ± 0.04	1.16 ± 0.06	97.51 ± 1.34
F12	268.91 ± 5.83	5.73 ± 0.47	0.20 ± 0.03	1.32 ± 0.19	98.21 ± 1.56

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.

The incorporation of non-volatile solvents such as propylene glycol and DMSO proved effective, with the solvents being well absorbed by the selected adsorbents, Avicel PH 102 or Neusilin. This absorption facilitated the creation of a flowable and compressible liquisolid (RLS) powder mass, which is a critical aspect of pharmaceutical formulation development. Flowability and compressibility (data not shown) are key parameters in ensuring the stability, manufacturability, and bioavailability of the final pharmaceutical product. The resulting RLS systems, supported by the synergy between the non-volatile solvents and adsorbents, offer a promising approach to enhancing the performance and reliability of the drug delivery system.

Comparative dissolution studies

The in vitro dissolution tests were performed in five different media to evaluate the dissolution profiles of the formulations under varying conditions. The dissolution profiles in three enzyme-free simulated gastrointestinal fluids are presented in Figure 2. Based on the similarity factor (f_2) calculations (Table 3), almost all RLS formulations exhibited dissolution profiles similar to the innovator across a pH range of 1.2–6.8. These results surpass the performance of the polymorph modification approach reported by Darusman et al. (2023), which failed to achieve a comparable dissolution profile to Amaryl® at pH 1.2 [19]. However, the test conditions in this study may not have been sensitive enough to detect differences between formulations. The stirring speed of 75 rpm, recommended in the USP monograph for glimepiride, may have caused excessive homogenization, masking potential variations in dissolution profiles.

To identify bioequivalent formulation candidates, additional comparative dissolution tests were conducted using biorelevant media, which better simulate gastrointestinal conditions. Unlike conventional media, biorelevant media not only reflect physiological pH but also incorporate components that mimic gastrointestinal fluids. This study used two biorelevant media under fasting conditions, as glimepiride is known to degrade in fed states [20-21]. The dissolution results in biorelevant media are shown in Figure 3.

The RLS formulation with Avicel PH 102 as the adsorbent demonstrated a dissolution profile comparable to the innovator in the FaSSGF medium. In contrast, formulations using Neusilin as the adsorbent showed higher dissolved glimepiride percentages but deviated from the innovator's profile. In the FaSSGF medium representing acidic gastric conditions, the formulation containing Neusilin®—an alkaline magnesium aluminum metasilicate [22]—was found to increase the microenvironmental pH, thereby enhancing the dissolution of glimepiride beyond that of the innovator product. This was reflected by an f_2 value of less than 50, indicating a significant difference in dissolution profiles. However, in alkaline conditions FaSSIF, Neusilin had no significant impact on the dissolution process, resulting in dissolution behavior similar to other formulations. In the FaSSIF medium, only three RLS formulations prepared with DMSO and Avicel PH 102 as the adsorbent achieved dissolution profiles similar to the innovator. Other formulations demonstrated lower dissolved glimepiride amounts. Among these three formulations, one (F7) failed to match the innovator's profile in conventional media at pH 4.5 and pH 6.8 based on (f_2) values (Table 3). This discrepancy occurred because the formulation with the lowest Avicel PH 102 ratio could not replicate the innovator's dissolution behavior in these media. Ultimately, two formulations (F8 and F9) were identified as closely resembling the innovator across various media, including biorelevant conditions. The use of biorelevant media proved more effective in distinguishing dissolution profiles among formulations, enabling the identification of those that truly resemble the innovator's dissolution characteristics [23].

