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# Physicochemical reports of gliclazide-carplex solid dispersions and tablets prepared with directly compressible co-processed excipients

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ABSTRACT

*Objectives:* The main goal of this research was to develop better tablet formulations by utilizing solid dispersions (SDs) and coprocessing excipients composite to achieve a better release rate of poor water-soluble gliclazide.

*Methods:* The solvent evaporation method made SDs of gliclazide with different carriers carplex 67, carplex 80, and carplex FPS 500 (weight ratio, 1:1). The drug release patterns of the SDs were all evaluated and optimized. The SDs were illustrated by using scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray powder diffraction (PXRD), and Fourier transform infrared spectroscopy (FTIR). Tablet batches FGC-1 to 8 were made using gliclazide-carplex 67 solid dispersions (GC67-SDs) and the co-processed composite of excipients, namely starch-MCC-povidone (SMP) and lactose-MCC-povidone-sodium starch glycolate (LMPS), prepared with coprocessing technology. We evaluated these batches by conducting physicochemical tests and comparing them to the existing commercial brand.

*Results:* In a water medium, the release of gliclazide from SDs peaked within the first 30 min, showing a roughly 5~6-fold increase compared to plain gliclazide. This quick dissolution rate may be due to the amorphization of the drug, which improved the specific surface area, and increased wettability caused by the hydrophilic properties of carplex particles. This has been confirmed through SEM, DSC, FTIR, and PXRD analysis. All FGC formulations had satisfactory pre-compression factor results, while the post-compression parameters indicated good mechanical strength and homogeneity across the blend. All produced tablets met the weight variation, friability, and disintegration time limit set by the compendia. Through in vitro drug release testing, it was discovered that all FGC tablet batches had consistent and nearly identical release results compared to SDs of gliclazide. However, the FGC-5 to 8 batches containing LMPS composites were determined to be the most effective formulations. In the first 30 min in a water medium, the percentage of drug generated from the FGC-8 tablets involving GC67-SDs and co-processed composite LMPS-4 is approximately 3.5 times higher than the average release of currently marketed products (MPs). After storing the selected FGC tablet batches for three months at 40 °C and 75 % RH, there were no noticeable alterations in the amount of drug and drug release profiles across the batches.

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*Conclusion:* Based on these findings, it appears that using the carplex silica-based SDs approach, along with gliclazide and co-processing excipients composite, could result in significant benefits compared to the current commercial brands. This approach could be effectively utilized to create solid dosage forms for drugs that have low solubility in water.

## 1. Introduction

Advanced pharmaceutical technology has shown significant interest in enhancing the dissolution rate and bioavailability of poorly water-soluble drugs, which has greatly impacted clinical therapy [1,2]. Designing drug formulations for these drugs was difficult because of their poor wettability and water solubility, which caused uneven oral bioavailability.

Gliclazide belongs to the second-generation hypoglycemic sulfonylurea and is used to treat type 2 diabetes mellitus [3,4]. It is vital to increase the solubility of gliclazide because it is a weakly water-soluble drug and has a low aqueous solubility [5–7]. Therefore, a well-designed formulation is crucial for effectively delivering gliclazide to the intended absorption site. It is generally known that increasing surface area can speed up dissolution and, as a result, increase bioavailability [8,9].

Various techniques are available to enhance solubility, including salt formation, particle size reduction, micronization, nanosuspension, and adding solvents or surfactants [10]. Moreover, some studies suggest that solid dispersions (SDs) formulation is one of the most effective solubility enhancement methods for hydrophobic drugs [11]. SDs are solid preparations of active ingredients in an inert carrier or matrix made through fusion, solvent, and melt-solvent methods. When SDs come into contact with water, the carrier dissolves or disperses, releasing the drug in tiny particles. Therefore, this method significantly increases the total surface area of the drug, which leads to an improvement in its dissolution rate and bioavailability [12,13]. Previous studies showed that silica-drug SDs prepared by the spray-drying process enhance the solubility of hydrophobic drugs [14]. The preparation of SDs by the co-grinding method showed similar results [15].

Moreover, many studies were performed to check the dissolution profile of SDs of gliclazide using different carriers such as PEG 6000 [16], silica and polyvinylpyrrolidone K30 [17], polyvinylpyrrolidone K90 [18], cross-linked swellable polymers, amorphous silica, and sodium lauryl sulfate [19], aerosil 380 [20] and those studies revealed significant enhancement of release kinetics of the drug. Porous and mesoporous silica materials have recently been found to be a step forward in enhancing drug dissolution and oral absorption since they have a large specific surface area [21].

The use of SDs formulation is highly beneficial in the dissolution rate and bioavailability for poorly soluble drugs, but there is limited understanding of how they can be transformed into final dosage forms such as tablets [22,23]. Even if used in small quantities, excipients can significantly impact the processability and effectiveness of the dosage form when designing and developing formulations [24]. To speed up production and make new materials for direct compression more affordable, the current compendial excipients are used to create custom diluents using the co-processing technique, which involves physically combining two or more excipients [25]. Co-processing has recently emerged as a potential method for creating high-performance, multifunctional diluents with the necessary physicomechanical properties [26,27]. Furthermore, the co-processing of excipients could speed up the conception of novel direct compression excipients by drastically lowering development time and expenditure [28].

In the current work, different grades of hydrated carplex silica (carplex 67, carplex 80, and carplex FPS 500) have been used as dispersing carriers to increase the dissolution rate of the poorly water-soluble gliclazide. There was no previous proof of using this silica carrier with gliclazide. The solvent evaporation process was used to prepare SDs of gliclazide with different carplex. The optimized SDs preparations were examined and categorized through a set of complementary techniques like SEM, FTIR, DSC, and PXRD. Furthermore, the prepared tablets using gliclazide-loaded SDs of carplex 67 and directly compressible co-processed excipients composite (SMP, starch-MCC-povidone; LMPS, lactose-MCC-povidone-sodium starch glycolate) were characterized physiochemically and compared to available marketed products (MPs) to explore the improved knowledge and new approaches to the management of diabetes by gliclazide.

