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Preparation and evaluation of glibenclamide binary solid dispersions prepared by fusion and solvent-fusion method

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ABSTRACT

Solid dispersions (SDs) of the poorly water soluble antidiabetic drug, glibenclamide(GLB), were prepared using polyethylene glycol 4000(PEG) through the fusion and solvent-fusion method. Solid-state analysis and the in vitro drug release profiles of the prepared formulations were assessed. Compressibility and flowability of the prepared solid dispersions were also evaluated. The dissolution rate of the prepared SDs was greatly superior to GLB. The release profile was more dependent on drug to hydrophilic polymer ratio than the preparation technique. The FTIR studies showed no interaction between drug and polymer. DSC thermograms of the prepared SDs showed no endothermic peak of GLB, which could be attributed to the gradual dissolving of the GLB in the melted PEG and/or drug amorphization. Moreover, prepared SDs were showed superior compressibility and flowability. According to the obtained results, GLB/PEG SDs both prepared successfully by fusion and solvent-fusion technique and showed improved flowability and dissolution. This will likely lead to an increase in drug bioavailability and glucose control performance in diabetic patients. There was no significant difference between the obtained result from fusion and solvent-fusion method. However, due to the lack of organic solvent as well as simple and economical manufacturing process fusion method is more reasonable.

Keywords: *Solid Dispersion; Glibenclamide; Fusion; Solvent-fusion; Dissolution.*

1. INTRODUCTION

Glibenclamide (GLB), a second generation hypoglycemic sulfonylurea, is used in the treatment of noninsulin dependent diabetes [1]. It belongs to Class II of biopharmaceutical classification system and tends to exhibit solubility or dissolution rate limited absorption as it may pass the absorption site before complete dissolution [2]. Therefore, the bioavailability of this drug can be improved via solubility and dissolution rate enhancement. Several attempts have been made to enhance the solubility of GLB by several techniques such as solid dispersions (SDs), lyophilization, liquisolid technique, complexation with cyclodextrin, nanosuspension and preparation of self-nanoemulsifying systems of GLB [3-7]. SDs were extensively studied as one of the most practical and effective strategies to improve dissolution rate and in turn bioavailability of poorly water-soluble drugs (particularly BCS class II drugs) [8]. The advantages of SDs include particle size reduction (possibly to molecular level), increase of wettability and porosity, decrease in drug crystallinity and sometimes dissapearance of drug crystalline structure and conversion into the amorphous state. Accordingly, the drug substance could disperse as separate molecules, amorphous particles or crystalline particles, whereas, the Carrier might present in the crystalline or amorphous state. Improvement in drug solubility and dissolution rate through SD technique has been shown by numerous studies [9-17]. Artificial hydrophilic polymers have been widely examined as Carrier substances for SDs. Polymer-based amorphous SDs have been considered as the major innovation in overwhelming limited aqueous solubility and oral absorption issues [18]. Different Carriers can be used in SD preparation and their choice influences the solubility of lipophilic drugs. Polyethylene glycols (PEG) are one of the most frequently used hydrophilic polymeric Carriers [19, 20]. Several conventional and novel methods have been proposed for the preparation of SDs including, hot-melt or fusion method, solvent method, solvent-fusion method, supercritical anti-solvent precipitation process, electrospraying technique and etc. [15, 21-25]. However, very few comparisons of the in vitro performance of conventional SDs are found in literature. Hence, in the present study attempts have been done to evaluate and compare binary SDs of GLB prepared by fusion and solvent-fusion as a conventional techniques using PEG as a hydrophilic Carrier. SDs of GLB with different drug to polymer ratios (1:3, 1:5 and 1:9) were prepared through fusion and solvent-fusion methods. In vitro drug release from SDs was performed and compared. The formulations were characterized by Fourier transformed infrared spectroscopy (FTIR), differential scanning colorimetry (DSC). Carr index and Hausner ratio were determined to evaluate the compressibility and flowability of the prepared SDs.

