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Optimization of solid dispersion technique and gliclazide to carrier (PVP K30) ratio for solubility enhancement

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Abstract

Background and objective: Poorly water-soluble dugs provide less dissolution rate and bioavailability; hence, it minimizes the pharmacological effect of orally administered medications. Gliclazide is a sulfonylurea antidiabetic medication of the second generation, used to treat type II diabetes mellitus. It belongs to the class II drugs of biopharmaceutic classification system, indicating that it has high permeability and poor aqueous solubility. The aim of this study is to determine an optimum solid dispersion method and drug to carrier ratio to improve the solubility of gliclazide.

Methods: Solid dispersions of gliclazide were formulated with polyvinyl pyrrolidone K30 using various drug to carrier ratios (1:1, 1:3, and 1:5) by utilizing kneading and solvent evaporation methods. Solubility and dissolution rate of solid dispersion formulas were compared with pure drug and co-ground mixtures. The formulations were further evaluated in terms of percentage of yield, drug content, FTIR, SEM, DSC, and XRD studies.

Results: The highest solubility improvement of gliclazide was obtained at the ratio 1:5 of gliclazide and PVP K30 utilizing solvent evaporation method, solubility increased about 2.54 folds (98.299 ± 5.77 µg/ml) as compared to pure gliclazide (38.739 µg/ml). Meanwhile, the greatest improvement in gliclazide dissolution rate was observed in the same solid dispersion formula that was about 105.76 % after 30 minutes. FTIR demonstrated no unwanted interaction between the drug and carrier. While, SEM, DSC, and XRD showed crystallinity of the drug was minimized and converted to amorphous form in solid dispersion formula.

Conclusion: Based on the investigations of this study, it can be concluded that the drug to carrier weight ratios and preparation methods had the influence on the drug solubility and the release rate. The obtained data revealed that the solvent evaporation is the best method of solid dispersion for enhancing gliclazide solubility using PVP K30 with the ratio 1:5 of the drug and carrier.

Keywords: Dissolution enhancement; Improving solubility; Solid dispersion; Polyvinyl pyrrolidone K30; Gliclazide.

Introduction

Pharmaceutical compounds with low aqueous solubility and dissolution rate properties lead to low bioavailability and reduced pharmacological effect when orally administered.[1] This is attributed to the concentration of poorly water soluble compounds that pass into circulatory system which might be much lower than the concentration in the gut due their low aqueous solubility.[2] It makes a limitation to the drug through ingestion of larger dose, which might result in appearance of unwanted effects, or creating an issue of increasing cost of medications. Therefore, pharmaceutical formulations of those compounds are often challenging and oral preparations of those drugs require

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significant effort.[3] Researchers have worked on many techniques to increase solubility and dissolution rate, and the efficient one is the carrier used technique (solid dispersion).[2,4] Dispersing the therapeutically active hydrophobic substance(s) in an inert hydrophilic carrier(s) in a solid matrix is described as Solid dispersion (SD). It is the most widely used method for increasing solubility, dissolution rate, and bioavailability of hydrophobic drugs. Dispersion of drugs through carriers could be prepared by fusion, solvent evaporation, solvent-melt, and kneading method.[5] Polymeric materials have essential role in preparing SDs.

Numerous of polymers can be utilized successfully for increasing solubility and dissolution rate of poorly water-soluble drugs. Polyvinyl pyrrolidone K30 (PVP K30) is produced from Vinylpyrrolidone polymerization. It is inert, harmless, biocompatible, and extremely soluble in water, as well as in a range organic solvent, hence, it can be utilized in a variety of industries such as pharmaceutics, biomedicals, cosmetics, and food.[6] Solubility and dissolution rate improvement of numerous class II drugs by SD technique have been successfully achieved by many researchers.[1,3] Gliclazide (Glz) is used to treat type II diabetes mellitus. Due to its good tolerance property and low probability of hypoglycemia, it is mostly prescribed for long-term treatment of type II diabetes.[7] It belongs to the class II of the biopharmaceutic classification system, indicating that it has high permeability and a poor aqueous solubility. This lead to the low rate and interindividual variability of Glzoral absorption.[8]

This study aimed to improve solubility and dissolution rate of Glz by using PVP K30 via SD techniques, and to evaluate the solid-state characteristics of the selected formula.

Methods

MATERIALS

Glz and PVP K30 were purchased from Apollo Healthcare, Singapore. 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 chemicals and organic solvents were of analytical grades.

METHODS

Preparation of Binary System

Co-grinding and SDs of Glz with PVP k30 were prepared in three different weight ratios (1:1, 1:3, and 1:5) (Table 1).

Table 1 Formulation codes of Glz binary mixtures

Formulation code	Carrier	Drug: carrier ratio w: w	Preparation method
Pc1	PVP K30	1:1	Co-grinding
Pc3		1:3	Co-grinding
Pc5		1:5	Co-grinding
Pk1	PVP K30	1:1	Kneading
Pk3		1:3	Kneading
Pk5		1:5	Kneading
Ps1	PVP K30	1:1	Solvent evaporation
Ps3		1:3	Solvent evaporation
Ps5		1:5	Solvent evaporation

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Preparation of co-grinding mixture

Co-ground formulation of Glz with PVP K30 in various weight ratios was prepared by accurately weighing specific quantity (as exhibited in Table 2) of each substance and followed by geometrical mixing and grinding in a glass mortar for 5 minutes. The milled products passed through the sieve no.60. The prepared powdered mixture was kept in desiccator over the experimental studies using silica gel.[9]

