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Self-Nanoemulsifying Drug Delivery System Combined with a Polymeric Amorphous System of Glibenclamide for Enhanced Drug Dissolution and Stability

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Cite This: *ACS Omega* 2024, 9, 43165−43174

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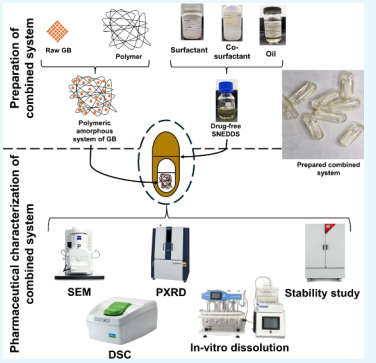
ABSTRACT: Self-nanoemulsifying drug delivery systems (SNEDDS) have been widely applied to improve the dissolution and bioavailability of hydrophobic medications like glibenclamide (GB). However, the acid liability of GB limits its loading in SNEDDS formulation owing to the expected drug degradation. The present study investigated the ability of a polymeric amorphous system (PAS) to amorphize raw GB and facilitate its integration within dispersed SNEDDS. Liquid-SNEDDS (L-SNEDDS), solid-SNEDDS (S-SNEDDS), and combined systems (SNEDDS + PAS) were prepared for this purpose. The physicochemical properties of the prepared formulations were examined using a zeta-sizer, SEM, DSC, PXRD, and dissolution apparatus. In addition, GB integrity within formulations following incubation in a stability chamber was also investigated. The prepared formulations were able to be dispersed within the nanosize range. SEM, DSC, and PXRD showed that freeze-drying (FD) was superior to the microwave (MW) method in GB amorphization. Even though L-SNEDDS and S-SNEDDS were able to increase the dissolution efficiency (DE) of GB, drug degradation was observed. However, PAS prepared using FD was able to increase the DE of GB from 2.5% to 84.2% and protect the drug from chemical degradation. The present study revealed that a combined system (SNEDDS + PAS) is a promising approach to enhance the stability of acid-labile drugs and facilitate the integration of amorphous drugs within a dispersed SNEDDS formulation.



1. INTRODUCTION

Glibenclamide (GB, Figure 1) is prescribed by medical staff for patients diagnosed with type 2 diabetes mellitus.[1,2] It belongs to the second generation of the sulfonylurea group that efficiently stimulates insulin secretion from beta cells of the pancreas.[3] However, the reported low drug solubility compromises its dissolution and absorption from the gastrointestinal tract.[4] Therefore, various oral drug carriers have been developed to combat this issue.[5−7]

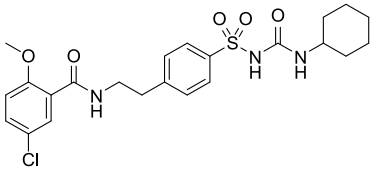


Figure 1. Chemical structure of glibenclamide.

Self-nanoemulsifying drug delivery systems (SNEDDS) have been widely applied to improve the dissolution and bioavailability of orally administered drug molecules owing to the reported advantages.[8,9] Following oral administration, nanoemulsions spontaneously form within the gastrointestinal tract through peristaltic movement.[10,11] This enhances drug integration within the lipid core and ensures the existence of drugs in the solubilized form within the gastrointestinal tract.[12]

Despite the advantages of the SNEDDS formulation, GB is susceptible to chemical degradation in the prepared formulation. This results from GB's exposure to the reported acidic microenvironment within the SNEDDS formulation, which is yielded by free fatty acids.[13] Therefore, an alternative strategy is required to avoid instability issues and retain the advantages of the SNEDDS formulation. Various studies have shown that solidifying the drug-loaded SNEDDS formulation significantly enhances drug stability.[14,15] However, this approach failed to retain the integrity of some therapeutic molecules within the SNEDDS formulation after solidification. This failure may be attributed to the intimate molecular interactions between the drugs and fatty acids, which can promote the chemical degradation of the loaded drug by the fatty acids.[13,16]

Received: August 8, 2024
Revised: September 28, 2024
Accepted: October 4, 2024
Published: October 10, 2024

Alternatively, drug separation from the formulation has been invented to avoid drug exposure to the acidic microenvironment of SNEDDS.[17,18] However, various studies have shown that the crystalline nature of drug molecules within raw material prevents their dissolution and incorporation into the SNEDDS formulation.[19,20] Therefore, drug amorphization is necessary to ensure a complete therapeutic outcome following oral administration.[15,20]

Polymeric amorphous systems (PAS) have been widely utilized to disrupt a drug's crystalline structure and convert it to an amorphous phase. They are usually prepared using a hydrophilic polymer to ensure the high absorption of water in vivo, which ensures rapid dissolution of the incorporated drugs.[21] Different types of instruments have been utilized for this purpose. Inter alia, microwave (MW), and freeze-drying (FD) technologies have been used widely owing to their effectiveness and simplicity.[22]

This study was designed to investigate the combined system's ability to enhance the dissolution profile and stability of acid-labile drugs. Liquid SNEDDS (L-SNEDDS), solid SNEDDS (S-SNEDDS), and combined systems (SNEDDS and PAS) were prepared. They were subjected to physicochemical characterization using a zeta-sizer, SEM, DSC, PXRD, and dissolution apparatus. Moreover, a stability study was performed to investigate drug degradation within the prepared formulations.

2. MATERIALS AND METHODS

2.1. Materials. Glibenclamide was acquired from Saudi Pharmaceutical Industries and Medical Appliances (Qassim, KSA). Cremophor EL (surfactant) was obtained from BASF (Ludwigshafen, Germany). Imwitor-308 (cosurfactant) was supplied by Sasol Germany GmbH (Germany). Kollidon (precipitation inhibitor) was acquired from BASF (Ludwigshafen, Germany). Capmul MCM (oil) was obtained from Abitec (Janesville, WI, USA).

