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DESIGN AND CHARACTERIZATION OF GLIMEPIRIDE HYDROTROPIC SOLID DISPERSION TO ENHANCE THE SOLUBILITY AND DISSOLUTION

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ABSTRACT
Background: Glimepiride lowers blood sugar levels in the body, and treats type 2 diabetes mellitus. But the main problem with the drug is its low aqueous solubility. The primary purpose of this study is to increase its solubility in an aqueous medium by using amphiphilic hydrotropic agents instead of harmful, volatile organic solvents. **Methodology:** A solubility study of Glimepiride was carried out using various hydrotropic agents at 10%, 20%, 30%, and 40%. In mixed hydrography, 30% of the hydrotropic agents were chosen for making blends due to their highest solubility. The blend's solubility was raised more than 50 times at fixed concentrations of urea (20%) and sodium acetate (10%) in a mixed hydrotropic solution. The solubility of Glimepiride in distilled water is 0.0038 mg/ml; in 30% urea, 49.512 ug/ml; and in 30% sodium acetate, 40.43 ug/ml. The optimized blend prepared hydrotropic solid dispersions by physical mixing and solvent evaporation. It was evaluated for drug content, FTIR, SEM, X-ray diffraction, and in vitro drug release studies. Finally, the drug release profile of the prepared tablet is compared with an already available consumer product. **Result**: HSD-5 showed an in-vitro drug release of 84.77±0.44 at 90 min, which is higher than the remaining formulations, and no significant change was found in drug content or drug release after 15, 30, and 45 days of stability studies. Scanning electron microscopy (SEM) showed homogenous solid dispersion, crystallinity was determined using X-ray diffraction, and FTIR showed good drug compatibility with carriers. The drug release profile of the prepared tablet was higher than that of the available consumer product. **Conclusion:** This study revealed that hydrotropic agents can potentially increase glimepiride's solubility and drug release. This approach can effectively enhance the solubility of poorly water-soluble drugs.

INTRODUCTION

Oral administration is a very convenient and easy ingestion route for all solid dosage forms, but for various poorly soluble drugs, bioavailability is limited by the dissolution rate. This is the main problem in developing pharmaceutical dosage forms [1].

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Throughout recorded history, diabetes mellitus has affected the lives of millions of people of all ages, sexes, races, and economic statuses [2]. Studies show that, between 2009 and 2034, the number of people with diagnosed and undiagnosed diabetes will increase from 23.7 million to 44.1 million in the United States [3-4]. Conventional treatment with sulfonylurea, glyburide, glipizide, and diet takes nearly 10 years to cure type 2 diabetes mellitus because of the poor aqueous solubility of drugs. So, there is a need to solubilize the drugs in aqueous medium [5].

Lipophilic drugs with poor aqueous solubility cause difficult problems during their spectrophotometric analysis in their formulation. Thus, their solubility must be enhanced to facilitate their estimation in dosage forms. Out of various methods available to increase the water solubility of lipophilic drugs, hydrotrope is the most advanced and successful method, in which the solubility of the poorly water-soluble drugs is increased by utilizing the highly water-soluble substances [6-7]**.**

Solubility behavior is the most challenging aspect for various new chemical entities, as 60% of the latest potential products possess solubility problems. This is the biggest reason for new drug molecules not reaching the market or not reaching their full potential. Various techniques enhance drug solubility, such as particle size reduction, nanosuspension, use of surfactants, salt formation, solid dispersion, etc. [8-9]. Hydrotropes are a diverse class of chemical compounds first described by Neuberg (1916) that cause several-fold increases in water solubility of sparingly soluble drugs used to designate the increase in solubility of poorly water-soluble drugs in concentrated solutions of hydrotropic agents [10-13]. The increase in water solubility is probably due to the formation of organized assemblies of hydrotrope molecules at critical concentrations [14-15]. Many drugs that are poorly soluble in water have been made soluble through the use of different hydrotropic solutions. Sodium salicylate, Sodium benzoate, nicotinamide, urea, sodium ascorbate, sodium ascorbate, sodium citrate, and sodium acetate are the most commonly used hydrotropic agents [16-17].

Glimepiride is a very poor water-soluble sulfonylurea with aqueous solubilities of less than 4 μg/mL at 310.15 K and 6.4 μg/mL at 298.15 K. This work aims to improve glimepiride's solubility, dissolution, and drug release by employing various highly water-soluble, non-toxic hydrotropic compounds [18].

MATERIALS AND METHODS

Materials

Supra Chemicals, Mumbai, kindly gifted glimepiride powder (raw material). Urea, sodium acetate, and sodium alginate from Loba Chemie, Mumbai, were hydrotropic agents. Cholesterol from Loba Chemie, Mumbai, methanol from Emplura, Mumbai, chloroform, and ethanol from Merk, Mumbai, of analytical purity were used as solvents. Potassium dihydrogen phosphate from disodium hydrogen phosphate from Loba Chemie, Mumbai, was used as a buffer.

Preparation of Hydrotropic solutions

Accurate weight quantities of urea, sodium acetate, and sodium citrate were added to 100ml of distilled water in volumetric flasks to prepare 10%, 20%, 30%, and 40% concentrations, and the solubility of Glimepiride was checked individually [19]. Among all these, the 30% concentration ratio exhibited the maximum solubility and was further chosen for mixed hypertrophy.

