Poly-2-ethyl-2-oxazoline as an Alternative to Poly(Vinylpyrrolidine) in Solid Dispersions for Solubility Dissolution Rate Enhancement of Drug

ABSTRACT

Poly(2-ethyl-2-oxazoline) (PEOX), a biocompatible polymer considered as pseudopolypeptide, was introduced as a potential alternative to the commonly used polymer, poly(vinylpyrrolidone) (PVP) for the preparation of solid dispersion with a poorly soluble drug. Glipizide (GPZ), a Biopharmaceutical Classification System class II model drug, was selected for solubility and dissolution rate study. GPZ-polymer solid dispersions and physical mixtures were characterized and investigated by X-ray diffractometry, differential scanning calorimetry, scanning electron microscopy, and FTIR spectroscopy. The impact of polymers on crystal nucleation kinetics was studied, and PEOX exhibited strong inhibitory effect compared with PVP. Solubility and dissolution behavior of the prepared solid dispersions and their physical blends were in vitro examined and evaluated. A significant enhancement in GPZ solubility was obtained with PEOX compared with the pure drug and solid dispersion with PVP. A big improvement in the intrinsic dissolution rate (45 times) and dissolved amount of GPZ (58 times) was achieved with PEOX in fasted state simulated intestinal fluid, against comparable enhancement observed with PEOX and PVP in phosphate buffer at pH 6.8. Lower molecular weight of PEOX-5K (5000 g/mol) was found to be superior to higher molecular weight PEOX-50K (50,000 g/mol) in the improvement of dissolution behavior. The findings of this study with GPZ as a model drug introduce lower molecular weight PEOX as a promising polymeric carrier toward better oral bioavailability of poorly soluble drugs.

Keywords

Solid dispersion, dissolution, solubility, amorphous, polymer, oxazoline, PEOX, glipizide.

1. Introduction

A great challenge for scientists is the search for pioneering drugs with an improved efficacy and less adverse effects for controlling diseases. An estimated 40% of FDA approved drugs and about 90% of the developmental drugs includes poorly soluble molecules (1). Moreover, many drugs in the market suffer from low aqueous solubility or low permeability (2). For poorly soluble drugs with good permeability, or Class II drugs according to the biopharmaceutical classification system (BCS), the main problem which limits their bioavailability is their low solubility in the gastrointestinal fluid and slow dissolution rate.

Many techniques have been applied to enhance the solubility and dissolution rate of poorly soluble drugs, such as decreasing particle size, inclusion complexes with cyclodextrins (3,4), nanocrystallization (5), salt formation (6), cocrystalization (7) and solid dispersion of drug in hydrophilic polymers (8). The later approach is getting more prevalent due to its broad usage, low cost and feasible industrial application.

Solid dispersion can be obtained when a poorly soluble drug is molecularly dispersed in hydrophilic polymer where the drug release profile is highly dependent on the type of interaction and molecular weight of the polymer (9-11). Amorphous drugs usually have higher water solubility over their crystalline forms, but they also have the tendency to recrystallize

during storage or in the supersaturation state. Polymers interacting favorably with the drug molecules have been shown to stabilize the amorphous drugs dispersed within their chains both in solution and in solid state. Due to their high molecular weight and slow relaxation, polymers reduce the diffusion of the drug molecules and prevent the ordered stacking required for their spontaneous crystallization. The “spring and parachute” effect is the main advantage of amorphous solid dispersions. Spring refers to the supersaturated state produced from the highly soluble amorphous drug, while “parachute” refers to the prolonged supersaturation. Spring is normally followed by a subsequent drop in concentration if drug crystallization occurs. In solid dispersions the polymer maintains the supersaturation by preventing drug crystallization (12). For oral rout of administration, spring and parachute effect ensures the stability of drug in the gastrointestinal fluid until it becomes totally absorbed (13).

The most two popular method for preparation of solid dispersions are the melting method and solvent method. In the melting method, the drug and polymer are melted together at a temperature above the melting point of both and then cooled to the ambient temperature. The basic requirement for this method is thermostability and miscibility in the molten form. The solvent method, on the other hand, is suitable for heat sensitive drugs and depends on dissolving both drug and polymer in an organic solvent and then evaporating the solvent at ambient temperature to produce a solid dispersion. The solvent must be able to dissolve both components, however, employing organic solvents in this method is considered the main disadvantage of this method.

Poly(2-ethyl-2-oxazoline), a nonionic polymer (Figure 1), has not been investigated before in the formation of solid dispersions; PEOX is soluble in water at temperature below its cloud point (T_c ~60 ^oC) and in many organic solvents. It is thermo-responsive, biocompatible and used in various biomedical applications, such as forming protein and small drug conjugates (14), drug loading and release from micellar drug carriers formed from PEOX block polymers (15).

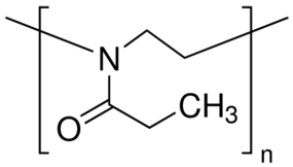


Figure 1: Chemical structure of PEOX

Glipizide (GPZ) is the selected model drug, it belongs to Class II according to the biopharmaceutical classification system (BCS) with very low, pH dependent water solubility (16) and good permeability. Glipizide is a second generation of sulfonylureas (Figure 2), a class of drug used to treat non-insulin dependent diabetes mellitus (NIDDM) or type 2 diabetes, which characterized in both tissue insulin resistance and insulin secretion deficiency (17).

