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RESEARCH ARTICLE

HYDROTROPIC SOLUBILIZATION: AN EFFECTIVE TECHNIQUE FOR ENHANCING THE SOLUBILITY OF ANTIDIABETIC DRUG GLIMEPRIDE

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Abstract

Solubility, a key physicochemical property, determines a substance's ability to dissolve in a solvent. Glimepiride, a BCS Class II drug for type 2 diabetes, exhibits very low aqueous solubility and high lipophilicity, which complicates formulation and may cause variable bioavailability and therapeutic failure. Hydrotropy which enhances aqueous drug solubility without micelle formation can allow higher drug loading with low toxicity. This study aimed to improve glimepiride's aqueous solubility and bioavailability using hydrotropic agents. Solubility was measured in water, saline phosphate buffer, ethanol, and methanol, and in solutions of five hydrotropic agents (sodium benzoate, mannitol, urea, sodium acetate, and sodium citrate at 10–40% w/v). Drug solubility was also evaluated in binary and ternary mixtures of these hydrotropic agents'. The *in vitro* dissolution of glimepiride was assessed for a physical mixture and for solid dispersions with sodium citrate prepared by solvent evaporation and kneading. Glimepiride solubility in water was 2.83 µg/ml. The greatest solubility enhancement (ratio 284.33) was achieved with 40% sodium citrate, yielding 803.79 ± 0.015 µg/ml. Production yields for the physical mixture and solid dispersions ranged from 95.44 ± 1.95% to 101.80 ± 2.36%, and drug content varied from 87.00 ± 0.32% to 101.34 ± 0.26%. The fastest and complete *in vitro* dissolution; 99.95 ± 0.78% (DE 80.51%) within 30 minutes was observed for the solid dispersion prepared by the kneading method, compared with 62.35 ± 0.54% (DE 50.95%) for the pure drug. FTIR analysis indicated hydrogen-bond interactions between glimepiride and sodium citrate. In conclusion, sodium citrate, enhance glimepiride's solubility and dissolution from solid dispersion especially by kneading method.

Keywords: Glimepiride, Solubility enhancement, Hydrotropic agents, Solid dispersions, *In vitro* drug dissolution.

1. Introduction

Solubility is the chemical property that describes the ability of a solute to dissolve in a solvent at equilibrium, resulting in a saturated solution. The drug-related characteristics like particle size and shape, surface area, pK_a, and polymorphism; solvent-related characteristics like polarity, pH, and volume; and environmental factors like temperature and pressure all influence the solubility of the drug [1,2]. The solubility of a drug is a fundamental property that affects its absorption and bioavailability. Approximately 40% of newly discovered drug candidates exhibit poor water solubility, posing significant challenges in formulation development. Poor solubility often leads to inadequate dissolution rates, resulting in low bioavailability and therapeutic failure [2-5]. The Biopharmaceutics Classification System (BCS) classifies drugs into four classes based on their aqueous solubility and permeability: Class I high solubility/high permeability; Class II low solubility/high permeability; Class III high solubility/low permeability; and Class IV low solubility/low permeability. Class II and IV face issues such as erratic absorption, dose dumping, and limited formulation options. Therefore, optimizing solubility is essential for consistent drug delivery and clinical efficacy [6-8].

The poor solubility and dissolution rate of Class II and IV drugs pose major challenges in developing suitable dosage forms and delivery systems. Techniques that are

used to overcome this problem include cryogenic technology [1,7], micronization and nanosizing [8], supercritical fluid technology [9], pH modification, cosolvency [2,9] and hydrotropy [2,10,11]. By dispersing the medication in a hydrophilic carrier, the solid dispersion technique increases wettability and decreases crystallinity. Methods for solid dispersions include solvent evaporation, melt extrusion, kneading, and spray drying [12]. Additionally, polymorphic modification and inclusion complexation with cyclodextrins and other complexing agents can enhance drug solubility via the formation of inclusion complexes that increase the drug's stability and aqueous solubility [13]. Surfactants reduce surface tension and form micelles that solubilize hydrophobic drugs. Overall, improving drug solubility and dissolution is essential for optimizing therapeutic outcomes [1].

Hydrotropic agents have emerged as a promising, cost-effective strategy to improve the solubility of poorly water-soluble drugs while avoiding the use of organic solvents. It also allows for higher drug loading and can be easily formulated into suitable dosage forms. Moreover, hydrotropic solutions exhibit minimal toxicity compared to conventional solubilizers [14]. Hydrotropic solubilization is defined as a strategy for solubilizing the low water-soluble drug by the addition of large amounts of a hydrotropic agent. Hydrotropy offers a unique mechanism where hydrotropes, usually aromatic sulfonates or salts, increase the aqueous solubility of hydrophobic drugs without forming micelles [15]. Hydrotropes are characterized by their ability to increase solubility through weak interactions such as π-π stacking, hydrogen bonding, and enhanced drug-water interactions. Unlike micelle formation in surfactants, hydrotropy involves molecular aggregation of the hydrotrope around the drug molecules, increasing their apparent solubility [14]. Recent studies highlighting the role of hydrotrope concentration and structure in solubilization efficiency. Common hydrotropes include sodium benzoate, sodium salicylate, urea, and nicotinamide. Recent research has explored novel hydrotropic agents like amino acid derivatives and ionic liquids for enhanced solubility profiles [16,17]. Hydrotropy has been successfully applied in the solubilization of drugs such as furosemide [2], rosuvastatin [4], artemisinin [18] and naproxen [19] demonstrating improved dissolution rates and bioavailability.