## 2. Materials & methods

### 2.1. Materials

Gliclazide supplied by Zhejiang Jiuzhou Pharmaceuticals China was a kind gift from Square Pharma Ltd., Bangladesh. We purchased carplex-67 from the German company Evonik. We procured maize starch, lactose, sodium starch glycolate (SSG), microcrystalline cellulose (MCC), povidone, ethanol (HYC Corp., China), methanol (Merck, Germany), and magnesium stearate from Jajco Trading in Bangladesh. The marketed products MP-1, MP-2, and MP-3 produced by the local companies were purchased from a nearby drug store. All experiments were conducted using Millipore-prepared distilled water. Additional analytical-grade chemicals were utilized as reagents in experiments.

### 2.2. SDs preparation

The SDs of gliclazide with different silica carriers carplex 67, carplex 80, and carplex FPS 500 were made with the solvent (ethanol) evaporation system and denoted as GC 67, GC 80, and GC FPS 500 respectively. Based on enhancement in dissolution rate (data not

shown), the drug-to-carrier ratio was optimized among different ratios of 3:1, 2:1, 1:1, 1:2, and 1:3. The optimized gliclazide-to-carplex ratio 1:1 (by weight) was used for further study here. Accurately weighted gliclazide powder was dissolved into a sufficient volume of ethanol, and the required quantity of carplex carrier was incorporated and dispersed into the drug solution. The disperse system was continually stirred for 30 h at 50 °C using an electromagnetic stirrer to permit suitable drug loading in carrier surfaces and remove all solvent from the dispersion system. The dried and hardened composite mixture was crushed to fine powders with a glass mortar and pestle. Finally, the composites were conserved in a screw-cap vial at ambient temperature for further use.

### 2.3. Solid state description of SDs by SEM, FTIR, DSC, and PXRD

The structure, surface, and longitudinal morphologies of plain gliclazide and SDs of gliclazide were examined using an SEM (SSX-500, Shimadzu, Tokyo, Japan). FTIR spectroscopy was performed to investigate the drug–carrier interactions in the SDs in a solid state. FTIR spectra were obtained using IR-Prestige 21, Shimadzu Co., Japan. Samples of gliclazide and SDs were set with potassium bromide and scanned from 4000 to 400 $cm^{-1}$ at ambient temperature.

Exstar SII DSC7020 (Hitachi High-Tech Science Corporation, Tokyo, Japan) generated the gliclazide and various SDs' thermograms. In sealed aluminum pans, 3–5 mg of samples were used. The samples were then heated from 0 to 300 °C at a scanning rate of 10 °C per minute while subjected to a 40 mL/min nitrogen purge, with an empty aluminum pan as a reference.

DSC was used with an X-ray diffractometer (RAD-C, Japan) to assess the physical condition of the drug in SDs. The samples were exposed to Cu–K radiation (30 kV, 50 mA) while being scanned from 2 to 40°, 2θ at a rate of 5°/min.

### 2.4. Percentage of yield and drug content of SDs

The yield percentage of SDs products was calculated from the practical mass of SDs and the theoretical mass of the drug with the carrier to determine the efficiency of the method used in this study. To analyze the drug content, samples of each SDs equivalent to 50 mg of gliclazide were dissolved and then the volume was made up to 25 mL with methanol. After being sonicated for 15 min, the solution was filtered through a Whatmann filter paper no. 1. The amount of drug was measured at 229 nm spectrophotometrically after appropriate dilution of the samples and filtration through 0.45 μm nylon syringe filter. Each sample was evaluated in parallel triplicate (n = 3) and backed to determine the drug content in SDs.

### 2.5. In vitro dissolution studies

The release of gliclazide from SDs and plain form was assessed using an in vitro dissolution investigation. It was directed with Apparatus 2 b y USP 24 standards. The dissolution medium was 900 mL of water and phosphate buffer (pH 7.4) that agitated at 75 rpm while being kept at 37 ± 0.5 °C. Accurately weighted 15 mg of gliclazide-equivalent sample of each SDs was added to the dissolution medium. A 10 mL sample was taken out at scheduled times (5, 15, 30, 60, 90, and 120 min) and filtered by a 0.45 μm nylon syringe filter. The filtrate samples were directly measured at 229 nm spectrophotometrically. The same procedure was followed for the dissolution of plain gliclazide. Dissolution investigations were carried out in triplicate (n = 3), and mean values were calculated to represent the release curves.

### 2.6. Preparation of co-processed excipients composite

Table 1 provides the composites' formula. Although the amounts of maize starch (MS) and Avicel PH 101 (MCC) varied, the amount of povidone (PVP) remained constant at 3 % in all composites. Additional four excipients composite were prepared (Table 2) using lactose instead of starch and sodium starch glycolate, while the concentration of PVP and MCC were the same as defined in Table 1. The dehydrated PVP was heated at 130 °C on a hotplate (TP-350 E+, MIULAB, China) and blended with MS/MCC and lactose/MCC/sodium starch glycolate for efficient dispersion. The mass was stirred vigorously for 15 min and heated at a predetermined sub-gelatinization temperature (55 °C) in a thermostatic water bath. The slurry was dried adequately at 60 °C, followed by a second drying cycle lasting 24 h on the dried mass after micronizing it with a mortar and pestle. The resulting composites were screened through a 40-mesh sieve, labeled, and stored in airtight containers for further use [29].