2.2. Ultra-Performance Liquid Chromatography (UPLC) Method. This study utilized a previously validated UPLC method to quantify the GB concentration.[23] An Ultimate 3000 UPLC system consisting of a quadratic pump connected to an automatic sampler, a column chamber, and a Photodiode Array (PDA) detector was used for drug analysis. The mobile phase composed of 46.9% acetonitrile and 53.1% of a 0.1% formic acid solution was eluted through a connected Acquity UPLC column BEH C_{18} at 0.3 mL/min. The column temperature was maintained at 38.8 °C. In addition, the GB concentration within samples was accurately measured using a connected PDA detector that was set at 228 nm.

2.3. Preparation of SNEDDS and S-SNEDDS Formulations. A drug-free SNEDDS formulation was prepared using Kolliphor-EL, Imwitor-308, and Capmul MCM in the following ratio: 2:1:1. After that, 5% (w/w) PVP K30 was dissolved within the prepared formulation to enhance the solubilization of GB and avoid drug precipitating during storage. GB was mixed with a drug-free SNEDDS formulation to prepare the L-SNEDDS formulation with a drug loading of 5 mg/g. The S-SENDDS formulation was prepared by mixing Syloid with an equivalent amount of L-SNEDS formulation.[24]

2.4. Preparation of PAS Systems. In the present study, two methods were utilized to prepare the PAS of glibenclamide (GB): MW and FD. A mixture of GB, poloxamer 188, and sodium bicarbonate for both methods was prepared and used in a 1:4:1 ratio, respectively. Poloxamer 188 was added as a hydrophilic polymer to enhance the amorphization of the drug,[25] while sodium bicarbonate enhances drug stabilization and solubilization.[26]

2.4.1. MW Method. 1 g portion of the aforementioned mixture was placed in a white porcelain dish and mixed well to obtain a consistent homogeneous blend. The PAS was prepared by utilizing a MW instrument (Samsung Model ME0113M1). The instrument was subjected to preheating before the experiment. The mixture in the porcelain dish was subjected to radiation with a power of 600 W for 3.5 min. The obtained melted blend was mixed at room temperature using a glass rod to ensure dispersion of GB in the prepared PAS formulation. The solidified formulation was crushed in a glass mortar and then sieved to obtain uniform powders by using a screen with a pore size of 315 μm.

2.4.2. FD Method. The mixed components were dissolved in 300 mL of Milli-Q water using a magnetic stirrer to prepare a clear solution. After that, the prepared solution was frozen at −60 °C as the primary step in the FD process. The frozen dispersions were subsequently subjected to FD for a minimum duration of 48 h at a temperature of −60 °C utilizing a freeze-dryer (Alpha 1−4 LD Plus, Osterode am Harz, Germany) to facilitate the sublimation of the solvent. The prepared PAS was ground and then sieved through a 315 μm mesh to obtain a uniform powder.

2.5. Particle Size (PS) and Zeta Potential (ZP). The prepared formulations were diluted (1:1000) using distilled water and mixed using a magnetic stirrer for 5 min to ensure SNEDDS dispersion. The PS and ZP values of the obtained dispersed system were measured using a Zetasizer instrument Model ZEN3600, Malvern Instruments Co. (Worcestershire, UK).[27]

2.6. Scanning Electron Microscopy (SEM). Images of pure GB and PAS were captured using scanning electron microscopy (SEM) to investigate the drug's integration within the formulation matrix. In addition, the syloid adsorbent and solidified SNEDDS were also examined to determine the impact of SNEDDS on the adsorbent. Samples were affixed to stubs and underwent gold sputter coating for a duration of 60 s at a 20 mA current in a Q150R sputter coater (Quorum Technologies Ltd., East Sussex, UK) within an argon environment. The SEM parameters were set as follows: EHT = 20.00 kV, WD = 9.5 mm, Signal A = SE1, and magnification = 1.00 and 5.00 KX for high- and low-resolution power, respectively. This preparation enabled the assessment of the surface texture and structure of the various PASs using SEM imaging technology (Carl Zeiss EVO LS10, Cambridge, MA, USA) in a high vacuum setting.[28]

2.7. Differential Scanning Calorimetry (DSC). Thermal analysis of glibenclamide, poloxamer 188, sodium bicarbonate, and the prepared PAS was performed using a DSC-8000 Perkins Elmer (Waltham, MA, USA) apparatus in a temperature range of 30−220 °C at heating rates of 10 °C/min. An accurately weighed amount of samples (2−3 mg) was placed and fixed within the sealed aluminum pan.[19]

2.8. Powder X-ray Diffraction (PXRD). Powder X-ray diffraction analysis was performed to examine the crystalline state of glibenclamide. The pure ingredients, physical mixture, PAS, and solidified SNEDDS formulations were analyzed using an X-ray diffractometer (Ultima IV, Rigaku Inc. Tokyo, Japan). The X-ray diffractometer scanned the PXRD for each sample from 3° to 60° at a rate of 1°/min. The samples were evaluated for their characteristic peaks by collecting data using

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monochromatic radiation at a 1.54 Å (Cu Kα' 1) 30 wavelengths.[29]

2.9. In Vitro Dissolution. The in vitro dissolution study was conducted to investigate the prepared formulations' impact on glibenclamide dissolution. Dissolution apparatus Type II (LOGAN Inst. Corp., NJ, USA) was used during the study, and the paddle was set to rotate at a 50 rpm speed. For each test, 2.5 mg of GB, either as a raw drug or within the various formulations, was placed in capsules and then surrounded with a sinker to avoid floating. The dissolution medium was preheated before the experiment at 37 ± 0.5 °C, which consisted of 900 mL of phosphate buffer (pH 6.8). Samples were withdrawn from the medium at predetermined intervals (5, 10, 15, 30, 45, and 60 min) using a 10 μm filter connected to the syringe. The in vitro dissolution profile was obtained by plotting the percentage of drug dissolved (based on cumulative drug released) against time intervals. This plot facilitates a comparison between raw GB and the various formulations. The drug concentration within the samples was measured using the UPLC method. The dissolution efficiency was calculated to investigate the impact of different formulations on the dissolution profile of glibenclamide.[6]