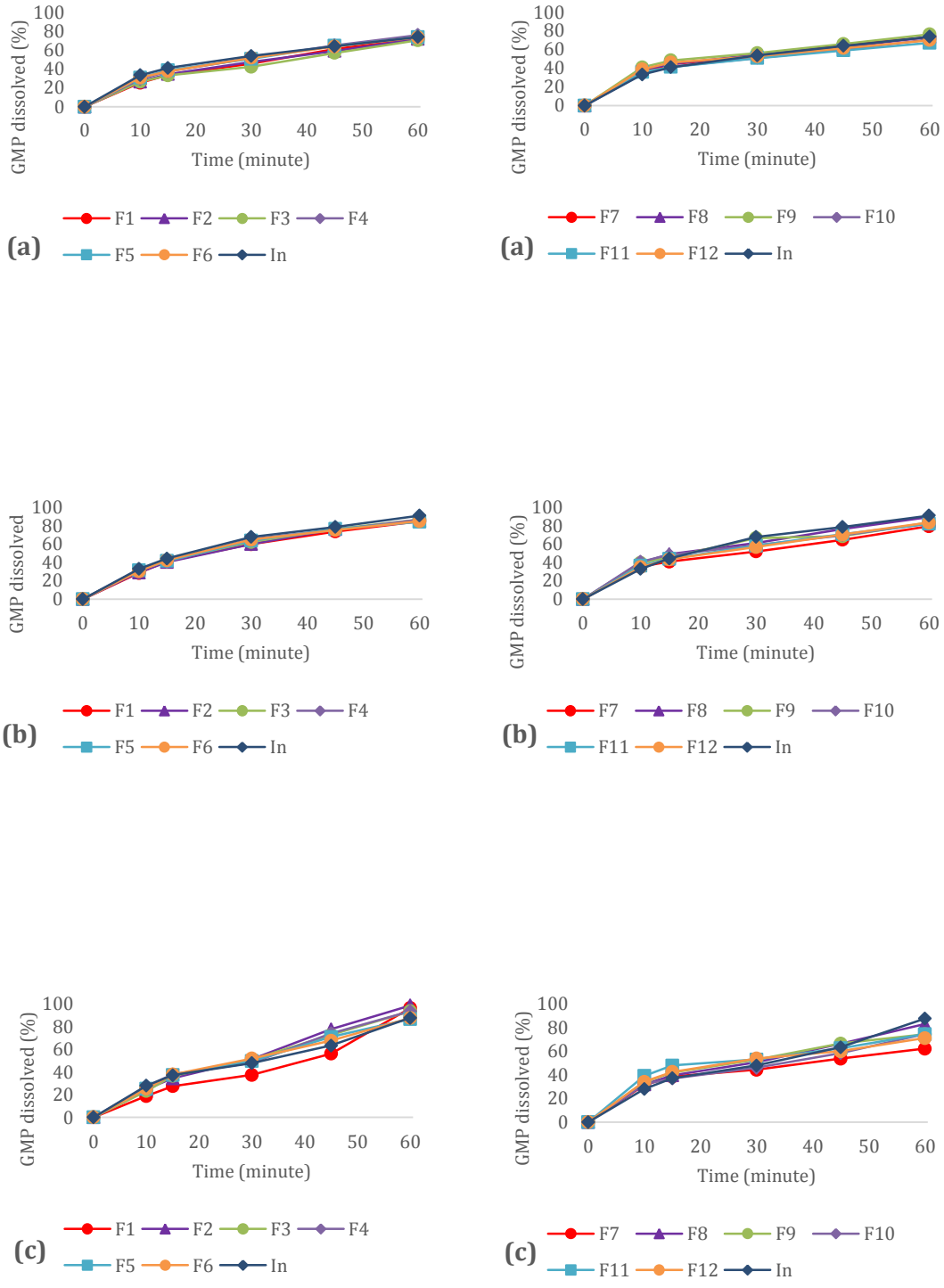


Fig. 2. Dissolution profiles of glimepiride refined liquisolid system tablets and Amaryl® in pH 1.2 (a), pH 4.5 (b) and pH 6.8 (c).

