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Physicochemical characterization of gliclazide–macrogol solid dispersion and tablets based on optimized dispersion

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Abstract

Background: This study investigated the physical interaction of gliclazide (GLC) with a hydrophilic carrier, that is, macrogol [polyethylene glycol (PEG)]. Different molecular weights of PEG (4000, 10,000, and 20,000) were used in different drug : carrier weight ratios (1 : 1, 1 : 2, 1 : 5, and 1 : 10). *Method*: Preliminary screening was done by phase solubility studies to characterize the liquid state interaction between the drug and the carrier. Solid dispersions (SDs) of GLC and PEG in different ratios were prepared by fusion technique and by physical mixing. The solid-state interaction between the drug and the carrier was examined by performing differential scanning calorimetry and Fourier transform infrared spectroscopic studies. SD with satisfactory characteristics was selected for the formulation of tablets by wet granulation method and compared with the commercial brand for in vitro dissolution. *Results*: It was evident from phase solubility studies that the drug solubility increased linearly with increasing PEG concentrations. In vitro dissolution of GLC improved significantly in the SDs prepared by fusion method as compared with the original drug and physical mixtures. Scanning electron microscopy images showed well-defined changes in the surface topography of GLC, thus confirming the effective formation of a fused binary system. The SD tablets showed a significant improvement in the drug release profile than that of the commercial brand. *Conclusion*: It was thus concluded that SD formulations of GLC can be successfully used to design a solid dosage form of the drug, which would have significant advantages over the current marketed tablets.

Key words: *Dispersion tablets; fusion method; gliclazide; macrogols; solid dispersions*

Introduction

Gliclazide (GLC), 1-(3-azabicyclo[3,3,0]oct-3-yl)-3-(*p*-tolylsulfonyl) urea (Figure 1), is an oral hypoglycemic second-generation sulfonylurea drug that is useful for a long-term treatment of noninsulin-dependent diabetes mellitus[1]. Previous studies showed that GLC possesses good general tolerability, low incidence of hypoglycemia, and low rate of secondary failure. In general, rapid gastrointestinal (GI) absorption is required for oral hypoglycemic drugs, to prevent a sudden increase in blood glucose level after food intake, in the treatment of patients with noninsulin-dependent diabetes mellitus[2]. However, the absorption rate of GLC from the GI tract is slow and varied among the subjects. Several studies on healthy volunteers and diabetic patients revealed that the time to reach plasma concentration (T_{max}) ranged from 2 to 8 hours following a single oral administration of 80 mg of GLC tablet[3]. This could be because it belongs to Class II of the biopharmaceutical classification in which the drug dissolution rate is the controlling step in drug absorption[4]. Slow absorption has been suggested to be due to poor dissolution of GLC owing to its hydrophobic nature and poor permeability across the GI membrane. Also, it is a weak acid with a good lipophilicity and a pH-dependent solubility. It is practically insoluble in acidic media, and its solubility increases as the pH becomes more alkaline. Therefore, a well-designed formulation capable of presenting a therapeutically effective amount of the hydrophobic drug to the desired absorption site in an absorbable form is necessary[5].

One technique that can be applied to increase the dissolution rate of hydrophobic drugs is the formation of solid dispersion (SD) with hydrophilic polymeric

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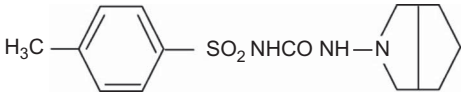

Figure 1. Chemical structure of gliclazide.

carriers[6]. The term SD refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. All drugs in SD might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be a molecular dispersion in the matrix, thereby forming a solid solution. Once the SD was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be significantly high[9–12]. SD techniques are very useful in pharmaceutical sciences because of the increasing number of novel drug candidates that are poorly soluble, but there is still limited information available on their ability to be processed into the final dosage forms[13–14].

Many substances can be used as carriers to prepare SDs among which one of the popular carriers used are polyethylene glycols (PEGs)[13–16]. They are often used as a vehicle because of low toxicity, low melting point, rapid solidification rate, high aqueous solubility, availability in various molecular weights, economic cost, and physiological tolerance. These and other properties make them a very suitable vehicle for formulations into dosage forms. The molecular size of various PEG grades favors the formation of interstitial solid solutions. They have been used as a carrier for increasing the dissolution rate of several poorly water-soluble drugs, such as nifedipine, phenytoin, rofecoxib, etodolac, and so on[16]. Although PEGs have been investigated for the development of oral drug delivery systems for many drugs, however, only few reports are available with GLC[17–19]. Also, it was noted that extensive research work has been carried out in the previous years on the complexation of GLC with cyclodextrins[20–26] to improve its aqueous solubility; but nothing has been reported as yet on binary systems of GLC with PEG, especially by the fusion method[25–27].

SD of GLC in PEG may enhance its dissolution and subsequent absorption from the GI tract and may also overcome the intervariability problems. The objective of this study was thus to investigate the inclusion mode between GLC and various grades of PEGs in different drug : carrier weight ratios. Dispersions were prepared by fusion technique and by physical mixing. The effects of polymer grade and concentration on the physical characteristics of the prepared dispersions and the in vitro drug release rate were investigated. The infrared (IR) spectroscopy and differential scanning calorimetry (DSC) studies were used to investigate possible interactions between the components. The surface topography of the polymeric systems was studied using scanning electron microscopy (SEM). Furthermore, the optimized GLC SD was formulated into tablets and compared for in vitro dissolution with that of marketed conventional GLC tablet.