2.10. Stability Study. This experiment was conducted to evaluate the stability of GB within the prepared formulations. The prepared formulations were placed in glass vials that were tightly locked by using a screwed cap. A stability chamber (Binder GmbH, Tuttlingen, Germany) was used for this study. Temperature was set at 40 ± 2 °C and 15 ± 5% relative humidity before the incubation of samples. The drug concentration within samples was measured at the beginning of the study to determine the initial drug concentration (0 Day). At the end of the experiment, the percentage of drug degradation was estimated using the developed UPLC method to assess the impact of different types of formulations on glibenclamide stability.[13]

3. RESULTS

3.1. Physicochemical Characterization. Table 1 summarizes the measured physicochemical properties of the prepared formulations. The results showed that glibenclamide loading within the prepared SNEDDS formulation resulted in an insignificant change in the particle size of the dispersed system. However, the particle size of the SNEDDS formulation was significantly reduced when it was dispersed with the prepared PAS and its solidified formulation. In addition, the incorporation of glibenclamide within the prepared SNEDDS showed an insignificant effect on the zeta potential value. On the contrary, solidified SNEDDS and the combined system had lower zeta potential values than the drug-free SNEDDS formulation.

Table 1. Physicochemical Properties of the Prepared Formulations

Physicochemical properties	Particle size (nm)	Zeta potential (mV)
Drug-free SNEDDS	124.4 ± 3.1	−16.4 ± 0.9
L-SNEDDS	122.4 ± 3.3	−16.6 ± 0.6
S-SNEDDS	137.6 ± 6.2	−25.5 ± 0.9
Drug-free SNEDDS + PAS-FD	93.7 ± 2.0	−23.6 ± 1.8

3.2. SEM. *3.2.1. Solidified SNEDDS Formulation.* SEM images of the Syloid adsorbent and S-SNEDDS formulation are captured to study the morphological characteristics (Figure 2). The Syloid adsorbent has an irregular shape with a smooth surface, as shown in Figure 2A,B. On the contrary, the S-SNEDDS formulation showed that the surface appearance of the Syloid adsorbent changed from smooth to rough, as depicted in Figure 2C,D. However, there is no sign of changes in the particle size following the adsorption of L-SNEDDS by Syloid.

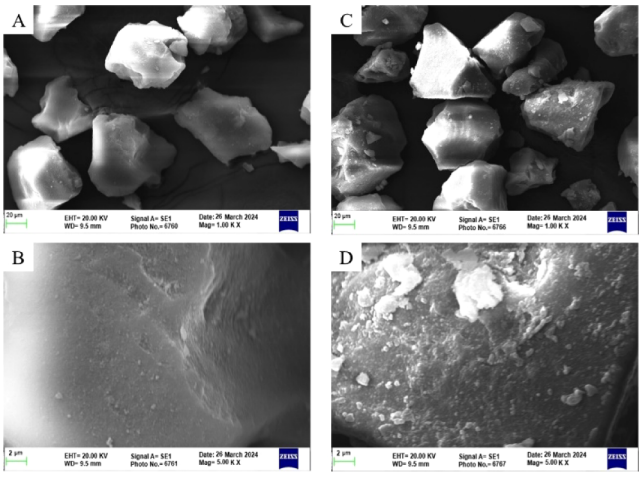

Figure 2. SEM images of A,B) Syloid adsorbent and C,D) S-SNEDDS at low and high magnification power, respectively.

3.2.2. Polymeric Amorphous System. Figure 3 shows the SEM images for glibenclamide along with the prepared PAS. Untreated glibenclamide appears as tiny crystals with sharp borders, indicating its crystalline structure. On the other hand, the captured images of PAS systems have large particle sizes and smooth surfaces. The distinctive crystalline structure of glibenclamide was completely absent in the captured images of PAS.

3.3. DSC. *3.3.1. Solidified SNEDDS Formulation.* Figure 4 presents DSC thermograms for GB, Syloid, and S-SNEDDS. The figure clearly shows that glibenclamide has a sharp endothermic peak at 175 °C. However, the Syloid adsorbent has a broad endothermic peak at 62 °C. In addition, the endothermic peak of the adsorbent in S-SNEDDS was detected at 47 °C.

3.3.2. Polymeric Amorphous System. Figure 5 shows the thermograms of glibenclamide and poloxamer 188, which have sharp endothermic peaks at 175 and 54 °C, respectively. In addition, sodium bicarbonate has two distinctive peaks at about 88 and 93 °C. Furthermore, the physical mixture and the prepared PAS have sharp endothermic peaks at around 52 °C. However, the characteristic melting peak of glibenclamide completely vanished.

3.4. PXRD. *3.4.1. Determining the Characteristic Peaks of Glibenclamide.* Figure 6 shows PXRD chromatograms of glibenclamide, poloxamer 188, and sodium bicarbonate. It was found that glibenclamide has different characteristic peaks around 19.2° and 23.1°. In addition, poloxamer 188 has two overlapping peaks with glibenclamide at 19.1° and 23.4°. In contrast, sodium bicarbonate exhibits noninterfering peaks with GB, predominantly above 30°. However, GB has four predominant characteristic peaks (Figure 7; indicated by gray rectangles) with high to moderate intensity at 10.9°, 11.7°, 21.0°, and 21.9° along with additional peaks with low intensity at 14.8°, 15.3°, and 28.1°.