**Table 1**
The composite SMP (starch-MCC-povidone).

| Composites | Primary Excipient | | | Classification |
|---|---|---|---|---|
| | Maize starch (%) | MCC 101 (%) | Povidone (%) | |
| SMP-1 | 87 | 10 | 3 | High starch-low MCC composite |
| SMP-2 | 67 | 30 | 3 | High starch-mild MCC composite |
| SMP-3 | 47 | 50 | 3 | Moderate starch-moderate MCC composite |
| SMP-4 | 27 | 70 | 3 | Low starch-high MCC composite |

**Table 2**
The composite LMPS (lactose-MCC-povidone-sodium starch glycolate).

| Composites | Primary Excipient | | | | Classification |
|---|---|---|---|---|---|
| | Lactose (%) | MCC 101 (%) | Povidone (%) | Sodium starch glycolate (%) | |
| LMPS-1 | 83 | 10 | 3 | 4 | High lactose-low MCC composite |
| LMPS-2 | 63 | 30 | 3 | 4 | High lactose-mild MCC composite |
| LMPS-3 | 43 | 50 | 3 | 4 | Moderate lactose-moderate MCC composite |
| LMPS-4 | 23 | 70 | 3 | 4 | Low lactose-high MCC composite |

### *2.7. Flowability of GC67-SDs and co-processed excipients*

The angle of repose, bulk density, tapped density, compressibility index, and Housner's ratio of the solid dispersions of GC67, and co-processed excipients composite were measured to check the flowability of powders before compression into tablets.

### *2.8. Moisture content (MC) and swelling capacity (SC)*

The moisture level of the composites was estimated using the 'loss on drying' approach. Samples (2 g) were dehydrated in a hot air oven at 100 °C till a consistent mass was recognized and assessed how much weight was lost. For SC, 5 g of the sample was taken in 50 mL of deionized water and allowed to forcefully shake the graduated cylinder for 5 min. The dispersion was allowed to settle down for 20 h and determined the SC as the sedimented mass's percentage volume growth.

$SC = 100\% \text{ x } [(V_2 – V_1)/V_1]$

$V_1$ was the preliminary volume of the deposit; $V_2$ was the final volume of the deposit.

### *2.9. Preparation of tablets using GC67-SDs and characterization*

Based on the physicochemical attributes and reproducibility of the data, the solid dispersions (SDs) of gliclazide with carplex 67 were selected for the preparation of tablets using the direct compression technique. The materials were weighed according to Table 3 formulations and blended for 10 min. After passing through 40 mesh sieves, we added magnesium stearate and compressed the powders into tablets using a single-punch compression machine (TDP-1.5, China). The prepared tablets were labeled FGC-1 to 8.

Various physicochemical properties of the tablets were examined based on the USP 24 method [30] to ensure quality. To assess the weight variations, 20 tablets were randomly chosen from each formulation and their weights were compared to the calculated mean weight.

The Monsanto tablet hardness tester was used to measure the fracture strength for every six tablets in each lot. The friability was determined using a tablet friability tester with 20 tablets for 4 min at a speed of 50 rpm. Additionally, the disintegration time at 37 ± 0.2 °C in water was measured using six tablets of each formulation.

The drug content was analyzed by dissolving a powdered mass of tablets containing 50 mg of gliclazide in methanol and increasing the volume to 25 mL. After sonication, filtration, and appropriate dilution, the sample was assessed spectrophotometrically at 229 nm. In vitro dissolution tests of SDs tablets and marketed products of gliclazide (80 mg) were conducted using 900 mL water as the dissolution medium. The sample was analyzed spectrophotometrically at 229 nm after proper dilution. The other investigation factors were unchanged, as stated for SDs earlier.

**Table 3**
Formulations of tablets covering the GC67-SDs and co-processed excipients.

| Formulation → Composition ↓ | FGC-1 | FGC-2 | FGC-3 | FGC-4 | FGC-5 | FGC-6 | FGC-7 | FGC-8 |
|---|---|---|---|---|---|---|---|---|
| GC67-SDs (equivalent to 80 mg drug) | 170 | 170 | 170 | 170 | 170 | 170 | 170 | 170 |
| SMP-1 (mg) | 120 | – | – | – | – | – | – | – |
| SMP-2 (mg) | – | 120 | – | – | – | – | – | – |
| SMP-3 (mg) | – | – | 120 | – | – | – | – | – |
| SMP-4 (mg) | – | – | – | 120 | – | – | – | – |
| LMPS-1 (mg) | – | – | – | – | 125 | – | – | – |
| LMPS-2 (mg) | – | – | – | – | – | 125 | – | – |
| LMPS-3 (mg) | – | – | – | – | – | – | 125 | – |
| LMPS-4 (mg) | – | – | – | – | – | – | – | 125 |
| Na-starch glycolate (mg) | 9 | 9 | 9 | 9 | 4 | 4 | 4 | 4 |
| Mg-stearate (mg) | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| The overall weight (mg) | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

### 2.10. Stability studies of SDs tablets

The selected batches of GC67-SDs tablets (FGC-1, 4, 5, 8) were tightly packed in airtight containers and then kept at 40 ± 2 °C and 75 ± 5 % RH for three months. The specimens were taken apart and assessed for hardness, disintegration time, the quantity of the drug, and drug dissolution rate following three months of storage. The substantial variance was then tested using statistical analysis of the data at a 5 % threshold of significance.

### 2.11. Statistical analysis

Data were presented as mean ± standard deviation (SD). A *t*-test was utilized to carry out statistical analyses. A value of $p < 0.05$ is considered significant.

## 3. Results

### 3.1. Percentage of yield and drug content of SDs

The percentage of yield of SDs of GC 67, GC 80, and GC FPS 500 was determined using actual and theoretical yield. The results showed a yield of 92.65 % for GC 67, 89.45 % for GC 80, and 90.62 % for GC FPS 500. This reflects that the formulation and method show a high level of proficiency. The SDs products have confirmed the level 89.33–94.21 % of the theoretically added amount of gliclazide in different dispersions. The GC67-SDs achieved the highest drug content at 94.21 %. This could be due to the highest adsorption efficiency of gliclazide to the surface of carplex 67.