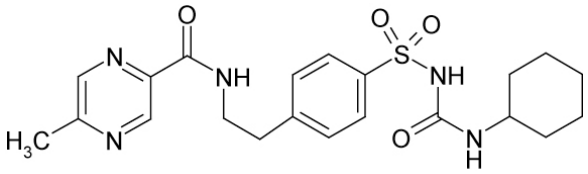


Figure 2: Chemical structure of Glipizide

To date, several attempts have been made to improve the solubility of glipizide, including preparation of solid dispersion with polyvinyl acetate phthalate, hydroxypropyl methylcellulose (18), poloxamer (19) and polyethylene glycol (20); formation of cyclodextrin complex (21-23), nanosuspension (24), microparticles (25) and co-solvent solubilization (26). In the present study, we aimed to introduce PEOX as a novel carrier for solid dispersion preparation and investigate glipizide-PEOX solid dispersion as a new model system and compare it with glipizide-PVP solid dispersion in terms of solubility and dissolution behavior.

2. Materials and methods

2.1. Materials

Glipizide and PEOX 50K were purchased from Sigma Aldrich (Germany). PVP M_w= 360000 was obtained from Scientific Polymer Products, INC (USA.) and PEOX 5K was obtained from Alfa Aesar (Germany). Methanol, chloroform, sodium hydroxide pellets, sodium chloride, sodium dihydrogen phosphate monohydrate and acetic acid were obtained from Merck (Germany). SIF® Powder instant biorelevant medium was purchased from Biorelevant.com (London, UK).

2.2. Preparation of solid dispersion and physical mixtures

Solid dispersion (SDs) of GPZ:polymers were prepared in different mass ratios by solvent evaporation method. Minimum volume of chloroform (0.8 mL) was used to dissolve 50 mg of glipizide with the corresponding amount of polymer. After complete dissolution, the solvent was removed by evaporating under hood at ambient temperature with continuous stirring, and resultant solid was kept under hood for 48-72 hours to make sure that no chloroform was remained. The obtained solid was then pulverized and homogenized with a mortar and pestle. The physical mixtures (PMs) were prepared by grinding the drug and polymer together using a mortar and pestle at the same mass ratio as the SDs.

2.3. Quantitative analysis

The amount of drug was determined in all prepared solid dispersions by UV-Visible spectroscopy. An appropriate amount of each SD was dissolved in DMSO and quantitative dilution was made with phosphate buffer at pH 7.4, absorbance was then measured at λ_{max} = 276 nm and glipizide amount were estimated from the constructed calibration curve.

2.4. Powder X-ray diffraction (PXRD)

XRD measurements were carried out using X-ray diffractometer (Bruker, Germany) operating at 20 kV and 5 mA with CuKα radiation, over the range of 2θ =2-40°.

2.5. Differential scanning calorimetry (DSC)

Thermal analysis of pure drug, polymers, PMs and SDs was performed on differential scanning calorimetry (TA Analysis). Samples (3-5 mg) were loaded into aluminum crucibles. The thermal behavior of each sample was investigated in a temperature range of 30-300 ˚C with 10˚C/min heating rate under a continuous flow of dry nitrogen at 50 mL/min.

2.6. Scanning electron microscopy (SEM)

The surface morphology of all substances was examined using a scanning electron microscope (Zeiss, Germany). Carbon double-sided adhesive tape was used to fix samples on the stage. Gold coating (~25 nm) was applied to make samples conductive and the samples were scanned at 10 – 25 kV.

2.7. Fourier transform infrared spectroscopy (FTIR)

Infrared spectra of studied solid dispersion were obtained using FTIR spectrometer (Nicolet iS10, Thermo Scientific, USA) over the wavenumber range of 4000-400 cm^{-1} with a resolution of 4 cm^{-1} and an accumulation of 64 scans.

2.8. Determination of solubility

The solubility of glipizide in its pure form, solid dispersion, and physical mixture with polymers was determined by shake flask method. The experiment conducted at a controlled temperature of 25 ˚C, by adding an excess amount equivalent to 5 mg glipizide to 2 mL of PBS (phosphate buffer saline) pH 7.4. Samples were shaken on a rotating shaker for 24 hours, then were left for rest vertically for 24 hours. The pH was double-checked before samples being centrifuged at 3500 rpm for 30 min. Aliquots of the supernatant fluid were diluted with phosphate buffer and the glipizide amount was determined by UV-Visible spectroscopy at 276 nm with respect to a calibration curve prepared at the same day of experiment. Experiments were performed in triplicate, and the solid state of the remaining solids was investigated using PXRD.

2.9. Dissolution test

Dissolution study was performed for pure glipizide, its solid dispersion and physical mixtures. Experiments were performed using Sirius GLpKa system equipped with UV fibre-optic spectroscopy probe. The dissolution procedure mentioned in a previous work was followed (27). Tablets of 3 mm diameter containing an equivalent to 5 mg of glipizide were created using a hydraulic press under a constant pressure of 0.1 ton. The tablets with their disc holders were held by an O-ring seal and placed in a glass vial. This insured a single side exposure to the dissolution medium with a total exposed surface area of about 0.07 cm^2. A volume of 1.5 mL of 0.125 M acetate-phosphate buffer pH 1.6 was introduced below the disc holder level, then the instrument added 13.5 mL of 0.15 M of KCl aqueous solution. Experiment then started, and the medium was stirred at a constant speed throughout the experiment time. After 30 minutes, 0.5 M KOH solution was automatically dispensed to adjust to the next pH. In all experiments, UV-Vis spectra were recorded at fixed intervals of 30 seconds.

The dissolution experiments were also performed in biorelevant media, FaSSIF (fasted state simulated intestinal fluid) which was prepared from SIF powder. FaSSIF medium is a phosphate buffer contains 3 mM of sodium taurocholate and 0.75 mM of lecithin adjusted to pH 6.5.