Materials and methods

Materials

GLC and the polymers, PEG 4000, PEG 10,000, PEG 20,000, and polyvinylpyrrolidone K 30 from Sigma Aldrich (Munich, Germany). Sodium starch glycolate (Explotab) and crosscarmellose sodium (Vivasol) were received as gift samples from JRS Pharma (Rosenberg, Germany). Microcrystalline cellulose (Avicel 102) was a gift sample from FMC, Brussels, Belgium. Diamicron 80 mg conventional GLC tablets (Serdia Pharmaceuticals Pvt. Ltd., Mumbai, India) were purchased from the market. Disodium hydrogen phosphate, sodium hydroxide, and talc were purchased from Loba chemie Ltd., Mumbai, India. Ultrapure water (Millipore, Billerica, MA, USA) and analytical grade reagents/chemicals were used throughout the study.

Phase solubility studies

Phase solubility studies were carried out according to the method reported by Higuchi and Connors[28]. Excess amount of drug (50 mg) was added in screw-capped conical flasks containing 50 mL of aqueous solution each of different concentrations (0.5, 1, 2, 5, and 10%, w/v) of PEG of different molecular weights (4000, 10,000, and 20,000). The suspensions were continuously stirred on an orbital shaker (maxQ 3000, Barnstead Lab-Line, Thermo Scientific, Waltham, MA, USA) at 25 ± 1°C and 200 rpm for 48 hours (this duration was previously tested to be sufficient to reach equilibrium). The suspensions were filtered through Whatman No. 40 filter (Whatman Ltd., Maidstone, UK). The filtrates were suitably diluted and analyzed spectrophotometrically (Shimazdu UV-1601, UV/Vis spectrophotometer, Shimadzu Corp, Kyoto, Japan) for the dissolved drug at 227 nm. All assays were performed in triplicate. The standard plot of GLC in distilled water over a concentration range of 0–20 μg/mL at 227 nm was linear with a correlation coefficient of 0.9999. The apparent stability constant and Gibb's free energy were calculated from the phase solubility diagram.

Preparation of solid dispersions by fusion method

Each SD preparation containing different weight ratio (1:1, 1:2, 1:5, and 1:10) of GLC in PEG of different molecular weights (4000, 10,000, and 20,000) was prepared by the fusion (melting) method. PEG was heated at a temperature of 75 ± 1°C using a thermostatically controlled water bath (Clifton, Nickel Electro Ltd., North Somerset, UK). GLC was dispersed in the melted polymer and the resulting homogenous preparation was cooled to room temperature with constant stirring. The solidified mass was stored at room temperature for 24 hours and later pulverized using a glass mortar and pestle. It was then sifted through 40 mesh sieve (Endecotts, London, UK), labeled, and stored in airtight containers until further evaluation.

Preparation of physical mixtures

PEG flakes were triturated in a mortar and passed through 40 mesh sieve. Physical mixture (PM) of previously sieved fractions of PEG and GLC having the same weight ratios as that of the above-mentioned fused SDs was obtained by blending the two components in geometric proportion in a mortar for 10 minutes to obtain a homogenous mixture. The resulting mixtures were sieved again through 40# sieve, labeled, and stored in airtight containers until further evaluation.

Physicochemical characterization of solid dispersions

Drug content of solid dispersions

Samples of PMs or SDs containing an equivalent of 40 mg of GLC were dispersed in a suitable quantity of methanol and sonicated (Elma Transonic, 460/H, Germany) for 30 minutes. The drug content of the filtered samples was determined at 227 nm by UV spectrophotometer after suitable dilution.

In vitro dissolution studies in distilled water

Pure drug, PM, and the prepared SD equivalent to 80 mg of GLC were used for the dissolution studies. The study was performed in 900 mL distilled water using USP 25 Type II (paddle) eight station dissolution apparatus (Erweka DT 80, GmbH, Heusenstamm Germany)[29]. The stirring speed employed was 100 rpm and the temperature was maintained at 37 ± 0.5°C. Powdered samples of each preparation, equivalent to 80 mg of GLC, were placed in the dissolution medium. Samples (5 mL) withdrawn at different time intervals were filtered and measured at 227 nm spectrophotometrically, after suitable dilution with the dissolution medium if needed, to determine the amount of drug released. An equal volume of fresh dissolution medium kept at the same temperature was added after each sampling to maintain the sink conditions. All studies were performed in triplicate.

Dissolution test in phosphate buffer pH 7.4

Dissolution study on pure drug and the optimized SDs (i.e., GLC and PEG 4000/10,000/20,000 in the ratio 1:2, w/w) prepared by fusion method was performed in phosphate buffer (pH 7.4), which is the dissolution medium recommended by USP XXV. The test conditions were maintained same as those mentioned above. Subsequently, the aliquots (5 mL) withdrawn at different time intervals were analyzed spectrophotometrically at 228 nm for drug release after suitable dilution with the dissolution medium. All assays were performed in triplicate. The standard plot of GLC in phosphate buffer (pH 7.4) over a concentration range of 0–20 μg/mL at 227 nm was linear with a correlation coefficient of 0.9998.