Glimepiride (GLP) is a third-generation hypoglycemic sulfonylurea used to treat type 2 diabetes mellitus by stimulating insulin release from pancreatic β-cells, thereby increasing circulating insulin and C-peptide levels. Its chemical name is 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrrolidinylcarbamoyl) ethyl] phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea (Figure 1), and its molecular weight is approximately 490.62 g·mol^{-1}. GLP is classified as Biopharmaceutical Classification System (BCS) class II, exhibiting low aqueous solubility and high permeability. Its solubility is very low (<0.004 mg/mL at 37°C in acidic and neutral media; ≈0.02 mg/mL at pH > 7) and it is lipophilic (log P ≈ 4.7) [20,21]. These physicochemical properties-poor water solubility and slow dissolution- complicate dosage form development and can lead to variable bioavailability, inconsistent clinical responses, and therapeutic failure [22–25].

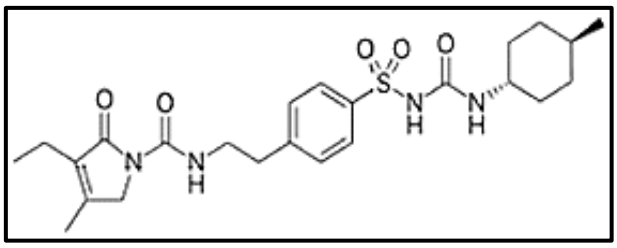

Fig. 1. Chemical structure of glimepiride (GLP)

The aim of this work was to enhance the aqueous solubility of the antidiabetic drug glimepiride (GLP) using the hydrotropic technique with various hydrotropes at different concentrations. This approach may improve GLP's bioavailability and, consequently, its effectiveness in controlling blood sugar levels.

2. Materials and methods

2.1. Materials

Pure Glimepiride (GLP) was obtained as a gift sample from MAF Company, Hadhramaut, Yemen. Sodium citrate was purchased from BDH Chemicals Ltd., Poole, England; sodium acetate was purchased from HiMedia Laboratories Pvt. Ltd, India; sodium benzoate and sodium chloride were purchased from Pure-Chemical; Potassium dihydrogen phosphate, disodium hydrogen phosphate, urea, and mannitol were purchased from Scharlau, Spain; methanol and ethanol were purchased from Pharmchem, Bahadurgarh, India. All chemicals used were of analytical grade.

2.2. Methods

2.2.1. Saturated solubility studies of GLP

Approximately 20 mg of (GLP) was added in excess to 50 ml of different solvents (water, ethanol, methanol, and saline phosphate buffer [SPB], pH 6.8) contained in amber glass bottles. The bottles were tightly sealed to prevent the evaporation and placed in a magnetic stirrer (Stuart CB162 hotplate, UK) at 100 rpm for 24 hours at a controlled temperature of 37 ± 1°C to attain equilibrium. After equilibration, the samples were centrifuged at 3000 rpm for 30 minutes to separate undissolved solids. The clear supernatant solutions were collected, suitably diluted with the respective solvents, and analyzed using a UV spectrophotometer at 226 nm. For every measurement, corresponding solvents served as blanks [26]. Each experiment was conducted in triplicate, and the

mean values with standard deviation (SD) were calculated.

2.2.2. Saturated solubility studies of GLP with hydrotropic agents

The saturation solubility of GLP in the presence of various hydrotropic agents was determined. The agents used were mannitol (M), sodium benzoate (SB), urea (U), sodium acetate (SA), and sodium citrate (SC). Solubility studies were conducted at concentrations of 10, 20, 30, and 40% w/v using distilled water as the solvent. Predetermined amounts of hydrotropic agents were dissolves in 100 ml of distilled water contained in amber glass bottles, after which an excess amount of GLP (approximately 10 mg) was added. The bottles were tightly sealed to prevent evaporation and placed on a magnetic stirrer at 100 rpm and 37 ± 1°C for 24 hours to reach equilibrium. Subsequently, the samples were centrifuged at 3000 rpm for 30 minutes to remove undissolved solids. The clear supernatant solutions were collected, suitably diluted with the respective solvents, and their absorbance was measured at 226 nm using a UV spectrophotometer. The solubility studies were performed in triplicate and the mean values with SD were calculated [11]. The following equation was used calculate the solubility enhancement ratios (SER):

$$\text{SER} = \frac{\text{solubility of drug in hydrtropic agent}}{\text{solubility in water}} \quad \ldots\ldots\ldots \text{(Eq.1)}$$

2.2.3. Saturated solubility studies of GLP with binary and ternary hydrotropic agents

GLP exhibited the highest aqueous solubility when mixed with sodium citrate at 40% w/v. Accordingly, the saturation solubility of GLP was investigated by using sodium citrate in combination with one or two additional hydrotropic agents at different weight ratios. The same experimental procedures as above were used, in which either two or three hydrotropic agents were mixed and dissolved in distilled water, an excessive amount of GLP was added, and the mixture was stirred at 100 rpm at a controlled temperature of 37 ± 1°C for 24 hours to reach equilibrium. Subsequently, the samples were centrifuged at 3000 rpm for 30 minutes, and clear supernatant solution was collected and suitably diluted with the respective solvents, and analyzed at 226 nm using a UV spectrophotometer. All experiments were conducted in triplicate, and the mean values with SD were calculated. Solubility enhancement ratios were also calculated [11].