3. Results and Discussion

3.1. Preparation and characterization of solid dispersion

Since glipizide has a melting temperature of about 215 ˚C and such high temperatures may cause polymer decomposition, "solvent method" was chosen for the preparation of SDs instead of melting method. The differences in solvent polarities, boiling points, and thus the evaporation rate at room temperature, in addition to many complex factors will affect the interaction of drug with polymer. Thus, several solvents and solvent mixtures were tested including methanol, acetone, acetonitrile, chloroform, acetonitrile-methanol mixture, and acetone-methanol mixture. GPZ was found to be dissolved at room temperature only in acetone-methanol mixture and in chloroform. The obtained SDs prepared in acetone-methanol mixture and chloroform both were examined using PXRD. According to glipizide X-ray diffractogram (Figure 3a), distinctive peaks at numerous diffraction angles (2θ) have proved the crystalline nature of GPZ raw material. This crystallinity was observed in SDs prepared in acetone-methanol mixture with the studied polymers at different weight ratios (data not shown). In contrast, chloroform has produced a solid dispersion of almost vanished crystallinity with PEOX at 1:3 weight ratio, proved by quite wide peaks of very small intensities (Figure 3a); whereas a fully amorphous solid dispersion characterized by a broad hump centred at 2θ of about 22˚ was obtained with PVP at 1:2 weight ratio (Figure 3b). A moderate decrease in glipizide crystallinity was observed in SDs attained with PEOX at 1:2 and PVP at 1:1 ratio. Interestingly, a new glipizide polymorph was found in GPZ-PEOX 1:2, indicated by two new peaks appeared at 2θ of 14.9˚ and 16.4˚ instead of a single peak at 15.7˚ (Figure 3a). Glipizide crystal structure remained unchanged in its physical blend with PEOX and PVP, demonstrated by GPZ characteristic peaks observed in their diffractograms (Figure 3).

a b

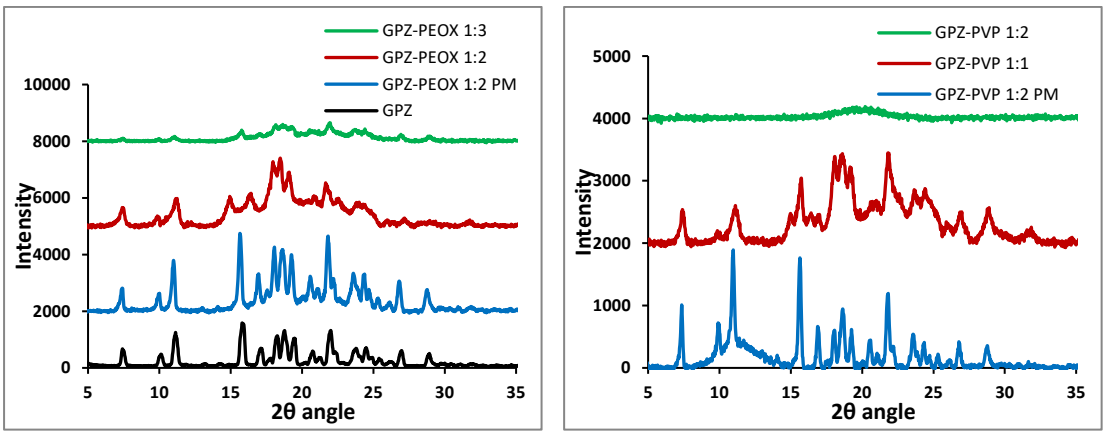


Figure 3: PXRD difractograms of glipizide solid dispersions prepared with PEOX and PVP compared to their physical mixture (PM) with GPZ. (PEOX and PVP has amorphous structure and thus were not included).

Differential scanning calorimetry experiments were also conducted to further investigate the thermal behavior of the prepared solid dispersions (Figure 4). The DSC thermogram of glipizide shows a single characteristic melting peak at 215 ˚C indicating its crystalline nature. The DSC curve of PEOX shows a broad endothermic peak at about 71 ˚C (Figure 4a) which corresponds

to its glass transition temperature (28). PVP thermogram (Figure 4b) shows a wide endothermic peak in the range 40-130 ˚C associated with the glass transition of PVP together with water loss from the polymer (29). The DSC thermograms of the GPZ-PEOX and GPZ-PVP physical mixtures showed the same broad endothermic peaks observed for the pure polymers in addition to reduced melting peaks corresponding to the crystalline drug at about 197 ˚C and 210˚C, for GPZ-PEOX and GPZ-PVP, respectively. On the contrary, GPZ endothermic peak disappeared or hardly detected in the solid dispersion thermograms, especially with GPZ-PEOX 1:3 and GPZ-PVP 1:2 indicating an amorphous nature of GPZ in these solid dispersions (Figure 4a,b).

a b

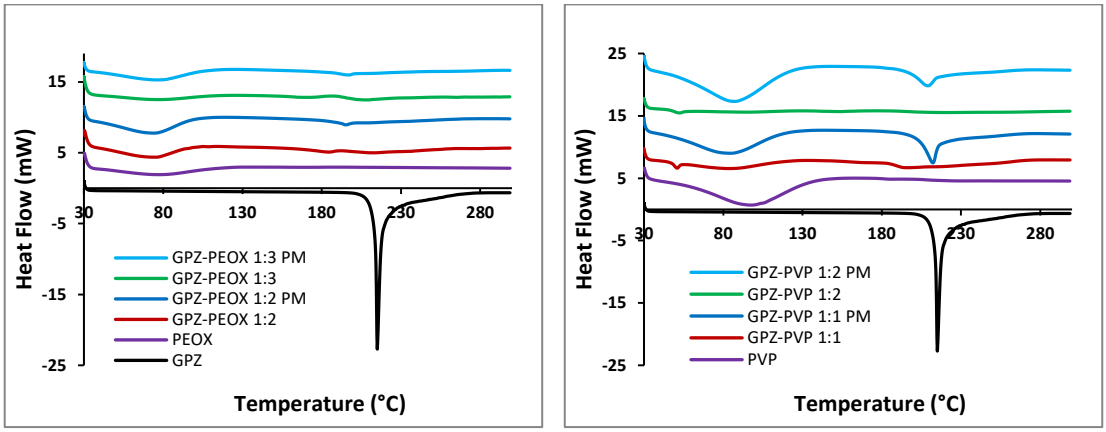
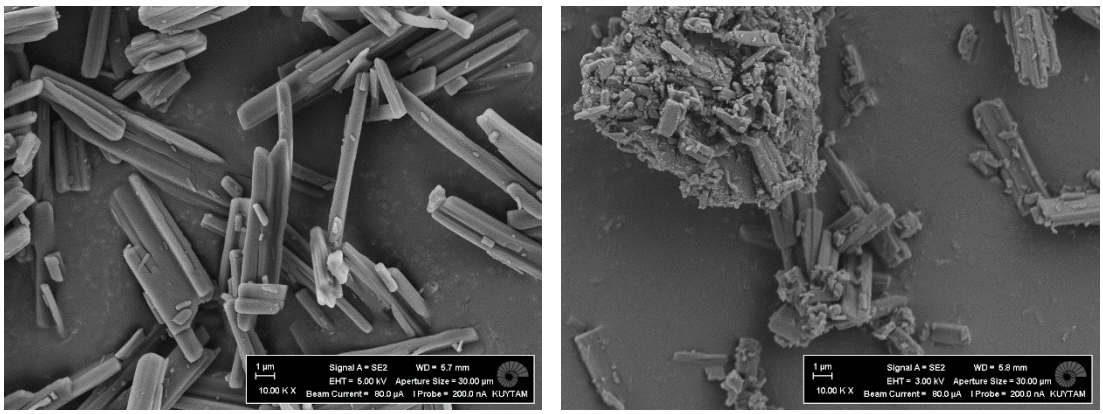