Preparation of SD by kneading method

An accurate weight, in the above Table 2, of Glz and PVP K30 with three distinct ratios was mixed geometrically in the glass mortar and powdered mixture was kneaded by the addition of small volume of acetone-water (50% V/V) for 20 minutes. To facilitate the evaporation of the solvents being used, the obtained thick paste was placed in an oven at 45 C^{o} ± 1 C^{o} for up to 16 hours. The dried samples were scraped, grinded, sieved through sieve no.60, and stored over silica gel in desiccator for 48 hours before using and during all the experimental studies.[10]

Preparation of SD by solvent evaporation method

Accurately weighted quantity of Glz and PVP K30 with numerous ratios, in the aforementioned Table 2, were separately dissolved in (35-45 ml) of appropriate solvents, followed by the addition of Glz solution into the carrier solution with continuous stirring using magnetic stirrer (300 rpm). The solution was evaporated to get dry dispersion using rotary evaporator (Stuart RE 300, UK) at temperature 45 C^{o} ± 1 $C^{o,}$ pressure 25 cm Hg, with the rotation speed of 60 rpm. Then, secondary drying was performed using an oven at 45± 1 ^{o}C for 15 hours. After scraping, crushing, and sieving, the dried samples were stored over silica gel in desiccator for 48 hours before using and during all the experimental studies.[10, 11]

Characterization of Prepared Formulations

Determination of percentage yield

Percentage yield (% yield) was estimated to determine the efficiency of the used technique. It was calculated by the following equation 1.[12]

$$\%yield = \frac{\text{Actual weight of formulated sample}}{\text{Theoretical weight of drug + Theoretical weight of carrier}} \times 100 \quad \ldots \text{Equation (1)}$$

Table 2 Compositions' weight of different drug to carrier ratios

Drug: carrier ratio	Drug weight	Carrier weight
1:1	600 mg	600 mg
1:3	600 mg	1800 mg
1:5	600 mg	3000 mg

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Saturation solubility study

Saturation solubility was performed by shake flask method. An excess amount (10 mg) of pure Glz and its equivalent weight in binary mixtures added into 25 ml volumetric flask and filled the volume to the level with distilled water. The prepared suspensions were shaken (200 rpm) using an orbital shaker (Stuart SSL1, UK) for 48 hours at room temperature (23 ± 2 ^{o}C). Then, aliquot of suspensions filtered through 0.45 µm syringe filter followed by suitable dilutions and absorbances was measured using UV/Visible double beam spectrophotometer (Jenway 6850, UK) at wavelength of 229 nm.[13, 14]

Determination of drug content

To calculate the percentage drug content (%DC), 5 mg of Glz in binary mixtures was dissolved in 5 ml of methanol and the volume was completed up to 50 ml with distilled water using volumetric flask. The solution was shaken for 15 minutes using magnetic stirrer, and filtered samples quantified using spectrophotometer.[5] The percentage of drug content was calculated using equation 2.[15]

In-vitro dissolution study of Glz binary mixtures

Glz binary mixture samples equivalent to 10 mg of pure Glz was placed in dissolution tester (HM L-TT-DS6I, UK) using type I basket apparatus. The basket was placed in 900 ml phosphate buffer solution pH 7.4, the temperature kept at 37 ± 1^{o}C with the rotation of 100 rpm. At times (2, 5, 10, 15, 30, 45, 60, and 90 minutes), 5 ml of solution was withdrawn, aliquots were filtered through 0.45 µm syringe filter and withdrawal volumes were replaced by5 ml of fresh phosphate buffer solution pH 7.4. Absorbances of filtered samples were measured spectrophotometrically at 225.3 nm.[7]

Factors affecting the dissolution of Glz in binary mixtures

In-vitro dissolution study was performed based on the factors affected on the dissolution of Glz in binary mixtures.[15] The factors are divided as the following:

Effect of drug: carrier ratio

The influence of Glz: carrier's ratios on release of Glz was studied for the samples (ps1, ps3, ps5), which are related to the solvent evaporation method.

Effect of preparation methods

The effect of preparation methods on dissolution of Glz was studied for pk5, pc5, and ps5 formulations, which related to the ratio 1:5. That ratio was selected because the highest solubility was obtained by this ratio in all methods.

Based on the solubility and dissolution studies, an optimum SD of Ps5 formula was selected for further evaluations and the results were compared with pure Glz and co-grounded mixture (Pc5).

Fourier transform infrared (FTIR) spectroscopic study

FTIR study was performed for pure Glz, PVP K30, Pc5 and Ps5 formula to detect the functional groups and incompatibility between them. The spectrum of samples was attained within the range of 400nm – 4000nm using FTIR spectrophotometer (Jasco 4600, Japan).[16]

$$\%DC = \frac{\text{Practical weight of Glz}}{\text{Theoretical weight of Glz}} \times 100 \qquad \text{..... Equation (2)}$$

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X-ray diffraction (XRD) study

Analysis of crystalline nature of the pure Glz and selected formula was performed using X-ray diffractometer (Shimadzu XRD-6000, Japan). Sample pattern was scanned using Cu-K radiation from the range of 5° to 80°at 2θ and at voltage 40 kV with the current of 30 mA. The scan speed and step of 10°/ minute and 0.04° were used, respectively.[17] The percent of crystallinity was calculated according to equation 3.[18] Area of peaks determined using an origin software program.