### 3.2. Particle morphology by SEM

From the SEM photograph, gliclazide was detected as crystalline in Fig. 1D, while the SDs of gliclazide with carplex seem spherical and cotton-like in Fig. 1A, B, and 1C, which might accelerate the rate of dissolution. Furthermore, the size of the particles of the SDs is comparatively smaller and this reduction may be due to the solvent evaporation method in the preparation of SDs.

### 3.3. Verification of interactions by FTIR spectrum

It is known that the major adsorption sites on a silica surface are hydroxyl groups and previous studies have documented the interaction of drugs with silica's silanol groups [15,31]. Fig. 2 displays the FTIR spectrum. The carbonyl (C═O) sulphonyl urea group

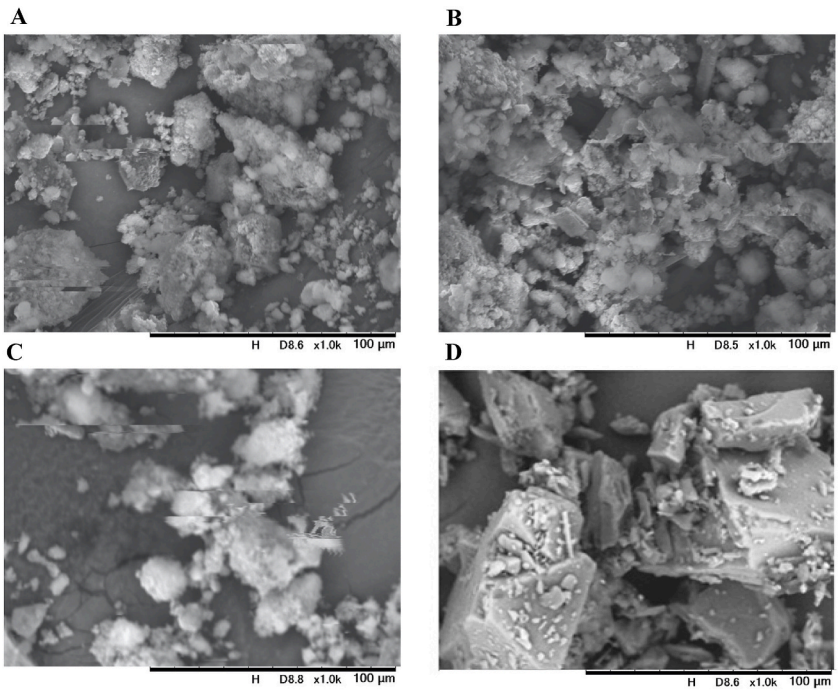


**Fig. 1.** SEM photographs of [A] GC 67 (gliclazide-carplex 67 solid dispersions); [B] GC 80 (gliclazide-carplex 80 solid dispersions); [C] GC FPS 500 (gliclazide-carplex FPS 500 solid dispersions) and [D] gliclazide.

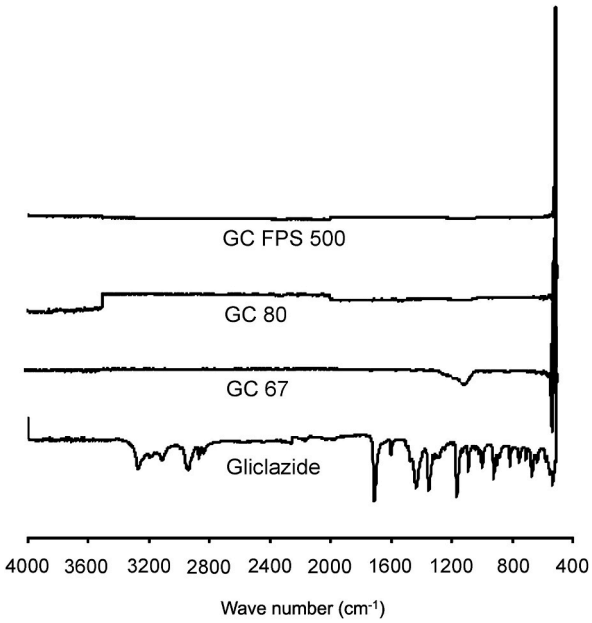


**Fig. 2.** FTIR spectrum of gliclazide, GC 67 (gliclazide-carplex 67 solid dispersions); GC 80 (gliclazide-carplex 80 solid dispersions) and GC FPS 500 (gliclazide-carplex FPS 500 solid dispersions).

absorbs at 1706 $cm^1$, which is a defining property of gliclazide in the FTIR spectrum [4]. This band nearly vanished from the spectra of all SDs. The secondary amine groups (–NH–) in gliclazide alone displayed *N*–H stretching vibrations at 3262 $cm^1$, but these vibrations vanished in the FTIR spectra of all SDs of gliclazide. This result raises the potential of weak hydrogen bonding between the NH and CO groups of the gliclazide and the silanol groups of the carplex during the solvent evaporation-based preparation of SDs [32].