2.2.4. Formulation of GLP with SC

2.2.4.1. Preparation of the physical mixture

The physical mixture of GLP and sodium citrate was prepared at a 1:4 (w/w) ratio. Each powder was passed through sieve No. 70 and then weighed separately. The powders were then mixed thoroughly using the geometric dilution technique, followed by passage through sieve No. 70 once again. The final mixture was stored in screw-capped glass vials in a desiccator [12].

2.2.4.2. Preparation of the solid dispersion by solvent evaporation method

GLP solid dispersion was made using the solvent evaporation method with sodium citrate at a weight ratio of 1:4 (w/w). The precisely weighed quantity of hydrotropic agent was dissolved in appropriate volume of distilled water. GLP was then weighed and dissolved in ethanol. The aqueous solution was then mixed with the drug's ethanoic solution and continuously stirred at room temperature until complete evaporation of the solvent. The solid mass was then crushed and sieved through sieve No. 70 after drying for 24 hours at 40°C in an oven. The prepared solid dispersion was stored in screw capped glass vials inside a desiccator [27].

2.2.4.3. Preparation of the solid dispersion by kneading method

Accurately weighed quantities of GLP and sodium citrate (1:4, w/w) were placed in a mortar and thoroughly mixed. The mixture was kneaded with warm distilled water to form a paste, dried in an oven at 40°C for 24 hours, then crushed and sieved through sieve No. 70. The resulting solid dispersion was stored in screw-capped glass vials inside a desiccator [12].

2.2.5. Evaluation of the prepared mixtures

2.2.5.1. Production yield

The following equation was used to determine the production yield of the solid dispersions and physical mixture of GLP with sodium citrate [8]:

$$\text{Production yield (\%)} = \frac{\text{weight of solid dispersion}}{\text{drug weight+hydrotopic weight}} \times 100 \quad \ldots\ldots\ldots \text{(Eq.2)}$$

2.2.5.2. Drug content of GLP

The amount of GLP in the solid dispersions and physical mixture was assessed. Each mixture was precisely weighed separately to determine how much GLP it contained (4 mg), which was then transferred to a 25 ml volumetric flask and dissolved in a small amount of methanol to bring the volume up to the required level. The resultant mixtures were centrifuged at 3000 rpm for 30 minutes, A specified volume of these solutions was diluted to 10 ml with SPB at pH 6.8, and the absorbance was measured using a UV spectrophotometer at a wavelength of 226 nm. The linear regression equation of glimepiride was used to calculate the drug concentration; $y = 0.0449x - 0.0023$ ($R^2 = 0.9994$). The percent drug content is calculated using the following equation [8]:

$$\text{\% Drug Content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100 \text{ . (Eq.3)}$$

2.2.5.3. In vitro dissolution rate studies

The dissolution rate studies of 4 mg of pure GLP, an equivalent amount from the physical mixture, and the solid dispersions were performed using the paddle method of the dissolution testing apparatus type 2 (United States Pharmacopeia, USP). The dissolution medium consisted of 900 ml of SBP at pH 6.8, maintained at 37 ± 0.5°C, with paddle rotation speed 75 rpm. The studies were conducted for one hour. Samples of 5 ml were withdrawn at predetermined time intervals of 5, 10, 15, 20, 25, 30, 45 and 60 minutes and replaced with fresh SPB at the same temperature to maintain a consistent volume throughout the experiment. The withdrawn samples were centrifuged at 3000 rpm for 30 minutes and were analyzed using UV spectrophotometer at 226 nm. The dissolved concentrations of GLP were calculated as the percentage amount released against time (minutes). The dissolution studies of each formulation were conducted in triplicate, and the mean values with SD were calculated [27].

2.2.6. Fourier transform infrared analysis (FTIR)

A Fourier-transform infrared (FTIR) spectrophotometer (PerkinElmer Spectrum Two™ FTIR) was used to obtain the FTIR spectra of pure GLP, sodium citrate, the physical mixture, and solid dispersions of GLP and sodium citrate (1:4, w/w). The spectra were recorded over the range of 4000 -450 cm^{-1} [11].

