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Enhancing gliclazide solubility using solid dispersions with carboxymethyl chitosan and polyvinylpyrrolidone K30 as polymeric carriers

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ABSTRACT

Background: Gliclazide (Glz) is a second-generation sulfonylurea antidiabetic drug, used to treat type II diabetes mellitus. Glz is a class II drug according to the biopharmaceutic classification system (BCS), indicating that it has high permeability and poor aqueous solubility.
Objective: This study aimed to improve the solubility of Glz *via* the solid dispersion method.
Methods: Solid dispersions of the drug were formulated using carboxymethyl chitosan (CMch) and polyvinyl pyrrolidone K30 (PVP K30) in varying drug to carrier ratios (1:1, 1:3, and 1:5 w/w) using kneading and solvent evaporation methods. The solubility of Glz solid dispersions was compared with the pure Glz and co-grounded mixtures of the drug.
Results: Both carriers exhibited a noticeable increment in solubility and dissolution rate compared to the drug alone. Glz: CMch (1:5 w/w ratio) formulation made by the kneading method exhibited an increased solubility by approximately nine folds (337.79 ± 4.22 µg/ml) as compared to Glz alone (38.74 ± 4.69 µg/ml). However, the greatest improvement in drug dissolution rate was observed in the dispersion made with 1:5 w/w drug to PVP K30 using the solvent evaporation method, and the percentage drug release reached 100% after 30 min. Solid dispersions characterization manifested the compatibility between the drug and carriers, with alteration in particle morphology, and reduction in drug crystallinity.
Conclusion: Overall, solid dispersion using CMch has shown to be an excellent approach for enhancing the solubility and dissolution of the class II drug Glz.

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Solid dispersion; gliclazide; solubility; class II drug; carboxymethyl chitosan; kneading; solvent evaporation; co-grinding

Introduction

Active pharmaceutical ingredients (APIs) of low aqueous solubility and dissolution rate have low bioavailability and compromised pharmacological effect following oral administration [1]. Thus, drug concentration in the blood circulation is usually much lower than its concentration in the gut [2,3], necessitating the ingestion of larger drug doses in order to achieve the desired therapeutic effect, which may cause undesirable side effects or inflated costs of medication [4]. The development of oral formulations of poorly soluble drugs is needed for the drug to be absorbed through human cells [1,5]. Researchers have worked on many techniques for increasing the solubility and dissolution rate of APIs, including the solid dispersion (SD) method, through which the hydrophobic drug is mixed with an inert hydrophilic carrier in the solid state [2,6]. Solid dispersions can be prepared by fusion, solvent evaporation, solvent-melt, or kneading method [7,8], and this technique dates back to 1961, when it was developed by Sekiguchi and Obi [9].

Polymeric carriers play an essential role in the preparation of SDs. Numerous polymers can be utilized, such as polyvinyl pyrrolidone K30 (PVP K30), which is produced through vinylpyrrolidone (VP) polymerization. These polymers are inert, harmless, biocompatible, and highly soluble in water and some organic solvents, which promotes their application in different types of industry such as pharmaceuticals, biomedicals, cosmetics, and food [10]. Moreover, PVP K30 has been widely used in many research papers for enhancing solubility [11–13].

Nowadays, the use of biocompatible and biodegradable polymers is increasing in drug formulations, aiming to enhance solubility, promote bioavailability, and control the release of APIs. Thus, the utilization of biopolymers such as chitosan is becoming more popular [14]. Nevertheless, the weak solubility of chitosan in an alkaline medium is a drawback of this polymer. Therefore, numerous water-soluble derivatives of chitosan have been developed; among these is carboxymethyl chitosan (CMch) [14,15]. CMch is a hydrophilic chitosan derivative with amphoteric characteristics. Interestingly, CMch has also been widely used for its antibacterial, anticancer, and fungicidal properties, in addition to its use for wound-dressing and as a water retention agent. Furthermore, CMch has applications in tissue engineering and in the preparation of polymeric drug delivery systems [16].

Gliclazide (Glz) is a second-generation sulfonylurea antidiabetic drug, used to treat type II diabetes mellitus [17]. Due to its good

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tolerance and low probability of causing hypoglycemia, it is mostly prescribed for long-term treatment of type II diabetes [18]. It belongs to class II of the BCS; thus, it has high permeability and a poor aqueous solubility, leading to inter-individual variability in bioavailability following oral administration [19].

Based on our knowledge, only a few studies have used CMch in order to improve solubility by SD systems [20,21]. The solubility study of Diflunisal indicates its improvement by 13-fold upon using CMch [21]. In addition to that, some other studies used CMch to improve the solubility of curcumin and cannabidiol, however, by using esterification and nanomicelle formation, respectively [22,23]. Moreover, and this is the first study that investigates the utilization of CMch for increasing Glz solubility. The aim of this study is to improve the solubility of Glz *via* different methods of SD by using various polymer carriers at different drug to carrier ratios (1:1, 1:3, and 1:5 w/w), and to study the effect of CMch for increasing the solubility of Glz as a model class II drug.

Materials and methods

Materials

Gliclazide (Glz) and polyvinyl pyrrolidone K30 (PVP K30) were purchased from Apollo Healthcare, Singapore. Carboxymethyl chitosan (CMch) was supplied by Santacruz Biotechnology, USA. Sodium dihydrogen phosphate anhydrous was purchased from Guangdong Guanghua Sci-Tech Co., Ltd., China. Disodium hydrogen phosphate anhydrous was purchased from Hangzhou Soya Co., Ltd., China. All other chemical reagents and organic solvents were of chemical analytical grades. Freshly prepared distilled water was used throughout the study.

Preparation of binary system

Co-grinding and SDs of Glz with PVP K30 and CMch were prepared in three different ratios (1:1, 1:3, and 1:5 w/w) (Table 1). These ratios were selected based on the previous literature and our previous study [24–26], where a number of various drug-to-polymer ratios were trialed and characterized. However, the three ratios presented in the manuscript (1:1, 1:3, and 1:5 w/w) demonstrated the most promising physicochemical properties and drug release profiles. Also, the 1:1 ratio represents a balanced polymer-drug interaction, while the 1:3 and 1:5 ratios allow us to evaluate the impact of progressively higher drug loading on formulation performance and stability. We could not use a higher ratio than 1:5 due to the characteristic polymer after drying (e.g. viscosity and hardness).

Table 1. Formulation code of binary mixture, where a drug (Gliclazide (Glz)) and two polymeric carriers (carboxymethyl chitosan (CMch) or polyvinyl pyrrolidone K30 (PVP K30)) were employed in a drug to carrier ratios (i.e. 1:1, 1:3, and 1:5 w/w) prepared *via* co-grinding (c), kneading (k), and solvent evaporation (s) methods.

Formulation code	Carrier	Drug: carrier (w/w)	Preparation method
Pc1	PVP K30	1:1	Co-grinding
Pc3		1:3	
Pc5		1:5	
Pk1		1:1	Kneading
Pk3		1:3	
Pk5		1:5	
Ps1		1:1	Solvent evaporation
Ps3		1:3	
Ps5		1:5	
Cc1	CMch	1:1	Co-grinding
Cc3		1:3	
Cc5		1:5	
Ck1		1:1	Kneading
Ck3		1:3	
Ck5		1:5	
Cs1		1:1	Solvent evaporation
Cs3		1:3	
Cs5		1:5	

Preparation of SD by co-grinding method

Glz with PVP K30 or CMch (1:1, 1:3, or 1:5 w/w) were mixed (geometric mixing) within a glass mortar, followed by grinding for 5 min and sieving (sieve no. 60). The mixtures were stored in a desiccator over silica gel for 48 h [27].