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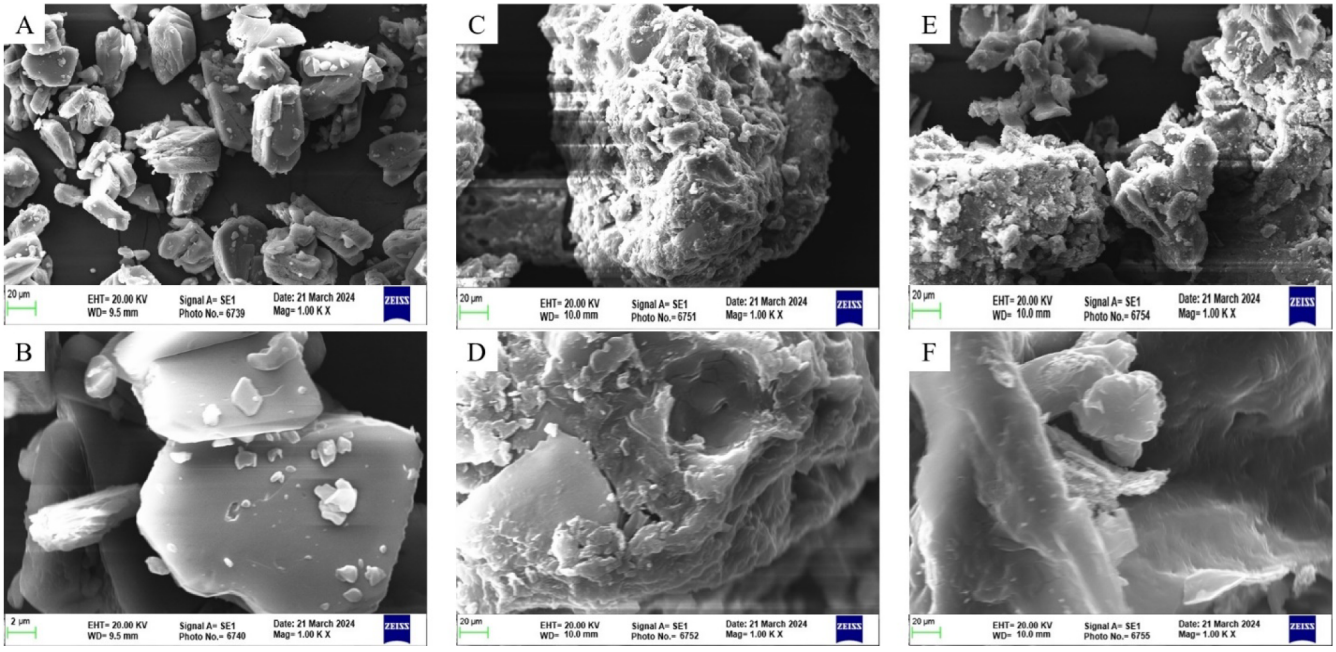

Figure 3. SEM images of A,B) untreated glibenclamide along with the PAS formulations prepared using C,D) MW method and E,F) FD method SNEDDS at low and high magnification power, respectively.

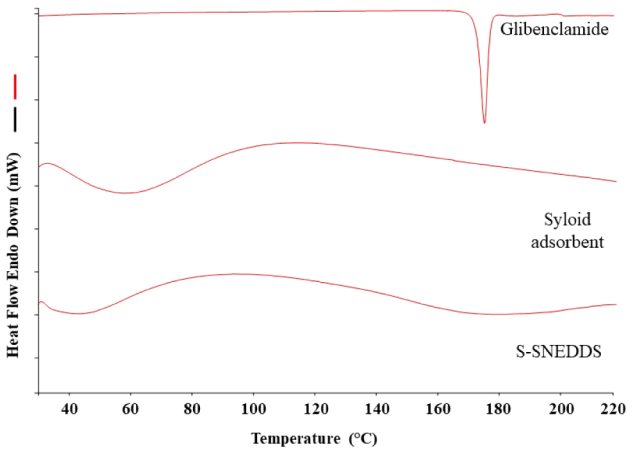

Figure 4. DSC chromatogram of glibenclamide, the Syloid adsorbent, and S-SNEDDS.

3.4.2. Determining the Amorphization of GB in S-SNEDDS. The PXRD analysis of the Syloid adsorbent is presented in Figure 7 to examine its crystalline structure. It is clear from the obtained spectrum that Syloid has two diffraction peaks at 38.1° and 44.3°. The spectrum of the S-SNEDDS formulation was compared against the raw Syloid adsorbent. The spectrum showed that the S-SNEDDS formulation has no impact on the diffraction peaks of Syloid. Moreover, the characteristic peaks of GB completely disappeared from the spectrum of drug-loaded S-SNEDDS.

3.4.3. Determining the Amorphization of GB in PAS. The PXRD spectrum of GB was compared to that of the physical mixture of the prepared PAS as shown in Figure 8. It is clear that the predominant characteristic peaks of GB were obviously observed in the physical mixture. Regarding PAS-MW, the spectrum showed that all characteristic peaks were retained with a reduction in peaks at 21.0° and 21.9°, whereas the peak at 28.1° was absent. In contrast, the PAS-FD