Mixed Hydrotrophy

Optimum concentrations of hydrotropic agents were used in mixed hypertrophy to reduce their toxicity. Glimepiride is more soluble in Urea and Sodium acetate than in urea, so these agents were used to prepare blends by different ratios of urea and sodium acetate to 100 ml of distilled water (total concentration kept 30%), as shown in Table 1 [20-21].

Table 1: Composition of blends of U-Urea and SA-Sodium acetate with 30% fixed concentration

Formulation code	Formula	Total concentration (30%)
Blend A	U+SA	15:15
Blend B	U+SA	20:10
Blend C	U+SA	10:20
Blend D	U+SA	25:5
Blend E	U+SA	5:25

Hydrotropic solid dispersion

Blend B, which combines urea and sodium acetate in a 20:10 ratio for maximum solubility, was chosen to make solid dispersions of various formulations using solvent evaporation and physical mixing methods, as indicated in Table 2.

Hydrotropic solid dispersion by Physical mixing method

A beaker was filled with various amounts of sodium acetate and urea that had been precisely weighed and mixed. Once

thoroughly mixed, add 100 mg of glimepiride and a small amount of water and stir until a semisolid consistency is achieved. After being placed on watch glasses, this solid mass was dried completely at a temperature of 90°C. Using a mortar and pestle, the dried solid dispersion was triturated and passed through sieve no. 60. For later usage, the finely ground solid dispersion was kept in glass vials in desiccators [22].

Hydrotropic solid dispersion prepared by solvent evaporation method: An accurate weight amount of urea and sodium acetate and 100 mg of Glimepiride was dissolved in the required quantity of methanol at room temperature for 4 to 6 h. The semisolid mass was obtained after evaporation of the solvent, then poured on watch glasses and kept in an oven at a temperature of 90ºC for 24 h. The dried mass was triturated and passed through sieve no.60, and fine solid dispersion was stored in glass vials in the desiccators [23-24].

Table 2: Optimized formula of solid dispersion prepared by physical mixing and solvent evaporation with various concentrations

S. No.	Formula	Ratio	Formula	Ratio
1.	HSD-1	1:3	HSE-1	1:3
2.	HSD-2	1:6	HSE-2	1:6
3.	HSD-3	1:9	HSE-3	1:9
4.	HSD-4	1:12	HSE-4	1:12
5.	HSD-5	1:15	HSE-5	1:15
6.	HSD-6	1:18	HSE-6	1:18

HSD – Hydrotropic solid dispersion, HSE – Solid dispersion by solvent evaporation

Physical characterization of hydrotropic solid dispersion

The prepared solid dispersion was evaluated in triplicate for physical and micrometric properties like bulk density, Hausner ratio, compressibility index, and angle of repose, and the average of three determinations was calculated [25].

Determination of drug content in different formulations

The prepared solid dispersions equivalent to 4 mg of pure drug were accurately weighed and transferred to a 100 ml volumetric flask containing 6.8 pH phosphate buffer, shaken properly, and sonicated for 20 min to dissolve the solid dispersion and then the volume was made up with phosphate buffer up to 100 ml. One ml of each solution was diluted to 10 ml and assayed for drug content using a UV spectrophotometer at 238 nm, and drug content was estimated by the following equation. Each sample was assayed in triplicate, and an average of three determinations was calculated [26].

$$\%\ drug\ content = \frac{Practical\ drug\ content}{Theoretical\ drug\ content} \times 100$$

Hygroscopicity

Accurately weighed (m1) 100 mg of prepared formula placed on watch glasses and subjected to ambient temperature 75% ±5 RH, 30ºC±2 for 2 days. The weight main (m2) was measured in triplicate, and the average percentage weight gain was calculated by using the formula [27].

$$\text{The percent mass gain } \left(\%\frac{\text{m}}{\text{m}}\right) = \frac{\text{m2} - \text{m1}}{\text{m1}} 100$$

Structural analysis of Glimepiride solid dispersion

Scanning Electron Microscopy (SEM)

Samples of solid dispersion and Glimepiride pure drug were mounted onto the stubs using double-sided adhesive tape and then coated with gold-palladium alloy (150-200 A°) using a fine coat ion sputter (Joel, JPC-1100). The samples were analyzed under the scanning electron microscope for external morphology [28-29].

X-ray diffraction studies (XRD)

X-ray diffraction of glimepiride and optimized (HSD-5) solid dispersions were carried out to assess the changes in the crystallinity when the drug was mixed with hydrotropic agents. Powder X-ray diffraction patterns were recorded using a powder X-ray diffractometer. The scanned range was 0- 50° [30-31].

Differential Scanning Calorimetry (DSC)

A shift in the peak or additional peaks at temperatures other than those corresponding to the drug and carrier indicated an interaction between the drug and polymer if any [32].

Fourier Transform Infrared (FTIR)

Infrared spectra of pure Glimepiride, urea, sodium acetate, and solid dispersion were recorded using an FTIR spectrometer to ascertain the presence of different functional groups. A small amount of the powdered solid (2-3 mg) was added to pure potassium bromide powder (KBr) and ground up as fine as possible. This was then placed in a small die and put under pressure to form a KBr pellet. The pellet was scanned from 400 to 4000 cm-1 [33-34].