Thermal analysis

Based on the results of the in vitro drug release, DSC study was performed on the optimized SD only. Sample of approximately 10 mg of GLC/PEG 20000/GLC:PEG 20000 PM (1:2, w/w)/GLC : PEG 20000 fused dispersion (1:2, w/w) was weighed and placed in pin-holed aluminum pans. DSC analysis was performed using DSC 141 Setaram Group Thermal Analyzer (France) under a nitrogen flow of 40 mL/min and heating rate of 10°C/min in a 20–250°C temperature range.

IR spectroscopy

IR spectra of GLC/PEG 20000/GLC : PEG 20000 PM (1:2, w/w)/GLC : PEG 20000 fused dispersion (1:2, w/w) were carried out using Fourier transform IR spectroscopy (FTIR) (Bruker IFS 125 FTIR, GmbH, Rheinstetten, Germany) based on the KBr disc method. The samples were scanned from 4000 to 400 cm^{-1} at room temperature.

Scanning electron microscopy

To observe the surface morphology of GLC and the optimized SD, that is, GLC : PEG 20000 fused dispersion (1:2, w/w), SEM studies were performed using Jeol JSM-5610 LV (Jeol Corp., Tokyo, Japan). The samples were prepared by spreading some powder onto a double-sided tape that was then attached to the brass sample holder and sputter coated for 120 seconds, with a thin gold palladium layer in an Auto sputter coater (E5200, BIO RAD, Watford, UK). The images were captured at an excitation voltage of 15 kV at varying magnifications (×50 to ×2000) from original magnification.

Tablet preparation and characterization

Tablets of the optimized SD, that is, GLC : PEG 20000 fused dispersion (1:2, w/w), containing an equivalent of 80 mg of GLC were formulated using the wet granulation technique. All the ingredients (Table 1) were passed separately through 40 mesh sieve. The required amount of SD and Avicel 102 were manually blended in

Table 1. Composition of GLC 80 mg SD tablets.

Components	Quantity (mg) per tablet
GLC : PEG 20,000 SD	240
Avicel 102	41
PVP K30	4.5
Isopropyl alcohol	q.s.
Ac-di-sol	8.5
Vivasol	20
Talc	6

a mortar for 10 minutes. Thereafter, the powder blend was granulated with 3% (w/v) solution of PVP K30 in isopropyl alcohol and passed through 16 mesh sieve. The granules were dried in a hot air oven at 50°C for 3 hours and passed again through 20 mesh sieve. Finally before tabletting, Ac-di-sol, Vivasol, and talc were added, the blend was efficiently mixed and compressed using a single-punch Erweka tablet press (Erweka EK-0, Motor Drive AR 402, Germany), using 9-mm diameter, circular, standard concave punches. The machine settings were adjusted to produce tablets having approximately the same hardness (4.0 kg/cc) and a target weight of 320 mg (±5%) per tablet.

The tablets were evaluated for physical properties using USP 25 methods. The disintegration time was determined for six tablets with USP disintegration apparatus (Erweka ZT31, Heusenstamm, Germany) at 37 ± 0.5°C in distilled water. Friability was determined by using an Erweka friabilator (Erweka, TAR 10) with 20 tablets for 4 minutes (100 revolutions). Thickness and hardness were measured using a vernier calliper and a Monsanto hardness tester, respectively. The drug content of SD tablets was determined using UV spectrophotometry as mentioned for the SDs after crushing the tablets and extracting a sample equivalent to 80 mg of GLC in methanol. In vitro dissolution studies of SD tablets and a commercial brand of GLC (80 mg) and Diamicron (Serdia Pharmaceuticals, Pvt. Ltd., Mumbai, India) were carried out using 900-mL distilled water as the dissolution medium. The test parameters were the same as that mentioned for the SDs before.

Results and discussion

Phase solubility studies

The plots of drug solubility against various polymer concentrations investigated at 25 ± 1°C are represented in Figure 2. The solubility curve was classified as A_L type according to Higuchi and Connors. Solubility of pure GLC in water at 25°C was found to be 6.14 µg/mL. The results showed that the solubility of GLC increased linearly with increasing carrier concentration, for all the

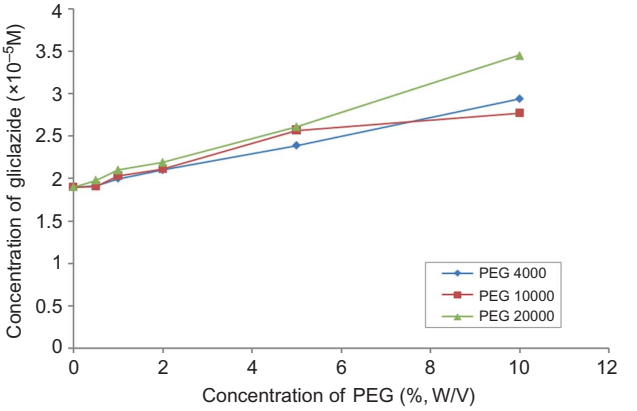

Figure 2. Phase solubility studies of gliclazide with various grades of PEG.

three grades of PEG studied (4000, 10,000, and 20,000). The extent of interaction between the drug and the carrier in aqueous media is characterized by the apparent stability constant Ks, calculated according to the equation given by Higuchi and Connors, Ks = slope/S_0(1 − slope); where S_0 is the intrinsic solubility of GLC in the absence of PEG (Y intercept). The values of Ks were found to be 61.94, 52.88, and 94.23 M^{-1} for PEG 4000, 10,000, and 20,000, respectively, whereas the Gibb's free energy ΔG° were found to be –10.22, –9.83, and –11.26 kJ/mol for PEG 4000, 10,000, and 20,000, respectively.