2. MATERIALS AND METHODS

2.1 Materials.

Glibenclamide was supplied from Mahban chemi Co., Ltd. (Iran), PEG 4000, monobasic potassium phosphate, sodium hydroxide and chloroform were purchased from Merck (Germany). Double distilled water was used throughout the study and all the other chemicals were of analytical grade.

2.2 **Preparation of GLB binary SDs and physical mixtures (PMs).** Binary SDs of GLB was prepared using PEG in different

drug to polymer ratios through fusion and solvent-fusion method (Table.1). Briefly, for fusion method, an accurately weighed amount of PEG was placed into a suitable glass beaker and heated to 65–70 °C using a hot plate until PEG melted. The required amount of sieved GLB powder was added to the molten vehicle with continuous stirring to ensure homogeneity. For solvent-fusion technique the GLB powder was dissolved in minimum amount of chloroform and poured into the molten PEG at this step. Then, after complete dispersion of GLB, the prepared SDs were slowly cooled at ambient temperature and pressure for 24 h. The residues were pulverized by mortar and pestle, passed through a 250 μm sieve (mesh size 60), and then stored in a desiccator at room temperature. For the preparation of relevant PMs, an accurately weighed amount of GLB and PEG were powdered separately in a mortar and passed through a 250 μm sieved and then mixed with spatula for 5 min.

Table 1. Theoretical composition, drug to polymer ratio and preparation method.

GLB: PEG	Method	Formulation code
1:0	-	GlB
1:3	Fusion	F3
1:5	Fusion	F5
1:9	Fusion	F9
1:3	Solvent-Fusion	SF3
1:5	Solvent-Fusion	SF5
1:9	Solvent-Fusion	SF9
1:3	Physical Mixing	PM3
1:5	Physical Mixing	PM5
1:9	Physical Mixing	PM9

2.3. Dissolution studies.

The drug release profile was determined by USP standard dissolution apparatus II, paddle stirrer (Pharmatest, Germany). The pure drug and prepared SDs and PMs all contained 10 mg of GLB were weighed and added into the dissolution medium (phosphate buffer pH 7.8, 900 ml, under stirring rate of 100 rpm at) maintained at 37 ± 0.5 °C. At the specified times (10, 20,30,45,60 Minutes) 3 mL of samples were withdrawn by using of 0.45 μm membrane filter and 3 ml of fresh buffer was replaced. Then assayed for GLB content by determining the absorbance at 230 nm using a UV-visible spectrophotometer (Cecil UV/VIS, UK). The stability studies on dissolution profile were Carried out after 6 month on the prepared SDs which were kept in the desiccator at room temperature. Finally, the cumulative amount of released drug was calculated and plotted vs. time. The reported results are the average of three independent experiments ±SD.

2.4. Fourier transformed infrared spectroscopy study (FTIR).

FT-IR spectra were obtained by an FT-IR spectrophotometer (PerklinElmer, USA) using the potassium bromide (KBr) disk method. Data were collected over a spectral region from 4000 to 400 cm^{-1} with a resolution of 2 cm^{-1}.

2.5. Differential scanning calorimetry (DSC).

The DSC thermograms of the prepared SDs and PMs as well as the pure drug and polymer were obtained using differential scanning calorimeter (PerklinElmer, USA). All accurately weighed samples (3–5 mg) were placed in sealed aluminum pans. The thermograms obtained at a heating rate of 10 °C/min, from 25 °C to 250 °C. An empty aluminum pan was considered as reference.

2.6. Flow properties

The flow properties of the pure drug, prepared SDs and PMs were characterized using Carr's index and Hausner's ratio. Samples were poured slightly through a glass funnel into a graduated cylinder exactly up to 10 ml mark and the weight of the powder required for filling the cylinder volume was measured. Then the cylinder was tapped from a height of 1 cm until the time were there was no decrease in the final volume. The bulk density (ρB) and tapped density (ρT) of plain GLB and SDs were determined, Carr's index and Hausner's ratio were calculated using ρB and ρT values as shown below [26].