Preparation of SD by kneading method

Glz and PVP K30 or CMch (1:1, 1:3, or 1:5 w/w) were mixed within a glass mortar and kneaded by the addition of a small volume of acetone and water (1:1 v/v) for 20 min. The acetone-water mixture prevents the thick paste from immediate drying. The paste was then placed in an oven at 45 ± 1 °C for 16 h. The resulting dried samples were scraped out, ground, sieved (through sieve no.60), and then stored over silica gel in a desiccator for 48 h [7].

Preparation of SD by solvent evaporation method

The drug mixture with the polymers was done as described for the two previous methods, followed by the addition of organic solvent (acetone 35 ml and methanol 54 ml) with continuous stirring using a magnetic stirrer (300 rpm) to obtain a clear solution. A rotary evaporator (Stuart RE 300, UK) was used at 45 ± 1 °C with a negative pressure and a rotation speed of 60 rpm to conduct the primary drying of the solvent for 1 h. Then, secondary drying was performed using an oven at 45 ± 1 °C for 15 h. As done with the previous two methods, the samples were collected, crushed, sieved, and stored over silica gel in a desiccator for 48 h [28,29].

The modified solvent evaporation method was used for CMch, which involved the dissolution of Glz in acetone and CMch in distilled water. The Glz solution was added to the CMch solution with continuous stirring using a magnetic stirrer (Stuart UC 152, UK). Then, the solution was dried at 50 ± 1 °C for 48 h, followed by sample collection, grinding, sieving and storage in a silica gel desiccator for 48 h [30].

Characterization studies

Determination of percentage yield

Percentage yield was estimated to determine the efficiency of the used SD technique. It was calculated using Equation (1) [31]:

$$\text{Percentage yield}(\%) = \left(\frac{\text{Actual weight of prepared formulatioin}}{\text{Theoretical weight of drug} + \text{Theoretical weight of carrier}}\right) \times 100 \quad (1)$$

Saturation solubility study

Saturation solubility was performed by the shake flask method. An excess amount (10 mg) of pure Glz or its equivalent weight in binary mixtures were added into 25 ml volumetric flask containing distilled water. The resultant suspensions were shaken (200 rpm) using an orbital shaker (Stuart SSL1, UK) for 48 h at 23 ± 2 °C. Then,

aliquots of suspensions were filtrated using a 0.45 µm syringe filter followed by suitable dilutions, and absorbance was measured using a UV/Visible double beam spectrophotometer (Jenway 6850, UK) at a wavelength of 229 nm [32,33].

Determination of drug content

For calculating the percentage drug content (% DC), Glz (5 mg) in binary mixtures was dissolved in methanol (5 ml), and the volume was made up to 50 ml with distilled water. The solution was shaken for 15 min using magnetic stirring, followed by filtration, dilution, and spectrophotometric analysis at 229 nm [7]. The drug content was calculated using Equation (2) [34]:

$$\%DC = \left(\frac{\text{Practical weight of Glz}}{\text{Theoretical weight of Glz}}\right) \times 100 \quad (2)$$

In-vitro dissolution study of Glz binary mixtures

An amount of binary mixture containing 10 mg of the drug was placed in the dissolution apparatus (HM L-TT-DS6I, type I basket, UK). The basket was placed in 900 ml phosphate buffer solution (pH 7.4), and the temperature was kept at 37 ± 1 °C and rotation speed of 100 rpm. At different time intervals (2, 5, 10, 15, 30, 45, 60, and 90 min), 5 ml was withdrawn, aliquots were filtered through a 0.45 µm syringe and the volumes taken were replaced with 5 ml of fresh phosphate buffer solution. Absorbance of filtered samples was measured at 225.3 nm [18]. The absorbance behavior of Glz is different in different media. In water, Glz has a peak absorbance at 229 nm, whereas in phosphate buffer it is 225.3 nm. This is attributed to the pH of the medium, which significantly affects the solubility of Glz. Phosphate buffer at pH 7.4 offers higher solubility when compared to media like 0.1 N HCl or distilled water [35,36].

Study of factors affecting drug dissolution in binary mixtures. A dissolution study was performed based on the factors expected to affect the dissolution of Glz in binary mixtures [34].

- *Polymer type*
  The influence of CMch and PVP K30 on the dissolution of Glz was studied on Ck5 and Pk5 formulations, which belong to the ratio 1:5 of the kneading method (Table 1).
- *Drug to carrier ratio*
  The influence of drug to carrier ratio on drug release was studied for the samples (Ck1, Ck3, Ck5) and (Ps1, Ps3, Ps5), which are related to the kneading and solvent evaporation method for CMch and PVP K30, respectively (Table 1).
- *Preparation methods*

  The effect of the preparation method of binary mixtures on the dissolution of Glz was studied for Ck5, Cc5, Cs5, Pk5, Pc5, and Ps5 formulations, which are related to the ratio of 1:5 (Table 1). That ratio was selected because the highest solubility was obtained by this ratio for both carriers and in all methods.

Based on the solubility study, CMch formulations were selected for further solid state characterizations.

Fourier transform infrared (FTIR) spectroscopic study

An FTIR study was conducted for raw Glz, CMch, and the selected formulations to detect the functional groups and compatibility between the drug and the excipients. A small quantity of sample was placed in the sample holder and the spectrum of the sample was attained within the range of 1100–4000 nm using an FTIR spectrophotometer (Jasco 4600, Japan) [16].

X-ray diffraction (XRD) study

An analysis of the crystallinity of the pure Glz and the selected SD formulations was performed *via* X-ray diffractometer (Shimadzu XRD-6000, Japan). The sample pattern was scanned from the range of 5 – 80° 2θ using Cu-Kα radiation at 40 kV and 30 mA. The scan speed and step of 10°/min and 0.04° were used, respectively [37]. The percentage crystallinity was calculated, as exhibited in Equation (3), in order to determine the influence of polymer proportion on the crystallinity of Glz [38].

$$\text{Crystallinity}(\%) = \left(\frac{\text{Area of crystalline peaks}}{\text{Area of all peaks}}\right) \times 100 \quad (3)$$

Scanning electron microscope (SEM) study

Surface morphology of the pure drug, carriers, and binary mixtures was studied using scanning electron microscopy (SEM; Tescan, Czech Republic). At room temperature, the samples were coated with gold under argon gas. The experiments were performed under negative pressure with an accelerating voltage of 5 – 30 kV and with various magnifications (500—3000×) [39].

Differential scanning calorimetry (DSC) study

The melting temperature and crystalline nature of raw Glz, carrier, and selected formulations were investigated using differential scanning calorimetry (DSC1 STAR^e system, Mettler-Toledo, USA). A small amount of powder (10 mg) was sealed into an aluminum crucible. An empty aluminum crucible was used as the reference, and thermal scanning was conducted between 25 and 250 °C at an increasing rate of 10 °C min^{-1} while nitrogen gas was used for the atmospheric surrounding of the crucible in order to prevent vapor condensation [3].

Statistical analysis

All experiments were conducted in triplicate, and whenever applicable, findings were presented as mean ± SD One-way analysis of variance (ANOVA) by using GraphPad Instat Demo was used to determine the statistical significance of differences between the compared groups. P values of less than 0.05 were considered significant.

Results

Determination of percentage yield

The yield was in the range of 74.31% to 99.45%, depending on formulation composition, indicating that recovery of the ingredients was generally high, and some formulations exhibited only minimal waste. However, the percentage yield of SDs using the solvent evaporation method (74.31–89.88%) was lower than those of co-grounded mixtures (95.30–99.45%).