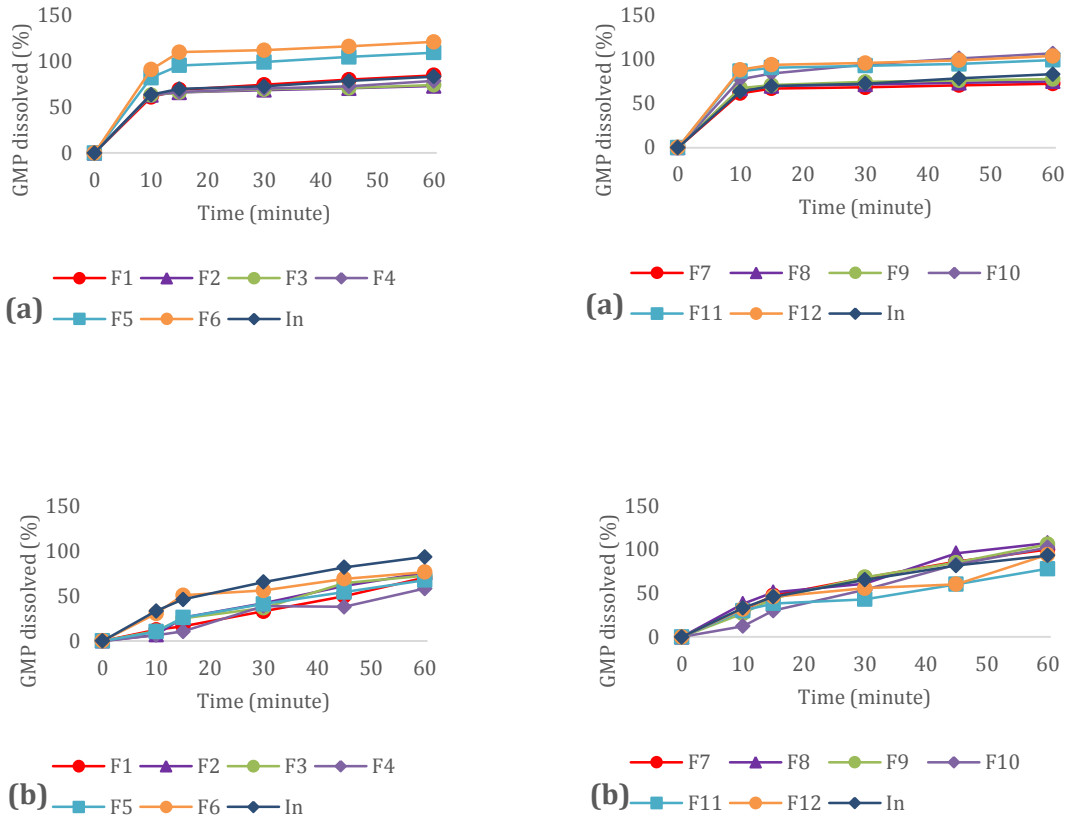


Fig. 3. Dissolution profiles of glimepiride refined liquisolid system tablets and Amaryl® in two biorelevant medium FaSSGF (a) and FaSSIF (b).

Table 3. Similarity factor (*f2*) for dissolution profiles of glimepiride refined liquisolid system tablets in gastrointestinal fluid.

Code	Similarity factor (*f2*)					
	pH 1.2	pH 4.5	pH 6.8	FaSSGF	FaSSIF	Comparison with innovator brand
F1	60.06	62.37	51.90	85.52	27.64	Not similar in 1 biorelevant medium
F2	62.39	64.17	53.50	59.54	32.98	Not similar in 1 biorelevant medium
F3	55.33	72.24	62.08	61.76	32.53	Not similar in 1 biorelevant medium
F4	75.49	74.08	62.69	70.09	23.32	Not similar in 1 biorelevant medium
F5	81.87	69.66	70.75	30.35	30.81	Not similar in biorelevant medium
F6	81.46	70.81	75.52	21.77	48.69	Not similar in biorelevant medium
F7	82.34	47.90	45.26	59.57	69.39	Not similar in 2 medium
F8	75.60	65.26	72.21	66.74	50.56	Similar
F9	64.13	59.43	56.57	72.75	58.19	Similar
F10	78.48	54.89	58.79	35.26	43.47	Not similar in biorelevant medium
F11	68.66	57.45	51.29	35.71	39.96	Not similar in biorelevant medium
F12	69.75	57.25	52.65	32.16	48.79	Not similar in biorelevant medium