Drug content of solid dispersions

UV analysis of the SD products confirmed that GLC could be found at a level of 98.5–102% of the theoretically added amount in the various dispersions and PMs.

In vitro dissolution studies in distilled water

The dissolution profiles of GLC, PM, and solid complexes prepared by fusion method using various grades of PEG in different drug–polymer weight ratios are shown in Figures 3–5. The results in terms of percentage of active ingredient dissolved at 15 and 60 minutes (DP_{15} and DP_{60}) are presented in Table 2. The reported values were obtained by calculating the arithmetic mean of three measurements, and standard deviation bars are omitted to avoid overlapping. The initial dissolution rate of GL was very slow with only about 5.74% of the drug dissolved in 15 minutes and 11.03% dissolution at the end of 1 hour. Rapid dissolution is the characteristic behavior of SDs. It was observed that the complexes showed a higher release compared with the pure drug and the corresponding PMs. The improvement in the dissolution rate of the dispersed systems may be attributed to the degree of crystallinity of the active

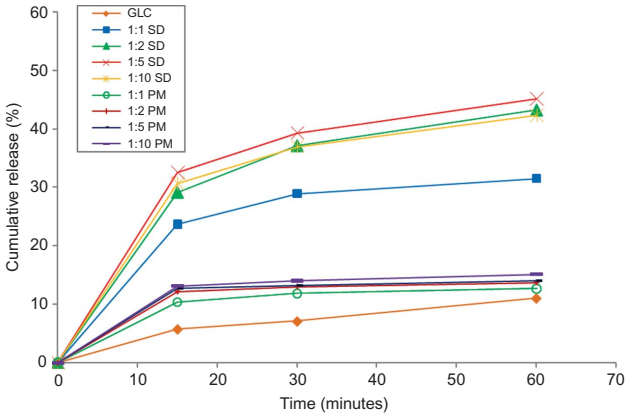

Figure 3. In vitro release profile in distilled water for GLC from physical mixtures and solid dispersions with PEG 4000 in different GLC : PEG (w/w) ratios.

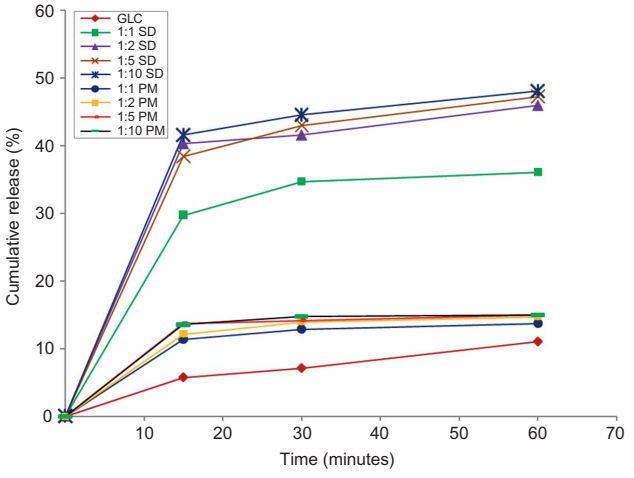

Figure 4. In vitro release profile in distilled water for GLC from physical mixtures and solid dispersions with PEG 10,000 in different GLC : PEG (w/w) ratios.

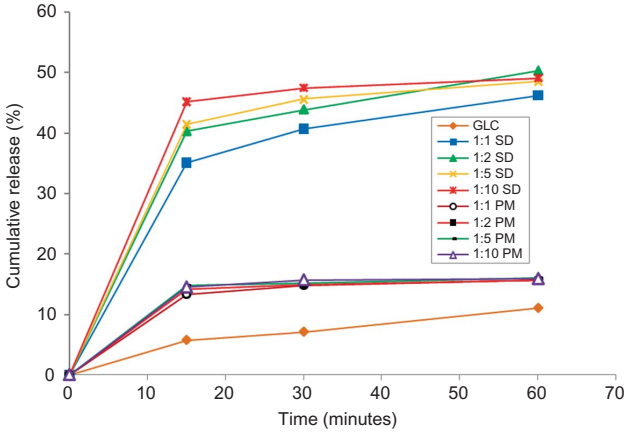

Figure 5. In vitro release profile in distilled water for GLC from physical mixtures and solid dispersions with PEG 20,000 in different GLC:PEG (w/w) ratios.

Table 2. DP_{15} and DP_{60} parameters for pure GLC, and various solid dispersions in distilled water.