Scanning electron microscope (SEM) study

To observe the shape and surface morphology of the pure drug, carrier, and selected binary mixture, scanning electron microscope (Tescan, Czech Republic) was used. At room temperature, the samples were coated with a coating of gold under Argon gas. The study was performed at a high vacuum with an accelerating voltage of 5-30 kV and with various magnifications (500x - 3000x).[19]

Differential scanning calorimeter (DSC) study

Melting temperature and crystalline nature of raw Glz, carrier, and Ps5 formula were evaluated via differential scanning calorimeter (DSC1 STAR^e system, Mettler-Toledo, USA). Exactly 10 mg of powder was weighted and sealed into an aluminum crucible. Samples were subjected to heating at rate 10 C° min^{-1} from the range 25 °C to 250 °C and nitrogen gas was used for atmospheric condition.[19]

Statistical Analysis

The data of experiments that carried out in triplicate were provided as mean ± Standard deviation, that was calculated using Microsoft excel 2019. Shapiro-Wilk test was used by Statistical Package for the Social Sciences (SPSS) software program to determine the normality of distribution of the data. The data was normally distributed because of the significance of the test was greater than 0.05. After that, one way Analysis of Variance (ANOVA) was used by using GraphPad Instat Demo to determine statistical significance of differences. *P* values of less than 0.05 were considered significant and consequently Tukey-Kramer multiple comparison posttest was used to make comparison between pairs of columns. Moreover, unpaired t-test was used to make comparison between each two groups of preparation methods (SDs and co-rounding) of dissolution test.

$$\%\text{of crystallinity} = \frac{\text{Area of crystalline peaks}}{\text{Area of all peaks}} \times 100 \qquad \text{..... Equation (3)}$$

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Results

CHARACTERIZATION OF PREPARED FORMULATIONS

Determination of Percentage Yield

The practical yield of each formulation was calculated by weighing each sample after storing in the desiccator for 48 hours. The percentage of yield of prepared formulations was varied between 74.31 to99.45% W/W.

Saturation Solubility

The solubility of pure Glz powder in distilled water was found to be 38.739 ± 4.686 µg/ml and its solubility in all binary mixtures can be seen in Figure 1. All formulations, excluding Pc1 formula, exhibited noticeable increment in solubility as compared to the pure Glz. Statistically, significant difference (P <0.0001) in solubility improvement observed among the SD and co-grounded formulas of Glz/ PVP K30 with the ratios 1:1 and 1:3. Whereas, non-significant difference (P = 0.297 detected among binary mixtures at the ratio 1:5.

Drug Content Analysis

The percentage drug content of binary systems is shown in Table 3.

The percentage of Glz content in all SDs formulations exhibited in the range of 92.46 – 101.93 %. Significant difference observed among the formulations of kneading (P = 0.0102) and co-grinding (P = 0.0089) mixtures of all three various ratios whereas non-significant difference (P = 0.0932) observed among the solvent evaporated formulas.

Table 3 Drug content analysis of Glz in binary mixtures of SDs and co-grinding formulas

Techniques	1:1 ratio	Percent drug content* 1:3 ratio	1:5 ratio	*P* value
Solvent evaporation	94.39 ± 2.274	97.90 ± 2.979	101.41 ± 4.068	0.093
kneading	92.46 ± 3.266	96.33 ± 2.756	101.93 ± 0.725	0.01
Co-grounding	93.96 ± 2.559	94.45 ± 2.729	101.57 ± 0.532	0.008

*Is the mean of three values ± standard deviation.

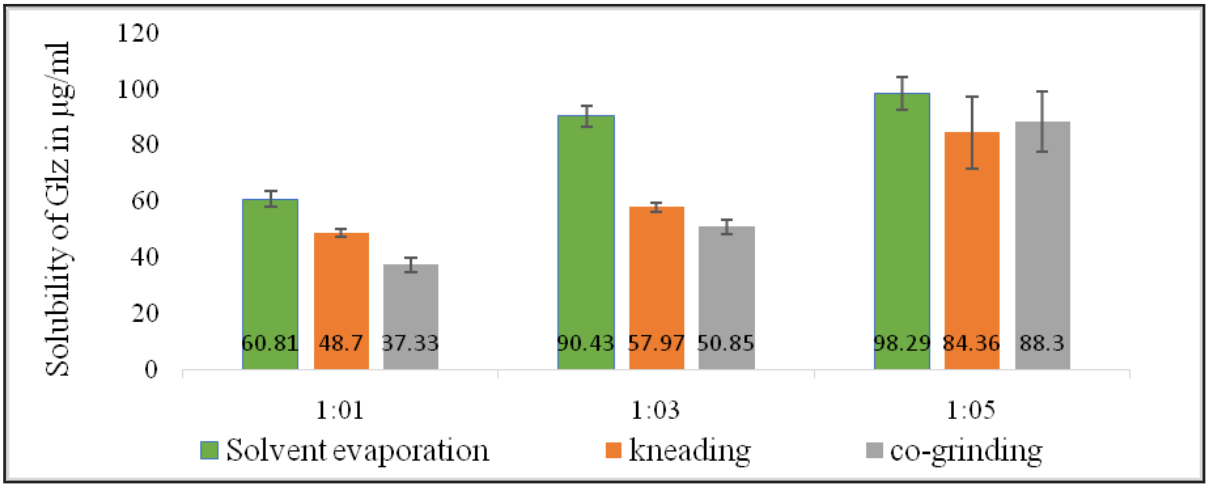

Figure 1 Solubility of Glz in binary mixtures of SDs and co-grounded formulas in each of the drug/carrier ratio

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In-Vitro Dissolution Study of Glz in Binary Mixtures

Effect of Glz: carrier ratios

Figure 2illustratesthat the Formula Ps5 had the highest percent of Glz release throughout the study. The batch Ps1, Ps3, and Ps5 showed a cumulative drug release of 50.166 % (P <0.05), 68.8 % (P <0.01), and 81.633 % (P <0.001), respectively, within 5 minutes as compared with pure Glz (13.203 %). Moreover, along the dissolution study the Formula Ps5 had the highest percent of release. For instance, the percent of Glz release from Ps5 was (113.966 %) as compared to Ps3 (99.766 %), ps1 (94.066 %), and plain Glz (63.166 %), after 90 minutes of the study.