Pharmacodynamic study

The pharmacodynamic test results in normoglycemic rats provided additional evidence for the equivalence of the RLS glimepiride formulations compared to the innovator product. The pharmacodynamic profiles of the RLS tablets and the innovator (Amaryl®) are illustrated in Fig. 4. The RLS tablets achieved a 20-50% reduction in blood glucose levels (RBGL) within the first 7 hours, similar to the innovator. However, this reduction was lower than that obtained with the Self-Nanoemulsifying Drug Delivery System (SNEDDS) approach, which reached 40-60% RBGL within 8 hours [24]. The reduction in RBGL observed with the developed RLS formulation was less pronounced compared to the SNEDDS, which can be attributed to the fundamental differences in drug delivery mechanisms. SNEDDS facilitates the formation of nanoparticles that enhance absorption, whereas the RLS system enhances solubility by adsorbing the drug in an amorphous state within the porous structure of the adsorbent, without generating nanoparticles. Despite this, all RLS formulations demonstrated pharmacodynamic profiles comparable to the innovator, as evidenced by the lack of significant differences in the area under the curve (AUC) values of the pharmacodynamic profiles ($p > 0.05$).

These pharmacodynamic results were consistent with the findings from comparative dissolution testing in three conventional media, which were also unable to differentiate the performance of the RLS formulations from the innovator. The testing conducted in this study, including comparative dissolution profiles and pharmacodynamic evaluations in normoglycemic rats, was unable to fully differentiate the performance of the RLS glimepiride formulations. These tests were designed as preliminary assessments to identify potential candidates for bioequivalence testing in humans. While the results demonstrated that the RLS formulations exhibit dissolution and pharmacodynamic profiles comparable to the innovator product (Amaryl®), the sensitivity of the methods used was insufficient to discern finer distinctions between the formulations. Further studies employing more sensitive techniques and human bioequivalence trials are essential to validate the findings and confirm the clinical equivalence of the RLS glimepiride formulations to the innovator product.

Solid state characteristic

Two formulations were selected for solid-state characterization of the glimepiride RLS system. Formulation F9 was selected based on its consistent dissolution profile across all tested media. In contrast, formulation F12—utilizing Neusilin® as the adsorbent but sharing the same solvent composition (DMSO) as F9—was included for comparative analysis to evaluate the influence of adsorbent type on the crystallinity and physicochemical characteristics of glimepiride within the RLS system.

Differential Scanning Calorimetry (DSC)

To investigate the transformations of glimepiride when incorporated into the RLS system, DSC analysis was conducted, as shown in Figure 5. The thermogram of pure glimepiride exhibited an endothermic peak at 207.66 °C, corresponding to its melting point. This is characteristic of glimepiride form I, as it lacks an additional exothermic peak near 140 °C, which would indicate the presence of form II [25]. The observed melting point aligns with values reported in the literature [19, 26-28].

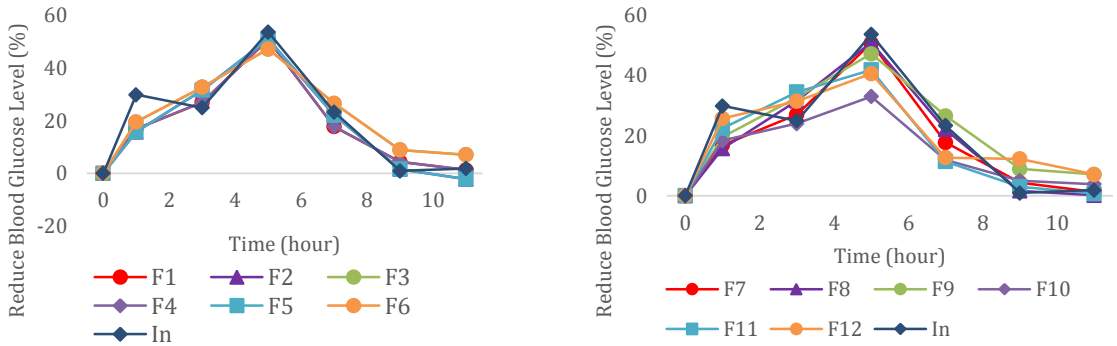


Fig. 4. Pharmacodynamic profiles of glimepiride refined liquisolid system tablets and Amaryl® in six normoglycemic rat subjects.