Compound[a]	Dissolution parameters[b]	
	DP_{15}	DP_{60}
Pure GLC	5.74 ± 1.61	11.03 ± 0.94
GLC : PEG 4000 (1:1, w/w) SD	23.68 ± 1.85	31.46 ± 0.97
GLC : PEG 4000 (1:2, w/w) SD	29.14 ± 1.09	43.23 ± 1.18
GLC : PEG 4000 (1:5, w/w) SD	32.59 ± 0.77	45.18 ± 1.46
GLC : PEG 4000 (1:10, w/w) SD	30.62 ± 1.53	42.32 ± 0.95
GLC : PEG 10,000 (1:1, w/w) SD	29.74 ± 1.41	36.08 ± 1.25
GLC : PEG 10,000 (1:2, w/w) SD	40.35 ± 0.93	46.02 ± 1.73
GLC : PEG 10,000 (1:5, w/w) SD	38.44 ± 1.18	47.27 ± 0.61
GLC : PEG 10,000 (1:10, w/w) SD	41.59 ± 1.39	48.08 ± 1.06
GLC : PEG 20,000 (1:1, w/w) SD	35.10 ± 1.18	46.2 ± 1.17
GLC : PEG 20,000 (1:2, w/w) SD	40.31± 0.62	50.31 ± 0.49
GLC : PEG 20,000 (1:5, w/w) SD	41.48 ± 1.44	48.52 ± 0.95
GLC : PEG 20,000 (1:10, w/w) SD	45.23 ± 1.75	49.13 ± 1.26

[a]SD indicates solid dispersions prepared by fusion method. [b]$n = 3$.

material, together with the increase in both wettability and solubility of the drug.

Dissolution test in phosphate buffer pH 7.4

In vitro release characteristics of the optimized dispersions with various PEG grades (1:2, w/w) were further evaluated in phosphate buffer pH 7.4, which is the officially recommended dissolution medium for GLC tablets in the USP 25. The drug : polymer ratio 1:2 (w/w) was considered to be optimum as there was no significant increase in dissolution observed beyond this ratio. Also the intention of the study was to further screen the polymer grades for compression into fast-dissolving tablets. A higher drug : polymer ratio would unnecessarily lead to bulky tablets. The results in terms of percent of active ingredient dissolved at 15 and 60 minutes (DP_{15} and DP_{60}) are presented in Table 3. It was observed that at pH 7.4 after 15 minutes only 12.36% of pure GLC was dissolved and at the end of 60 minutes only 26.86% of the drug went into solution, whereas in the case of all the GLC : PEG SDs prepared by the fusion method, 100% drug release was obtained at the end of 60 minutes (Figure 6). The comparative release studies indicated that the release of the active material was

Table 3. DP_{15} and DP_{60} parameters for pure GLC, and optimized solid dispersions in phosphate buffer pH 7.4.

Compound[a]	Dissolution parameters[b]	
	DP_{15}	DP_{60}
Pure GLC	12.36 ± 0.83	26.89 ± 0.95
GLC : PEG 4000 (1:2, w/w) SD	85.91± 1.17	99.25 ± 1.29
GLC : PEG 10,000 (1:2, w/w) SD	87.26 ± 1.43	100.37 ± 1.68
GLC : PEG 20,000 (1:2, w/w) SD	87.72 ± 0.84	101.97 ± 0.62

[a]SD indicates solid dispersions prepared by fusion method.[b]$n = 3$.

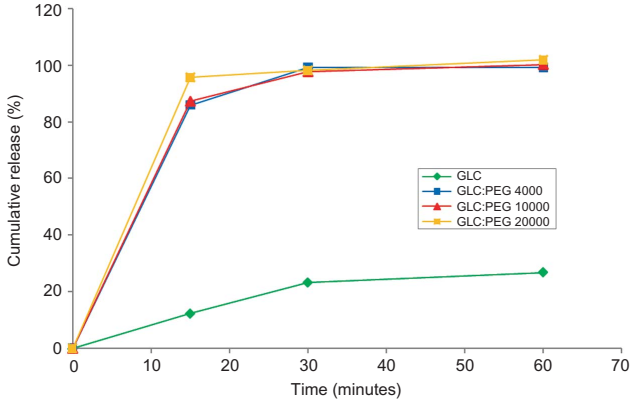

Figure 6. In vitro release profile in phosphate buffer (pH 7.4) for GLC and optimized solid dispersions with PEG of different grades in 1:2 (w/w) ratio.

strongly affected by the method of formulation and the pH of the dissolution medium. An overall increase in the dissolution rate was noted in the alkaline medium compared with that in distilled water, which may be due to the ionization of the drug as it is a weak acid.

Thermal analysis

The DSC enables quantitative detection of all processes in which energy is required or produced (i.e., endothermic and exothermic phase transformations). The thermograms for pure GLC, PEG 20,000, PM of GLC and PEG 20,000 (1:2, w/w), and fused SD of the same in 1:2 (w/w) ratio are presented in Figure 7. The DSC of pure GLC shows a sharp melting endotherm at 175°C with enthalpy of fusion (ΔH) of 117.7624 J/g, whereas the glass transition temperature (T_g) was found to be 172.1°C. The thermogram of pure PEG 20,000 depicts an endothermic peak at 60°C representative of its melting point, whereas ΔH and T_g were found to be 226.9788 J/g and 57.53°C, respectively. The DSC pattern of the PM shows the presence of the typical melting endotherm of the two compounds, except with the difference that the drug-melting endotherm had slightly shifted from its original position of 175°C to 162.5°C. There was also a reduction in the enthalpy values to 106.84 and 157.4014 J/g for GLC and PEG 20,000, respectively. This slight shift and reduction in ΔH values could be due to a weak interaction between the drug and the polymer. The thermogram of the fused SD exhibited almost complete disappearance of the endothermic peak characteristic of GLC, and the ΔH for PEG 20,000 was further reduced to 144.5224 J/g. This decrease in enthalpy of fusion value (Δ ΔH = −82.4564 J/g) for the polymer can be due to a decrease in PEG crystallinity, resulting in an increased dissolution rate. Also, the disappearance of GLC endotherm could be attributed to its amorphous