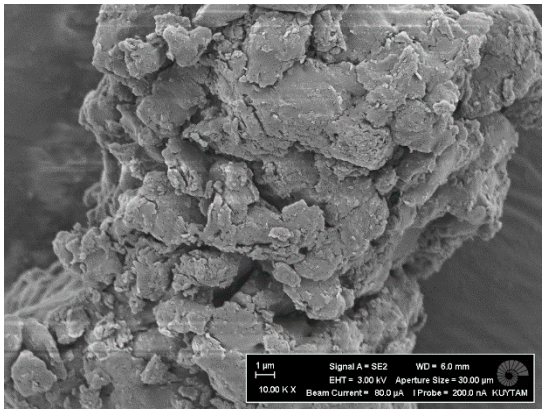
Figure 4: DSC curves of pure drug and its solid dispersions and physical mixtures (PM) prepared with PEOX and PVP.

Moreover, SEM study was performed to observe the morphology of the solid dispersion and compare it to the plain drug and the physical mixture of drug and polymers. As shown in Figure 5a, Glipizide found to have rectangular crystals of different sizes, which appear clearly in physical mixtures sticking to the polymer particles (Figure 5b,e). On the contrary, the morphology of solid dispersions was completely altered with no noticeable drug crystals found in none of the prepared solid dispersions (Figure 5c,d,f,g). The homogeneous dispersion of glipizide within polymer matrix was so clear in all studied solid dispersions.

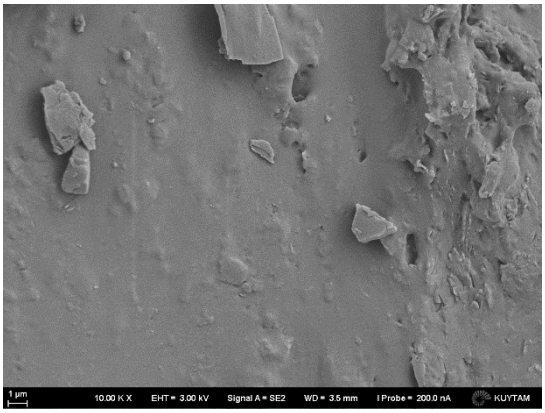
a: pure glipizide b: GPZ-PEOX 1:2 PM



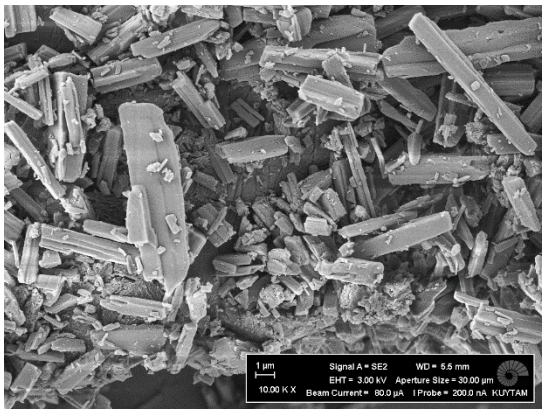
c: GPZ-PEOX 1:2 SD



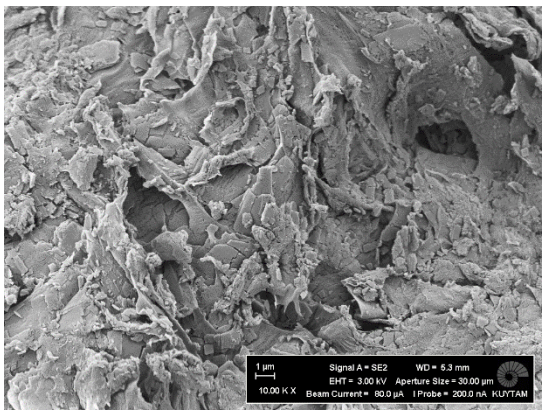
d: GPZ-PEOX 1:3 SD



e: GPZ-PVP 1:1 PM



f: GPZ-PVP 1:1 SD



g: GPZ-PVP 1:2 SD

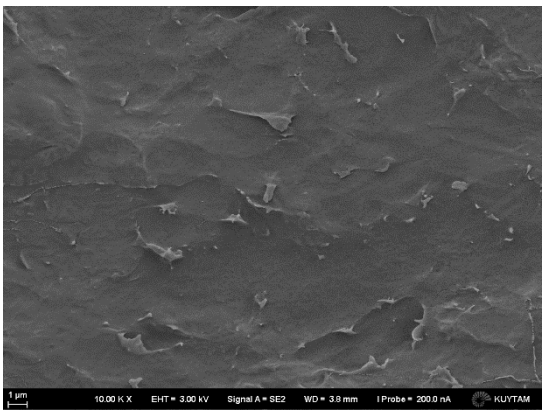


Figure 5: SEM images of pure drug and its solid dispersions and physical mixtures prepared with PEOX and PVP.