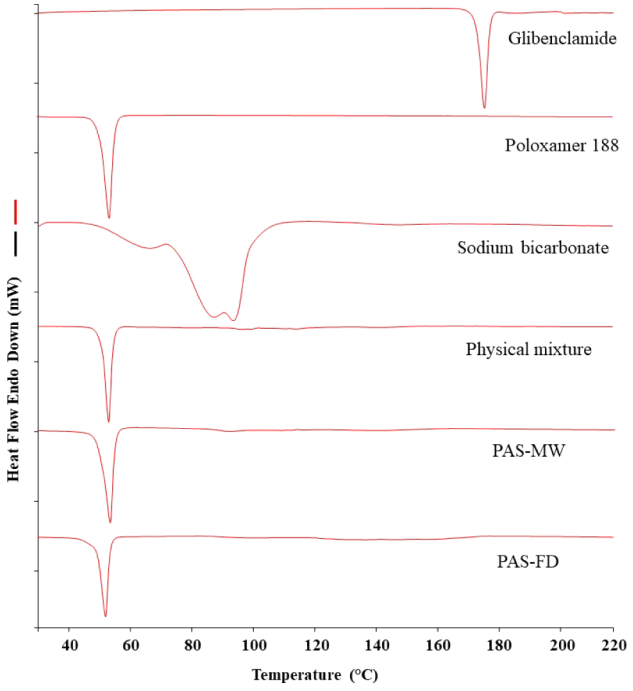

Figure 5. DSC chromatogram of glibenclamide, poloxamer 188, sodium bicarbonate, and PAS formulations, along with the physical mixture of their ingredients.

spectrum showed a remarkable reduction and absence of the characteristic peaks of GB within the prepared formulation.

3.5. In Vitro Dissolution Study. *3.5.1. SNEDDS Formulations.* The in vitro dissolution study presented in Figure 9 revealed that the total percent of glibenclamide dissolved from the raw material at the end of the experiment was 4.1%, with a dissolution efficiency value of 2.5%. However, L-SNEDDS and S-SNEDDS formulations significantly increased glibenclamide dissolution efficiency by about 24 and 19 times

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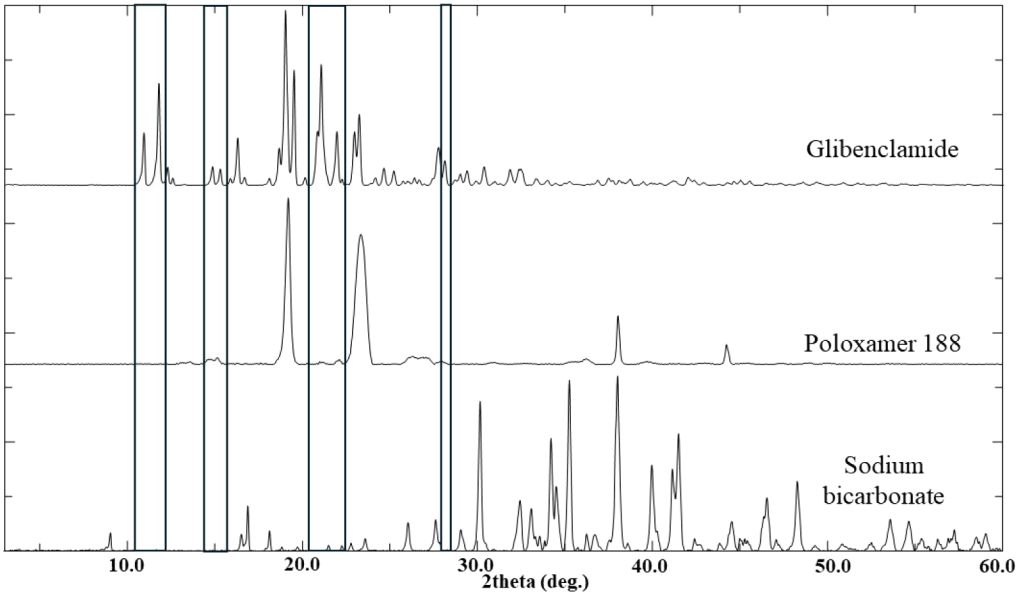

Figure 6. PXRD spectra of glibenclamide, poloxamer 188, and sodium bicarbonate.

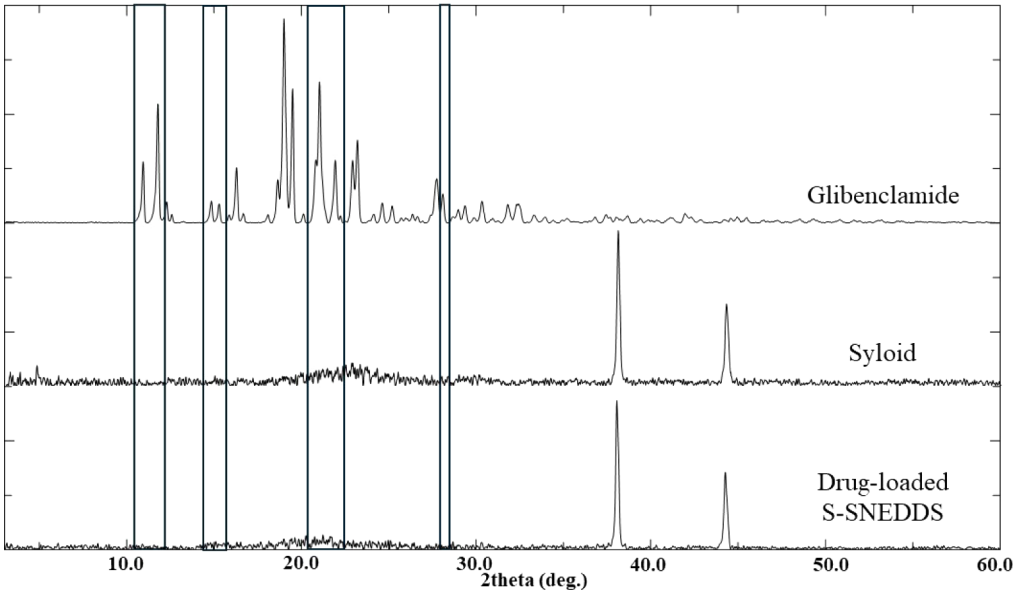

Figure 7. PXRD spectra of glibenclamide, Syloid, and S-SNEDDS formulation.

compared to the raw drug. Even though combining drug-free SNEDDS with the raw drug was able to increase the dissolution efficiency of the pure drug by about 1.5-fold, it failed to produce an outstanding increment in dissolution efficiency compared with L-SNEDDS and S-SNEDDS formulations.