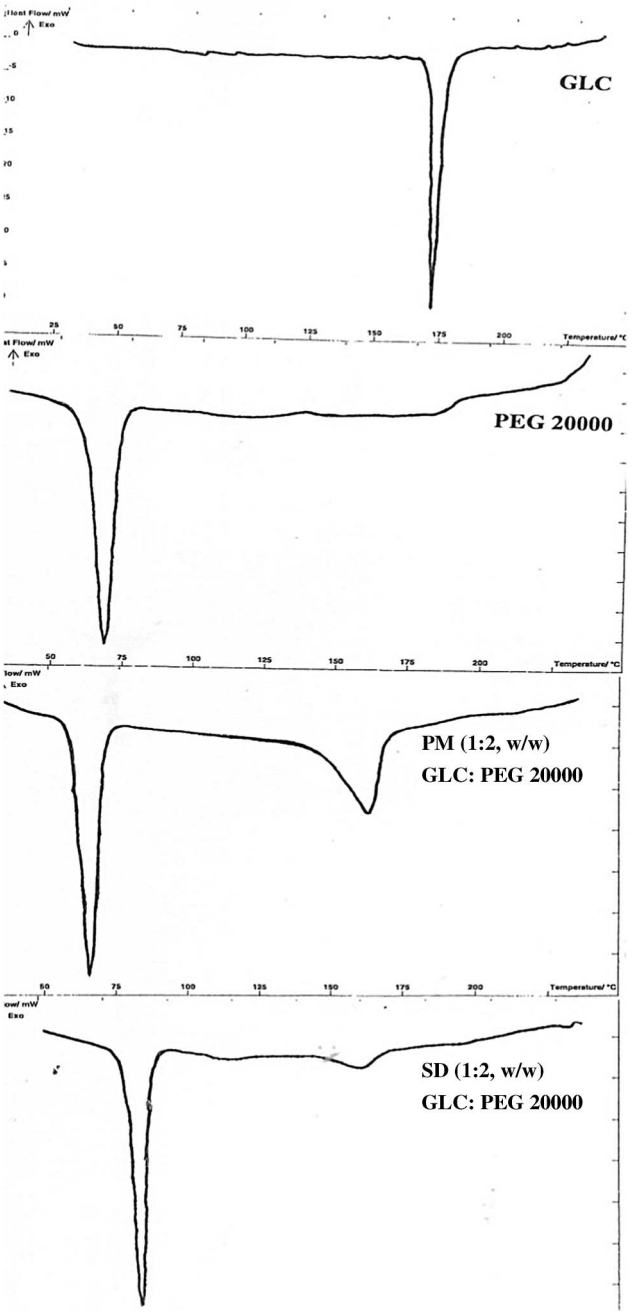

Figure 7. DSC thermograms of GLC, PEG 20,000, and binary systems with PEG 20,000 (PM and SD in 1:2, w/w ratio).

character in the fused state, strongly indicating that the drug is well dispersed in the polymer matrix and its recrystallization is restrained. The results of thermal analysis are thus suggestive of maximal complex formation in the fused dispersed state.

IR spectroscopy

The interaction between the drug and the carrier often leads to identifiable changes in the IR profile of the SD.