Carr's index **(CI)** = [1- (ρB/ ρT)] ×100

Hausner's ratio **(HR)** = ρT/ ρB

3. RESULTS

3.1. Dissolution studies.

The in vitro drug release profiles of the pure drug (GLB) as well as PM and SDs both prepared by fusion and solvent fusion methods are represented in Figure 1, 2. The pure GLB showed only 17% and 32% drug release after 60 and 120 min respectively in phosphate buffer (pH 7.8). The best PM with the highest ratio of polymer (PM9) showed a relative improvement in drug release performance (53% and 66% drug release after 60 and 120 min respectively). The increase in dissolution performance of drug probably ascribed to an improvement of wetting and to local solubilization by the excipients in the diffusion layer [8]. Within the first 10 min, the prepared SDs showed higher burst release in the following order: F9 > SF9 > SF5 > F5 > F3 > SF3. This enhanced drug release performance could be due to the solubilizing and wetting effect of PEG, formation of amorphous complex, as well as substantial reduction of particle size during the formation of SDs. Similar observations have been reported for naproxen-PEG, glibenclamide-polyglycolized glycerides and ezetimibe-PVP solid dispersions [8, 27, and 28]. SDs in 1 to 9 drug to polymer ratio (F9 and SF9) showed the best release rate profile. Based on the obtained results, it seems that polymer ratio plays a more important role than the preparation technique in this study. The stability studies on dissolution profile of the prepared SDs after 6 month showed no significant difference (ANOVA, $p > 0.05$) in the dissolution profiles compared to the observed value throughout the study period (data not shown).

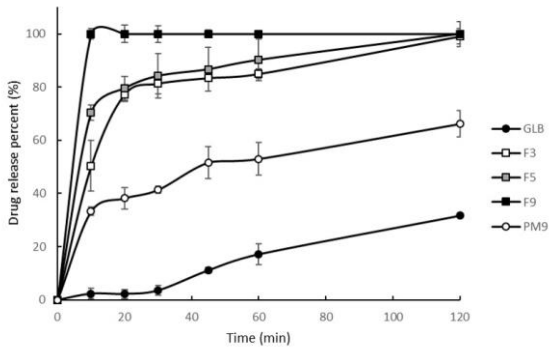

Figure 1 . Comparative dissolution profiles of GLB and the prepared formulations by fusion technique. Key: pure GLB (●); PM9 (○); F3 (□); F5 (🔲); F9 (■). Each point refers to mean ± S.D. (n = 3).

3.2. Fourier Transformation Infrared Spectroscopy (FTIR).

Possible interactions between the drug and polymer were assessed by Fourier-transform infrared spectroscopy (FT-IR) analysis. FT-IR spectra of the pure drug, physical mixture and the prepared formulations are shown in Figure 3. The FT-IR spectrum of pure GLB showed characteristic amide peaks at 3318, and 1715 cm^{-1}, urea carbonyl stretching (urea N–H stretching) vibrations at 1618, and 1527 cm^{-1}, SO_2 stretching vibration at 1160, 1342 cm^{-1}. Important vibrations detected in the spectrum of PEG were the C–H stretching at 2,890 cm^{-1}, C–O stretching at 1,120 cm^{-1} and–OH stretching at 3 400cm^{-1}.Comparing the spectra for the prepared formulations with those for the physical mixture and pure drug and polymer clarified the maintenance of major bands. The spectra of PM and the prepared SDs were equivalent to the spectra obtained by the addition of polymers and the crystalline drug spectrum. These findings indicated that no chemical interaction occurred between the drug molecules and polymer during the solid dispersion preparation process. Similar results were reported for valdecoxib solid dispersions [19].