Effect of preparation methods

Figure 3 displays the amount of Glz released from the different binary systems of various preparation methods. The dissolution rate of pure Glz within 5 minutes was 13.203 %, while its dissolution was 81.633% (P <0.001) in Ps5, 58.3% (P <0.01) in Pk5, and 53.2% (P <0.01) in Pc5 batches. After 30 minutes, however, all the prepared binary mixture statistically (P <0.001) had the same enhancing impact on pure Glz.

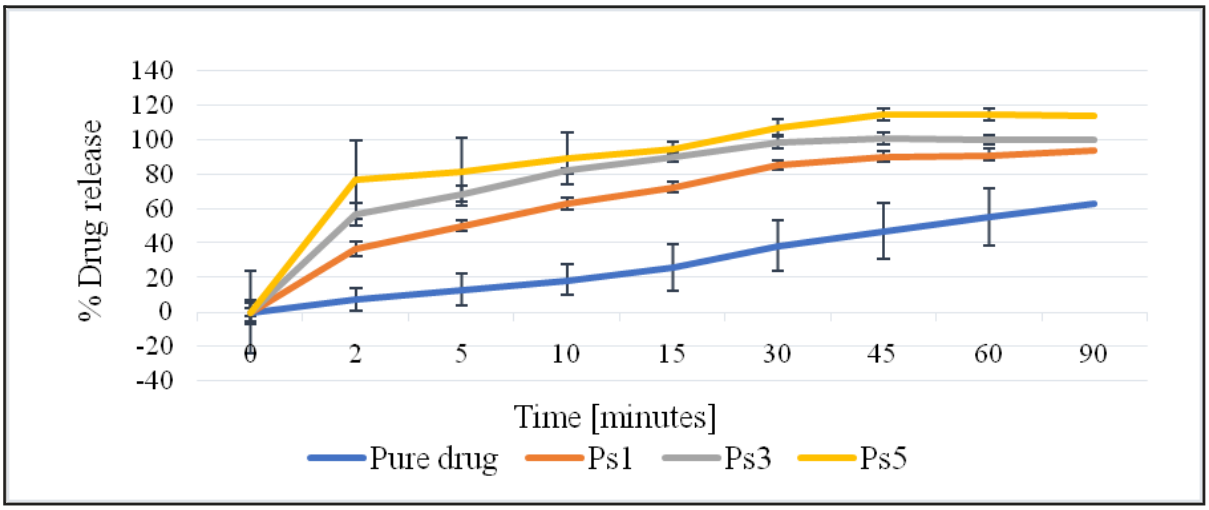

Figure 2 Effect of Glz: PVP K30 ratios on the percentage of Glz released from the solvent evaporated formulas

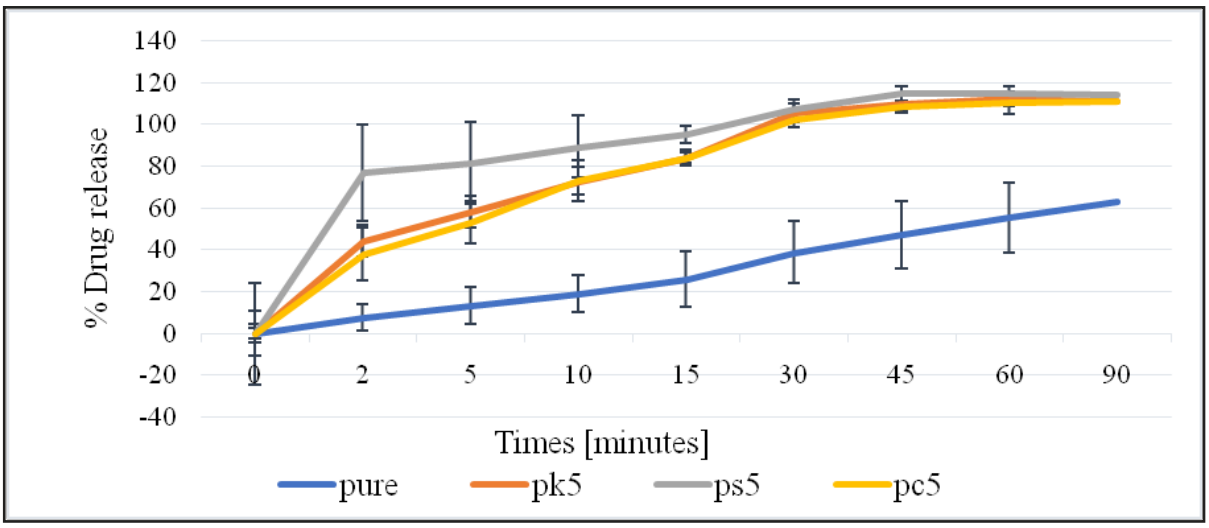

Figure 3 Effect of preparation methods on Glz release profile

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Figure 4 A and B illustrate the comparison of the drug release between the co-ground and SD mixtures. Non-significant differences observed. between solid dispersion and co-grinded formulations.