Infrared spectroscopy measurements were performed to investigate the possible interactions between the drug and studied polymers in the solid dispersion. Hydrogen bonding could be expected between the amine group of glipizide and carbonyl group of PEOX and PVP. Those interactions could be distinguished by peak broadening and absorption bands shifting of the interacting groups (30). The spectrum of glipizide showed characteristic peaks at 1688 cm^{-1} (secondary amide C=O stretch), 1649 cm^{-1} (C=N stretch), 1527 cm^{-1} (secondary amide N-H

bending), 2943 cm^{-1} and 2854 cm^{-1} (C-H stretch), 3324 cm^{-1} and 3249 cm^{-1} (N-H stretch). The characteristic peaks of the PEOX spectrum at 1629 cm^{-1}, 2976 cm^{-1} and 2938 cm^{-1} were attributed to (C=O stretch) and (C-H stretch), respectively. As shown in Figure 6, there was no shifting nor broadening in the present peaks, which means that no significant interaction takes place between glipizide and PEOX with regard to hydrogen bonding formation. The same result was found in GPZ-PVP solid dispersion (data not shown).

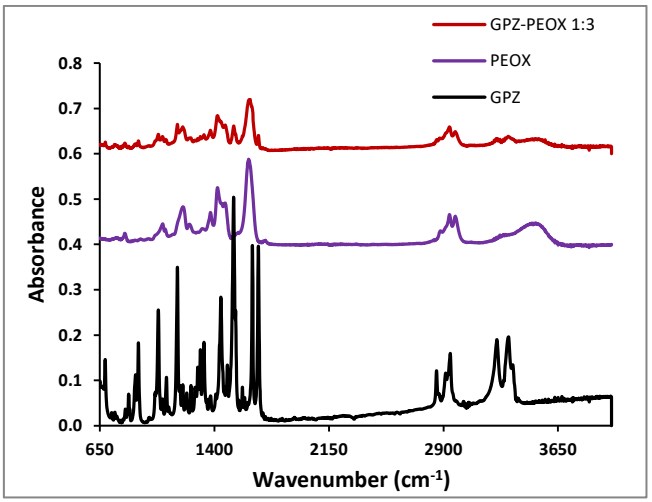


Figure 6: FTIR spectra of glipizide, PEOX and its SDs with drug.

3.2. Equilibrium solubility study

Shake flask method was applied to determine the equilibrium solubility of glipizide in solid dispersions and binary mixtures with the studied polymers. Solubility measurements were performed in PBS with pH 7.4 and ionic strength of 0.15M, from which the effect of medium pH is eliminated as glipizide will be ionized to the same extent in all samples; and thus, differences in solubility will be only attributed to the solid state of the drug. As shown in Table 1, there was no significant change observed in solubility between pure glipizide (95.3 μg/mL) and its physical mixtures with polymers, which can be explained by the proven crystalline nature of GPZ in its physical mixtures. The solubility obtained from GPZ-PEOX 1:3 solid dispersion was 239 μg/mL, about two times higher than that obtained from the physical mixture of drug with PEOX (130 μg/mL); whereas GPZ-PEOX 1:2 and GPZ-PVP 1:2 have shared the same value of solubility enhancement over their physical mixtures (Figure 7). In fact, GPZ-PVP 1:2 was expected to give the highest solubility value as the drug was completely amorphous, but it was not the case. This might be due to the transformation of the amorphous glipizide to the less soluble crystalline form during the 48 hours required for equilibrium. The XRD diffractograms obtained for the remaining solid collected after solubility measurements confirm this recrystallization (Figure 8). The diffractogram of GPZ-PVP 1:2 clearly shows a complete transformation of amorphous glipizide to its original crystalline state, whereas a different polymorph of less crystallinity was observed in the solids collected from GPZ-PEOX, as reveled from the wider peaks found at the diffraction angles (2θ) of 14.9° and 16.4° (figure 8). These findings were in accordance with the relative improvement in solubility found with

PEOX solid dispersions that could be due to its ability to prolong the time required for the crystalline conversion of GPZ, whereas PVP could not prevent this transformation.

Table 1. Solubility results of drug, solid dispersions and physical mixture with PEOX and PVP.

	Solubility ± SD (mg/mL) (*n*=3)	
	Solid dispersion	**Physical mixture**
GPZ	0.0953 ± 0.010	
GPZ-PEOX 1:2	0.210 ± 0.001	0.126 ± 0.001
GPZ-PEOX 1:3	0.239 ± 0.001	0.130 ± 0.009
GPZ-PVP 1:1	0.182 ± 0.008	0.111 ± 0.003
GPZ-PVP 1:2	0.170 ± 0.008	0.110 ± 0.003

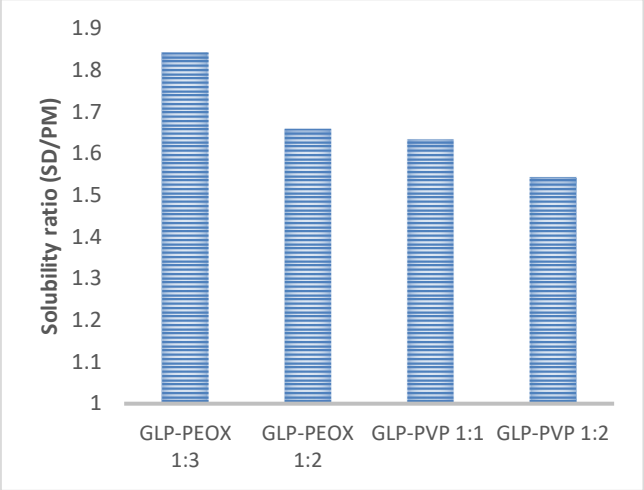


Figure 7: Enhancement ratio of GPZ solubility obtained from SDs and physical mixtures prepared using PEOX and PVP.