Solubility study

The solubility of pure Glz powder in water was found to be poor (38.739 ± 4.686 µg/ml). By contrast, the solubility of the drug in the

binary mixtures was much higher (Figure 1); thus, all SDs and co-grounded formulations excluding the Pc1 formulation, demonstrated a noticeable increment in Glz solubility compared to the drug alone. The highest drug solubilities were obtained when the CMch carrier was used in the binary mixtures. There was a significant difference ($p < 0.001$) between the saturation solubility of Glz in CMch and PVP K30 at drug to carrier ratios of 1:1, 1:3, and 1:5 using co-grinding and SD methods. The highest increase in solubility was obtained in the Ck5 formula, where the solubility was 337.788 µg/ml with an 8.72 fold increase in solubility compared to pure Glz.

Drug content analysis

The drug content of mixtures prepared using CMch was in the range of 74 to 87% (Table 2), which was lower than values obtained by using PVP K30 (92–101%). The results of drug content demonstrated uniform drug distribution in the formulations. However, the amount of Glz that was contained in the PVP K30 formulations was higher than that in CMch. This might be attributed to the difficulty of dissolving CMch in methanol since carbohydrates have limited solubility in commonly used organic solvents [40].

In-vitro dissolution of Glz prepared in binary mixtures

Effect of polymer type

Figure 2 reveals that both polymers had a substantial influence on drug dissolution, leading to enhanced release. The release of Glz was 105.77% ($p < .001$) in the Pk5 formula and 86.5% ($p < 0.01$) in the Ck5 after 30 min as compared to 38.70% for the non-polymeric formulations (i.e. pure drug). It was demonstrated that pure Glz exhibited a slow dissolution even after 30 min. Throughout the dissolution study, dissolution of Glz using PVP K30 was greater than its dissolution using CMch. We visually noted that PVP K30 dissolved faster than CMch in the dissolution medium.

Effect of Glz to carrier ratio

Figure 3(A) illustrates the influence of Glz to CMch ratio on dissolution of the drug in the binary systems. It was shown that when the amount of CMch was increased, the drug release from the SD also increased. Compared to unprocessed Glz (13.303%), formulation Ck5 had the highest release (52.53%) ($p < .05$) after the first 5 min. Moreover, the results of cumulative drug release in PVP K30

Table 2. The drug content in the binary mixture where the drug (Gliclazide (Glz)) was incorporated with carboxymethyl chitosan (C) or polyvinyl pyrrolidone K30 (P) in a 1:1, 1:3, and 1:5 w/w ratio using kneading (k; Ck1, Ck3, and Ck5), solvent evaporation (s; Cs1, Cs3, and Cs5) and co-grinding (c; Cc1, Cc3, and Cc5) methods.

Formulations	Drug content (%)	Formulations	Drug content (%)
Ck1	87 ± 1.94	Pk1	92.46 ± 3.27
Ck3	80 ± 1.27	Pk3	96.33 ± 2.76
Ck5	81 ± 1.90	Pk5	101.93 ± 0.73
Cs1	87 ± 2.92	Ps1	94.39 ± 2.27
Cs3	74 ± 2.28	Ps3	97.90 ± 2.98
Cs5	77 ± 0.72	Ps5	101.41 ± 4.07
Cc1	87 ± 3.38	Pc1	93.96 ± 2.56
Cc3	87 ± 3.14	Pc3	94.45 ± 2.73
Cc5	87 ± 4.58	Pc5	101.57 ± 0.53

Note: Data are mean ± *SD*, $n = 3$.

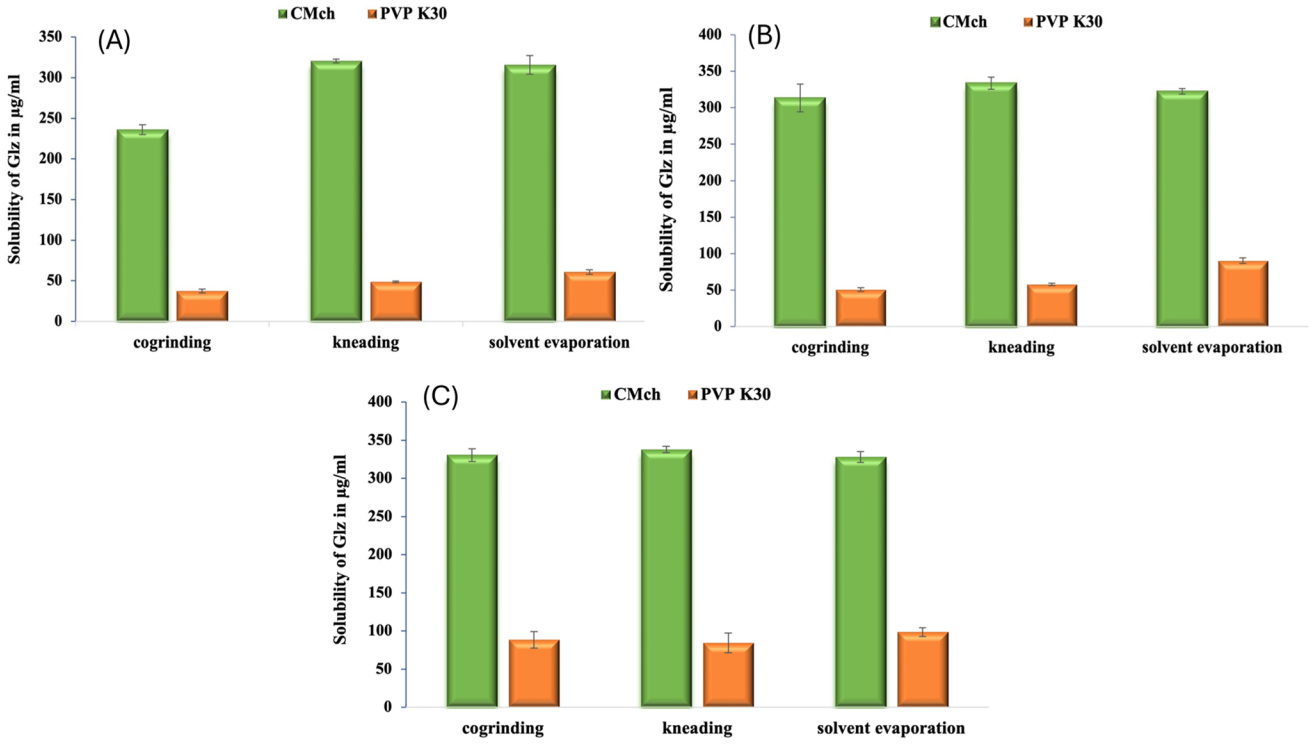

Figure 1. Saturation solubility study of gliclazide in the binary mixtures prepared *via* co-grinding, kneading and solvent evaporation methods. The binary mixtures of the drug and polymeric carriers (carboxymethyl chitosan (CMch) or polyvinyl pyrrolidone K30 (PVP K30)) were combined together at weight ratios of (A) 1:1 w/w, (B) 1:3 w/w, and (C) 1:5 w/w. Data are mean ± SD, $n = 3$.