3.5.2. PAS + Drug-Free SNEDDS Formulations. Figure 10 shows the dissolution profile of GB in the media from the drug-free SNEDDS formulation combined with pure drug, PAS-MW, and PAS-FD formulations. At the end of the experiment, about 66.8% and 94.7% of glibenclamide were dissolved from the combined system using the PAS prepared with MW and FD, respectively. Additionally, it was found that both systems were able to enhance the dissolution efficiency of glibenclamide by about 20 and 33 times, respectively.

3.5.3. Comparing L-SNEDDS against the Combined System. The dissolution profile of L-SNEDDS was compared against the combined system (SNEDDS + PAS-FD) and is presented in Figure 11. The calculated dissolution efficiency of the developed L-SNEDDS formulation in the initial phase (0−10 min) was 51.8 ± 3.84%, while it was lower in the case of the combined system by 34.3 ± 3.71%. On the other hand, the estimated dissolution efficiency during all experiments was higher in the case of the combined system by 1.4-fold compared to L-SNEDDS.

3.6. Stability Study. Figure 12A displays the percentage of intact GB at the beginning and end of the stability study. The analyzed data revealed that the percentage of intact glibenclamide significantly decreased to 23.4% and 49.0% within L-SNEDDS, and S-SNEDDS formulations, respectively. In contrast, there was no significant difference in the percentage of intact GB at the beginning and end of the experiments in the PAS. Figure 12B,C shows chromatograms obtained from samples at Days 0 and 30, respectively. It is clear

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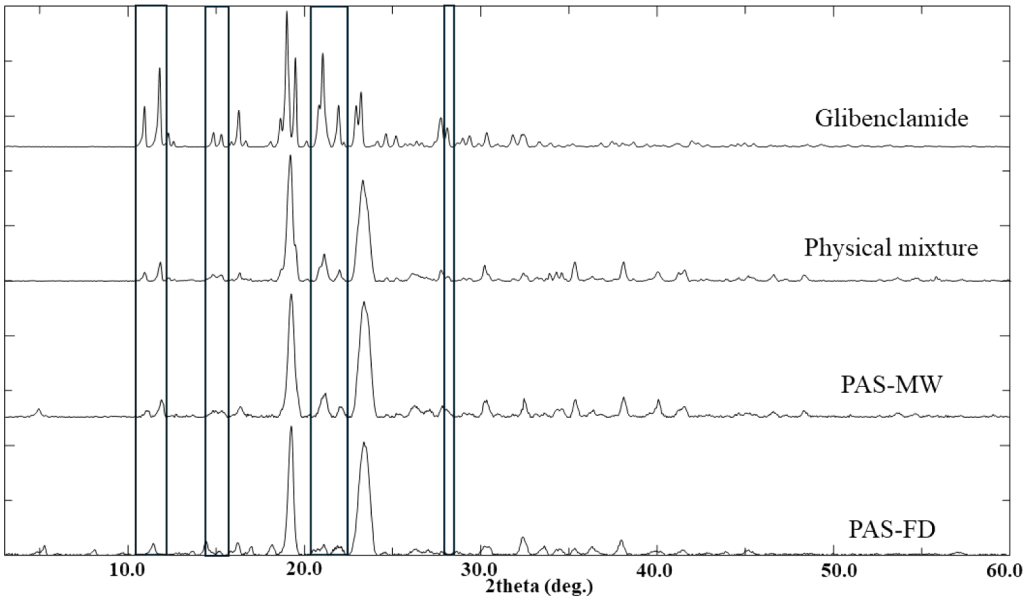

Figure 8. PXRD spectrum of glibenclamide, physical mixture, and prepared PAS.

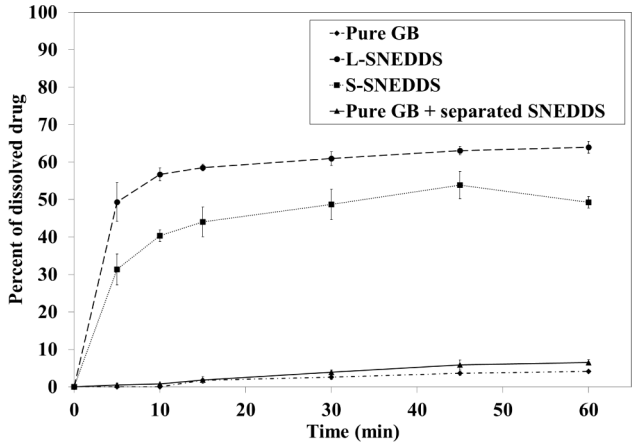

Figure 9. In vitro dissolution profile of glibenclamide, L-SNEDDS, S-SNEDDS, and drug-free SNEDDS + pure GB.

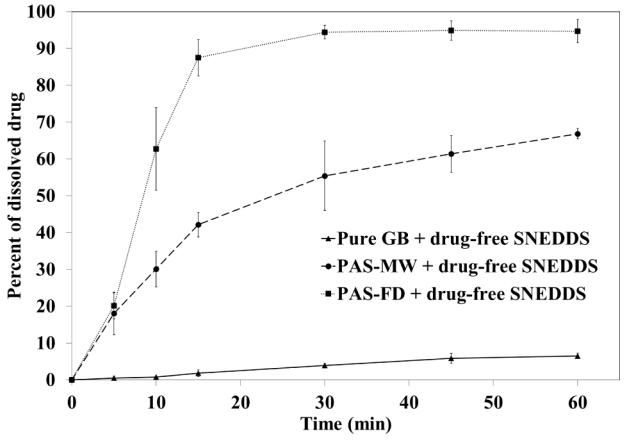

Figure 10. In vitro dissolution profile of drug-free SNEDDS combined with pure GB, PAS-MW, and PAS-FD.

from the figures that the UPLC method can separate GB from the formed degradation products.