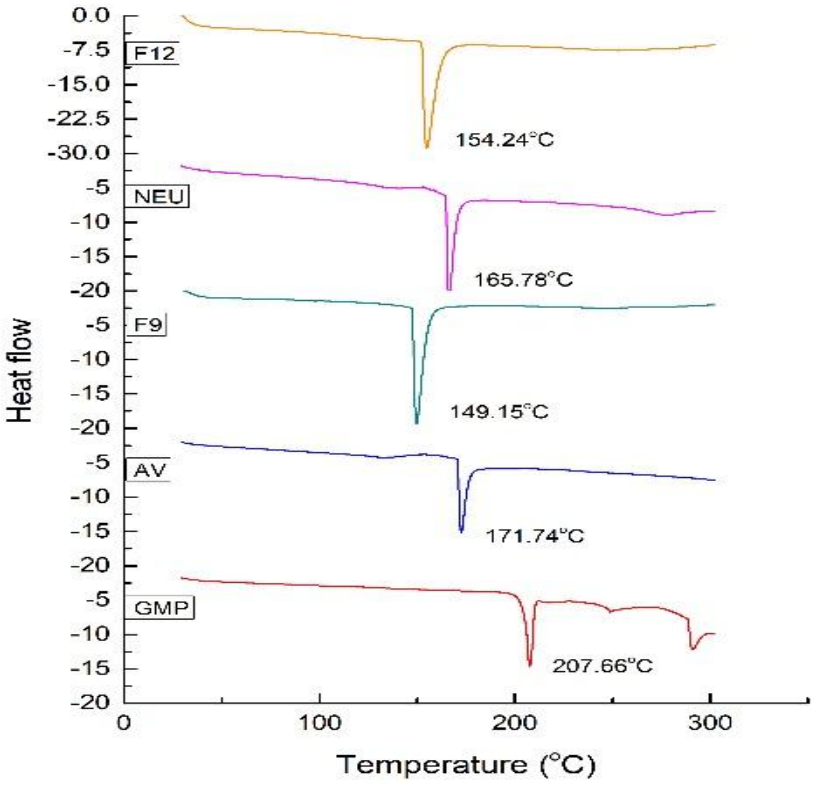


Fig. 5. Thermograms of pure glimepiride (GMP), adsorbent Avicel PH 102 (AV), Neusilin (Neu), refined liquisolid system formulations F9 and F12.

The endothermic peaks of the adsorbents, Avicel PH 102 and Neusilin, were observed at 171.74 °C and 165.78 °C, respectively. These values are lower than the commonly reported melting points of above 200 °C [29]. This discrepancy can be attributed to differences in the sources of raw materials, production processes, moisture content, and testing methods. Similar deviations in the melting point of Avicel PH 102 below 200 °C have been reported in other studies [30].

Notably, in the thermograms of the RLS formulations F9 and F12, the original endothermic peaks of crystalline glimepiride disappeared, and new peaks emerged at 149.15 °C and 154.24 °C, respectively. This shift indicates that glimepiride transitioned into an amorphous state in the RLS system mediated by DMSO. The amorphous state alters the physical properties of glimepiride, as evidenced by the lower melting point, which facilitates the dissolution process.

The transformation into an amorphous structure and the reduction in crystallinity have been observed in other studies where glimepiride interacted with different components using various methods [5, 24, 27, 31-33]. Additionally, interactions with compounds such as arginine, meglumine, and metformin in combination tablets have also been shown to enhance glimepiride dissolution [34-36]. DSC analysis effectively revealed the structural changes in glimepiride during its incorporation into the RLS system, highlighting the drug's transition to an amorphous form, which contributes to its improved dissolution properties.