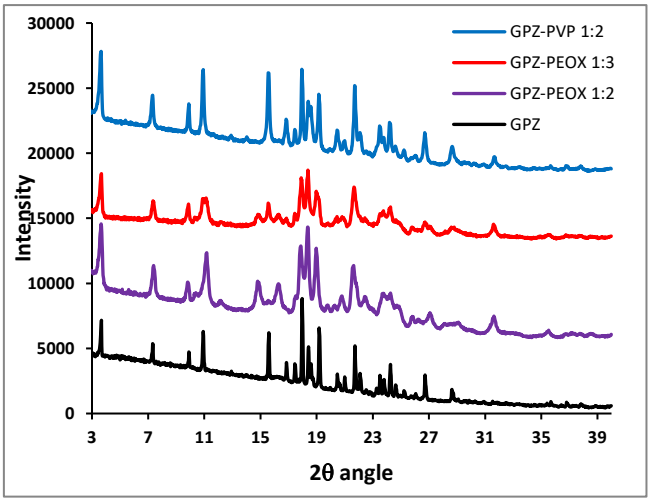


Figure 8: PXRD diffractograms obtained from the remaining solid after solubility measurements of the SDs and pure drug.

3.3. Dissolution study in buffer medium

In case of poorly soluble drugs, the rate of oral absorption is usually limited by the dissolution rate of drug in the gastrointestinal tract. However, the dissolution rate of a drug substance is highly related to its physical properties such as: crystallinity, amorphism, polymorphism, being a hydrate or solvate, the particle size and surface area. In addition, there are extrinsic factors affecting the dissolution rate such as stirring speed, temperature, medium viscosity, pH and the ionic strength in case of ionizable compounds. Noyes and Whitney have expressed the dissolution rate in the following equation:

$$\frac{dm}{dt} = \frac{A.D_{aq}(S-C)}{h} \qquad (1)$$

Where D_{aq} = diffusivity in aqueous solution (cm^2/min), the particles surface area A (cm^2), C = concentration of substance dissolved in the bulk medium at a particular time (mg/mL), S = equilibrium solubility at the pH of microenvironment close to the solid surface, and h = the thickness of diffusion layer (cm). By using pellets with a fixed surface area, A = 0.07 cm^2, we have studied the dissolution rate of the substance that is continuously released from the surface exposed to the dissolution media.

The intrinsic dissolution rate (IDR) is defined as the maximum dissolution rate divided by the surface area (mg/min/cm^2). According to this definition, IDR should be measured at sink state (when C ~ 0 the dissolution rate is at its maximum value), a state that refers to the infinite dilution of the drug in the solution, at least three to five times below the equilibrium solubility. Since we are employing only small volumes of dissolution media, 15 mL, the dissolution is considered to happen under non-sink condition. Thus, to obtain the IDR, calculation was made only at the beginning of the experiment when the amount of drug dissolved in the bulk solution is extremely low and sink condition is still in effect. The accumulated amount dissolved in the dissolution medium was plotted against time, and the IDR was calculated by dividing the slope of the regression line obtained with time points up to 5 min after deducting the lag time divided by the surface area of the disc (0.07 cm^2).

First, the dissolution test was performed in buffer at a full sequence of pHs (1.5, 4.0, 5.5, and 6.8) which are typically simulating the pH values of gastrointestinal tract (GIT), staying for 30 minutes at each pH value, so that drug dissolution is monitored over the entire pH range encountered in the GI tract.

As shown in figure 9, the dissolved amount of pure glipizide was negligible at all pH sectors. However, a significant difference in dissolution profile was observed with solid dispersions compared to the pure drug, starting from the acidic medium, pH 1.5, moving towards higher pH values. The dissolved amount of glipizide was found to increase as the pH increased from 1.5 to 6.8 where a jump in dissolved amount is clearly seen. This was an expected behavior since dissolution process is highly dependent on the ionization status of the drug. Glipizide pKa value was determined to be 5.23, accordingly, glipizide exists almost in its neutral form at the acidic pH. As pH goes higher to 6.8 the drug starts to ionize more and thus a higher amount of drug is expected to move into the solution (Figure 9). The bump shown in first acidic section with GPZ-PVP 1:2 corresponds to an instantaneous fast release of drug due to high solubility

of the amorphous drug followed by a nonstable supersaturation and drug precipitation to its solubility limit.

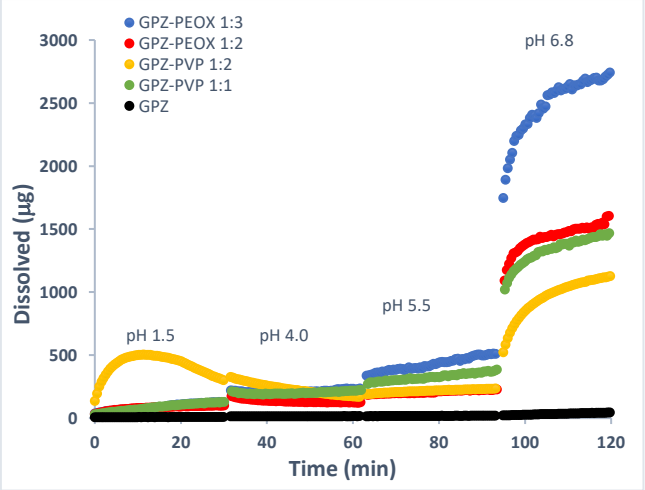


Figure 9: The dissolution profile of GPZ and its SDs with PEOX 1:2, PEOX 1:3, PVP 1:1 and PVP 1:2 at full sequence of pHs (1.5, 4.0, 5.5 and 6.8) each pH lasts for 30 minutes.