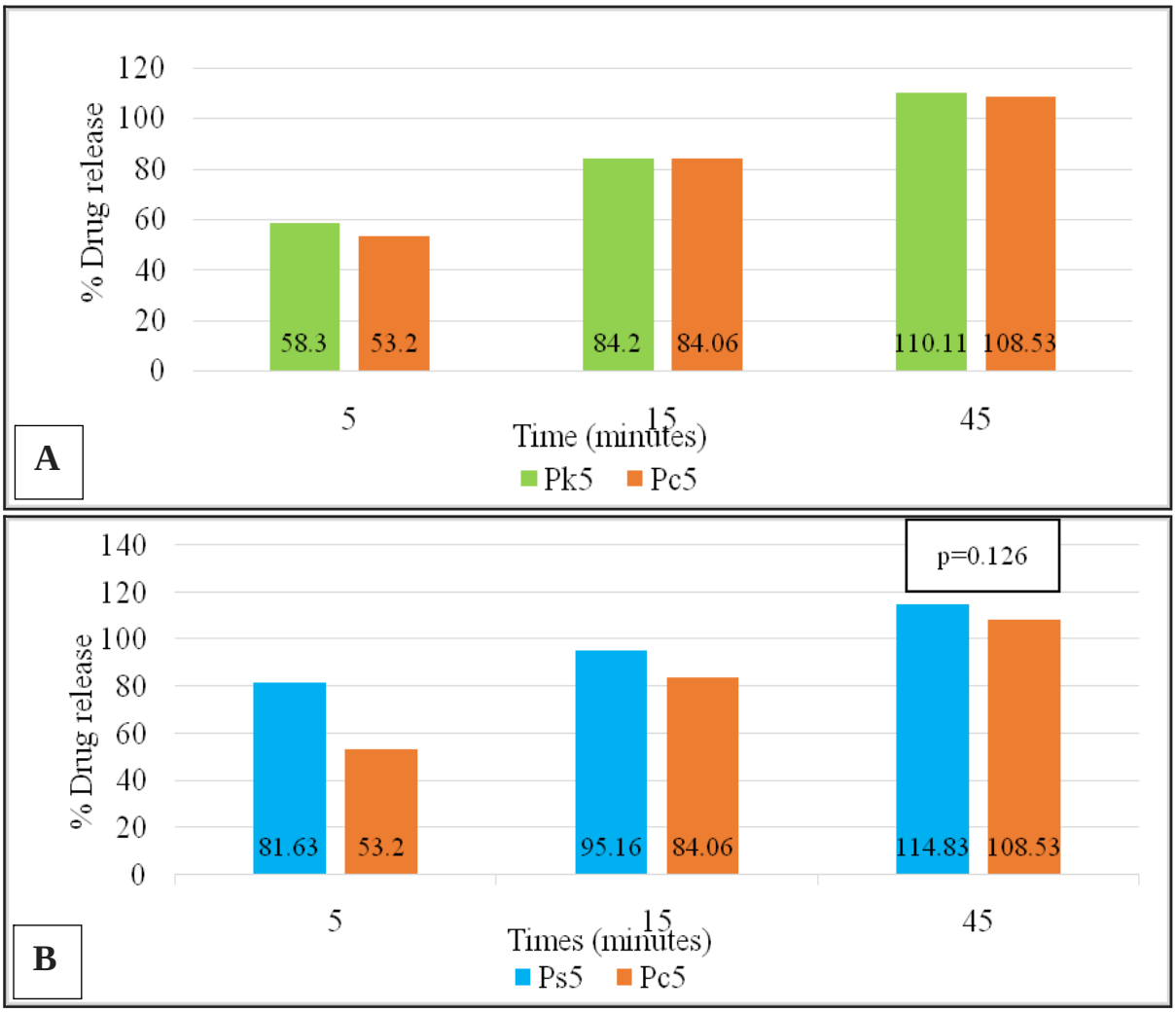

Figure 4 Comparison of Glz release rate between SD and co-ground formula. A: kneaded and co-ground formulas. B: solvent evaporated and co-ground formulas

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Fourier Transform Infrared (FTIR) Spectroscopic Study

The infrared spectrum of pure Glz, PVPK30 and Ps5 formula are expressed in Figure 5, the main peaks of Glz functional group at wave number 1704 $cm^{-1}$and 3264 cm^{-1} demonstrated the carbonyl and amino group, respectively, as well as Peaks absorption at 1158 cm^{-1} and 1343 cm^{-1} shows the sulfonyl group.

X-Ray Diffraction Study

The XRD diffractogram of pure Glz, PVP K30, Ps5 and Pc5 batches are illustrated in Figure 6. The pure Glz displayed sharp and intense diffraction peaks at 2θ, values of 10.48° - 29.2°.