2.2.7. Data analysis of in vitro dissolution rate of GLP

2.2.7.1. Dissolution profile similarity analysis (f2)

The similarity factor f2 was calculated to compare the dissolution profiles of GLP alone (reference) with the formulations of GLP with SC physical mixture and solid dispersions prepared by solvent evaporation and kneading methods (test). The dissolution studies were conducted over a 1-hour period. The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error. f2 values between 50 and 100 indicate that two dissolution profiles are similar. Equation 4 was used to calculate the similarity factor f2. Where (n) is the number of sampling time points, (Tt) is the percent dissolved of the reference at time t, and (Rt) is the percent dissolved of the test at time t [27].

$$f2 = 50\log\left[\sqrt{\left\{1+\frac{1}{n}\sum_{t=1}^{n}(Rt-Tt)^2\right\}} \times 100\right]. \text{ (Eq.4)}$$

2.2.7.2. Dissolution efficiency (% DE)

The dissolution efficiency (%DE) of the pure GLP, the physical mixture, and the solid dispersions of GLP with SC were calculated using equation 5. Where y is the percent dissolved at each time (expressed as %), t is the time up to which the area under the dissolution curve is calculated (1 h) [27].

$$DE\ (\%) = \frac{\int_{t1}^{t2} y.dt}{y100.t} \times 100 \text{ ……. (Eq.5)}$$

3. Results and Discussion

3.1. Saturated solubility studies of GLP

GLP's saturation solubility was assessed over a 24-hour period in water, saline phosphate buffer (pH 6.8), and methanol. The solubility values of GLP in these solvents are shown in Table 1. GLP exhibited a poor water solubility (~ 2.827 µg/ml) due to its inability to effectively break the hydrogen-bonded lattice structure of water. In neutral saline phosphate buffer (pH 6.8), its solubility increased to 17.916 µg/ml. These outcomes are consistent with previous findings [3]. According to the biopharmaceutical classification, GLP is classified as a Class II drug because of its poor solubility in water and high partition coefficient value (log P ≈ 4.7), indicating good solubility in lipophilic solvents. This classification highlights the challenges in formulating GLP for effective oral delivery. Consequently, researchers are exploring various strategies to enhance its solubility and bioavailability, including hydrotropic solubilization.

Table 1: Saturation solubility of GLP in different solvent

Solvent	Solubility of drug µg/ml ±SD
Distill water	2.827 ±0.008
Saline Phosphate buffer 6.8	17.916 ±0.085
Methanol	70.520 ±0.005
Ethanol	73.590 ±0.005

3.2. Saturated solubility studies of GLP with hydrotropic agents

The study investigated the effects of various hydrotropic agents at different concentrations, including mannitol (M), sodium benzoate (SB), urea (U), sodium acetate (SA), and sodium citrate (SC), on the solubility of GLP. The concentrations of these agents ranged from 10% to 40% w/v [4]. Table 2 illustrates the aqueous solubility of GLP in (µg/ml) versus concentrations in % w/v of these hydrotropic agents. GLP exhibited the highest aqueous solubility (246.18 µg/ml ± 0.0133) with the addition of sodium citrate 10% w/v, witch further increased to 803.79 µg/ml ± 0.0147 at 40%w/v. The solubility also increased by the addition of sodium acetate to the aqueous solution of the drug 114.27 µg/ml ± 0.0067 at concentration of 10% w/v up to 310.65 µg/ml ± 0.0089. However, the drug's aqueous solubility didn't improve significantly with mannitol, sodium benzoate, or urea compared to SC and SA. The order of increasing aqueous solubility was: SC > SA > U > M > SB. The aqueous solubility enhancement ratios of these hydrotropic agents were calculated and are shown in Figure 2.

Table 2: The Solubility of GLP in hydrotropic agents

Hydrotropic agent	Solubility µg/ ml ±SD *(SER)			
	*10%	*20%	*30%	*40%
SB	9.63 ± 0.004 (3.41)	11.16 ± 0.004 (3.95)	12.50 ± 0.005 (4.42)	14.09 ± 0.004 (4.985)
M	7.39 ± 0.008 (2.61)	14.53 ± 0.003 (5.14)	16.98 ± 0.004 (6.01)	20.00 ± 0.003 (7.076)
U	27.53 ± 0.004 (9.74)	36.80 ± 0.003 (13.02)	68.96 ± 0.006 (24.39)	84.49 ± 0.008 (29.885)
SA	114.27 ± 0.007 (40.42)	187.86 ± 0.003 (66.45)	231.31 ± 0.008 (81.82)	310.65 ±0.009 (109.887)
SC	246.18 ±0.013 (87.08)	433.26 ± 0.008 (153.26)	662.66 ± 0.015 (234.40)	803.79 ±0.015 (284.33)

*(W/V), SB; sodium benzoate, M: mannitol, U: urea, SA: sodium acetate, SC: sodium citrate, *Solubility enhancement ratio

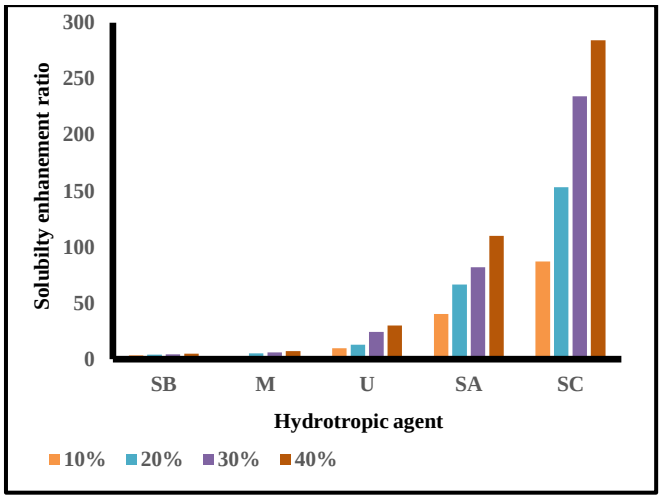

Fig. 2: Solubility enhancement ratio of GLP in the presence hydrotropic agents at concentration 10-40 % w/v.