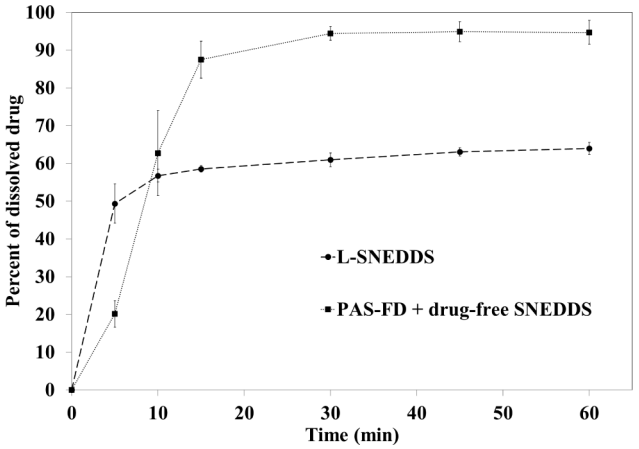

Figure 11. In vitro dissolution profile of L-SNEDDS + drug-free SNEDDS combined with PAS-FD.

4. DISCUSSION

Innovation in developing oral pharmaceutical formulations has become a crucial area of research. This aims to tackle the critical drawbacks of limited drug solubility and overcome physiological barriers.[30,31] Notably, SNEDDS has been extensively utilized in recent decades owing to its purported capacity to enhance medication dissolution within the gastrointestinal tract as well as its permeability across the physiological intestinal membrane barrier.[11] Disappointingly, oils (the main component of SNEDDS) innately comprise free fatty acids, which omits its usage because of the anticipated degradation of acid-labile medications.[19] Therefore, this work explores the influence of numerous approaches that enable the usage of SNEDDS for acid-labile medications.

First, the traditional forms of SNEDDS (liquid and solid) were prepared as a control approach to the proposed combined system (SNEDDS + PAS). To evaluate the prepared combined system, PAS's influence on GB's physical state was examined. Herein, the impact of the combined system on the dissolution profile and stability of GB was investigated to

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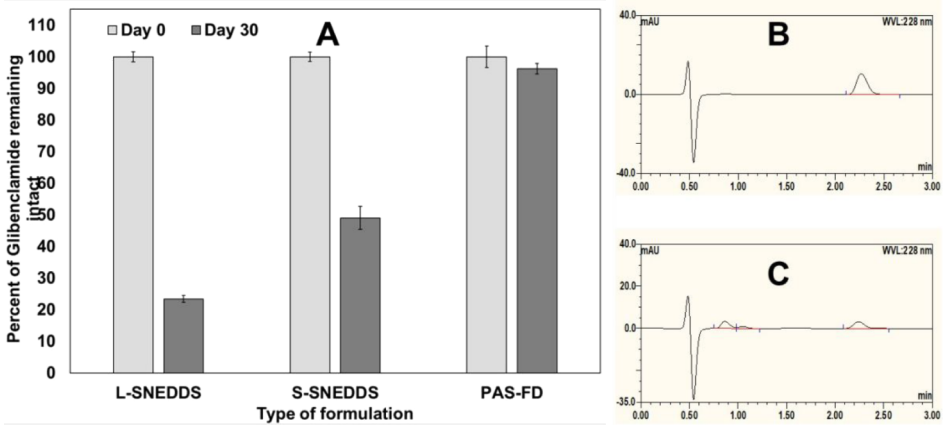

Figure 12. A) The stability study showing the percentage of intact GB within the L-SNEDDS, S-SNEDDS, and FD-PAS formulations. B and C) Chromatograms of GB-loaded formulation at Days 0 and 30, respectively.

confirm its suitability for acid-labile drugs. Finally, a stability study was performed to explore the influence of all formulations on GB's degradation.

The emulsification examination revealed that a nanosized emulsion system was attained, ensuring a promising dispersion propensity of L-SNEDDS. The obtained results revealed that the prepared SNEDDS could substantially augment the oral bioavailability of GB; this is supported by formerly published data.[32,33] Furthermore, further examination revealed that the dispersed SNEDDS exhibited a negative surface charge. This finding agrees with formerly published articles that are portentous in suggesting that free fatty acids are responsible for this finding.[34]

The results of in vitro dissolution showed that the L-SNEDDS formulation have the ability to improve GB's dissolution efficiency 24 times compared to the raw GB. However, L-SNEDDS showed a remarkable drug degradation. The reported acidic microenvironment in SNEDDS could be the main factor leading to the degradation of the incorporated acid-sensitive drug (GB). The reported abundance of fatty acids is the key factor for this acidic microenvironment, which is responsible for the detected drug degradation.[26,35]

Therefore, a traditional solidified approach was used to mitigate the detected instability within L-SNEDDS. The current study revealed that S-SNEDDS improved the dissolution efficiency of GB 19 times compared to that of the pure drug. SEM images revealed that L-SNEDDS was completely absorbed by the SYLOID absorbent, and the prepared S-SNEDDS did not affect the integrity of the SYLOID adsorbent. This ensured the physical stability of S-SNEDDS by avoiding particle aggregation during storage.[36] Moreover, DSC and PXRD analyses revealed that GB was completely dissolved within the core of the SYLOID adsorbent, with no evidence of crystallization. This might be ascribed to the reported solubilization of the drug within L-SNEDDS during the adsorption process, whereas GB molecules uniformly dispersed on the surface of the adsorbent.[37]

Even though S-SNEDDS increased the percentage of intact GB from 23.4% to 49.0%, the overall improvement was considered to be insufficient. This might be ascribed to the interaction between GB and SNEDDS due to their direct contact within the SYLOID adsorbent.[18] The present results align with reported studies that revealed the inability of S-SNEDDS to protect loaded drugs from chemical degradation.[38] Therefore, an alternative approach is demanded to resolve the drawbacks associated with the traditional solidification approach.

