POLYMER STRUCTURE AND PROPERTY EFFECTS ON AMORPHOUS SOLID DISPERSIONS WITH HALOPERIDOL: POLY(N-VINYL PYRROLIDONE) AND POLY(2-OXAZOLINES) STUDIES

Xiaoning Shan, Adrian C. Williams, Vitaliy Khutoryanskiy

School of Pharmacy, University of Reading, Reading RG6 6AP, Berkshire.

Background: Amorphous solid dispersions are defined as physical mixtures of poorly-soluble drugs with some hydrophilic materials to improve the solubility and dissolution profiles of hydrophobic drugs. In some studies, the reduction of drug crystallinity in solid dispersions with various polymers has been explored and related to the chemical structure and properties of water-soluble polymers. However, systematic studies into the effects of polymer structures on their ability to reduce drug crystallinity are currently lacking because there are limited opportunities to vary polymer structures in a controlled manner; most studies use commercially available polymers. Poly(2-oxazolines) are an emerging class of polymers, currently attracting substantial interest due to a number of unique physicochemical properties and lack of toxicity. Recently, poly(2-oxazolines) were used to prepare solid dosage forms as individual polymers and also in combination with some other pharmaceutical excipients. Using different water-soluble poly(2-oxazolines) to design solid dispersions offers interesting and previously unexplored opportunities to understand the effect of polymer molecular structure and hydrophilic-hydrophobic balance on the crystallinity of a dispersed drug.

Methods: Poly(2-methyl-2-oxazoline) (PMOZ), poly(2-propyl-2-oxazoline) (PnPOZ) and poly(2-isopropyl-2-oxazoline) (PiPOZ) were synthesized by hydrolysis of 50 kDa poly(2-ethyl-2-oxazoline) (PEOZ) and subsequent reaction of the resulting poly(ethylene imine) with acetic, butyric and isobutyric anhydrides, respectively. These polymers were characterized by ^{1}H-NMR, FTIR spectroscopy, powder X-ray diffraction, and differential scanning calorimetry. The poly(2-oxazolines) as well as poly(N-vinyl pyrrolidone) (PVP) were used to prepare solid dispersions with haloperidol (HP), a model poorly soluble drug. Dispersions were investigated by powder X-ray diffractometry, differential scanning calorimetry and FTIR spectroscopy. Dissolution studies were carried out on HP and polymer-HP solid dispersions and analyzed by UV-Vis.

Results: Increasing the number of hydrophobic groups (-CH_2- and -CH_3) in the polymer resulted in greater inhibition of crystallinity of haloperidol in the order: PVP > PnPOZ=PEOZ > PMOZ. Interestingly, drug crystallization inhibition by PiPOZ was lower than with its isomeric PnPOZ because of the semi-crystalline nature of the former polymer. Crystallization inhibition was consistent with drug dissolution studies using these solid dispersions, with exception of PnPOZ, which exhibited lower critical solution temperature that affected the release of haloperidol.

Conclusions: Polymer structure and properties were found to influence the crystallinity of the drug and its release from solid dispersions. By synthesizing polymers with equivalent degrees of polymerization, the effects of polymer hydrophobic-hydrophilic properties, their semi-crystalline nature, hydrogen bonding strengths, and lower critical solution temperature (influencing polymer solubility) on the structure of solid dispersions and drug release have been demonstrated. Our studies show that, when selecting a carrier for solid dispersions, it is important to consider not only the hydrogen bonding capabilities of the polymer but also its broader properties including their semi-crystallinity, steric properties and lower critical solution temperatures.