Drug release studies

In-vitro drug release of all formulations was studied using a type I dissolution test apparatus. pH 6.8 phosphate buffer was used as a dissolution medium. Solid dispersions equivalent to 4 mg pure drug were accurately weighed, placed in a dialysis membrane, then tied properly, and put in the basket. The stirrer was adjusted at 50 rpm. Temperature (37±0.50°C) was maintained throughout the experiments. Samples (5 ml) were withdrawn from the dissolution medium at 10min, 20min, 30min, 40min, 60min, 70min, 80min, and 90min time intervals and replaced with the same buffer volume after each withdrawal. The samples were analyzed using a UV spectrophotometer to measure the amount of drug release by measuring the absorbance after the appropriate dilution buffer. The amount of drug release obtained using the formula below [35].

$$Amount\ of\ drug\ release = Concentration \times dissolution\ bath\ volume \times dilution\ factor/1000$$

$$Cumulative\ percentage\ drug\ release = \frac{Volumes\ of\ samples\ withdrawn(ml)}{Bath\ volume(v)}\ x\ P(t-1) + pt$$

P (t-1) = Percentage release before t; Pt = Percentage release at time t.

Preparation of Glimepiride Tablets

The Glimepiride solid dispersions HSD-5 and excipient were weighed accurately, blended for proper mixing, and then lubricated by further mixing with magnesium stearate. The mixture blend was subjected to drying to remove the moisture at 40-45oC and then directly compressed by using a rotary punching machine with 3mm flat surface punches with a compression force of 3-5kg/cm^2 [36] shown in Table 3. Finally, the drug release profile of the prepared tablet is compared with already-available consumer products.

Table 3: Composition of Glimepiride Tablets

S.No.	Ingredients	Quantity(mg)
1.	Solid dispersion	37
2.	Avicel pH 101	156
3.	Magnesium stearate	02
4.	Talc	5
Total weight of tablet (mg)		200

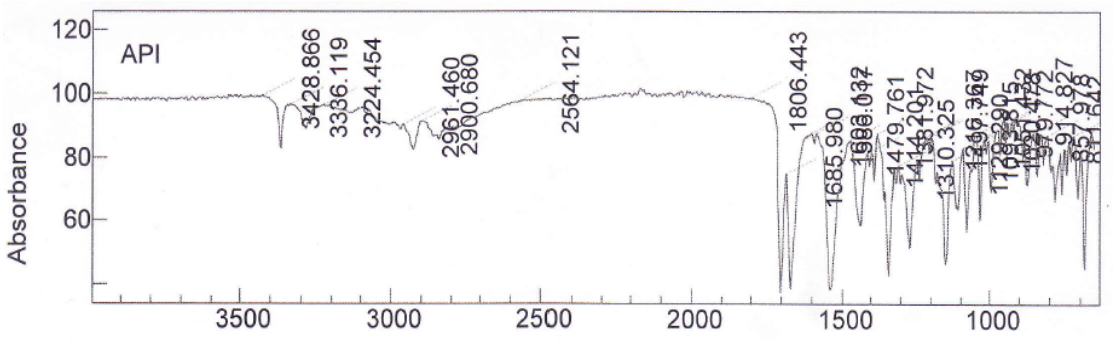
RESULTS AND DISCUSSION

Organoleptic properties

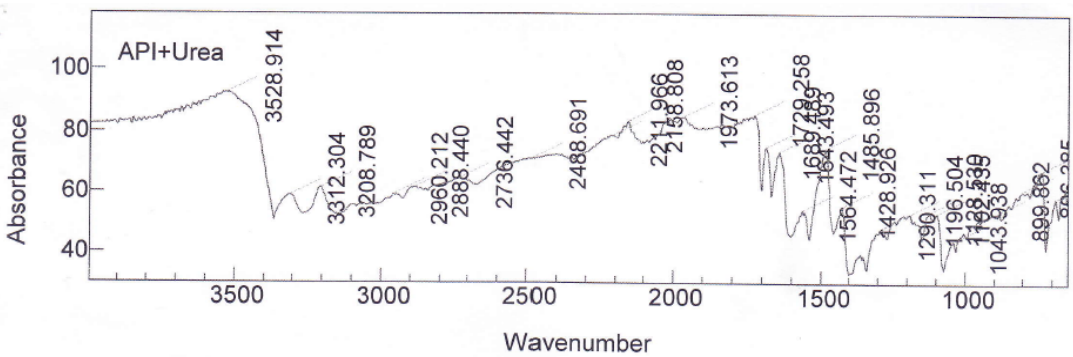
Glimepiride is a white, almost white crystalline powder, and all the prepared formulations are white crystalline powders.

Drug-excipient compatibility studies by FT-IR

From the spectra, the characteristic absorption peaks of GLMP (Glimepiride) at 3428 cm-1 (N-H stretch) were identified. It shows a strong absorption peak at 1806 cm-1 (C=O) and 1310 cm-1 (S=O). These characteristic peaks were also found in the drug with the hydrotropic agent mixture, which indicates no drug-excipient interaction shown in Figure 1.



(A)