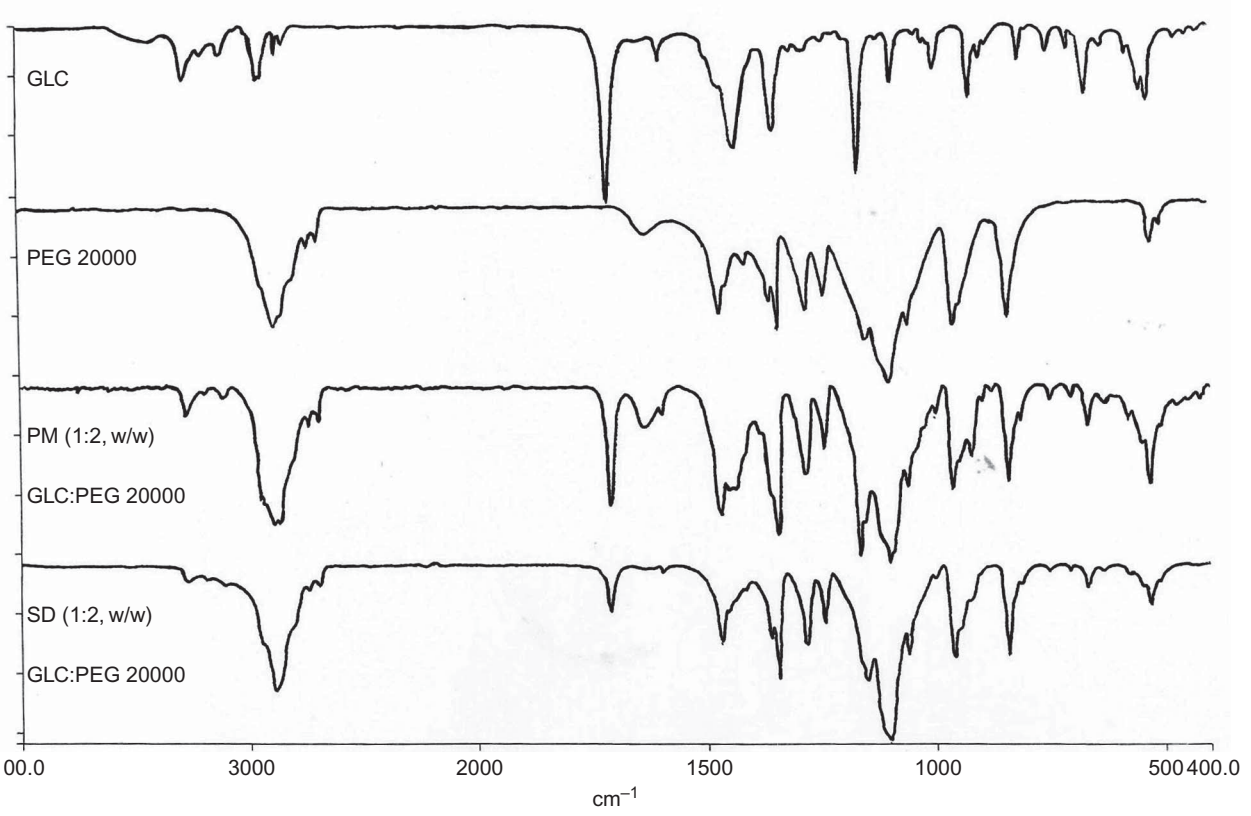

Figure 8. FTIR spectra of GLC, PEG 20,000, and binary systems with PEG 20,000 (PM and SD in 1:2, w/w ratio).

FTIR spectra were used to confirm the formation of SD of GLC in PEG 20,000 (1:2, w/w) prepared by the fusion method. The spectra of the dispersion were also compared with that of GLC, PEG 20,000, and the corresponding PM (Figure 8). The intense peaks that appeared in the spectra of GLC and PEG 20,000 were due to asymmetric stretching vibrations of the functional groups. The IR spectrum of pure GLC showed characteristic peaks at 3290, 1750, and 1200 cm^{-1} because of stretching of the –N–H– (amide), –C=O (carbonyl), and –S=O (sulfonyl) groups, respectively, whereas the PEG 20,000 spectrum showed a characteristic broad spectra of O–H stretching vibration from 3300 to 3600 cm^{-1}, C–H stretching of OC_2H_5 groups from 2800 to 2900 cm^{-1}, and C–O stretching from 1000 to 1200 cm^{-1}. The spectrum of the GLC : PEG 20,000 PM showed a summation effect, that is, simple superposition of the peaks because of the functional groups of the two compounds, indicating the presence of GLC in crystalline state and no formation of a new structure. However, it was observed that, in the spectrum of GLC : PEG 20,000 SD, the presence and absence of characteristic peaks associated with specific structural characteristics of the drug molecule were noted. The carbonyl group peak was significantly reduced in intensity, but appeared at the same frequency, Also, the characteristic –S = O sulfonyl group peak and amide –N–H stretching vibration seen in the pure drug spectrum could not be detected in that of the SD. This could be attributed to the physical interaction of the drug with the polymer moiety. However, the disappearance of –NH– peak of GLC could be due to hydrogen bonding between the hydrogen atom of the –NH– group of GLC and one of the ion pairs of oxygen atom in PEG 20,000. These interactions could be responsible for the improved wettability, aqueous solubility, and dissolution enhancement of the drug.

Scanning electron microscopy

Figure 9 reveals the surface topography studies performed on pure GLC (as received from the supplier), PEG 20,000, and the optimized SD [i.e., GLC : PEG 20,000 fused dispersion (1:2, w/w)]. (a) GLC was observed as irregular shaped crystals with rough surface; whereas, (b) PEG 20,000 appeared as smooth-surfaced waxy flakes. The photomicrographs of (c) GLC : PEG 20,000 fused dispersion exhibited well-scattered agglomerates of the drug in the polymer matrix that appeared in the form of smooth, uniform, and homogeneously mixed

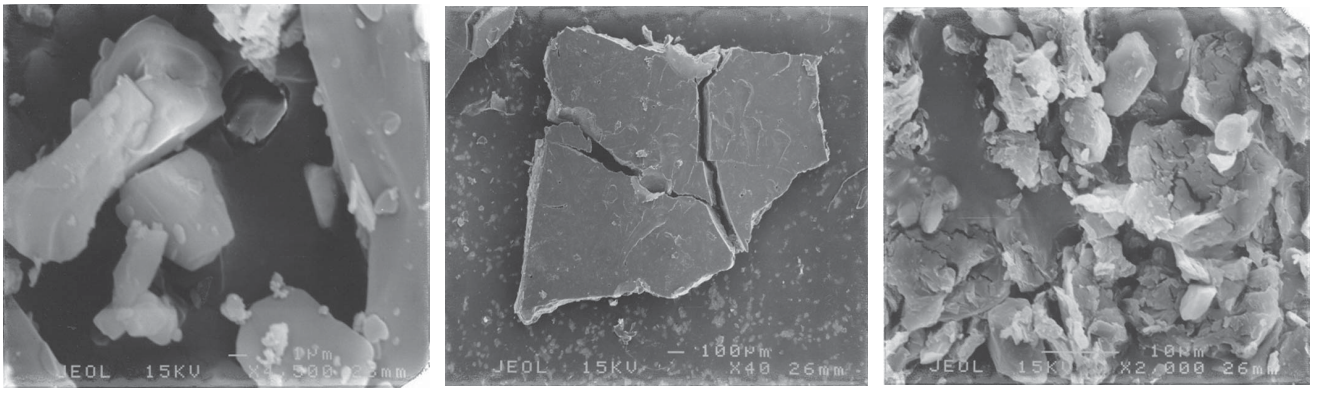

Figure 9. SEM images of (a) GLC, (b) PEG 20,000, and fused dispersion 1:2 (w/w) (c) GLC : PEG 20,000.