Fourier Transform Infra-Red Spectroscopy

FTIR analysis was conducted to assess the compatibility of the components used in the RLS formulation. As illustrated in Figure 6, the FTIR spectra of the primary individual ingredients and the final RLS formulation were compared. Glimepiride displayed two characteristic NH stretching vibrations at 3287 and 3369 cm^{-1}, which are attributed to the urea functional group and are indicative of its form I polymorph [25]. Additional absorption bands appeared at 1702 and 1670 cm^{-1}, corresponding to carbonyl stretching, while peaks at 1343 and 1150 cm^{-1} were associated with the sulfonamide moiety. These spectral features are consistent with previously reported data, 2020 [5, 24, 26]. The characteristic absorption bands corresponding to Avicel PH 102 and Neusilin, observed in formulations F9 and F12, showed the absence of glimepiride's distinct peaks. This indicates that the drug was effectively incorporated into the RLS system. The FTIR results confirmed that there were no significant interactions between the drug and the excipients, suggesting good compatibility within the formulation.

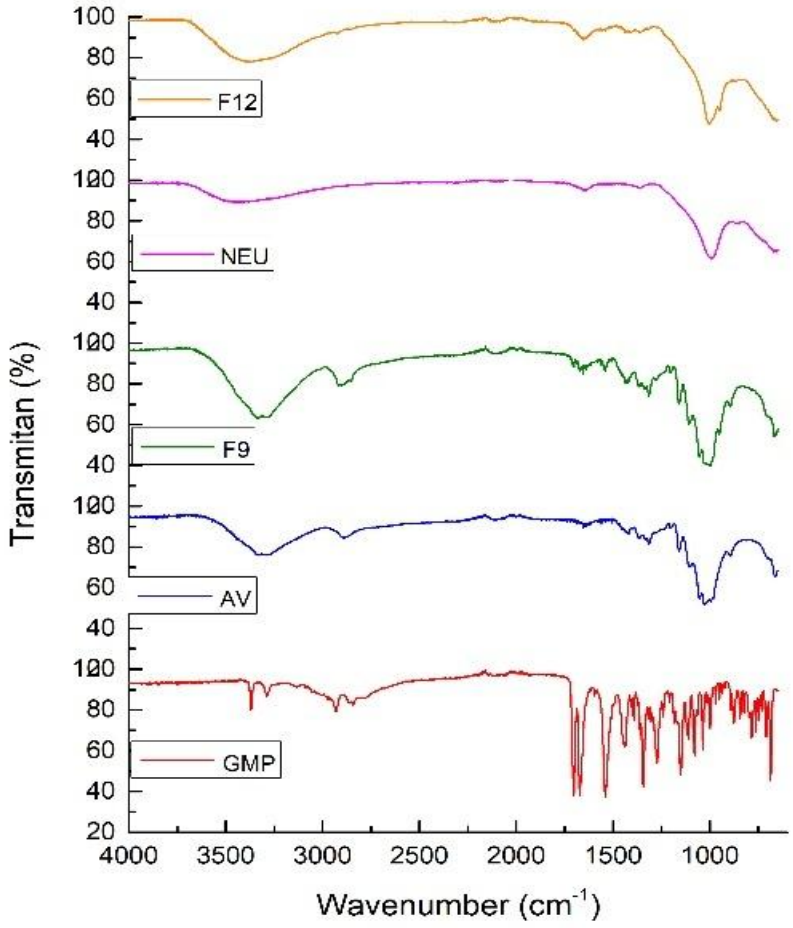


Fig. 6. Infrared spectrum of pure glimepiride (GMP), adsorbent Avicel PH 102 (AV), Neusilin (Neu), refined liquisolid system formulations F9 and F12.