3.3. Saturated solubility studies of GLP with binary and ternary mixtures of hydrotropic agents

The aqueous saturation solubility of GLP was evaluated using binary mixtures of two hydrotropic agents (M, SA, U, SB, and SC) at a 1:1 weight ratio (20%:20% w/v). Table 3 shows that mixing SC with SA, U, or M produced solubility values of 513.85 ± 0.0124, 420.91 ± 0.0074, and 407.05 ± 0.0106 µg/ml, respectively, compared with 433.26 ± 0.0080 µg/ml for SC alone (20% w/v). In contrast, combining SC with SB markedly reduced solubility to 11.68 ± 0.0033 µg/ml. SA alone (20% w/v) yielded a solubility of 187.86 ± 0.0030 µg/ml; SA mixed with M or U produced drug solubility values of 236.92 ± 0.0035 and 176.44 ± 0.0078 µg/ml, respectively. Other binary hydrotropic combinations generally result in decreased GLP solubility.

Ternary mixtures containing SC and two additional hydrotropic agents (M, SA, U, and SB) were evaluated at weight ratios of 3.5:0.25:0.25, 3:0.5:0.5, 2.5:0.5:1, 2.5:1:0.5, 2:1:1, and 1:1:1 (w/w) to cover possible combinations [4]. As shown in Table 4, the highest solubility among these mixtures occurred when SC was present at 35% w/w (3.5:0.25:0.25), although this remained lower than the solubility achieved with SC alone at 40% w/w. Overall, SC alone provided the greatest enhancement of GLP's aqueous solubility.

Table 3: The Solubility of GLP in binary mixture of hydrotropic agents

Binary Hydrotropic Agents	Total Concentration (% W/V)	Ratio	Solubility µg/ml ± SD	*SER
SC & SA	40	1:1	513.85 ±0.012	181.764
SC & U	40	1:1	420.91 ± 0.007	148.889
SC & M	40	1:1	407.05 ± 0.011	143.986
SC & SB	40	1:1	11.68 ± 0.003	4.133
U & M	40	1:1	44.96 ± 0.006	15.903
U & SA	40	1:1	236.92 ± 0.004	83.806
U & SB	40	1:1	7.69 ± 0.003	2.720
M & SA	40	1:1	176.44 ± 0.009	62.411
M & SB	40	1:1	11.09 ± 0.003	3.923
SB & SA	40	1:1	11.48 ± 0.003	4.061

*(W/V), SB; sodium benzoate, M: mannitol, U: urea, SA: sodium acetate, SC: sodium citrate, *Solubility enhancement ratio

Table 4: The Solubility of GLP in ternary mixture of hydrotropic agents

Ternary Hydrotropic Agents	Total Concentration (% W/V)	Ratio	Solubility µg/ml ± SD	*SER
SC & SA & U	40	3.5:0.25:0.25	661.46 ±0.009	233.98
SC & SA & M	40	3.5:0.25:0.25	677.36 ±0.009	239.603
SC & U & M	40	3.5:0.25:0.25	710.23 ±0.017	251.231
SC & SA & U	40	3:0.5:0.5	580.46 ±0.005	205.327
SC & SA & M	40	3:0.5:0.5	601.85 ±0.004	212.894
SC & U & M	40	3:0.5:0.5	591.44 ±0.010	209.209
SC & SA & U	40	2.5:1:0.5	500.47 ±0.007	177.031
SC & SA & M	40	2.5:1:0.5	558.47 ±0.006	197.548
SC & SA & U	40	2.5:0.5:1	538.77 ±0.004	190.579
SC & SA & M	40	2.5:0.5:1	458.52 ±0.010	162.192
SC & SA & U	40	2:1:1	415.05 ±0.006	146.818
SC & SA & M	40	2:1:1	418.54 ±0.005	148.053
SC & SA& U	40	1:1:1	333.51 ±0.007	117.973
SC & SA & M	40	1:1:1	348.56 ±0.007	123.298
SC & SA & SB	40	1:1:1	7.63 ±0.004	2.699
SC & M & U	40	1:1:1	266.37 ±0.017	94.225
SC & M & SB	40	1:1:1	7.90 ±0.003	2.794
SC & U & SB	40	1:1:1	5.26 ±0.003	1.862

SB; sodium benzoate, M: mannitol, U: urea, SA: sodium acetate, SC: sodium citrate *Solubility enhancement ratio

3.4. Evaluation of the prepared mixtures

3.4.1. Production yield

The percent production yield values for GLP formulations with SC are presented in Table 5 and ranged from 95.44 ± 1.95% to 101.80 ± 2.36%. These results were consistent with previously reported yields values [12].

3.4.2. Drug content of GLP

The calculated drug content of GLP was 87.00 ± 0.0032% for the physical mixture, 101.34 ± 0.0026% for the GLP solid dispersion prepared by the solvent evaporation method (SDE), and 94.37 ± 0.0025% for the solid dispersion prepared by kneading method (SDK); Table 5. The drug content uniformity determination indicated that the drug was uniformly dispersed throughout the films and fell within the acceptable range established by the British Pharmacopoeia (85–115%; Appendix XII C: Consistency of Formulated Preparations).