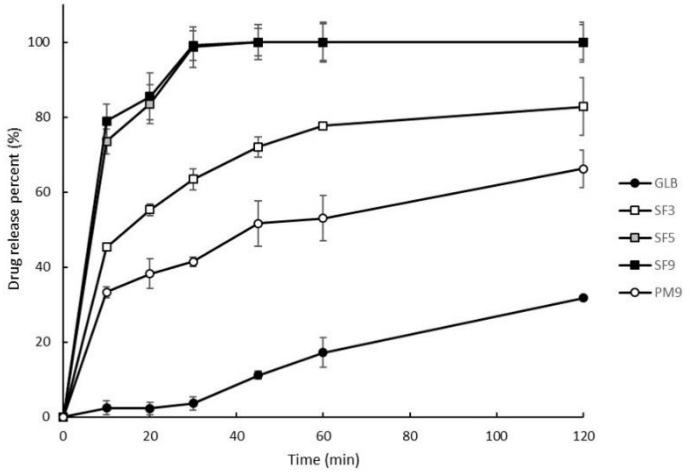

Figure 2. Comparative dissolution profiles of GLB and the prepared formulations by solvent-fusion technique. Key: pure GLB (●); PM9 (○); SF3 (□); SF5 (▣); SF9(■). Each point refers to mean ± S.D (n = 3).

3.3. DSC studies.

The DSC thermograms of the pure drug (GLB) and polymer (PEG) as well as physical mixture (PM) and solid dispersions prepared by fusion (F) and solvent-fusion (SF) method all in 1: 5 ratio is represented in figure 4. As could be seen in this figure, GLB and PEG showed a single endothermic melting peak at 177°C and 69°C respectively. The DSC curve of the both SDs prepared by fusion and solvent-fusion method, displayed a melting endotherm of PEG only. This could be ascribed to the gradual dissolving of the GLB in the melted PEG and/or drug amorphization. Therefore no distinct endothermic peak could be detected for the pure drug in both prepared solid dispersions with DSC. The DSC thermogram of the PM also showed similar results, owing to the dilution effect of polymer and/or the slow dissolution of the GLB in the molten PEG upon heating. Similar observations were also reported by Rodriguez and Bartsch *et al.* [29, 30].

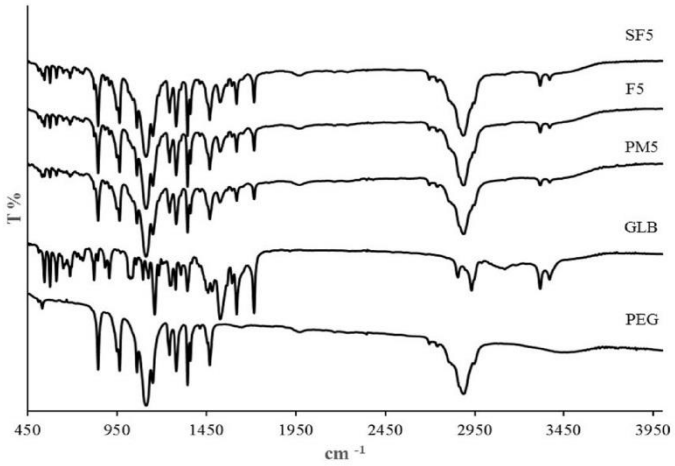

Figure 3. FTIR spectra of the pure drug (GLB) and polymer (PEG) as well as physical mixture (PM) and solid dispersions prepared by fusion (F) and solvent-fusion (SF) method all in 1: 5 ratio.