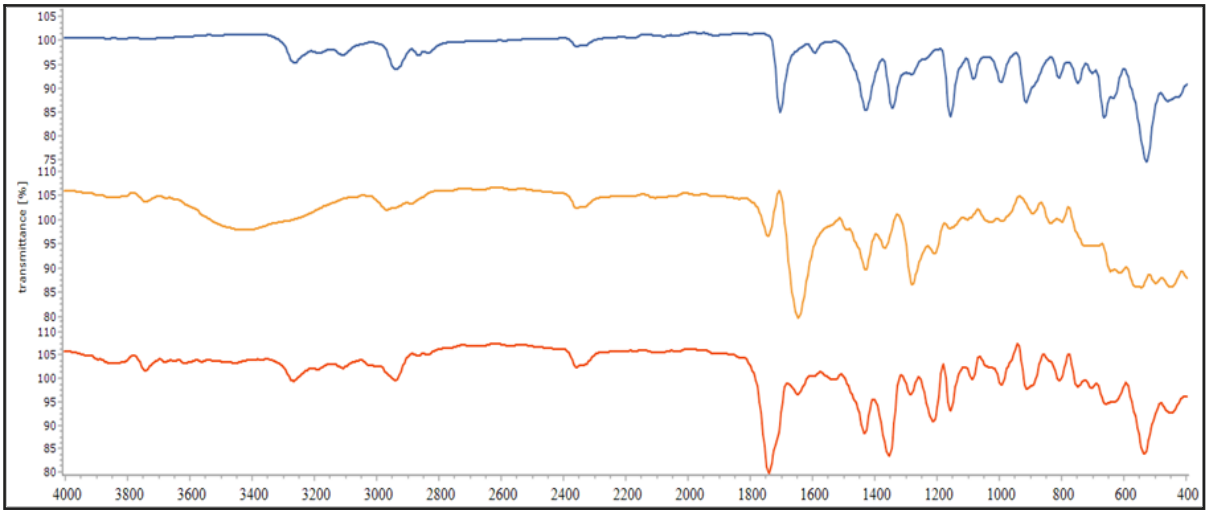

Figure 5 FTIR spectra of pure Glz (blue line), PVP K30 (orange line), and Ps5 formula (red line)

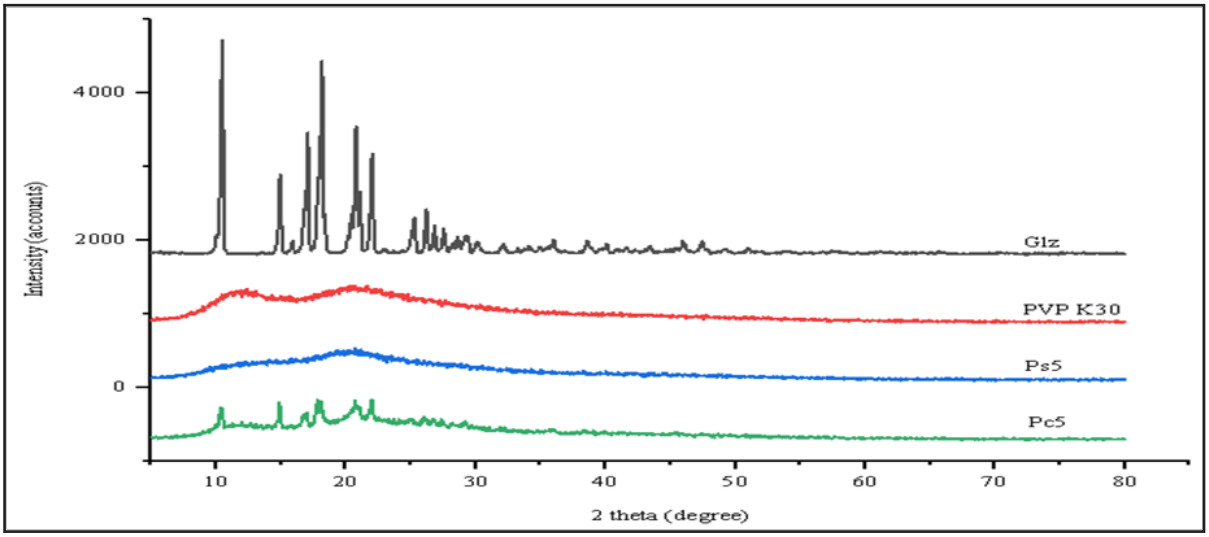

Figure 6 XRD pattern of pure Glz, PVP K30 carrier, and the selected formula (Ps5) of SD and co-grounded mixture (Pc5)

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Scanning Electron Microscope (SEM) Study

The surface morphology of unprocessed drug, PVP K30, Ps5 and Pc5 batches are depicted in Figure 7, it was found that Glz particles varied in size, and had an irregular shape which were angular, whereas, PVP K30 particles were in spherical shape. The particles of the Ps5 formula were appeared as a rough surface. Meanwhile, surface particles of Pc5 batch appeared smoother and some fractured PVP K30 particle detected in the micrograph.