### *3.4. DSC confirms changes in crystallinity*

The DSC thermogram of pure gliclazide showed a sharp endothermic peak starting at 175.6 °C, indicating crystallinity. In contrast, the thermograms of various SDs displayed broader curves with smaller endothermic peaks that corresponded to the melting of pure crystalline gliclazide (Fig. 3). The melting points of various SDs were varied and lower than pure gliclazide due to varying drug sizes. Gliclazide endotherm shifted to lower temperatures and the peak area decreased significantly in the SDs batches. The decrease in endotherm intensity observed in SDs is believed to be responsible for the faster release of gliclazide from these samples. This faster release is due to reduced drug crystallinity. This finding is consistent with the earlier hypothesis that the production of SDs causes the

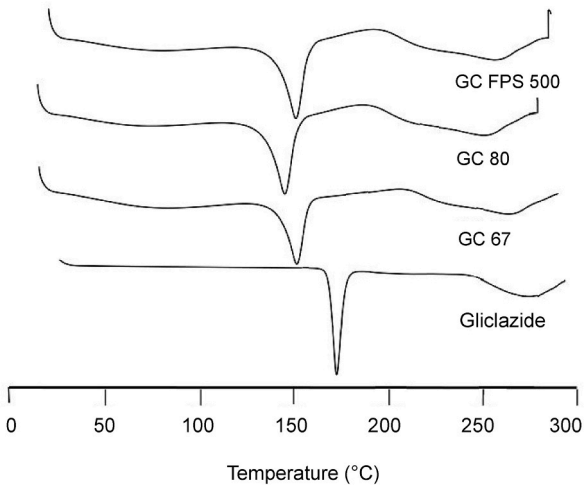


**Fig. 3.** DSC thermogram of gliclazide; GC 67 (gliclazide-carplex 67 solid dispersions); GC 80 (gliclazide-carplex 80 solid dispersions) and GC FPS 500 (gliclazide-carplex FPS 500 solid dispersions).

drug to change from its crystalline state to an amorphous state [13,33,34]. Moreover, the decrease in the drug crystallinity in SDs is caused by its reduced melting point when it is absorbed onto the silica surfaces [35,36]. However, the broad peak in SDs remained prominent at lower temperatures, so the possibility of the presence of crystallinity of the drug in SDs is not ruled out.

### 3.5. PXRD results justify changes in crystallinity

The PXRD patterns for gliclazide and its various SDs are shown in Fig. 4. The diffraction pattern of pure gliclazide showed several distinct and highly intense peaks that demonstrated its crystalline nature. Amorphous drugs dissolve more quickly than crystalline due to their higher internal energy and more molecular mobility, improving their thermodynamic characteristics [37]. The PXRD patterns of gliclazide and SDs batches were almost identical with sharp peaks at different diffraction angles (2θ). However, the peak heights of the SDs batches were lower than those of the pure gliclazide. This suggests that the SDs batches have smaller crystal sizes and lower crystallinity than plain gliclazide. Therefore, PXRD analysis revealed weaker diffraction peaks of the drug in the SDs, justifying the amorphization of the drug crystals [38].

### 3.6. Dissolution studies of the GC-SDs in water and phosphate buffer medium

The dissolution studies were accomplished to evaluate the drug release pattern of various SDs over plain gliclazide. The drug release in the first 5, 15, 30, 60, 90, and 120 min were displayed in Fig. 5. The results showed a decrease in the rate of drug release in the following order: GC 67 P > GC 80 P > GC FPS 500 P > GC 67 W > GC FPS 500 W > GC 80 W > GP > GW (after 30 min). The gliclazide-loaded SDs in carplex (GC-SDs) demonstrated an identical improvement in dissolution rate compared to plain gliclazide at every time point in both the water and phosphate buffer (pH 7.4) medium. The drug release from plain gliclazide was 4.76 % and 15.45 % at 30 min in water and phosphate buffer medium, respectively. The drug release of GC-SDs in a water medium showed around 5~6 times improvement at 30 min, while in a buffer medium, it was about 2.5~3 times better than plain gliclazide, depending on the type of carriers used. These comparative studies revealed that the release rate of gliclazide is affected by its SDs formulation and the pH level of the dissolution medium [23]. This significant enhancement in drug release compared to plain gliclazide confirms the superiority of carplex as a carrier for enhancing the release rate of drugs in both media. The drug release from GC-SDs decreased slightly further after 60 min in phosphate buffer, which may be attributed to analytical errors.

### 3.7. Evaluation of physical characteristics of GC67-SDs and co-processed excipients

The GC67-SDs and co-processed excipients composite were evaluated for the physical properties presented in Table 4. The data from compressibility index, Hausner ratio, angle of repose, and moisture content reflected that GC67-SDs and co-processed composite showed suitable flow property that was essential for the tableting process. The swelling capacity of GC67-SDs and different composites

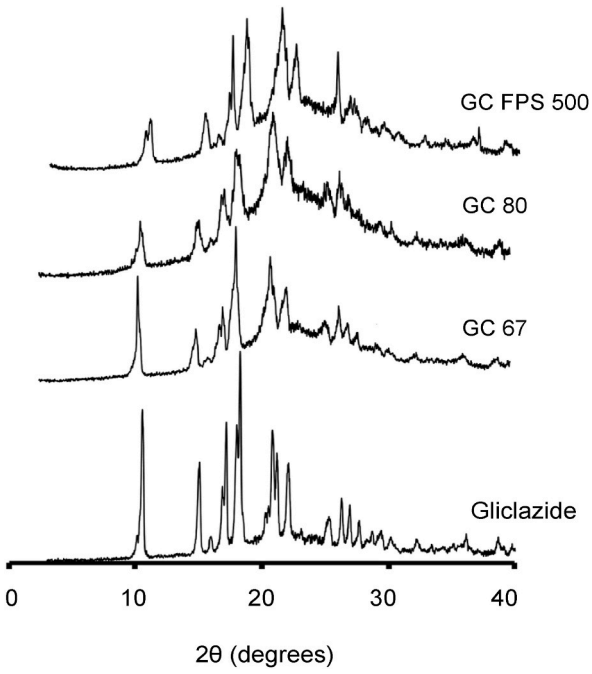


**Fig. 4.** PXRD diffraction patterns of gliclazide; GC 67 (gliclazide-carplex 67 solid dispersions); GC 80 (gliclazide-carplex 80 solid dispersions) and GC FPS 500 (gliclazide-carplex FPS 500 solid dispersions).