Since the major part of glipizide dissolution takes place at the intestinal pH value 6.8, we have focused on the dissolution rate at that pH value. The dissolution rate of the crystalline plain drug was too slow and did not exceed 1.3 µg/min with an IDR of about 19.3 µg/min/cm^2. As expected, the dissolution rate was improved dramatically with solid dispersions and has reached 85.3 µg/min and 124.0 µg/min with GPZ-PEOX 1:3 and GPZ-PVP 1:2, respectively, with a great enhancement over the dissolution rate of pure drug reached to 65 and 95 times with respect to the mentioned solid dispersions. The accumulated dissolved amount after 30 min was also improved with about 38 and 50-fold increasing in GPZ-PEOX 1:3 and GPZ-PVP 1:2, respectively, compared to the dissolved amount of crystalline drug. Inferior enhancement in the dissolution rate was achieved with GPZ-PEOX 1:2 and GPZ-PVP 1:1 as can be seen from table 2. This improvement in the dissolution behavior is mainly attributed to the solid state of glipizide in the solid dispersions, which was mostly amorphous. The polymer, on the other hand, helps to keep the dissolved drug from being precipitated to its original crystalline form. To prove this concept, experiments were performed on physical mixture of pure glipizide with polymers. As seen in table 2, the existence of polymer with crystalline glipizide had a negligible effect on the dissolution rate of glipizide.

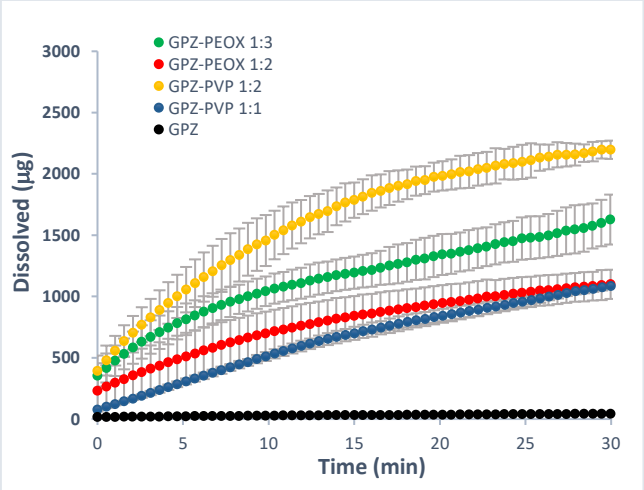


Figure 10: The dissolution profile of GPZ and its SDs with PEOX 1:2, PEOX 1:3, PVP 1:1 and PVP 1:2 at pH 6.8

Table 2. Dissolution results of glipizide compared to its solid dispersions and physical mixtures (PM) with PEOX and PVP at pH 6.8

	Dissolved amount ± SD (µg)	Absolute dissolution rate ± SD (µg/min)	IDR (µg/min/cm^2)
GPZ	42.7 ± 8.4	1.3 ± 0.2	19.3
GPZ-PEOX 1:2	1099.0 ± 119.1	52.9 ± 4.1	755.4
GPZ-PEOX 1:3	1627.3 ± 203.7	85.3 ± 3.0	1218.8
GPZ-PVP 1:1	1085.5 ± 19.4	44.8 ± 5.4	640.0
GPZ-PVP 1:2	2196.6 ± 74.7	124.0 ± 13.8	1771.2
GPZ-PEOX 1:2 PM*	83.4	3.2	45.1
GPZ-PEOX 1:3 PM*	87.5	2.1	30.1
GPZ-PVP 1:1 PM*	183.3	6.3	90.0
GPZ-PVP 1:2 PM*	192.3	4.5	64.1

* average of two replicates.

3.4. *Dissolution study in FaSSIF medium*

To further evaluate the dissolution improvement of GPZ solid dispersions, the effect of surfactants usually found in the intestinal fluids at the fasted state on the dissolution behavior was examined by performing the dissolution test in FaSSIF medium. Surfactants are known to promote wetting and facilitate the solubilization (31). However, the dissolution behavior of pure glipizide has not significantly changed in FaSSIF, as the dissolved amount after 15 min in FaSSIF was identical to that obtained in the normal buffer. Similarly, the dissolved amount from GPZ-PEOX 1:2 and GPZ-PVP 1:1 in FaSSIF was too close to that observed in the buffer (± 100 µg). Interestingly, a great improvement in the IDR was obtained with PEOX 1:3 solid dispersion in FaSSIF, whereas no significant difference was observed in IDR with GPZ-PVP 1:2 (Figure 11). However, the wetting effect of surfactant has accelerated the disintegration of GPZ-PEOX 1:3 disc, as a result, fine undissolved particles were noticed in the solution during the last part of the experiment. Consequently, the comparison of dissolved glipizide will be

assessed at the time point 15 min to ensure correct calculation of the amount exists in the solution. Beyond the expectations, the amount dissolved from GPZ-PVP 1:2 reached a plateau quickly after 15 min, with a value of 1143.4 µg compared to 2097.1 µg dissolved from GPZ-PEOX 1:3 after the same period. This might be due to fast transformation of the amorphous drug dispersed in PVP chains to the less soluble crystalline glipizide with help of surfactant. A similar observation was reported previously with celecoxib. Taylor *et al* have proved the impact of surfactants on the nucleation behavior of celecoxib and thus crystallization of its amorphous solid dispersion (32). These findings make PEOX the premier polymer to form solid dispersion and enhance the solubility and dissolution rate of glipizide in biorelevant media.