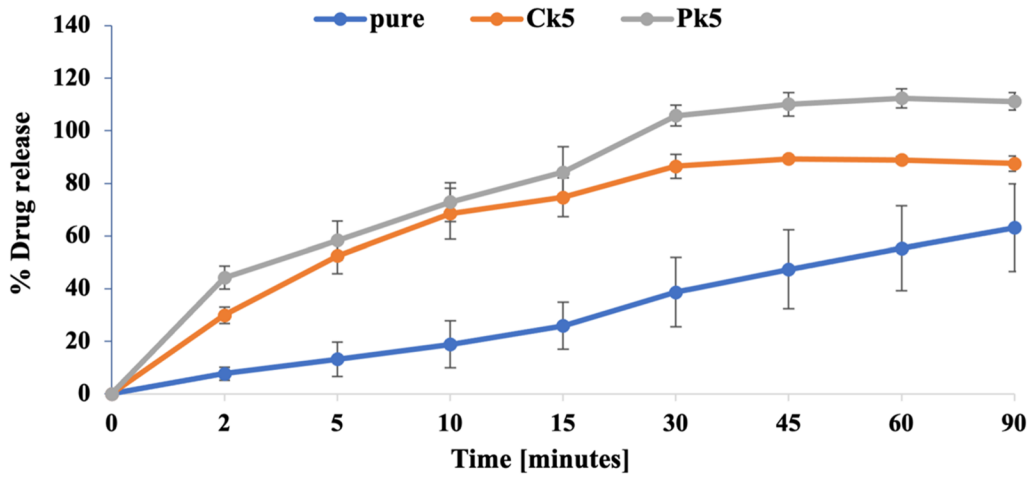

Figure 2. The release profile rate of a pure gliclazide (Glz) alone, the binary mixtures prepared *via* kneading (k) method using 1:5 w/w ratio of a drug Glz with carboxymethyl chitosan (Ck5) and Glz with polyvinyl pyrrolidone K30 (Pk5). Data are mean ± SD, $n = 3$.

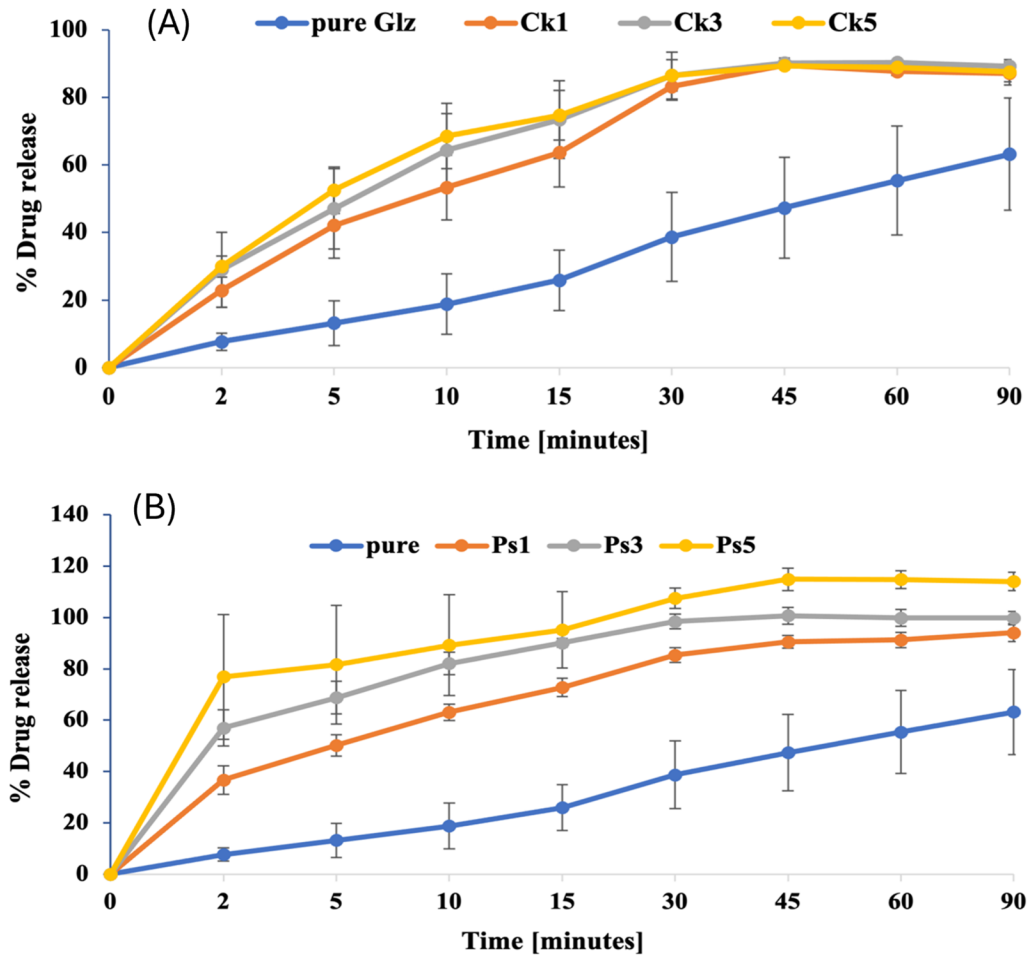

Figure 3. The drug (Gliclazide (Glz)) release profile when used as a control (pure) and its release from a binary mixture when prepared *via* kneaded (k) and solvent evaporation (s) methods to characterize the effect of (A) Glz to carboxymethyl chitosan (C) in a 1:1, 1:3, and 1:5 w/w ratios (Ck1, Ck3, and Ck5), and (B) Glz to polyvinyl pyrrolidone K30 (P) in a 1:1, 1:3, and 1:5 w/w ratios (Ps1, Ps3, and Ps5). Data are mean ± SD, $n = 3$.

formulations are shown in Figure 3(B). The highest release was demonstrated by Ps5 formulation, being 81.633% ($p < .05$) within 5 min. The dissolution and solubility findings indicate that by increasing carrier concentration, both solubility and dissolution of Glz increased.

Effect of preparation method

Figure 4(A) displays the amount of Glz released from various techniques containing CMch at 1:5 w/w. The amount of Glz released after 5 min was found to be 52.53% for Ck5, 40.47% for Cs5, and 21.47% for Cc5 as compared to 13.20% for pure Glz. Thus,