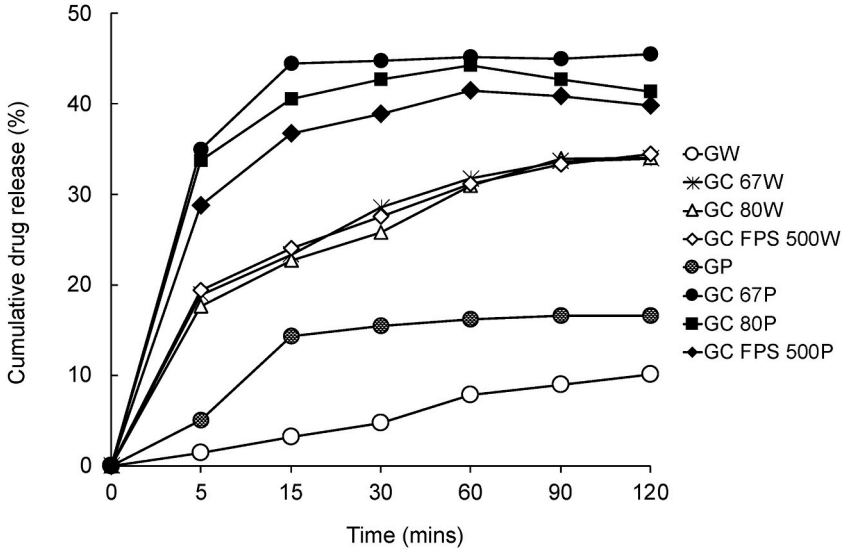


**Fig. 5.** The release patterns of gliclazide and its different SDs in both water and buffer medium. GW: gliclazide in water; GC 67 W: gliclazide loaded carplex 67 SDs in water; GC 80 W: gliclazide loaded carplex 80 SDs in water; GC FPS 500 W: gliclazide loaded carplex FPS 500 SDs in water; GP: gliclazide in phosphate buffer; GC 67 P: gliclazide loaded carplex 67 SDs in phosphate buffer; GC 80 P: gliclazide loaded carplex 80 SDs in phosphate buffer; GC FPS 500 P: gliclazide loaded carplex FPS 500 SDs in phosphate buffer; SDs: solid dispersions; data are expressed as mean ± SEM (n = 3).

**Table 4**
Physical characteristics of GC67-SDs and co-processed excipients.

| Properties→ Sample ↓ | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Carr's Index (%) | Hausner's Ratio | Angle of Repose | Moisture Content (%) | Swelling Capacity (%) |
|---|---|---|---|---|---|---|---|
| GC67-SDs | 0.28 ± 0.02 | 0.034 ± 0.01 | 16 ± 0.07 | 1.19 ± 0.10 | 29.44 ± 0.2 | 2 ± 0.01 | 50 ± 0.04 |
| LMPS-1 | 0.66 ± 0.02 | 0.77 ± 0.00 | 15 ± 0.03 | 1.17 ± 0.04 | 26.60 ± 2.05 | 1 ± 0.01 | 21 ± 0.01 |
| LMPS-2 | 0.52 ± 0.13 | 0.62 ± 0.02 | 18 ± 0.03 | 1.23 ± 0.04 | 28.67 ± 0.93 | 3 ± 0.02 | 26 ± 0.02 |
| LMPS-3 | 0.47 ± 0.03 | 0.53 ± 0.03 | 12 ± 0.03 | 1.13 ± 0.03 | 30.00 ± 1.88 | 2 ± 0.01 | 32 ± 0.08 |
| LMPS-4 | 0.45 ± 0.05 | 0.56 ± 0.10 | 18 ± 0.08 | 1.23 ± 0.12 | 28.98 ± 0.85 | 2 ± 0.01 | 61 ± 0.10 |
| SMP-1 | 0.46 ± 0.10 | 0.52 ± 0.10 | 12 ± 0.03 | 1.14 ± 0.04 | 28.81 ± 5.18 | 2 ± 0.11 | 24 ± 0.07 |
| SMP-2 | 0.42 ± 0.06 | 0.47 ± 0.06 | 11 ± 0.02 | 1.12 ± 0.02 | 29.76 ± 4.12 | 1 ± 0.09 | 33 ± 0.14 |
| SMP-3 | 0.36 ± 0.04 | 0.41 ± 0.02 | 13 ± 0.06 | 1.16 ± 0.06 | 29.76 ± 4.12 | 1 ± 0.04 | 56 ± 0.19 |
| SMP-4 | 0.39 ± 0.03 | 0.43 ± 0.02 | 10 ± 0.02 | 1.11 ± 0.02 | 30.29 ± 2.32 | 2 ± 0.01 | 44 ± 0.19 |

Data are expressed as mean ± SD (n = 3).

of SMP and LMPS was at perfect level (21–61 %). This indicates that it could effectively absorb water molecules, which benefitted the dissolution process. Among all of the direct compressible co-processed excipient composites, LMPS-4 was selected as the best one due to its suitable flow property ($\Theta < 30^{\circ}$), acceptable moisture content (2 %), and higher swelling capacity (61 %).