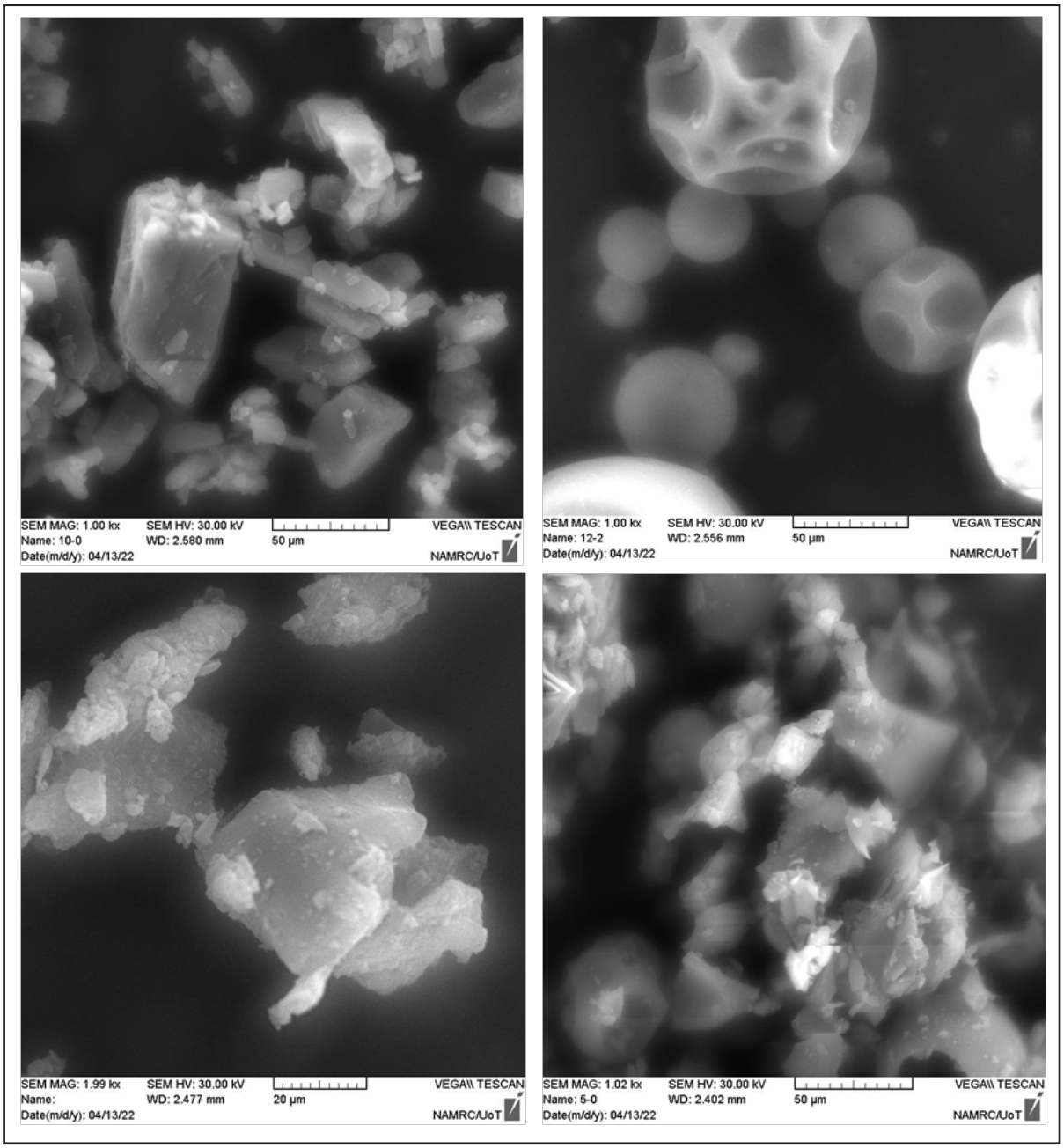

Figure 7 SEM images of pure Glz, PVP K30,Ps5 and Pc5 formula

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Differential Scanning Calorimeter (DSC) Study

Thermogram of Glz raw material, Figure 8, displays single and sharp endothermic peak at 171.26 ^{o}C with the enthalpy of fusion (ΔH) 136.73 J/g. Whereas, the melting peak of Glz in the ps5 formula became absent.

Discussion

CHARACTERIZATION OF PREPARED FORMULATIONS

Determination of Percentage of Yield

The percent yield of products demonstrated the most effective recovery of the ingredients in the formulas. However, the % yield of SDs (74.31 -89.88%) were lower than those of co-grounded mixtures (97.90-99.45%). The reasons behind that could be attributed to the physical characteristic (sticky nature) of the used carrier and multi-step process of the applied SD methods.

Saturation Solubility Study

The solubility study of pure Glz powder exhibited poor solubility in distillated water. The highest increase in solubility was obtained in the formulas (Pc5, Pk5, and Ps5) with the ratio 1:5 of the drug and polymer, meanwhile, the solubility of Glz was highest in the formula Ps5 where the increase in solubility compared to pure Glz. The increased water solubility of Glz in SD could be attributed to the hydrophilic effect and surfactant properties of PVP K30.[1]

Another important factor affecting the performance of the SD is the drug/ carrier ratio, as the concentration of polymer increased, the solubility of Glz was also increased, indicating higher ratio of hydrophilic parts to the hydrophobic part of drugs. An increment in the carrier proportion could improve the hydrophilicity of the particle, which minimizes aggregation of the drug after exposed to the liquid medium, resulting enhancement of poorly water soluble drugs.[20]

Drug Content Analysis

The content of Glz was found in the range of 92.46% - 101.93 % in all prepared formulations which was within the range specified by the United State Pharmacopoeia (90 % - 110 %).[15] The percentage of drug content demonstrated the uniform distribution of Glz within the prepared formulations.

In-Vitro Dissolution Study of Glz in Binary Mixtures

Effect of drug: carrier ratio

It was determined from the dissolution study, when the amount of carrier in the formulations increased, the drug release

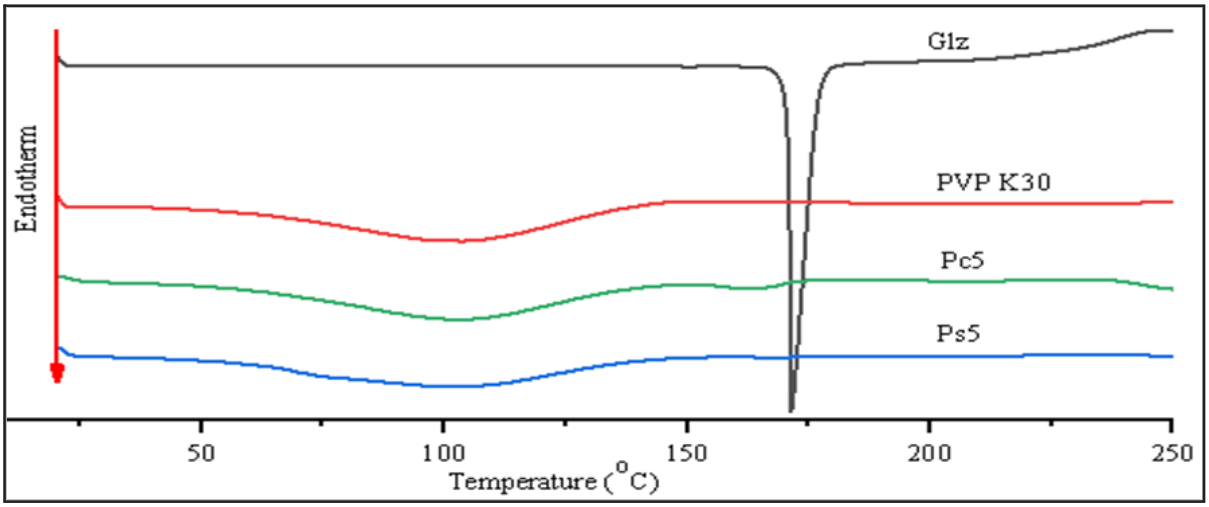

Figure 8 DSC thermograms of pure Glz, PVP K30, and Ps5.