mass. The individual surface properties of GLC were lost during melting and solidification process indicating the formation of effective SD system. Thin-layered wrinkles on the smooth surface of the SD are one of the surface characteristics that would form during the resolidification of melted mass of drug–PEG 20,000 mixture. The dispersed particles presented a surface morphology similar to that of pure PEG 20,000, and it was impossible to distinguish the presence of GLC crystals among the polymer particles, indicating that the drug was adsorbed into the polymer matrix at a molecular level. The microscopic evidence of this new arrangement of the drug and PEG particles in the fused form might be responsible for the enhanced drug dissolution rate found for SD systems, in comparison with pure GLC.

Tablets of solid dispersion and characterization

For formulation of GLC tablets, optimized SD with satisfactory in vitro release performance was used. This dispersion was prepared by fusion method with GLC : PEG 20,000 in the ratio 1:2 (w/w). For the formulation of granules, the wet granulation technique was used. The lubricated granules were compressed using a single-punch, motor-driven tablet compression machine. It is evident from the physical results given in Table 4 that the formulated tablets exhibited good technological properties with regard to weight, hardness, diameter, thickness, disintegration, and friability. The low friability obtained confirmed the suitability of wet granulation technology using PVP K30 in isopropyl alcohol as the binder. The use of superdisintegrants (Ac-Di-Sol and Vivasol) for the preparation of fast-dispersing tablets was found to be highly effective as well as commercially feasible. It is generally observed that the incorporation of higher concentrations of PEG usually strengthens the binding properties and prolongs the disintegration time of tablets. However, in the present formula, the GLC : PEG ratio used was only 1:2 (w/w) and hence the effect of the superdisintegrants used was more pronounced. The prepared tablet formulation fulfilled the USP requirements. Good uniformity in drug content was found among different tablets. In vitro dissolution studies for SD tablets confirmed the results obtained with solid binary mixtures (Figure 10). A significant enhancement in the dissolution characteristics with SD tablets ($DP_{15\ min}$ =

Table 4. Technological Characterization of GLC 80 mg SD tablets (1:2 w/w Drug:PEG 20,000 fused dispersion)*.

Weight variation	2.1 ± 0.4%
Diameter	9.0 ± 0.04 mm
Thickness	4 ± 0.03 mm
Hardness	3.5 ± 0.5 kg/cc
Friability	0.18 ± 0.1%
Disintegration	10.3 ± 0.5 minutes
Content uniformity	98.82 ± 1.36%

All values represent mean ± SD (n = 3).

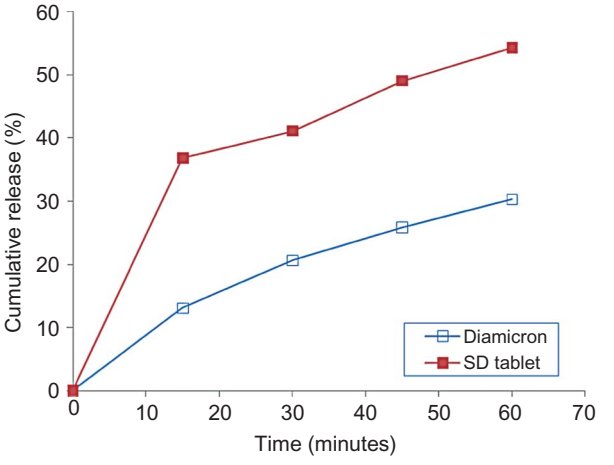

Figure 10. In vitro release profile of GLC (dose = 80 mg) in distilled water from Diamicron tablets and solid dispersion tablets (GLC : PEG 20,000, w/w) prepared by fusion method.

36.73%) was observed in contrast to the marketed brand ($DP_{15\,min}$ = 13.05%). The dissolution of Diamicron tablets and those prepared with SD was intentionally studied in distilled water to reflect the enhanced aqueous solubility of GLC in fused state with PEG. This would not have been possible if the study was performed in phosphate buffer, as the drug shows pH-dependent solubility, where the solubility increases with increase in pH. The SD tablets thus certainly performed better compared with the commercial formulation that is evident by the similarity factor (f_2 = 31.83) and difference factor (f_1 = 102.22) calculated according to Moore and Flanner[30].

Conclusion

The study confirms that Macrogols (PEGs) can be used successfully to prepare suitable SDs of GLC by the fusion method. Although dispersions prepared with all the PEG grades tested (4000, 10,000, and 20,000) showed remarkably significant increase in dissolution compared with the original drug; however, dispersions with PEG 20,000 showed comparatively reproducible and better results. As demonstrated by the DSC, FTIR, and SEM studies, a decreased crystallinity of GLC and surface morphology of the polymeric particles explained this improved dissolution rate. All the complexes prepared showed remarkable increases in the water solubility of the drug. Also, the optimized binary system along with the use of superdisintegrants could be used for the formulation of GLC with good technological properties and enhanced dissolution.

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