**Table 5**
Evaluation properties of GC67-SDs compressed tablets.

| Properties→ Formulation ↓ | Wt. variation (%) | Diameter (cm) | Friability (%) | Hardness (kg/cm$^2$) | D.T. (sec) | Drug content (%) |
|---|---|---|---|---|---|---|
| FGC-1 | 2.81 ± 1.07 | 1.02 | 0.16 | 5.50 ± 0.50 | 66.5 ± 2.54 | 97.43 ± 2.45 |
| FGC-2 | 0.4 ± 0.15 | 1.02 | 0.17 | 3.83 ± 0.21 | 39.5 ± 1.74 | 96.91 ± 2.71 |
| FGC-3 | 1.6 ± 0.41 | 1.03 | 0.18 | 3.66 ± 0.25 | 45 ± 2.07 | 95.12 ± 3.05 |
| FGC-4 | 2.52 ± 1.05 | 1.03 | 0.22 | 3.66 ± 0.29 | 34.5 ± 1.36 | 98.05 ± 1.67 |
| FGC-5 | 1.5 ± 0.31 | 1.02 | 0.24 | 3.66 ± 1.04 | 30 ± 0.00 | 97.17 ± 1.98 |
| FGC-6 | 2.57 ± 0.85 | 1.02 | 0.25 | 3.33 ± 0.19 | 22 ± 0.00 | 96.30 ± 2.65 |
| FGC-7 | 1.75 ± 1.15 | 1.02 | 0.36 | 3.16 ± 0.20 | 24 ± 2.66 | 97.05 ± 2.12 |
| FGC-8 | 2.24 ± 0.76 | 1.02 | 0.38 | 3.33 ± 0.23 | 13 ± 4.24 | 98.21 ± 1.10 |
| MP-1 | 0.46 ± 0.09 | 0.89 | 0.11 | 4.41 ± 0.1 | 380 ± 2.02 | 96.96 ± 2.55 |
| MP-2 | 1.50 ± 0.15 | 0.81 | 0.38 | 3.75 ± 0.60 | 330 ± 3.10 | 99.26 ± 1.22 |
| MP-3 | 1.30 ± 0.23 | 0.89 | 0.10 | 4.20 ± 0.57 | 309 ± 4.49 | 99.70 ± 1.38 |

Data are expressed as mean ± SD (n = 3).

### 3.8. GC67-SDs tablets using co-processed excipients and evaluation

The GC67-SDs with co-processed excipients were transformed into tablets through the direct compression technique. Table 5 shows the evaluation parameters for all designed formulations (FGC-1 to 8) and marketed products (MPs, MP-1 to 3). The drug level of the FGC tablets when compared to the marketed products (96.96 %–99.70 %) was found to be within the range of 95.12 %–98.21 %. A very good uniformity of drug content indicates the good homogeneity of gliclazide among all SDs tablet formulations.

The weight variation, diameter, friability, hardness, and disintegration time of all GC67-SDs tablets were in compliance with the compendial limit. The weight variation of SDs tablets and MPs was in the ranges of 0.4 % and 2.81 %, indicating that the variance of each formulation was within the limit (<7.5 %). The percentage of weight loss values of all formulas was within the acceptable limit (0.16 %–0.38 %). The SDs tablets showed good mechanical strength (3.16–5.50 kg/cm$^2$) compared to MPs ranging from 3.75 to 4.41 kg/cm$^2$. The disintegration time of the SDs tablets ranged from 13 to 66 s and when compared to values for the MPs ranged from 309 to 380 s, exhibiting a little variation but within the acceptable limit.

Fig. 6 shows the cumulative gliclazide release percentage in water for GC67-SDs tablets (FGC-1 to 8). The prepared tablets showed about 27–35 % and 33–39 % drug release during 30 and 60 min, respectively. The drug release from each formulation was demonstrated at a considerably higher rate than the MPs at every time point. The MPs demonstrated about 13.5 % drug release even after 2 h of the dissolution trial. Accordingly, dissolution rates of FGC-8 were roughly 3.5 times higher than MPs at 60 min. This notable increase in dissolution rate is due to the hydrophilic carplex carrier's ability to increase the wettability and dispersibility and reduce the aggregation of the hydrophobic gliclazide drug particles [20].

Studies at 40 °C and 75 % RH revealed no significant changes in disintegration time, hardness, and gliclazide content in some selected FGC tablet batches (FGC-1, 4, 5, 8). The drug release patterns showed no noticeable change ($p < 0.05$) during storage at 40 °C and 75 % RH for three months. The similarity factor (f2) value for the tablet batches was found to be between 85 and 87. This suggests that the dissolution profiles observed during the initial and 3-month stability tests were comparable.

## 4. Discussion

A crucial and limiting step in the effectiveness of oral medication is the release of the drug [39,40], particularly for medications with poor solubility and high permeability [41]. The relatively low water solubility of the BCS class II medication gliclazide played a limiting role in its bioavailability [19]. To get over this constraint, an effective and stable gliclazide tablet formulation with more release rate was designed using solid dispersions (SDs) and a co-processing excipients technology.

Gliclazide-loaded SDs with carplex (GC-SDs) were prepared and conducted in vitro analysis to determine if their dissolution rate could be improved in a water medium. Additionally, the drug release in water and phosphate buffer medium pH 7.4 was compared to examine the impact of pH on gliclazide solubility (Fig. 5). Previous studies have shown higher drug release using a buffer medium with pH 7.4 [42,43]. The findings from GC-SDs supported the pH-dependent solubility of gliclazide, as higher gliclazide release patterns were observed in the buffer compared to the water medium. This could be caused by the ionization of gliclazide since it is a weak acid [23].

There could be several reasons for the improvement that is seen, such as the reduction in particle size or an increase in surface area of gliclazide by the SDs technique [13]. These factors were confirmed by SEM when compared to the pure drug (Fig. 1). The increase in dissolution rate observed in SDs could be due to the amorphization of gliclazide, as confirmed by DSC and PXRD analyses (Figs. 3 and 4). These results confirmed previous studies that demonstrated significantly increased drug dissolution rates using amorphous formulations [44]. The FTIR spectrum of SDs indicates a weak interaction (hydrogen bonding) between the silanol groups of carplex and the carbonyl groups and amino groups of gliclazide (Fig. 2). This interaction could potentially enhance the drug's wettability properties and lead to a higher rate of drug dissolution [45,46]. It is evident that carplex has significantly improved drug dissolution, which is determined by the ratio of drug to carrier used and the method used to prepare the SDs. This finding supports earlier studies that solvent evaporation is the most effective way to enhance the dissolution rate [47]. This method also ensures a uniform distribution of the drug in the hydrophilic carrier surfaces, which promotes rapid dissolution once the system comes into contact with the dissolution medium.