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from the SD was also increased. This is in accordance with the solubility result, it indicates that by raising the concentration of the carrier both the solubility and dissolution rate of Glz increased. When compared to unprocessed Glz (13.303 %), ANOVA statistical analysis revealed that formula Ps5 had the highest percent of release (81.63 %) (*P* <0.001) after the first 5 minutes. SDs formulated with larger quantities of hydrophilic carrier may provide larger available space for enclosing hydrophobic drug particle, resulting in quicker hydration of the drug molecules and subsequently greater wettability and dissolution rate of the drug obtained.[21] Furthermore, as confirmed in XRD and DSC studies, the transition of crystalline nature of drug in the binary system of SD into amorphous form promotes the drug release rate and solubility compared to the pure Glz.

Effect of preparation methods

From the obtained results the dissolution rate of Glz in the Ps5 formula using the solvent evaporation technique was higher than kneaded and co-grounded mixtures, as compared to the pure drug. This might be attributed to the complete dissolution of Glz in drug/carrier solution and the use of heat in rotary evaporator process. Heating may induce conformational modifications and flexibility in the cavity of the carrier, thereby enhancing the interaction between the polymer and drug.[19] Concerning the mixtures that have been co-grounded also had an influence on improving dissolution and solubility which might be due to the micronization and proper distribution of pharmaceutical ingredient onto the surface of the hydrophilic polymer.[22]

Fourier Transform Infrared (FTIR) Spectroscopic Study

The band of the main functional groups of the drug was shifted slightly toward higher wave numbers in the spectrum of SD formula, which suggested a type of interactions (physical interaction) between the Glz and PVP K30. It is possible that enhanced wetting properties, solubility, and release rate of APIs were related to an interaction occurred between drug and carrier in the solid state.[23]

X-Ray Diffraction (XRD) Study

The crystalline nature of the drug is revealed by the presence of numerous sharp and intense peaks in the diffractogram.[24,25] Crystallinity degree of Glz in the Ps5 batch and in the pure Glz was 3.1% and 75.2%, respectively. The diffraction pattern of the co-ground mixture (Pc5) showed all the characteristic peaks of Glz but with noticeable reduction in their intensity. In contrast, the crystalline peaks in Ps5 formula exhibited the absence of all gliclazide's distinctive peaks. Crystallinity influences peak height, therefore, the proportionate lowering in Glz peak intensity in Ps5 formula indicated that the crystallinity of the drug was decreased and the drug was extensively converted to an amorphous form.[20,26] It has been proved that the amorphous or semi-crystalline nature of the drug product have more internal energy and faster molecular mobility, causing them to disintegrate at a faster rate when compared to the raw pharmaceutical substance.[10, 27]

Scanning Electron Microscope (SEM) Study

In SEM of co-grinded formula, some carrier particles could be observed as spherical smooth and fractured surfaces, whereas, the drug and carriers' particles in the photomicrograph of solid dispersion (ps5) formula appeared as aggregates and adhere with one another, making it impossible to distinguish between the particles of Glz and carrier specifically. Additionally, the particle surface was shown to be rough and a new solid shape was created.

The appearance of rough surface in SD could be due to the greater cohesion between the drug and carriers and/or adsorption of the drug particles to the surface of polymer.[28] The miscibility of the active agents into the carrier gave the SD the appearance of being aggregated with a rough surface, hence, when SDs come

into contact with a dissolution medium, their surface property helps the drug to dissolve more quickly.[29]

Differential Scanning Calorimeter (DSC) Study

The sharp and single endothermic peak of pure Glz at 171.26 ^{o}C indicating crystalline characteristics in nature. The obtained result of DSC study is in accordance with the study conducted by Zhou et al.(2021), they found the melting point of Glz at 171.03 ^{o}C.[30] The melting temperature of Glz in the co-grounded mixture was lowered to 167.67 ^{o}C with the reduction of peak area, whereas its melting peak disappeared in Ps5 solid dispersion formula. Also, DSC results support those finding from SEM, as in the photomicrograph, it was not possible to differentiate pure components in SD and the rough surface was appeared. Moreover, the absence of melting peak in DSC thermogram demonstrated that the crystallinity of Glz in SD was reduced which is further reinforced the XRD results which exhibited the disappearance of sharp characteristic peak of Glz in the selected formula of SD.

Conclusion

Based on the findings of this study, it can be concluded that PVP K30 carrier can be utilized effectively to formulate appropriate SD of Glz. SDs exhibited noticeable increment in solubility and dissolution rate compared to the raw Glz, the highest enhancement was observed in the SD prepared at the ratio 1:5 of Glz and PVP K30 by using solvent evaporation technique. The FT-IR study demonstrated that the Glz was compatible with the utilized polymer, and the decreased crystallinity of Glz and surface morphology of the binary mixtures explained the increased solubility and dissolution rate of the drugs. *In vivo* study using animal model requires to make correlation between solubility and dissolution rate enhancement with increasing rate and extend of drug absorption.

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Competing interests

The authors declare that they have no competing interests.

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