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Poly(2-Ethyl-2-Oxazoline) as an Alternative to Poly(Vinylpyrrolidone) in Solid Dispersions for Solubility and Dissolution Rate Enhancement of Drugs

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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.

Introduction

Preparation of solid dispersion (SD) is one of the prominent methods to enhance solubility, dissolution rate, and, thus, bioavailability of poorly soluble drugs. SD consists of at least 2 different components, mostly a hydrophilic polymer and a hydrophobic drug.[1] An estimated 40% of the Food and Drug Administration–approved drugs and about 90% of the developmental drugs includes poorly soluble molecules.[2] Drugs with low aqueous solubility and good permeability, or class II drugs according to the Biopharmaceutical Classification System, have dissolution-related bioavailability problems. The dissolution improvement of such drugs will directly reflect on their bioavailability.[3,4]

SD 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.[5-7] 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. Owing 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 SDs. “Spring” refers to the supersaturated state produced from the highly soluble amorphous drug, while “parachute” refers to the prolonged supersaturation. “Spring” is typically followed by a subsequent drop

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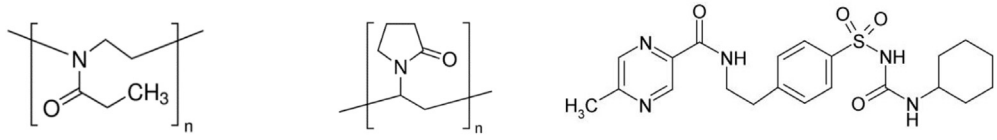

Figure 1. Chemical structure of (a) PEOX, (b) PVP, and (c) GPZ.

in drug concentration upon crystallization of the drug. In SDs, the polymer maintains the supersaturation by preventing drug crystallization.[8] For oral route of administration, "spring and parachute" effect ensures the stability of drug in the gastrointestinal (GI) fluid until it becomes totally absorbed.[9]

The 2 most popular methods for preparation of SDs 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 drugs and polymers in an organic solvent and then evaporating the solvent at ambient temperature to produce a SD. The solvent must be able to dissolve both components. However, using organic solvents is considered as the main disadvantage of this method.[10]

Many polymers have been used for the formation of amorphous SDs including cellulose derivatives such as hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, and synthetic polymers such as poly(vinylpyrrolidone) (PVP), poloxamer, and polyethylene glycol.[11] Poly(2-ethyl-2-oxazoline) (PEOX) is one of the biocompatible synthetic polymers and considered as pseudo polypeptide. It is nonionic polymer, soluble in water at temperature below its cloud point (T_c ~60°C) and in many organic solvents (Fig. 1a). PEOX has recently received significant attention for its biomedical applications such as forming protein and small drug conjugates[12] in addition to drug loading and release from micelles prepared from PEOX block polymers.[13] Good cytocompatibility has been proved *in vitro* for PEOX,[14,15] and no adverse effects were reported with respect to *in vivo* toxicity on rats after repeated intravenous injections of PEOX doses as high as 2 g/kg[16]; in addition, a very well oral toleration of PEOX with LD_{50} value exceeding 4 g/kg in rats was reported in an early cyclopedia.[17]

Despite similar hydrophilic properties and excellent water solubility of PEOX (Fig. 1a) and PVP (Fig. 1b), there are significant differences in the chain dynamics in aqueous solutions originating from their different chemical structures. Because the nitrogen end of the strong amide dipole is on the PEOX backbone, the PEOX backbone (−N−C−C−) is stiffer than the PVP backbone (−C−C−) resulting in more extended chains in aqueous solutions. The extended PEOX chains can get closer to each other, and the amide dipoles interact strongly. This strong interaction slows down the relaxation of the PEOX backbones.[18] These dynamic properties are expected to have a potential impact on its ability to stabilize the saturated solution induced after dissolution of amorphous drugs by inhibiting both the crystal nucleation and the crystal growth of the drug molecules.[19]

However, the exploration of PEOX's ability to maintain the supersaturation of a drug in comparison to the most chemically close polymer, PVP, has not been undertaken so far. This work reports the first investigation of SD of PEOX with a poorly soluble drug for which we anticipate better "parachute" effect based on the dynamic properties of PEOX chains in aqueous solutions as an alternative to the commonly used polymer, PVP, for the preparation of SDs.

Glipizide (GPZ), a Biopharmaceutical Classification System class II drug (low aqueous solubility and high permeability), was selected as a model drug in this study. GPZ is a second generation of sulfonylureas (Fig. 1c), a group of drugs used to treat noninsulin-dependent diabetes mellitus or type 2 diabetes, which is characterized in both tissue insulin resistance and insulin secretion deficiency. GPZ immediate-release tablets are available in 5 mg and 10 mg strengths, and the recommended starting dose is 5 mg, given 30 min before breakfast.[20] Several attempts have been made to improve the solubility of GPZ, including SD,[21-23] formation of cyclodextrin complex,[24-26] nanosuspension,[27] microparticles,[28] and cosolvent solubilization.[29]

In this study, GPZ-PEOX and GPZ-PVP SDs were prepared and thoroughly characterized using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and FTIR. The impact of PEOX and PVP on the crystallization behavior of GPZ and their ability to improve its supersaturation and dissolution profile in phosphate buffer and fasted state simulated intestinal fluid (FaSSIF) were investigated.

Materials and Methods

Materials

GPZ and PEOX-50K (M_w ~ 50,000 g/mol) were purchased from Sigma-Aldrich (Steinheim, Germany). PVP M_w = 360,000 g/mol was obtained from Scientific Polymer Products, and PEOX-5K (M_w ~ 5000 g/mol) was obtained from Alfa Aesar (Karlsruhe, Germany). Chloroform, sodium hydroxide, hydrochloric acid, acetic acid, sodium chloride, potassium chloride, and sodium dihydrogen phosphate monohydrate were obtained from Merck (Darmstadt, Germany) and used without further purification. SIF® Powder instant biorelevant medium was purchased from Biorelevant.com (London, UK).

Preparation of Solid Dispersion and Physical Mixtures

SDs of GPZ:polymer were prepared in different mass ratios by solvent evaporation method. Chloroform (0.8 mL) was used to dissolve 50 mg of GPZ with various amounts of polymer. After complete dissolution, the solvent was removed by evaporating under hood at ambient temperature with continuous stirring, and the resultant solid was kept under vacuum for 48-72 h to ensure no residual chloroform was present in SDs. The solids were then carefully collected by a spatula and well pulverized with a mortar and pestle until homogeneous powder was obtained. The particle size was less than 200 μm as determined by optical microscopy. 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.

Powder X-Ray Diffraction

PXRD measurements were carried out using X-ray diffractometer (Bruker, Bremen, Germany) operating at 20 kV and 5 mA with CuK_α radiation, over the range of $2\theta = 2°$-40°.