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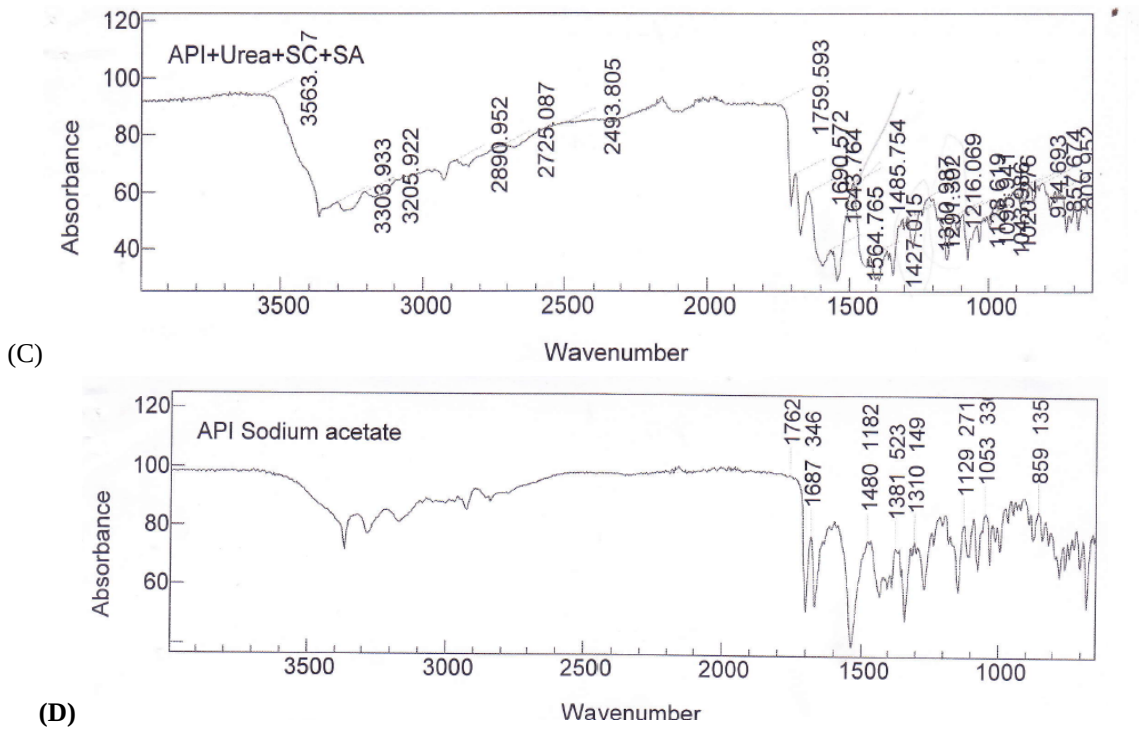


(C)

(D)

Figure 1: Fourier Transform Infrared Spectroscopy (A) Glimepiride (B) Glimepiride, Urea (C) Glimepiride, urea, sodium acetate and sodium citrate (D) Glimepiride and sodium acetate

Preliminary solubility studies of the drug: Table 4 shows the solubility of Glimepiride in water as 0.0038 mg/mL. The study states that the drug is practically insoluble and slightly soluble in methanol and ethanol. As the pH increased, the solubility of the drug also slightly increased.

Melting point: Glimepiride's melting point was found to be 205 ^{o}C±1, which is within the range and confirms the drug.

Preparation of calibration curve in mixed hydrotropic agents: It obeys beer's law in the 5-50 ug/ml concentration range with a correlation coefficient r2 = 0.9977, shown in Figure 2.

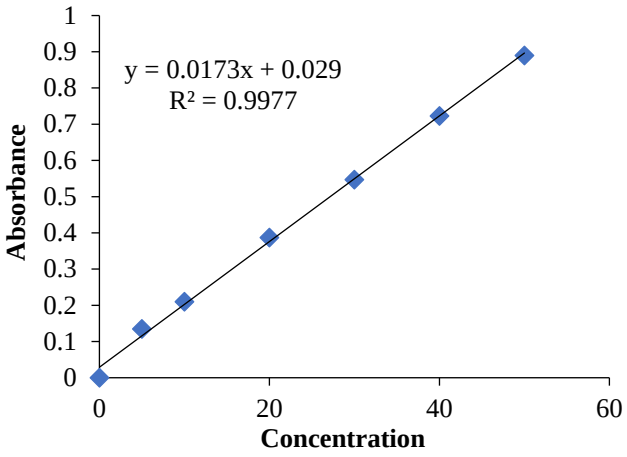


Figure 2: Calibration curve of Glimepiride

Evaluation of prepared formulations

Hydrotropic Solubilization: Table 5 shows the solubility of Glimepiride in 40% urea and 40% sodium acetate solutions as 51.172 ug /ml and 44.44 ug /ml, respectively. The study shows that this increase in the concentration of hydrotropic agents increases solubility.

Mixed Hydrotropy: The solubility of Glimepiride was found to be 64.513 ug /ml in a 20:10 ratio of urea and sodium acetate solutions (Table 6). Hence, the same combination was used to prepare the solid dispersion.

Table 4: Solubility of Glimepiride in different mediums

Solvent	Solubility(mg/ml)	Description
DM water	0.0038	Practically insoluble
Methanol	0.146	Slightly soluble
Ethanol	0.080	Very slightly soluble
1.2 pH buffer	0.094	Very slightly soluble
6.8 pH buffer	0.285	Slightly soluble
7.4 pH buffer	0.121	Slightly soluble

Table 5: Equilibrium solubility of Glimepiride in urea solution at different concentrations (average of 3)

S. No.	Concentration	Solubility in Urea (ug/ml)	Solubility Enhancement Ratio	Solubility in sodium acetate (ug/ml)	Solubility Enhancement Ratio
1.	10%	21.812	5.739	19.18	5.739
2.	20%	29.771	7.83	22.27	7.832
3.	30%	49.512	13.02	40.43	13.025
4.	40%	51.172	13.20	44.44	13.204

Table 6: Solubility enhancement of Glimepiride in mixed hydrotropic agents

Blends	Formula	Total concentration (30%w/v)	Solubility* (ug/ml)	Solubility enhancement ratio
1.	U+SA	15:15	28	7.36
2.	U+SA	20:10	64.513	16.97
3.	U+SA	10:20	22.276	5.8
4.	U+SA	25:5	35.302	9.28
5.	U+SA	5:25	44.25	11.64