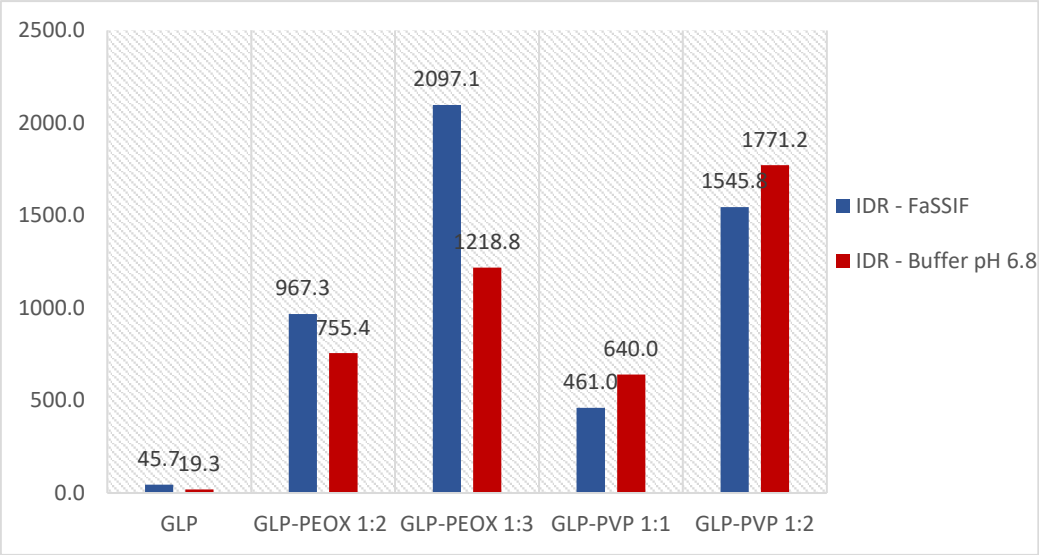


Figure 11: The intrinsic dissolution rate (IDR, µg/min/cm^2) of GPZ obtained from pure drug and its SDs with PEOX and PVP in buffer and FaSSIF medium.

3.5. *Effect of PEOX molecular weight on dissolution*

The previously discussed results were obtained with PEOX 5K. To investigate the effect of polymer molecular weight on the dissolution behavior of glipizide, PEOX 50K was also tested in terms of solubility and dissolution rate. The solubility of glipizide in PEOX solid dispersions was not affected by the molecular weight of PEOX, and thus solubility cannot interpret differences in the dissolution behavior of GPZ-PEOX 5K and 50K. Predictably, the IDR of glipizide with GPZ-PEOX 50K was significantly lower than that obtained with GPZ-PEOX 5K (Figure 12). This is in line with a previous work that proved the dependency of celecoxib dissolution rate on the molecular weight of PVP (11), and can be explained by increased viscosity at the tablet surface which results in less diffusion rate of glipizide and consequently lower dissolution rate.

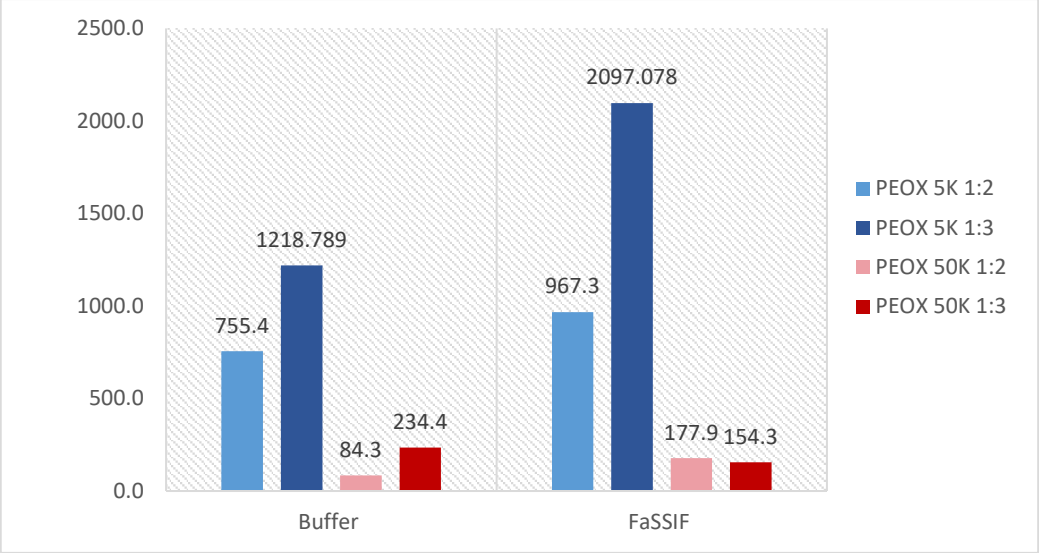


Figure 12: The IDR (μg/min/cm^2) obtained for GPZ-PEOX 5K and 50K in buffer and FaSSIF medium

4. Conclusion

In this work PEOX was employed for the first time to obtain solid dispersion with glipizide, a class II model drug, to enhance its solubility and dissolution rate. At the same time, solid dispersion with PVP was also prepared to compare the behavior of PEOX to well-known polymer in the pharmaceutical field. GPZ-PEOX solid dispersion with a slight crystallinity proved by XRD and DSC, was obtained with mass ratio 1:3 drug-polymer, whereas 1:2 mass ratio was enough to attain an amorphous solid dispersion with PVP. About 2.5 times enhancement in glipizide equilibrium solubility was obtained with PEOX 1:3 compared to about 1.8 times with PVP 1:2 with respect to the pure drug. Glipizide dissolution was greatly improved in GPZ-PEOX 1:3 solid dispersion compared to the pure drug, in buffer at pH 6.8 and in FaSSIF. In addition, two different molecular weights of PEOX were examined, and dissolution was significantly enhanced with PEOX 5K over PEOX 50K. These findings reflect a great biomedical improvement to the dissolution of glipizide in the body and subsequently to its bioavailability.

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