X-ray diffraction

XRD analysis was performed to evaluate the crystallinity of the obtained products and to corroborate the findings from the DSC study. The XRD diffractograms are shown in Figure 7. The diffraction pattern of pure glimepiride confirmed its crystalline nature, with prominent peaks appearing at 2θ values of 13.32, 18.01, and 20.97. In contrast, the F9 formulation exhibited a dominant peak at a 2θ angle of 22.3, corresponding to the most intense peak of Avicel PH 102, its primary component. Notably, no distinctive peaks corresponding to glimepiride were detected, indicating the drug was no longer in its crystalline form. The diffraction pattern of Neusilin displayed only a few low-intensity peaks, and the F12 formulation showed a halo pattern characteristic of an amorphous structure. These observations align with the DSC results, supporting the conclusion that glimepiride was molecularly dispersed within the carrier matrix and transitioned into an amorphous state.

Scanning Electrone Microscopy

As illustrated in Figure 8, pure glimepiride particles displayed an irregular crystalline morphology, consistent with the observations reported [37]. In contrast, Avicel PH 102 exhibited a porous particle structure. In the RLS formulations (F9 and F12), the drug appeared to be embedded within the excipient matrix, suggesting that glimepiride was initially dissolved in DMSO and subsequently adsorbed onto the carrier. These morphological findings are in agreement with previous studies on clopidogrel [29] and fexofenadine [38] formulated as liquisolid systems.

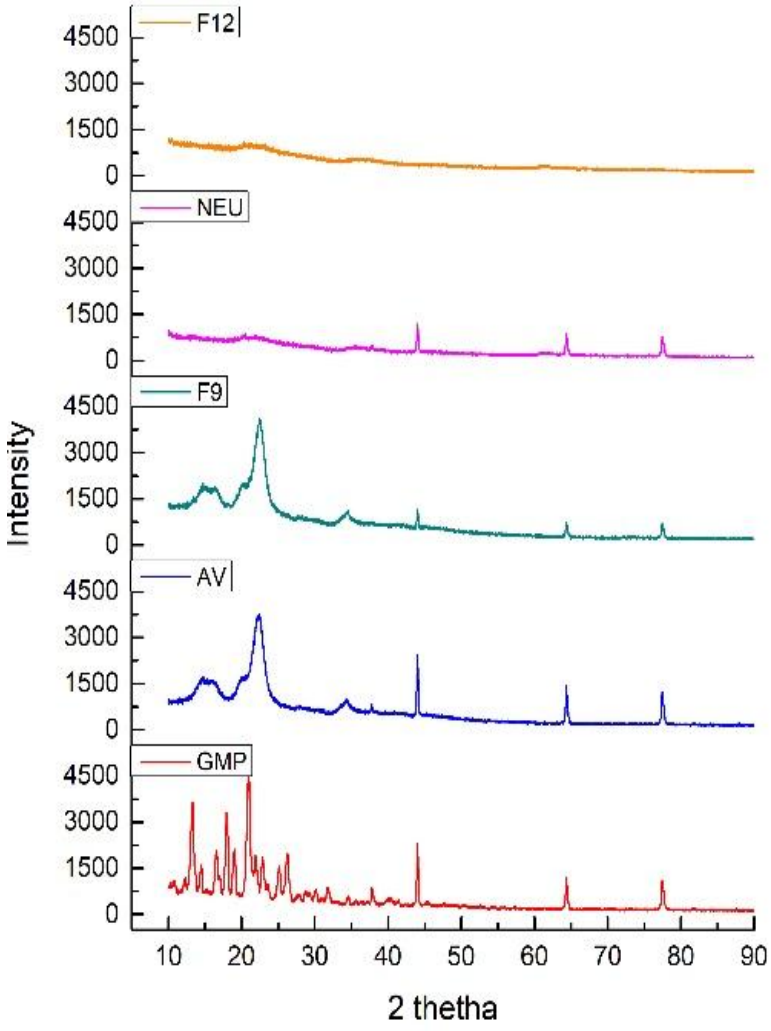
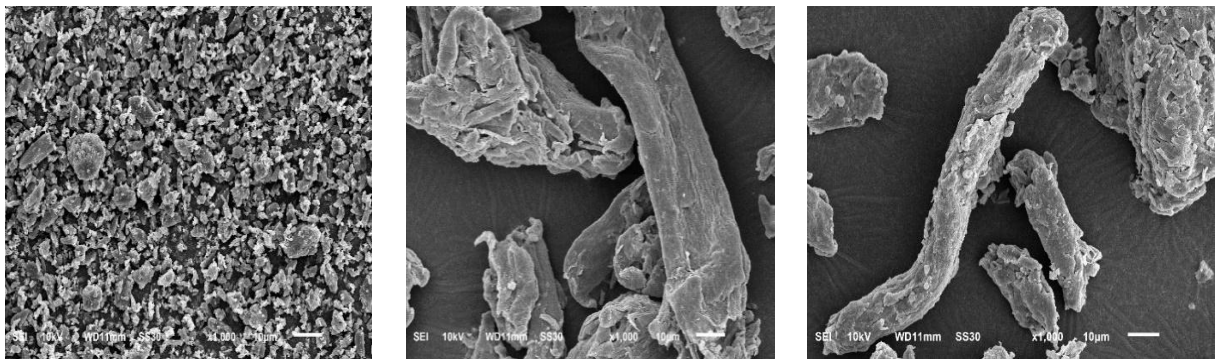
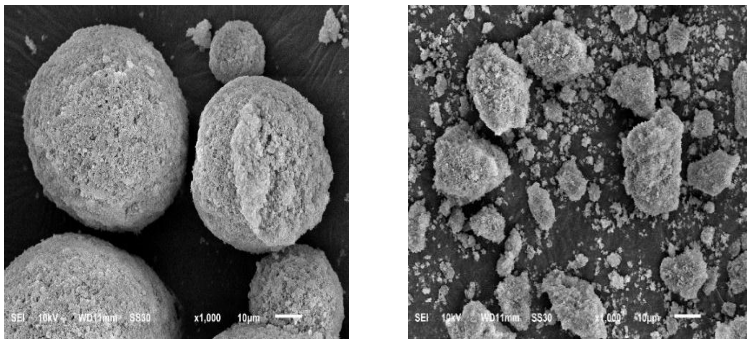