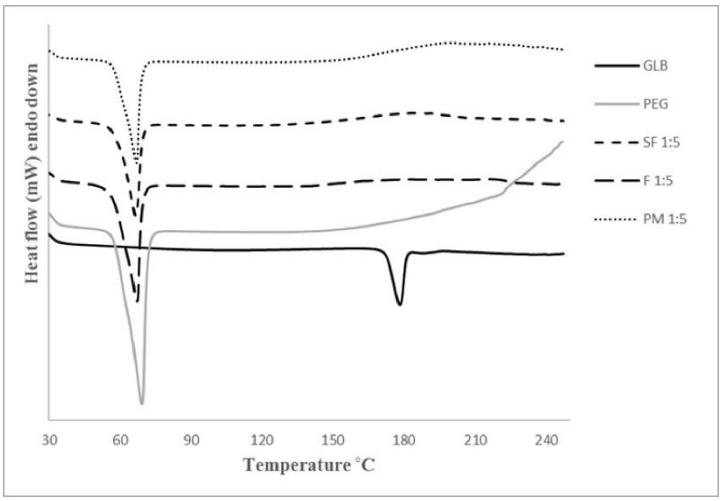

Figure 4. DSC thermograms of the pure drug (GLB) and polymer (PEG) as well as physical mixture (PM) and solid dispersions prepared by fusion (F) and solvent-fusion (SF) method all in 1: 5 ratio.

3.4. Flow properties.

The bulk density, tapped density, Carr's index and Hausner's ratio of GLB and the prepared formulations are shown in Table 2. The Carr index was found in the range of 36.57 % and the calculated Hausner's ratio was in the range of 1.57. The poor flow of pure GLB could be due to the asymmetrical shape and high fineness of the powder. The Hausner's ratio less than 1.34 and Carr's index less than 25 are considered as an acceptable flow characteristics of powder. According to the obtained results all of the prepared SDs with both fusion and solvent-fusion technique represent a better flow characteristics compared to the pure drug and PM, which had very poor flow properties. The improved flow characteristics of the prepared SDs might be due to the regular and larger size of particles [31].

Table 2. Flow properties of the pure drug (GLB), PM and the prepared SDs.

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner ratio	Carr's index (%)	Flow character
GLB	**0.40±0.01**	**0.63±0.07**	**1.57**	**36.57**	very poor
F3	**0.50±0.02**	**0.64±0.05**	**1.28**	**22.23**	Passable
F5	**0.48±0.09**	**0.64±0.14**	**1.32**	**24.28**	Passable
F9	**0.49±0.05**	**0.64±0.09**	**1.30**	**23.20**	Passable

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner ratio	Carr's index (%)	Flow character
SF3	**0.92±0.18**	**1.18±0.20**	**1.29**	**22.42**	Passable
SF5	**0.48±0.26**	**0.60±0.08**	**1.25**	**20.22**	Fair
SF9	**0.45±0.09**	**0.57±0.14**	**1.27**	**21.33**	Passable
PM3	**0.65±0.14**	**0.98±0.05**	**1.5**	**33.33**	very poor

4. CONCLUSIONS

SDs of GLB-PEG were successfully prepared by fusion and solvent fusion technique. The dissolution rate of GLB was improved by increasing the concentration of the hydrophilic Carrier (PEG) in both PMs and SDs. The fastest dissolution rate was found for SDs with the highest ratio of PEG prepared by fusion technique (F9). The release profile was more dependent on drug to hydrophilic Carrier ratio than the preparation technique. Stability studies of SDs did not show any noteworthy change in the dissolution profile after 6 months study. From FTIR spectroscopy, it was concluded that there was no chemical interaction between GLB and PEG in the prepared SDs and in physical mixture. No endothermic peak of GLB was present in the DSC thermograms of SDs prepared by both techniques suggesting the gradual dissolving of the GLB in the melted PEG and/or absence of crystalline structure of GLB. All of the prepared SDs demonstrated a better flow characteristics in comparison with the pure drug and PM. Altogether, there was no substantial difference between the obtained result from fusion and solvent- fusion method. The improved physicochemical and flow properties as well as dissolution characteristics of SDs prepared by fusion and solvent-fusion technique would likely be beneficial for better drug bioavailability and glucose control in diabetic patients. In conclusion, it seems that the fusion method is preferred due to the lack of organic solvent and simple manufacturing process.

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6. ACKNOWLEDGEMENTS

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