Table 5: The Production yield and drug content of GLP physical mixture and solid dispersions

Solid Dispersion	Production Yield (%) Mean ± SD	Drug content (%) Mean ± SD
GLPPM	99.33 ±3.02	87.00 ±0.32
GLPE	101.80 ±2.36	101.34 ±0.26
GLPK	95.44 ± 1.95	94.37 ±0.25

GLPPM: physical mixture, GLPE: solvent evaporation method, GLPK: kneading method

3.4.3. In vitro dissolution rate studies

Figure 3 presents cumulative dissolution profiles of pure GLP, the physical mixture (GLPPM), the solvent-evaporation solid dispersion (SDE), and the kneading solid dispersion (SDK) over 60 minutes. SDK released GLP significantly faster than the other formulations ($p < 0.05$), showing the highest percent dissolved at all sampling time and approaching complete dissolution within 30 minutes. Pure GLP exhibited the slowest release of about 62.35 ± 0.54% within 30 minutes, and complete dissolution was not achieved after 1 hour (67.88 ±0.25%). After 30 minutes, dissolution percentages were 83.83 ± 1.47% (GLPPM), 69.09 ± 1.10% (SDE). A complete drug dissolution was achieved by GLPK of 99.90 ± 2.83% within 25 min. It was reported that the improvement in drug dissolution from the SC-containing solid dispersions is likely due to decreased particle size, enhanced wettability, prevention of drug aggregation, and possible changes in crystallinity [12,27]. However, the unexpectedly lower dissolution from SDE versus GLPPM could be explained by poor SC solubility in ethanol during solvent evaporation, which would limit SC incorporation into the dispersion and reduce its ability to enhance GLP dissolution [29]. Dissolution rate improved significantly in hydrotropic solution compared to pure water. Hydrotropic agents disrupt intermolecular forces among drug molecules, form reversible complexes or aggregates with them, and modify solvent polarity, thereby enhancing the dissolution of hydrophobic drugs [24,28].

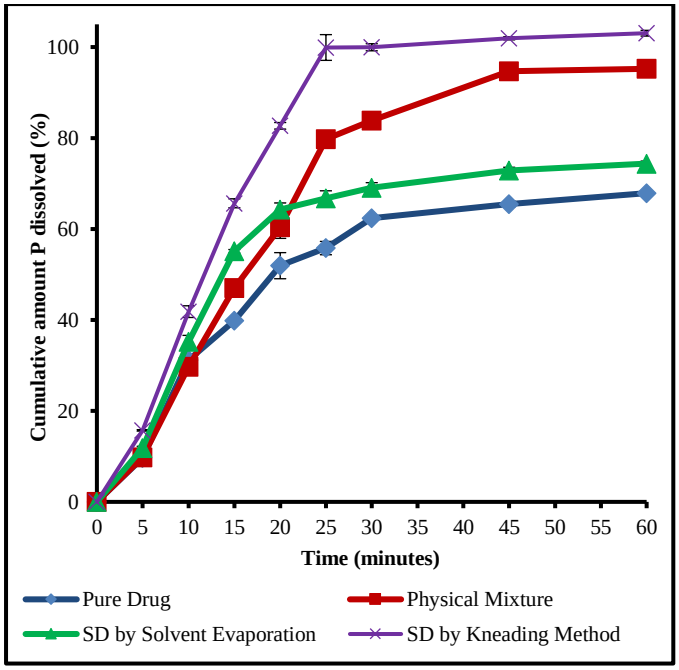

Fig. 3: The dissolution rate profiles of GLP: glimepiride, GLPPM: physical mixture, GLPE: solvent evaporation method, GLPK: kneading method

3.5. Data analysis of in vitro dissolution rate of GLP

Table 6 presents the calculated dissolution profile similarity (f_2) and dissolution efficiency (DE) for the *in vitro* dissolution data. Dissolution profiles of GLPPM, GLPE, and GLPK were compared to pure GLP. Both GLPPM and GLPK exhibited f2 and DE values that deviated from GLP by more than 10%, suggesting a significant difference in dissolution behavior. Conversely, GLPE didn't differ from GLP, with an f_2 of 53.08 and a DE of 58.46% compared to GLP's DE of 50.95%.

Table 6: The dissolution rate of pure GLP, physical mixture and solid dispersions with sodium citrate.

Formula	Cumulative amount GLP dissolved (%) / minute Mean ±SD								f_2	DE (%)
	5	10	15	20	25	30	45	60		
GLP	9.66 ±0.04	31.20 ±0.24	39.8 ± 0.26	51.9 ± 2.87	55.8 ±1.46	62.3 ±0.54	65.49 ±0.68	67.88 ±0.25	-	50.95
GLPPM	9.82 ±0.64	29.70 ±0.28	47.07 ±0.48	60.43 ±2.50	79.75 ±1.10	83.83 ±1.47	94.67 ±0.95	95.22 ±1.10	37.80	68.44
GLPE	11.83 ±0.40	35.20 ±1.41	55.10 ±0.38	64.29 ±1.43	66.76 ±1.63	69.09 ±1.10	72.85 ±0.72	74.38 ±0.56	53.08	58.46
GLPK	15.73 ±0.15	41.82 ±1.29	65.64 ±0.99	82.69 ±0.72	99.90 ±2.83	99.95 ±0.78	101.93 ±0.35	103.06 ±0.62	26.70	80.51

GLP: glimepiride, GLPPM: physical mixture, GLPE: solvent evaporation method, GLPK: kneading method, f2: similarity factor, DE: dissolution efficiency.