Fig.7. Diffractogram of pure glimepiride (GMP), adsorbent Avicel PH 102 (AV), Neusilin (Neu), refined liquisolid system formulations F9 and F12.



A B C



D E

Fig. 8. Microphotograph of (A) pure glimepiride, (B) Avicel PH 102, (C) refined liquisolid system F9, (D) Neusilin, and (E) refined liquisolid system F12.

Conclusion

Refined liquisolid system of glimepiride using DMSO and Avicel PH 102 exhibited dissolution profiles similar to the innovator product (Amaryl®) in both conventional and biorelevant media. The formulations demonstrated comparable hypoglycemic effects to Amaryl® in normoglycemic rats, indicating their therapeutic potential. The use of DMSO in the system induced the transformation of crystalline glimepiride into an amorphous state, enhancing its dissolution and solubility. The scientific contribution of this study lies in the development of a simplified formulation strategy that successfully achieves dissolution performance comparable to that of the innovator product. The system addresses several limitations commonly associated with nanoparticle-based delivery systems, including formulation instability, challenges in large-scale manufacturing, high production costs, and concerns related to potential toxicity and unintended side effects. The technique represents a promising method for improving the performance of poorly soluble drugs, offering simplicity, efficiency, and scalability for pharmaceutical development.

Conflicts of interest

The authors declare there are no conflicts of interest.

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Authors' contributions

The authors confirm contribution to the paper as follows: study conception and design: YNW, SS; data collection: AS, DNW; analysis and interpretation of results: YNW, SS, MP; draft manuscript preparation: YNW, AS. All authors reviewed the results and approved the final version of the manuscript.

Ethical considerations

The research plan was authorized by the local Health Research Ethics Committee in the Dian Nuswantoro University Health Faculty Number 636/EA/KEPK-FKes-UDINUS/VII/2024.

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