The disintegration time of the FGC-5 to 8 tablets ranged from 13 to 30 s, and the FGC-1 to 4 values ranged from 34 to 66 s (Table 5). The rapid disintegration of FGC-5 to FGC-8 tablets can be explained by the use of co-processing excipients composite containing superdisintegrants like sodium starch glycolate (SSG). The combination of the ingredients in LMPS composite may create a synergistic effect, leading to the tablets' porous nature and high swelling capacity. This allows water molecules to be absorbed rapidly into the tablet matrix, leading to a faster structural collapse, as it has been confirmed through disintegration studies. So, it reflects that the co-processing excipients composite with SSG might help to enhance the disintegration time of gliclazide tablets.

A considerably higher hydrochlorothiazide (HCTZ) dissolution rate was found when a hydrophilic carrier was co-processed with MCC compared to Tabletose-80 [48]. Our study revealed that all FGC batches had consistent and almost identical release results compared to the SDs of gliclazide (Figs. 5 and 6). The dissolution rate of gliclazide in the first 30 and 60 min was observed more for FGC-5 to FGC-8 formulations when compared to FGC-1 to FGC-4 batches. This might be due to the porous nature of the composite structure and the combined intrinsic swelling tendencies of the excipients in the formulations. Consequently, the water penetration into the tablet matrix might be quicker and collapse the structure faster due to superdisintegrants in the LMPS composite and offered drug release. The design of drug release from SDs tablets used to improve the dissolution rate of BCS class II drugs is consistent with previous reports on porous tablet formulations [49,50]. This finding reflects the significance of adequately selecting and optimizing excipients for composite used in poor water-soluble drug formulation. Furthermore, the co-processed excipients composites SMP and

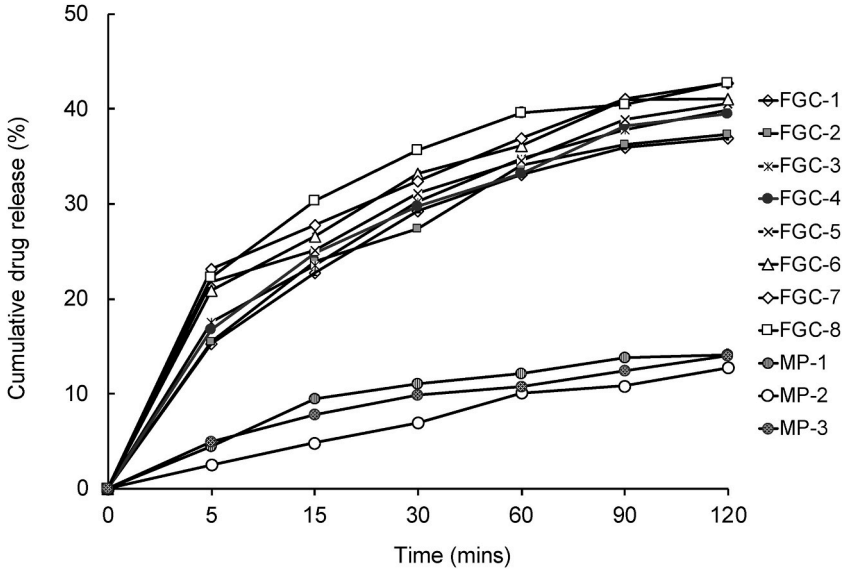


**Fig. 6.** Gliclazide release patterns of the various FGC tablets in the water medium;
FGC: formulated gliclazide carplex 67 tablets; MP: marketed products; data are expressed as mean ± SEM (n = 3).

LMPS are likely to be used in tablet formulations as cost-effective materials compared to commercial direct compressible excipients.

Clinically used gliclazide tablets typically require 2–8 h to reach maximum plasma concentration, which could be considered a shortcoming. This latency in achieving maximum concentration results from the drug's low dissolution rate. Notably, the percentage release of gliclazide from SDs and SDs tablets reached its highest within the first 30 min, about 3~4 fold higher than commercial brands in water medium (Figs. 5 and 6). Thus, the gliclazide tablets made with carplex 67 and co-processed excipients could provide a potential improvement and ensure the proper release of gliclazide, which might lead to better clinical outcomes.

This research has discovered that utilizing the solid dispersions technique with carplex and incorporating co-processing excipients technology is promising to enhance the dissolution rate of poorly water-soluble gliclazide tablets. By taking this approach, it is possible to generate drug formulations that are both cost-effective and stable. This can significantly improve our understanding of the best strategies for treating diabetes with gliclazide.

## 5. Conclusion

According to the report, it was found that carplex can effectively be used to prepare acceptable solid dispersions (SDs) of gliclazide using the solvent evaporation method. The SDs prepared using all carplex grades tested (67, 80, and FPS 500) demonstrated a significant increase in dissolution rate compared to conventional gliclazide. This enhanced dissolution rate was attributed to the reduced crystallinity of gliclazide and surface morphology of the carplex silica particles, as confirmed through solid-state characterizations. Furthermore, the findings suggest that a composite of optimized co-processed excipients could be utilized as direct compressible materials in gliclazide tablet formulation for SDs, and this can assist in achieving similar dissolution patterns to those seen in traditional SDs. This could significantly improve the bioavailability of gliclazide and eliminate the limitations associated with traditional tablet formulations.

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## Data availability statement

The data related to this research is provided within the article.

## CRediT authorship contribution statement

**Subrata Paul:** Formal analysis, Investigation, Methodology, Writing - original draft. **Kaniz Fatema Asha:** Data curation, Formal analysis, Investigation. **Israt Zerin Alam:** Formal analysis, Investigation, Data curation. **Md Ashraf Ali:** Investigation, Methodology. **Md Elias Al-Mamun:** Software, Writing - review & editing. **Md Bytul Mokaddesur Rahman:** Conceptualization, Funding acquisition, Resources, Supervision, Writing - original draft, Writing - review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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