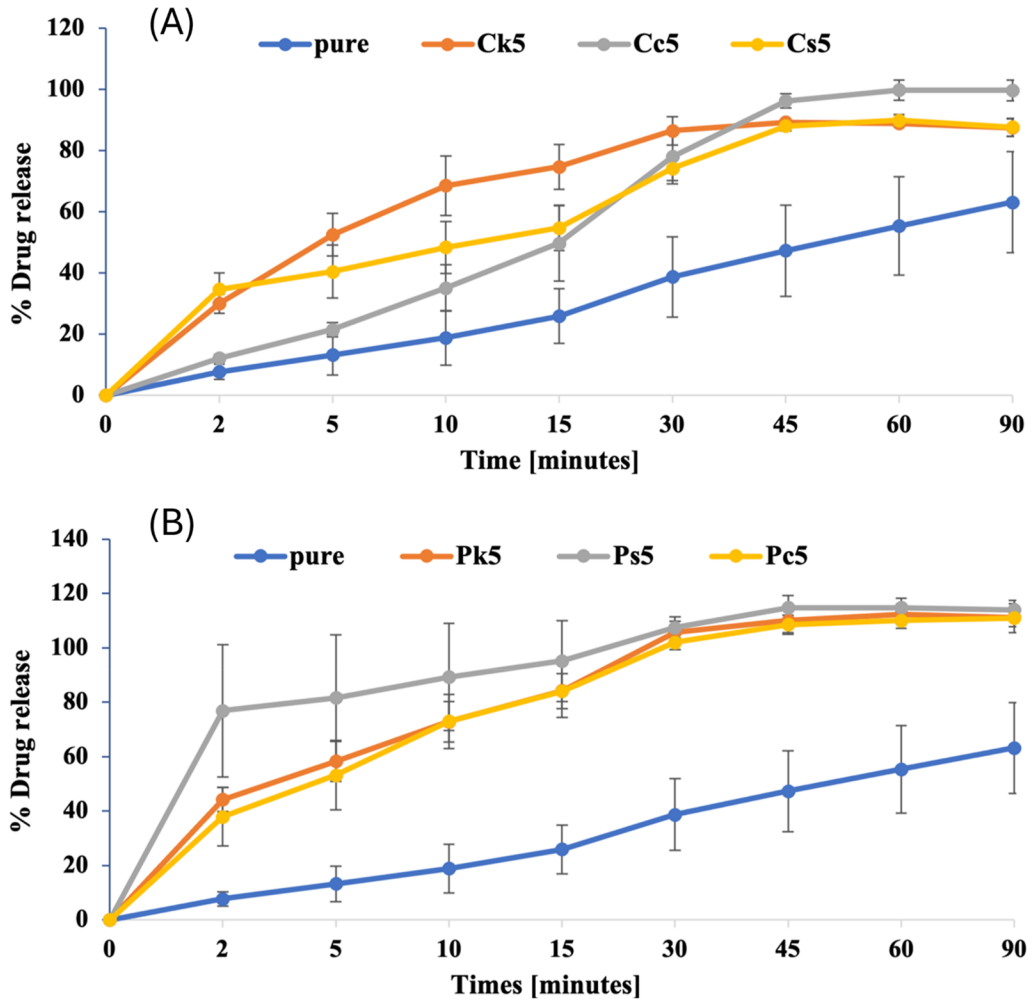

Figure 4. The drug (Gliclazide (Glz)) release profile when used as a control (pure) and its release from a binary mixture when prepared *via* kneaded (k), solvent evaporation (s), and co-grinding (c) methods to characterize the effect of (A) Glz to carboxymethyl chitosan (C) 1:5 w/w ratio (Ck5, Cc5, and Cs5), and (B) Glz to polyvinyl pyrrolidone K30 (P) in a 1:5 w/w ratio (Pk5, Ps5, and Pc5). Data are mean ± SD, $n = 3$.

cumulative drug release from CMch formulations using the kneading method was higher than from solvent evaporation mixtures. As shown in Figure 4(B), drug release within the first 30 min was highest from PVP K30 formulations using the solvent evaporation method. In terms of solubility and release of Glz in PVP K30 formulations, the solvent evaporation method was superior to the kneading method.

Our dissolution study findings can be summarized: (i) CMch is able to act as a carrier in the SD system for improving the dissolution of the drug Glz; (ii) the higher the concentration of the polymer, the faster the drug dissolves; (iii) the SD technique offered a significant influence on increasing the drug release when compared to the co-grinding method or when the pure Glz was used.

Solid state characterization of Glz/CMch binary mixtures

Based on the solubility study, CMch formulations were selected for further solid state characterization because the solubility of Glz in these polymer mixtures was significantly higher than that of PVP K30. However, the dissolution rate of Glz in PVP K30 formulations was higher, and the dissolution rate of Glz in CMch was still substantially higher than that of pure Glz. The selected formulations are based on the methods of preparation (Ck5, Cs5, and Cc5) and different drug to carrier ratios of kneaded mixtures (Ck1, Ck3, and Ck5).

Fourier transform infrared (FTIR) spectroscopic study

The infrared spectrum of pure Glz is exhibited in Figure 5. It provides main peaks at wave number 1704 cm^{-1} and 3264 cm^{-1} which indicate the carbonyl and amino groups, respectively, as well as the peaks absorption at 1158 cm^{-1} and 1343 cm^{-1} indicating the sulfonyl group. In the spectra of all binary mixtures, the carbonyl band of Glz showed up as a 'shoulder' on the 1740 cm^{-1} band of CMch. Additionally, the band of the main functional groups of Glz was shifted slightly toward higher wavenumbers, which may suggest an interaction (e.g. physical interaction) between Glz and the carrier.

X-ray diffraction (XRD) study

The XRD diffractogram of Glz, CMch, and various preparation methods are illustrated in Figure 6. The unprocessed Glz displayed sharp and intense diffraction peaks at 2θ, values of 10.48, 17, 17.08, 18.16, 20.80, 22.04, 25.28, 26.20, 26.84, 27.52, 28.64, and 29.2°, clearly demonstrating the crystalline nature of the drug. The crystalline nature of the drug can be evidenced by the presence of the numerous sharp and intense peaks in the X-ray diffractogram [41,42]. Pure CMch showed three main crystalline peaks with the highest intensity at 2θ of 20, 31.52 and 45.32°. In the spectrum of the co-ground sample, most of the drug's prominent peaks were presented but with considerable reductions in their

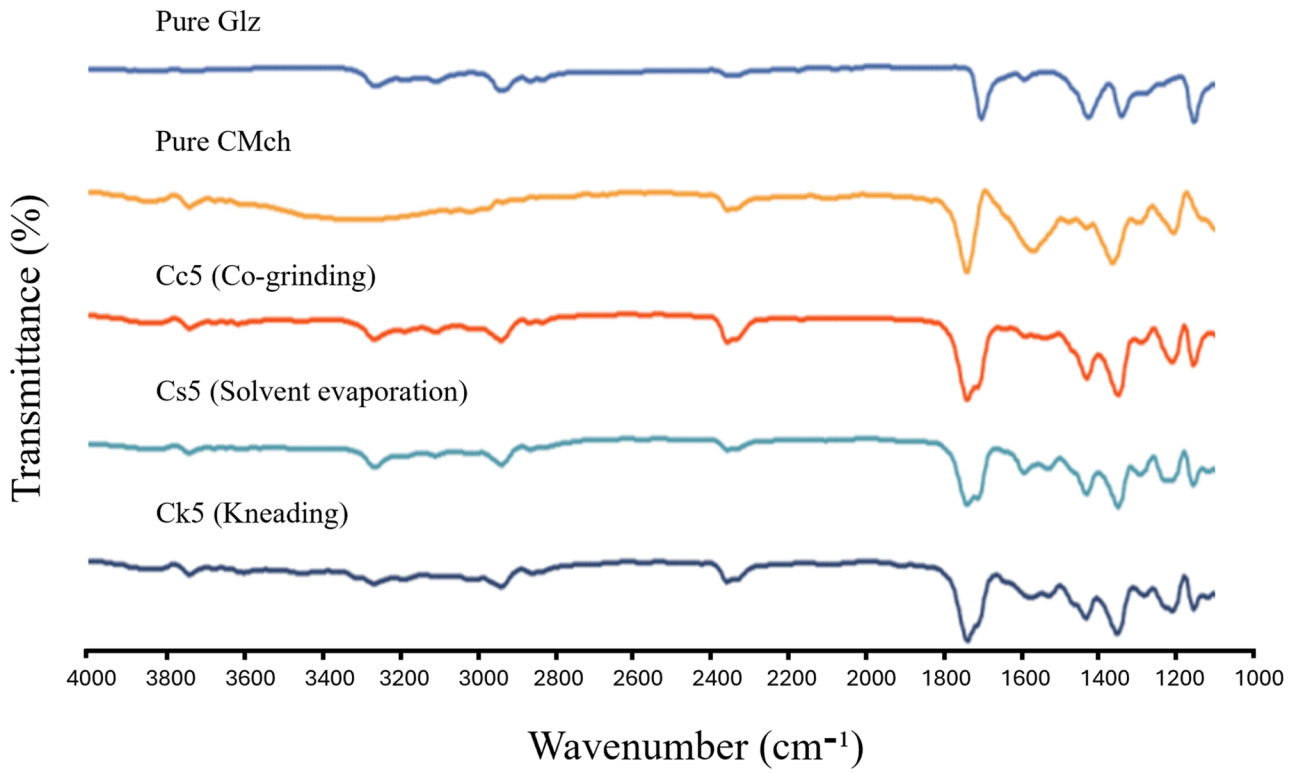

Figure 5. FTIR spectrum of pure gliclazide (Glz) and spectra of different formulations at a ratio of 1:5 w/w. Pure Glz, carboxymethyl chitosan (CMch), and formulations prepared using Glz and carboxymethyl chitosan (C) in a 1:5 w/w ratio *via* co-grinding (Cc5), solvent evaporation (Cs5), and kneading (Ck5) methods. These results are typical of three such different experiments.