*solubility is the average of 3 determinations *U = Urea, SA = Sodium Acetate

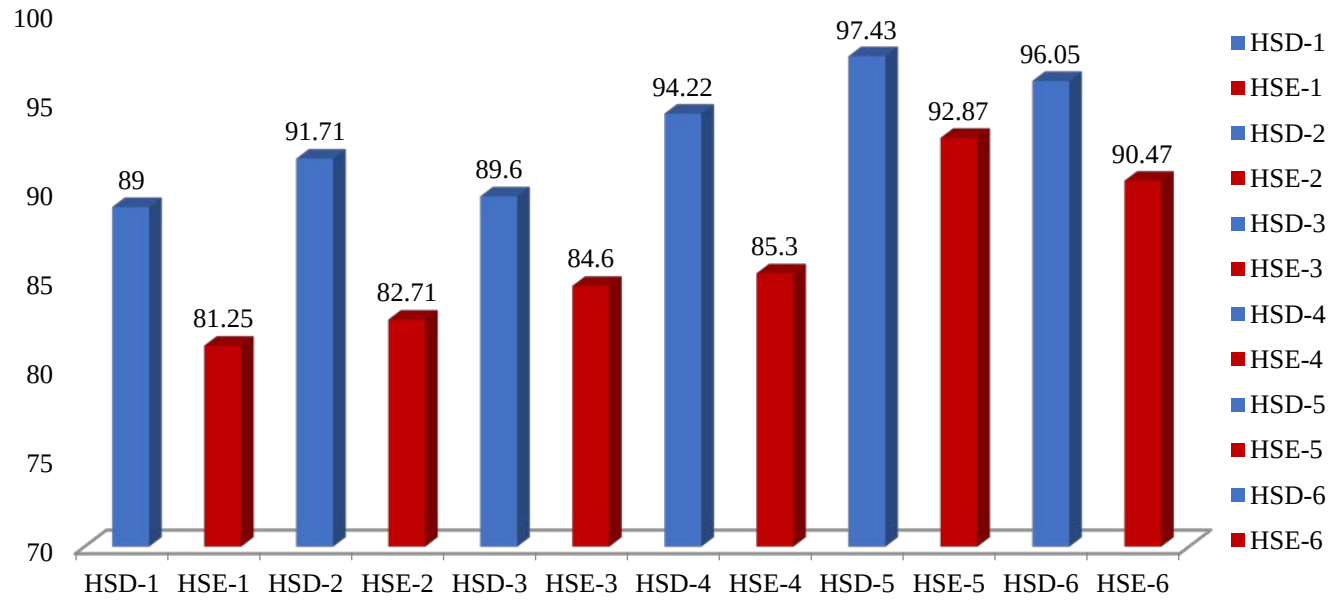


Figure 3: Percentage yield of HSD & HSE (HSD = Hydrotropic solid dispersion by physical mixing, HSE = Solid dispersion by solvent evaporation)

Determination of percentage yield: The percentage yield of the HSD formulations ranged from 89.00±0.25 to 97.43±0.06 and 81.25±0.25 to 92.87±0.06 of the HSE formulations.

Micrometric properties: The micrometric properties of the prepared formulations are shown in Table 7. Bulk densities range from 0.136±0.001 to 0.267±0.005 g/ml and 0.135±0.0 to 0.263±0.005 ug/ml of HSD and HSE, respectively, and tapped densities range from 0.158±0.001 to 0.301±0.004 g/ml and 0.151±0.001 to 0.289±0.005 ug/ml of HSD and HSE, respectively. Hausner ratio values ranging from 1.09±0.005 to 1.16±0.0 of HSD and 1.09±0.005 to 1.15±0.005 of HSE show low to moderate inter-particle friction, thus indicating good flow properties. The compressibility of HSD and HSE ranged from 8.78±0.73 to 14.08±0.55 and 9.59±0.31 to 13.79±0.59, respectively. Also, the angle of repose ranged from 10.38±0.317 to 17.39±1.088 of HSD and 13.23±0.57 to 17.30±0.839 of HSE, indicating good flow properties.

Table 7: Micrometric properties of hydrotropic solid dispersion prepared by physical mixing method ((n=3 mean ± SD)

Formula	Bulk density(gm/ml)	Tapped density (g/ml)	Hausner ratio	Compressibility index (CI)	Angle of repose
HSD-1	0.136±0.001	0.158±0.001	1.16±0.0	14.06±0.22	10.74±0.95
HSD-2	0.187±0.005	0.206±0.001	1.09±0.005	8.78±0.73	12.58±1.140
HSD-3	0.173±0.004	0.208±0.005	1.14±0.03	13.32±0.24	10.38±0.317
HSD-4	0.226±0.0	0.258±0.001	1.13±0.005	12.44±0.44	14.74±0.819
HSD-5	0.259±0.005	0.301±0.004	1.16±0.01	14.08±0.55	13.66±1.358
HSD-6	0.267±0.005	0.297±0.05	1.11±0.0	10.12±0.01	17.39±1.088
HSE-1	0.135±0.0	0.151±0.001	1.11±0.01	11.08±1.19	11.08±1.06
HSE-2	0.179±0.005	0.208±0.005	1.15±0.005	13.79±0.59	13.23±0.57
HSE-3	0.178±0.010	0.200±0.0005	1.11±0.005	11.24±0.56	17.30±0.839
HSE-4	0.212±0.0005	0.234±0.005	1.09±0.005	9.59±0.31	15.80±1.69
HSE-5	0.259±0.0005	0.289±0.005	1.11±0.0	10.27±0.09	20.08±0.5
HSE-6	0.263±0.0005	0.278±0.005	1.05±0.005	11.65±0.25	18.25±1.03