3.6. Fourier transform infrared analysis (FT-IR)

The FTIR spectra of GLP and its mixtures with SC prepared by physical mixing (GLPPM), solvent evaporation (GLPE), or kneading (GLPK) were examined for spectral changes indicating drug-excipient interaction. The GLP spectrum showed two N-H stretching peaks around 3369.48 and 3288.63 cm^{-1} were the characteristic of asymmetric and symmetric primary amines R-NH_2. At 2930.77 and 2842.64 cm^{-1}, corresponding to asymmetric and symmetric aliphatic -CH_3 stretches. The strong sharp band at 1704.50 cm^{-1} assigned to the urea carbonyl. N–H bending band at 1672.16 cm^{-1}. Peaks between 1589 and 1493 cm^{-1} attributable to benzene ring skeletal vibrations and C=C stretching. Sulfonamide (SO_2–NH): asymmetric and symmetric S=O stretches near 1344.44 and 1151.71 cm^{-1}, respectively. These two peaks serving as a fingerprint of the sulfonylurea moiety [11,12,24].

Sodium citrate exhibited O-H Stretching at 3446.60, 3369.33, and 3286.04 cm^{-1}. A strong asymmetric stretching peak at 1582.37 and symmetric stretching at 1417.57 cm^{-1} were characteristic of the carboxylate anion -COO-. The separation ($\Delta \approx 180$ cm^{-1}) indicates ionic bonding between sodium and citrate. Peaks in the region 1300-780 cm^{-1} correspond to skeletal vibrations of the citrate backbone, including C-O stretching, C-H bending, and C-C stretching modes [3].

The FTIR spectrum GLP in the GLPPM showed that the drug's distinctive peaks remained at the same wavelengths, indicating that no interaction occurred. However, the FTIR spectrum of GLP in GLPE showed the appearance of new, slightly broad peak and a reduction in the intensity of carbonyl group at 1704.50 cm^{-1} and N-H bending band at 1672.16 cm^{-1}. Similarly, the FTIR spectrum of GLP showed only one broad peak at 3369 cm^{-1} and a distinctive reduction in the peak intensities of the carbonyl group at 1704.50 cm^{-1} and N-H bending band at 1672.16 cm^{-1}. These observations were indicating the inclusion of GLP in the matrix of SC and the presence of intermolecular hydrogen bonds.