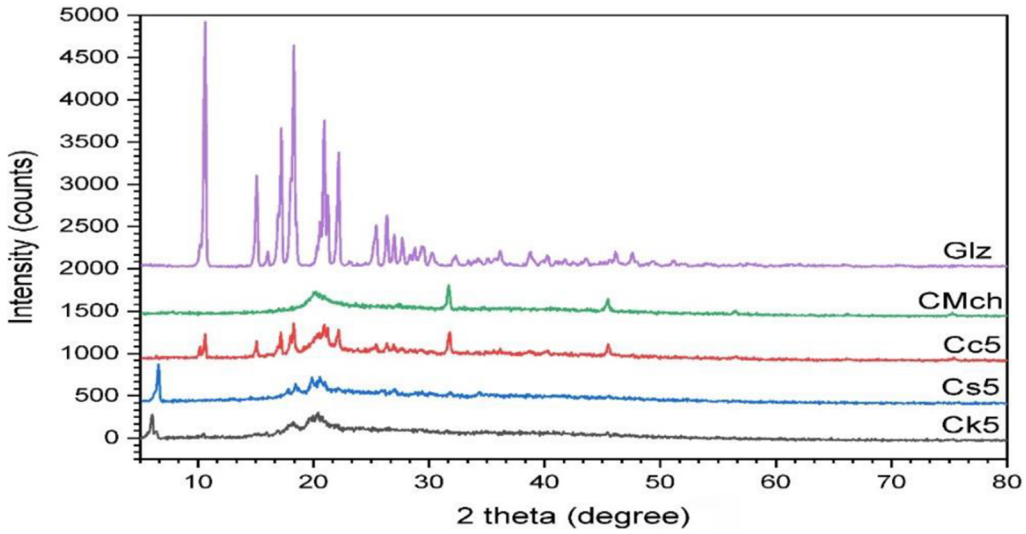

Figure 6. XRD pattern of pure gliclazide (Glz), carboxymethyl chitosan (CMch) alone, and a binary mixture where Glz and carboxymethyl chitosan (C) were prepared in a 1:5 w/w ratio using co-grinding (Cc5), solvent evaporation (Cs5), and kneading (Ck5) methods. These results are typical of three such different experiments.

intensity. However, several peaks disappeared in SDs, and a reduction in peak intensity in SDs was observed.

Moreover, as shown in Figure 7, the level of crystallinity of raw Glz and drug in CMch mixtures at three different ratios was found to be in the following order: Ck5< Ck3< Ck1< pure Glz, with the respective levels of 26, 31, 52, and 75%.

Scanning electron microscopy (SEM) study

Surface morphology of raw Glz particles and the various binary mixtures are shown in Figure 8. It was found that Glz particles varied in size and had irregular angular shapes. The polymer CMch was composed of irregularly shaped particles, and some particles had flake-like shapes. SEM of the co-ground formulations revealed that their surfaces were apparently smooth, whereas the surfaces of the particles of SD formulations were apparently rough with a new solid shape.

The morphology of SD with varying drug to carrier ratios was observed in Figure 9 with no obvious differences, which demonstrated that the drug to carrier ratio had no apparent effect on particle morphology in the SD system.

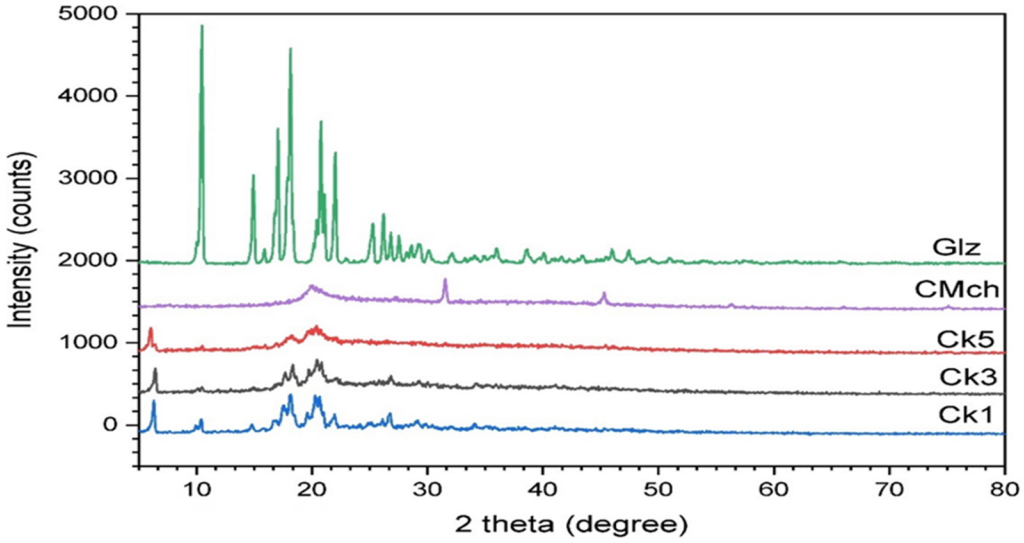

Figure 7. XRD pattern of pure gliclazide (Glz), carboxymethyl chitosan (CMch) alone, and a binary mixture where Glz and carboxymethyl chitosan (C) were prepared in 1:1, 1:3, and 1:5 w/w ratio using a kneading (k) method (Ck1, Ck3, and Ck5). These results are typical of three such different experiments.