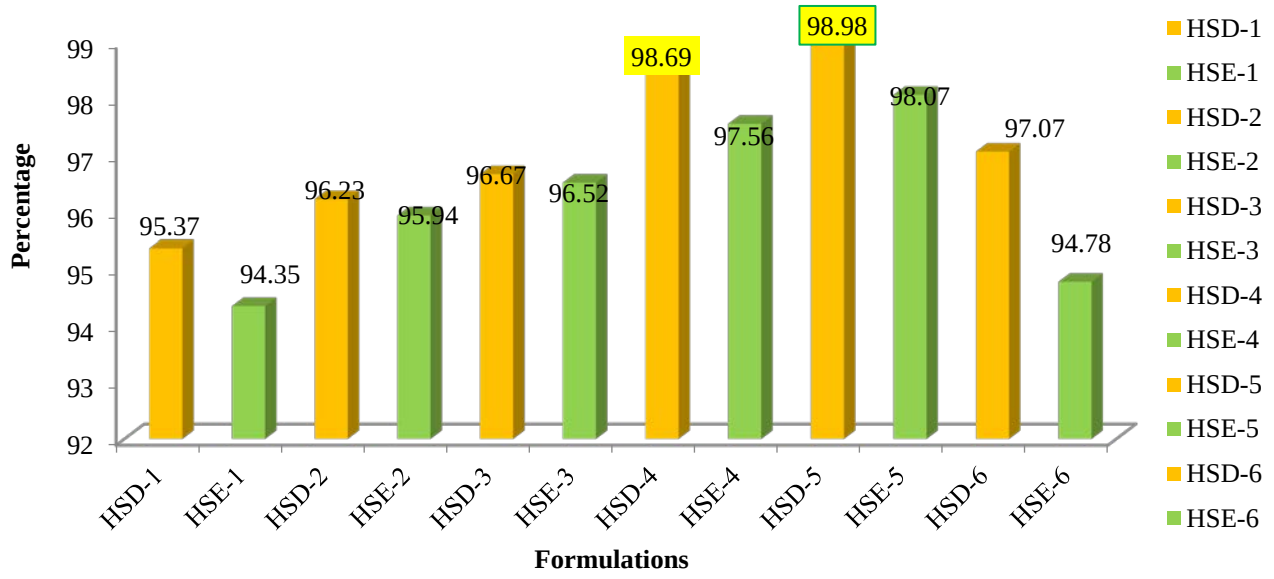


Figure 4: Percentage of drug content of HSD and HSE formulations

Hygroscopicity: Percentage mass gain was found to range from 0.5±0.1 to 8.3±0.1 for HSD and 0.4±0.1 to 3.43±0.30 for HSE. These are slightly hygroscopic because of urea and sodium acetate (Table 8).

Structural analysis of solid dispersion:

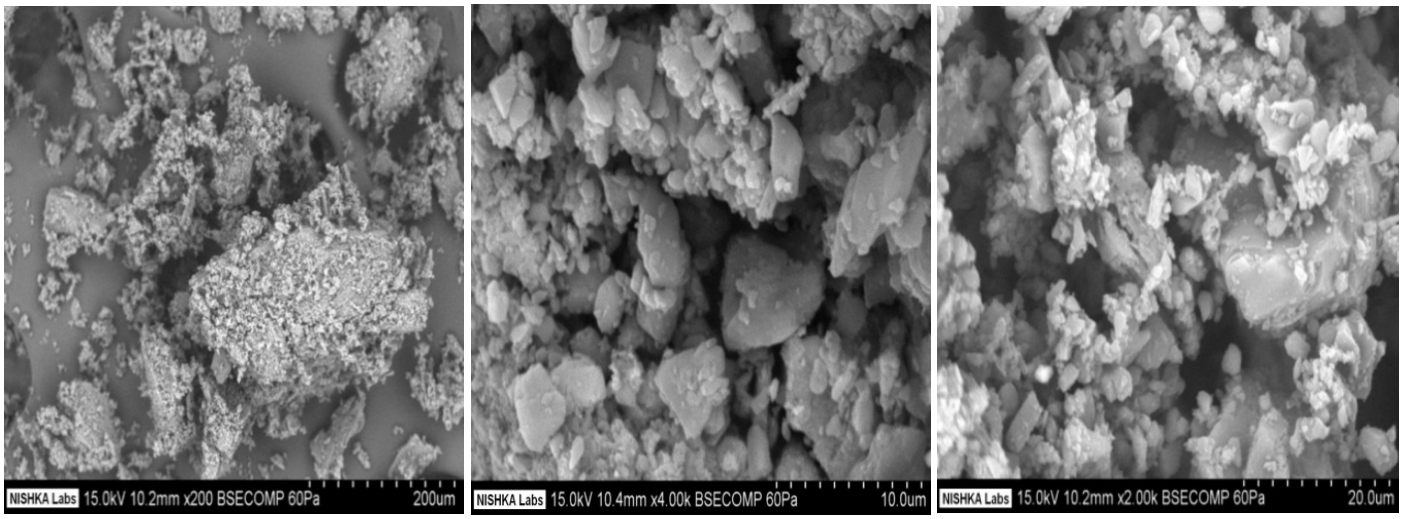
Scanning Electron Microscopy: The shape of the Glimepiride was irregular, and agglomerates appeared to exhibit homogenous solid dispersion. The particle size is very small, which leads to enhanced dissolution compared to the pure drug shown in Figures 5a, 5b, and 5c