Alternatively, the separation of drugs from the SNEDDS formulation has been invented to avoid exposure of acid-labile drugs to the acid microenvironment within the SNEDDS formulation.[17] In vitro dissolution of combined raw GB and SNEDDS was achieved to explore GB's ability to be partitioned within the dispersed SNEDDS. However, it was found that SNEDDS was unable to enhance the dissolution of pure GB. By the end of the experiment, the total percentage of GB dissolved in the dissolution media reached 3.8%, resulting in only a 1.5-fold improvement in dissolution efficiency. This might be ascribed to the presence of the GB in its crystalline state, preventing its dissolution and ability to be combined within the SNEDDS formulation.[39] Therefore, drug amorphization is necessary to ensure a complete therapeutic outcome following oral administration.[20]

Polymeric amorphous systems (PAS) usually convert drugs from crystalline to amorphous states. PAS consists of a porous system comprising a polymeric matrix where drugs are dispersed at the molecular level.[40] In this study, the PAS of GB was prepared using MW and FD methods. Moreover, sodium bicarbonate was incorporated into the prepared PAS at an equimolar ratio to GB owing to its ability to create an alkaline microenvironment that facilitates GB dissolution.[41]

Physicochemical examination of the dispersed combined system showed a substantial decline in the particle size compared to L-SNEDDS. This might be ascribed to the integration of poloxamer in SNEDDS following dispersion, as well as its emulsification activity.[20] In addition, SEM images of glibenclamide and the prepared PAS were captured to investigate the method's ability to encapsulate GB within the polymeric matrix. The absence of GB's crystalline structure indicates that the drug is successfully incorporated within the polymer matrix.[28]

Thermal analysis of the PAS was performed to explore the physical state of GB within the prepared PAS. The DSC spectrum showed that GB has a sharp melting point at 175 °C, which is in synchronization with formerly published papers and indicates the purity of the raw drug material.[42,43] In addition, the disappearance of the GB endothermic peak corresponds to either the drug's amorphization or the dilution effect produced by an incorporated polymer.[44] Thus, PXRD scanning was

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performed to indicate polymorphism changes in the drug within the prepared PAS.

PXRD assessment was used to evaluate the crystalline nature of GB within the PAS. The MW and PD methods disrupted GB crystallinity in the prepared PAS. The intensity of the characteristic diffraction peaks of GB prepared by the MW method was reduced, indicating partial amorphization. The current result concurs with a formerly published paper, which revealed that MW was not able to disrupt the crystalline structure of the used drug completely.[45] This might be ascribed to the energy power and rapid heating and cooling spent during PAS preparation by using the MW radiation method. However, further increments in MW radiation power and time could result in polymer burning and drug degradation.[46] However, in the present study, the absence of a drug degradation peak indicates that the power used during MW did not affect the integrity of GB. This could be ascribed to the presence of sodium bicarbonate, which generates an alkaline microenvironment where the drug is stable.[47]

On the contrary, GB's distinctive diffraction peaks were remarkably reduced in PAS prepared by the PD method. This might be ascribed to the solubilization of the drug (GB) and polymer (poloxamer) in the solution, whereas GB is homogeneously distributed in the polymer matrix. The sublimation process enables the evaporation of water from the frozen PAS and leaves amorphous drugs homogeneously dissolved and distributed in the polymer matrix.[48,49]

The in vitro dissolution revealed that the combined system (PAS−PD + SNEDDS) was able to intensify GB dissolution efficiency compared with the counterpart combined system (MW-PAS + SNEDDS). This harmonized with the current result of PXRD, indicating approximately complete amorphization of GB within the polymeric matrix using the PD method.[50] Furthermore, the used polymer (poloxamer) during the preparation of PAS significantly intensifies the dissolution efficiency of GB compared to L-SNEDDS. This could result from the reported precipitation inhibition activity of poloxamer present in the combined system, which could significantly boost GB oral bioavailability.[51] In addition, the stability study offers additional advantages in terms of drug stability compared to the traditional S-SNEDDS formulation. This resulted from avoiding long-term exposure of acid-labile drugs to free fatty acids within the components of SNEDDS.[19]

The proposed combined system (SNEDDS + PAS) provides numerous advantages in terms of improving the dissolution and stability of acid-labile drugs. This overcomes the reported limitations of traditional solidification, which include drug precipitation and drug degradation. Therefore, additional investigations are mandatory to inspect the suitability and application of the combination system for acid-labile drugs.

5. CONCLUSIONS

This study demonstrates the significant potential of combination systems (SNEDDS and PAS) to enhance the acid-labile drug dissolution profile and stability. The present results showed that the SNEDDS formulation enhanced the dissolution efficiency of GB by more than 20-fold compared with pure GB. However, remarkable drug degradation was observed. The PAS, using the FD method, was able to convert the drug from a crystalline to an amorphous state, as confirmed by SEM, DSC, and PXRD. The in vitro dissolution study revealed that the PAS enhanced the dissolution efficiency of GB when combined with SNEDDS with outstanding stability during storage. This resolves the instability issues associated with the traditional solidification approach. This innovative combined system has the potential to utilize the advantages of SNEDDS formation to enhance oral drug delivery, offering more effective and reliable therapeutic outcomes.

■ ASSOCIATED CONTENT

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

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Funding

The authors extend their appreciation to the Researchers Supporting Project number (RSP2024R171), King Saud University, Riyadh, Saudi Arabia.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors extend their appreciation to the Researchers Supporting Project number (RSP2024R171), King Saud University, Riyadh, Saudi Arabia.

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