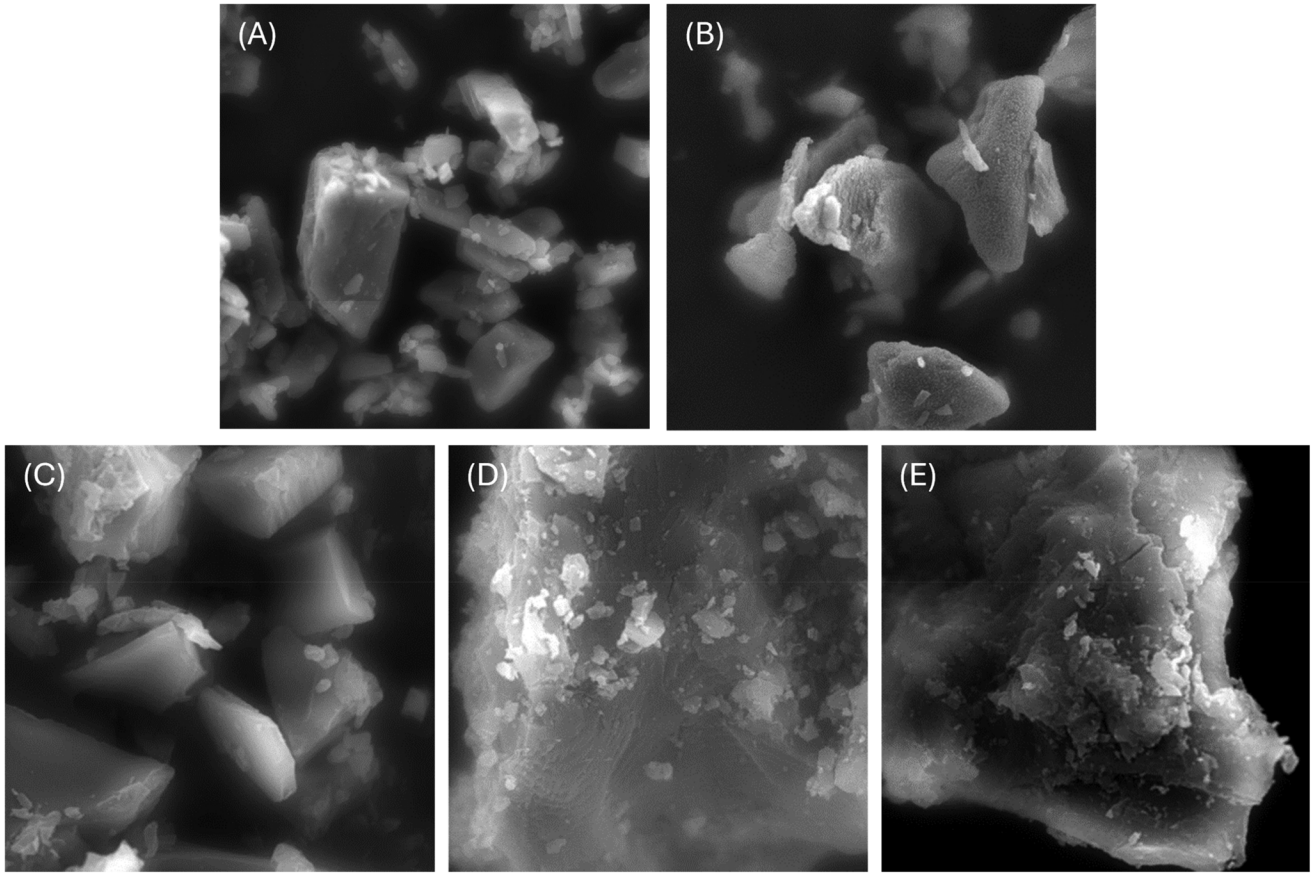

Figure 8. SEM images of (A) pure gliclazide (Glz), (B) pure carboxymethyl chitosan (CMch), and a binary mixture of Glz and CMch prepared *via* (C) co-grinding, (D) kneading, and (E) and solvent evaporated method. These images are typical of three such different experiments.

Differential scanning calorimeter (DSC) study

The thermogram of raw Glz (Figure 10) displayed a single and sharp endothermic peak at 171.26 °C with the enthalpy of fusion (ΔH) being 136.73 J/g, indicating drug crystalline characteristics. This finding consolidated our earlier findings of XRD and SEM. The melting peaks of Glz in all the formulations made by different methods and various drug to carrier ratios were shifted lower with a reduction in peak area (Figure 10 and Figure 11). The peak of Glz

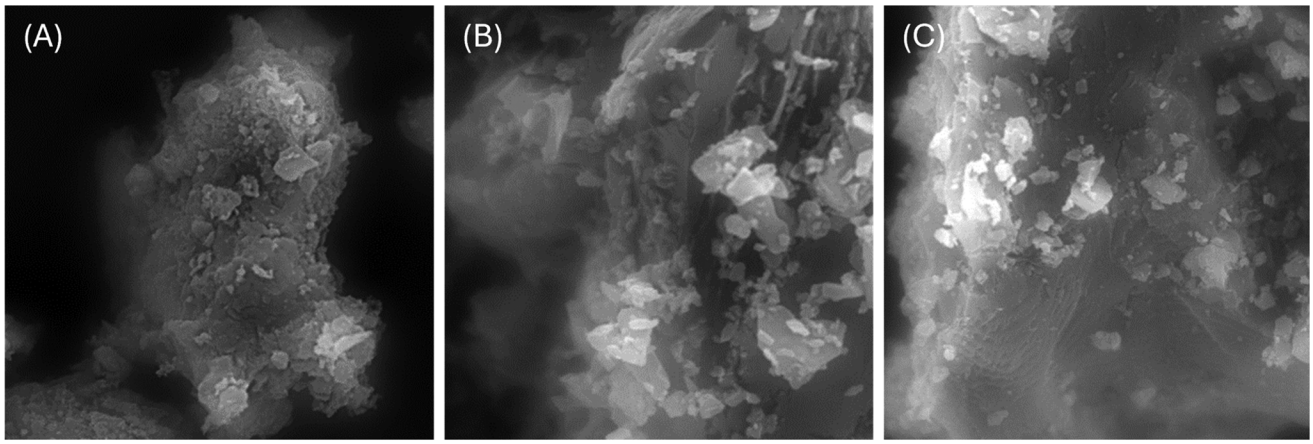

Figure 9. SEM images of a binary mixture of gliclazide (Glz) and carboxymethyl chitosan (CMch) prepared *via* kneading method in a (A) 1:1, (B) 1:3, and (C) 1:5 w/w ratio. These images are typical of three such different experiments.

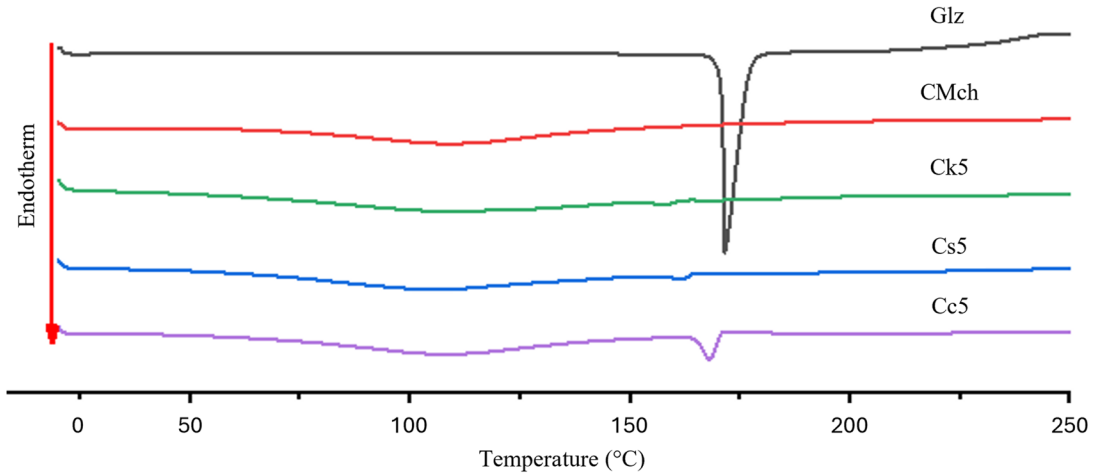

Figure 10. DSC thermograms of pure gliclazide (Glz), carboxymethyl chitosan (CMch) alone, and a binary mixture where Glz and carboxymethyl chitosan (C) were prepared in a 1:5 w/w ratio using co-grinding (Cc5), solvent evaporation (Cs5), and kneading (Ck5) methods. These results are typical of three such different experiments.

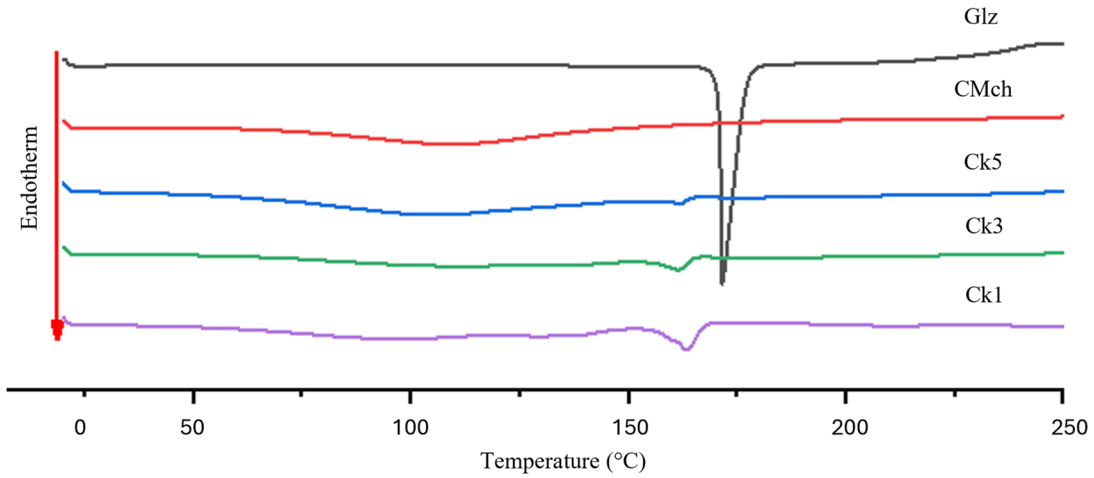

Figure 11. DSC thermograms of pure gliclazide (Glz), carboxymethyl chitosan (CMch) alone, and a binary mixture where Glz and carboxymethyl chitosan (C) were prepared in 1:1, 1:3, and 1:5 w/w ratio using a kneading (k) method (Ck1, Ck3, and Ck5). These results are typical of three such different experiments.