X-ray diffraction studies: The presence of crystallinity was further verified by contrasting a few representative peak heights in the solid dispersion's diffraction with that of the pure Glimepiride. Glimepiride exhibited many peaks in the fingerprint region, with a sharp peak in the 2θ diffraction angle at 10.96, 13.89, 18.27, 23.05, 28.22, and 30.06°. HSD solid dispersion diffractograms revealed fewer, weaker peaks. The absence of the Glimepiride characteristic peaks (10.96, 113.89, 18.27, 23.05, 28.22, and 30.06°) indicates that the drug is in an amorphous form, as shown in Figure 6.

Table 8: Mass gain of the HSD & HSE

S. No.	Formulation	Initial weight (mg)	% weight gain	Formulation	Initial weight(mg)	% weight gain
1.	HSD-1	100	0.5±0.1	HSE-1	100	0.23±0.15
2.	HSD-2	100	1.36±0.55	HSE-2	100	0.4±0.1
3.	HSD-3	100	1.9±0.1	HSE-3	100	0.83±0.05
4.	HSD-4	100	5.16±0.2	HSE-4	100	1.6±0.529
5.	HSD-5	100	6.2±0.1	HSE-5	100	0.5±0.26
6.	HSD-6	100	8.3±0.1	HSE-6	100	3.43±0.30

(n=3 mean ± SD)



(a) **(b)** **(c)**

Figure 5: (a) Glimepiride (Raw material); (b) Glimepiride solid dispersion at a magnification of 10 µm (c) Glimepiride solid dispersion at a magnification of 20µm