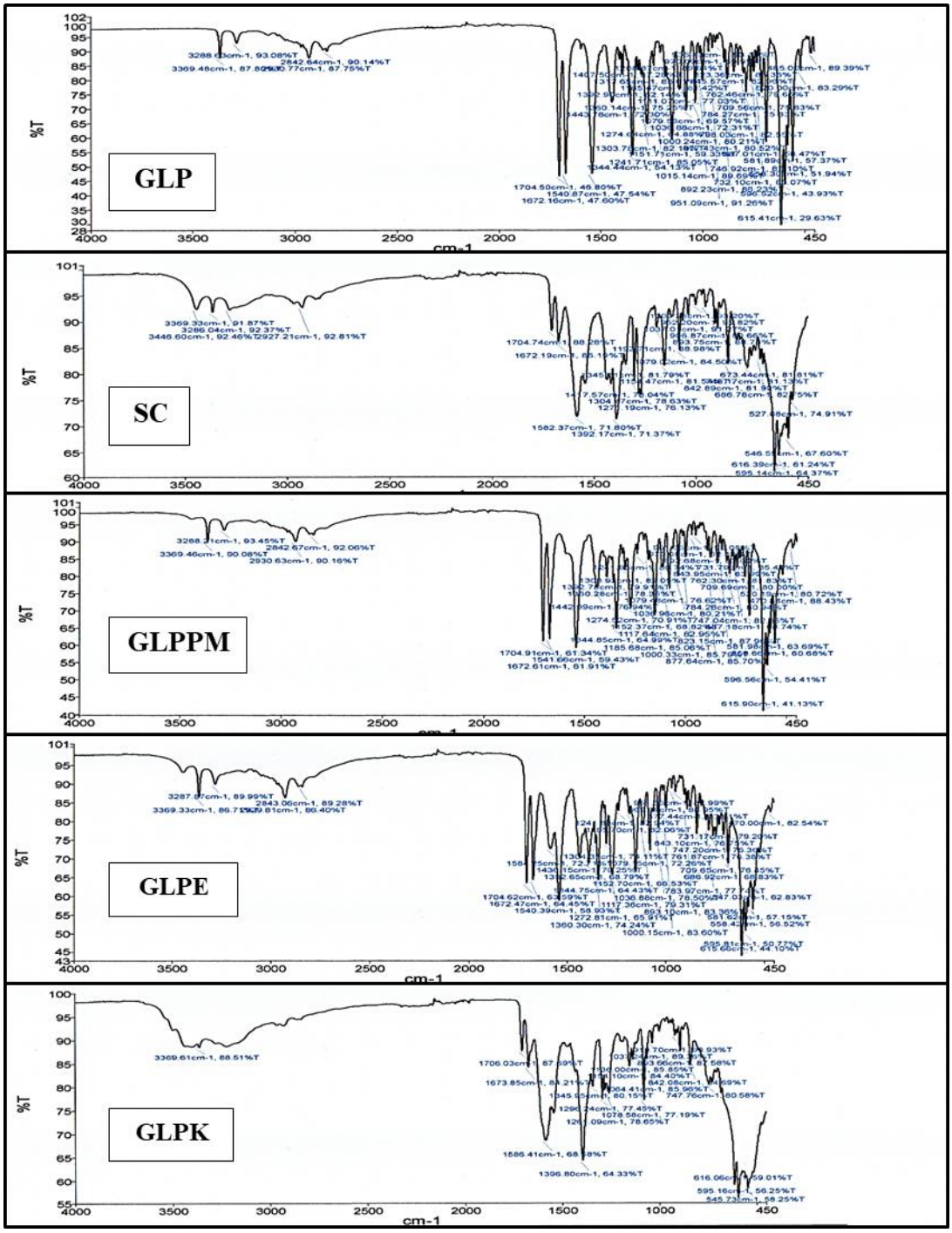

Fig. 4: The FTIR spectra of GLP: glimepiride, GLPPM: physical mixture, GLPE: solvent evaporation method, GLPK: kneading method

4. Conclusion

Glimepiride exhibits low aqueous solubility, which presents challenges for formulating it into a suitable dosage form. Enhancing the solubility of poorly soluble drugs remains essential for improving oral bioavailability and therapeutic efficacy. Hydrotropy offers a viable and cost-effective approach for enhancing the solubility of poorly soluble drugs. Among the five hydrotropic agents tested, sodium citrate provided the highest drug solubility value and enhancement ratio. The solid dispersion of glimepiride and sodium citrate prepared by the kneading method showed the fastest and most complete drug *in vitro* dissolution compared to the physical mixture and solid dispersion prepared by solvent evaporation.

5. Conflict of interest

The authors declare no conflicts of interest.

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مقالة بحثية

الذوبانية الهيدروتروبية: تقنية فعالة لتحسين ذوبانية دواء مضاد السكري جليمبيريد

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المُلخّص

الذوبانية، هي خاصية فيزيائية كيميائية، تحدد قدرة المادة على الذوبان في المذيب. جليمبيريد، وهو دواء من الفئة الثانية وفقًا لنظام تصنيف الأدوية (BCS) لعلاج مرض السكري من النوع الثاني، يتمتع بذوبانية مائية منخفضة جدًا ونفاذية عالية، مما يعقد عملية تركيبه الى شكل دوائي ويمكن أن يسبب تباينًا في التوافر البيولوجي وفشلًا علاجيًا. ان تعزيز الذوبانية المائية للأدوية باستخدام الهيدروتروبي يسمح بتحميل دوائي أعلى مع سمية منخفضة. هدفت هذه الدراسة إلى تحسين الذوبانية المائية والتوافر البيولوجي للجليمبيريد باستخدام العوامل الهيدروتروبية. وقد تم قياس الذوبانية في الماء، ومحلول الفوسفات الملحي، والإيثانول، والميثانول، وفي محاليل من خمسة عوامل هيدروتروبية (بنزوات الصوديوم، المانيتول، اليوريا، أسيتات الصوديوم، وسيتريت الصوديوم بنسبة 10-40% وزناً/حجماً). وكذلك تم تقييم ذوبانية الدواء في خليط من العوامل الهيدروتروبية الثنائية والثلاثية. وكما تم تقييم الذوبان في المختبر للجليمبيريد من المزيج فيزيائي والمتشتتات الصلبة مع سترات الصوديوم المحضرة بطرق تبخر المذيب والعجن. حيث كانت ذوبانية الجليمبيريد في الماء 2.83 ميكروغرام/مل. وتم تحقيق أكبر تحسين باستخدام 40% سترات الصوديوم، والذي ادى للحصول على ذوبانية 803.79 ± 0.015 ميكروغرام/مل (نسبة 284.33). تراوحت إنتاجية الخلطات الفيزيائية والمتشتتات الصلبة بين 95.44 ± 2.01% إلى 101.80 ± 2.99%، وتفاوت محتوى الدواء بين 87.00 ± 3.02% إلى 101.34 ± 2.36%. أسرع وأكمل ذوبانية في المختبر؛ 99.95% ± 0.78 (DE% 80.51) خلال 30 دقيقة لوحظ في التشتت الصلب المحضر بطريقة العجن، مقارنةً بـ 62.35% ± 0.54 (DE% 50.95) للدواء النقي. أشارت تحليل FTIR إلى تفاعلات الروابط الهيدروجينية بين الجليمبيريد وسيتريت الصوديوم. في الختام، ان سترات الصوديوم عزز بشكل كبير من ذوبان الجليمبيريد وانحلاله من المتشتتات الصلبة، خاصة بطريقة العجن.

الكلمات المفتاحية: الجليمبيريد، تحسين الذوبانية، العوامل الهيدروتروبية، المشتتات الصلبة، الذوبانية في المختبر.

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