was more noticeable in the co-ground mixture (Cc5; Figure 10) than those in SD methods. The results of SEM were in agreement with the DSC study. It was possible to differentiate pure components of both Glz and the polymer in binary mixtures formulated by the co-ground method. Moreover, the enthalpy of fusion was remarkably reduced with increasing the proportion of

CMch in formulations prepared by the kneading method. For instance, the enthalpy of fusion in Ck1, Ck3, and Ck5 was 25.64, 11.62 and 4.57 J/g, respectively.

Discussion

The higher percentage yield of the formulations was obtained for the co-grounded mixtures compared to the SD; it could be attributed to the physical characteristics (sticky nature) of the carriers used and the multi-step process of the applied SD methods. The solubility of the drug was significantly increased while using CMch as an excipient. The result of increasing solubility of Glz by CMch is in agreement with that of Lucio et al. who found that solubility of Diflunisal increased by 13 folds upon using CMch [21]. It is possible that the protonation of RCOOH and NH2 groups of CMch in alkaline or neutral media of the dispersion has enhanced the solubility of the carrier, and caused a conformational stretch of CMch chains, resulting in producing a polymer-rich microenvironment surrounding the drug, hence, improving drug wettability and solubility [16,21]. Likewise, the solubility of the drug PVP K30 mixtures using the solvent evaporation method was maximized (98.299 µg/mL) when the drug to carrier ratio was 1:5. Increased drug solubility when included with PVP K30 in SD could be attributed to the hydrophilic effect and surfactant properties of this polymer [1]. Another important factor that affects the performance of SD is the drug to carrier ratio. As the concentration of polymer was increased, the solubility of Glz increased. Increasing the carrier proportion to be higher than that of the drug causes diminished or abolished crystallinity of the drug, resulting in significant enhancement in solubility and dissolution. Furthermore, increasing the carrier proportion in the formulation improved the overall hydrophilicity of the particles, resulting in minimized aggregation of the drug in the liquid medium and enhanced solubility [43].

The polymer type plays a crucial role in the dissolution improvement of the drug and drug release rate. The solubility of Glz improved higher in CMch compared to PVP k30; this might be due to the relative viscosity of both carriers or the relative crystallinity degree of Glz in the mixtures of different carriers. The aforementioned behavior explains why Glz dissolution is not necessarily correlated with drug solubility. The findings are consistent with those reported by Soliman et al. who attempted to improve the solubility of Diacerein by employing various carriers [39]. Moreover, the carrier to drug ratio has a significant effect on dissolution and drug release profile. SDs formulated with larger quantities of hydrophilic carriers may provide larger space for enclosing hydrophobic drug particles, resulting in rapid hydration of the drug molecules and subsequently greater wettability and faster dissolution of the drug [44]. Furthermore, the obtained results demonstrated the method of preparation has a great impact on the dissolution and cumulative drug release. The kneading method provides higher cumulative drug release compared to the solvent evaporation method using CMch as a carrier. It is likely that drug precipitation in the solvent evaporation method using CMch has reduced the solubility and dissolution of Glz compared to the same formulations using the kneading method. In contrast, the solvent evaporation method was superior to enhance solubility and drug release using PVP. This might be attributed to the complete dissolution of Glz in the medium, and the provision of heat in the solvent evaporation method was helpful to aid subsequent drug dissolution, since heating has an effect on the polymorphic changes of some materials. It has previously been reported that heating may induce conformational modifications and flexibility in the cavity of the carrier, thereby enhancing the interaction between the polymer and the drug [39]. Consequently, Glz solubility, dissolution, and release were affected not only by formulation but also by the method used to prepare the solid dispersion. Co-grinding is expected to improve Glz dissolution. A previous study has reported that increased dissolution might be due to micronization and appropriate distribution of the drug onto the surface of hydrophilic polymers [45].

Solid state characterization of Glz/CMch binary mixtures using FTIR spectroscopy demonstrated a shift of the main functional group of the drugs, indicating physical interaction between Glz and the carrier. Also, it is confirmed by DSC results as the peak of the drugs reduces and the melting point shifts to lower in SD formulations, suggesting a possible interaction between Glz and the polymers [33,46]. The hydrogen atom of the amine group of Glz was predicted to form the hydrogen bond with an oxygen atom of the carbonyl group of the polymer and/or the C=O and S=O groups of Glz with one of the hydrogen atoms of the carrier [18]. Enhanced wetting properties, solubility, and release rate of APIs were related to an interaction occurring between the drug and carrier in the solid state [47]. The lack of any extra peaks in binary systems suggested that Glz and polymers did not interact chemically [48].

The percentage of crystallinity for assessing the influence of carrier proportions on the drug diffractive peaks demonstrated that the greater the concentration of the carrier, the greater the reduction in drug crystallinity. Crystallinity influences peak height; therefore, the proportionate lowering in Glz peak intensity in the binary mixtures indicated that drug crystallinity was decreased by partially converting into amorphous [43]. The appearance of rough surfaces of the SD formulations using SEM could be due to the greater cohesion between the drug and the polymer [46]. Additionally, the rough surface indicated that the Glz surface was uniformly covered by the carrier. The solubility of APIs into the carrier causes the drug solid dispersion to aggregate with a rough surface being observed; hence, the rough surfaces in SDs can motivate drug dissolution [49].

Furthermore, the lowest melting peak was observed in Glz dispersed in CMch (1:5 w/w) because a lower concentration of the drug will absorb a lower amount of energy to undergo melting [28]. The great reduction in the endothermic peak and enthalpy of fusion was revealed to be advantageous in terms of converting crystalline drug into amorphous form, justifying the greater solubility and dissolution of the drug in a 1:5 w/w ratio formulation.

Conclusion

Based on the findings of this study, it can be concluded that CMch as biopolymer can be utilized effectively to formulate solid dispersions by kneading and solvent evaporation methods. SDs showed substantial enhancement in solubility and dissolution compared to the Glz raw material and co-ground samples. The highest improvement in solubility was observed in SD prepared with CMch at 1:5 drug to carrier using kneading technique. The FT-IR study demonstrated that the Glz was compatible with the hydrophilic carriers used in this study. Overall, the manifestations of decreased crystallinity of Glz by the XRD and DSC studies, as well as the surface morphology changes of the binary mixtures justified the increased solubility and dissolution rate of Glz. *In vivo* studies using appropriate animal model are required in the future to correlate the enhanced solubility and dissolution with increasing rate and extent of drug absorption.

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Author contributions

CRediT: **Berivan Ajeel Ibrahim**: Data curation, Formal analysis, Methodology, Writing – original draft; **Nozad Rashid Hussein**: Conceptualization, Project administration, Supervision, Visualization; **Huner Kamal Omer**: Investigation, Software, Validation; **Abdelbary Elhissi**: Resources, Validation, Writing – review & editing; **Iftikhar Khan**: Project administration, Visualization, Writing – review & editing.

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Data availability statement

The authors declare that all the supporting data are contained within the paper.

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