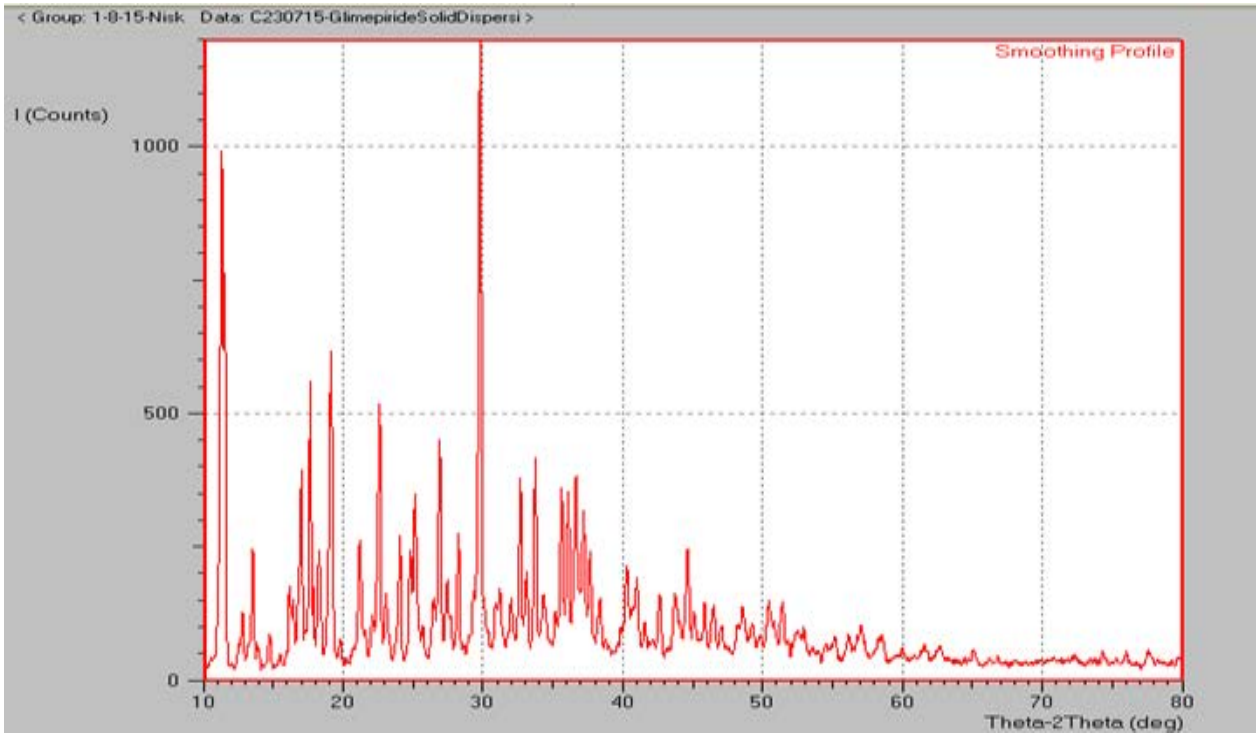


Figure 6: X-ray diffraction of Glimepiride Solid Dispersion

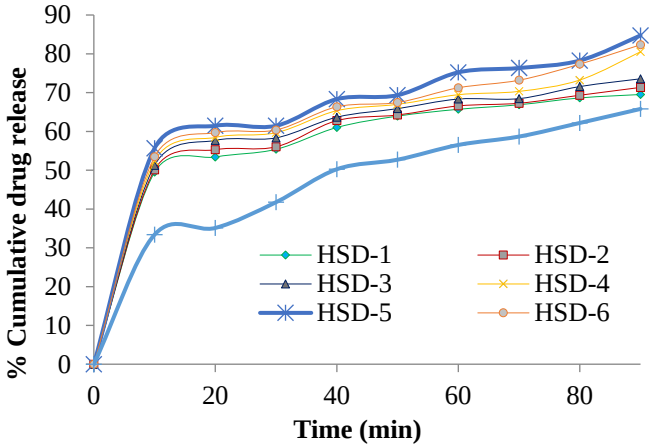


Figure 7: % Cumulative drug release of HSD with Glimepiride

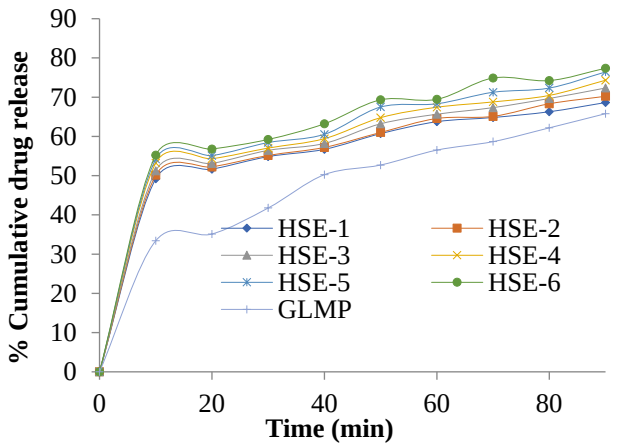


Figure 8: % cumulative drug release of HSE with Glimepiride

Stability testing: Optimized formulation HSD-5 was performed following ICH guidelines for accelerated stability studies. Formulations were taken in 10ml glass vials, plugged and sealed. Vials were kept at room temperature, at 40ºC with 75% RH and 55ºC. The samples were withdrawn at different time intervals, and drug content was determined by UV. The percentage of drug release of the optimized solid dispersion (HSD-5) was consistent for 60 days (Tables 9 and 10). It was observed that there was no significant difference after 2 months. Hence, it is clear that the prepared formulation is stable enough for further proceedings (Figure 9).

Table 9: % drug content of the optimized solid dispersion

S. No.	Frequency of testing	% drug content(n=3)
1.	After 30 days	98.94±0.14
2.	After 45 days	98.92±0.60
3.	After 60 days	98.99±0.91

(n=3, mean ± SD)

CONCLUSION

The present work found higher drug content in solid dispersion using solvent evaporation techniques where the drug is evenly distributed throughout the formulation. The prepared solid dispersions of Glimepiride have shown the highest solubility due to the synergistic effect of hydrotropic agents such as urea and sodium acetate. The HSD-5 formulation showed better physiochemical properties. Glimepiride tablets were prepared by using the HSD-5 solid dispersion. Glimepiride's solubility, dissolution, and drug release remarkably increased by employing highly water-soluble, non-toxic hydrotropic compounds. Reduction of particle aggregation, absence of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles may be responsible for the enhanced solubility and dissolution rate of Glimepiride, and the use of water-soluble hydrotropic agents have the great advantage of reducing the dose of the drug.

Table 10: % drug release of the optimized solid dispersion (HSD-5) (n=3 mean ± SD)

Time (min)	After 30 days	After 45 days	After 60 days
10	50.64±0.99	51.21±0.36	50.99±0.75
20	56.14±0.30	56.43±0.15	57.12±0.12
30	57.36±0.27	58.19±0.44	58.18±0.26
40	62.11±0.44	61.99±0.32	60.34±0.56
50	64.49±0.14	64.21±0.19	63.96±0.43
60	66.20±0.54	67.41±0.43	67.21±0.26
70	69.05±0.29	68.29±0.99	68.16±0.67
80	76.25±0.28	77.21±0.22	76.45±0.78
90	84.08±0.06	85.04±0.35	84.19±0.58

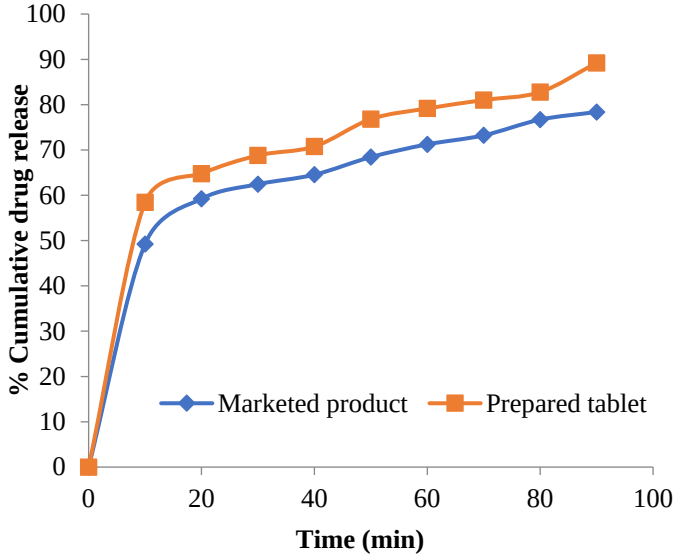


Figure 9: comparative % cumulative drug release of prepared tablet and marketed product

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FINANCIAL ASSISTANCE
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The authors declare no conflict of interest

AUTHOR CONTRIBUTION
All authors contributed to the study design**.** Devakmma Lakumalla gathered the relevant literature, prepared the material, and performed the study methods. Neeraja Podichety and Ravi Kumar Maddali worked on analyzing the results. Devakmma Lakumalla and Neeraja Podichety prepared the final manuscript, which all authors approved.

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