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Dissolution performance of binary amorphous drug combinations—Impact of a second drug on the maximum achievable supersaturation

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ABSTRACT

An increased number of amorphous formulations of poorly water soluble drugs are being introduced into the market due to their higher transient solubility and thus faster absorption and higher bioavailability. While most amorphous drug products contain a single drug substance, there is a growing trend towards co-formulating compounds in the same dosage form to improve patient compliance. The purpose of the present work was to evaluate the dissolution behavior and maximum achievable solution concentrations of amorphous solid dispersions of co-formulated ritonavir and lopinavir, and to compare the results with individual amorphous solid dispersion formulations. Dispersions of ritonavir and lopinavir were prepared in polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose acetate succinate (HPMCAS) at a 20% (w/w) total drug loading, both alone and in combination, at three different lopinavir:ritonavir weight ratios. Amorphous films containing both drugs, but no polymer, were also prepared. The dissolution behavior of the dispersions and the amorphous films in non-sink conditions was evaluated, using ultracentrifugation to separate any colloidal material from molecularly dissolved drug. Nanoparticle tracking analysis was used to characterize colloidal material formed during the dissolution process. Results from the dissolution study revealed that, although supersaturated solutions resulted following dissolution, the maximum achievable concentration of each drug, when present in combination, was dramatically lower than when the individual dispersions were dissolved. The maximum achievable solution concentration for systems containing both drugs was found to decrease as the mole fraction of the drug in the amorphous phase decreased. The type of polymer used to formulate the dispersion also appeared to influence the dissolution behavior whereby the HPMCAS dispersions dissolved rapidly, resulting in the generation of a nanodroplets, while the PVP dispersions did not produce as many colloidal species. These results highlight the need to consider potential decreases in achievable supersaturation for formulations containing more than one amorphous compound.

1. Introduction

Amorphous formulations are increasingly generating interest among pharmaceutical scientists as a means of formulating poorly water soluble drugs, due to their ability to generate higher temporary drug concentrations upon dissolution relative to formulations containing the crystalline form (Newman et al., 2015). This increase in concentration can also result in a corresponding increase in the bioavailability (Shah et al., 2013). Several commercial amorphous solid dispersions have reached the patient in recent years including Sporanox®, Kaletra®, Incivek® and Belsomra®.

The main drawback of amorphous formulations is the possibility of crystallization of the amorphous solid into its crystalline counterpart during the lifetime of the product, driven by the higher free energy of the amorphous form (Shibata et al., 2014). This process can be often circumvented by blending the drug with polymers with high glass transition temperatures (T_g), which kinetically stabilize the system against crystallization through drug-polymer intermolecular interactions, and by decreasing molecular mobility (Prasad et al., 2014; Trasi and Taylor, 2012). The polymer type, amount, and presence of other excipients in the amorphous solid dispersion (ASD) formulation, as well as the dissolution media and conditions, all influence the dissolution performance of the amorphous formulation (Konno et al., 2008; Saeio et al., 2007; Shi et al., 2014). Some polymers dissolve very rapidly (resulting in fast release of the drug) while

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others have a slower dissolution rate (resulting in a correspondingly slower release of the drug) (Six et al., 2004). Under non-sink dissolution conditions, the drug concentration upon ASD dissolution typically exceeds the crystalline solubility, hence the solution is supersaturated. Some ASD formulations dissolve to yield sufficiently high concentrations that the amorphous solubility is exceeded, leading to liquid liquid phase separation (LLPS) and the formation of a disordered drug-rich colloidal phase (Aisha et al., 2012; Frank et al., 2012; Ilevbare and Taylor, 2013). Thus the amorphous solubility of the drug dictates the maximum free drug concentration that can be achieved using any formulation strategy (Raina et al., 2015, 2014). The free drug concentration is important since it not only determines the supersaturation, but it is this parameter that determines the rate of passive diffusion of the drug through the intestinal membrane. This can be evaluated *in vitro* by studying the drug membrane transport using a diffusion cell and an artificial membrane (Raina et al., 2014).

While most amorphous drug products contain a single drug substance, there is an increasing trend towards co-formulating compounds in the same dosage form to improve patient compliance. Some disease conditions such as human immunodeficiency virus (HIV) and hepatitis infections, cancer, and tuberculosis frequently require more than one drug in the treatment protocol. Hence two or more drugs may need to be administered in the same dosage form or dosed concurrently. Kaletra®, marketed by Abbvie, is one such formulation, whereby ritovanir and lopinavir are co-formulated in amorphous form for the treatment of HIV. When two or more drugs are administered in a single dosage form they are called fixed dose drug combinations (FDC). The main benefits of FDCs are increased compliance and convenience to the patient. From 1990 to 2013, the FDA has approved 131 FDC products, all consisting of active pharmaceuticals that have been previously approved (Kararli et al., 2014).

Combination products can be delivered in various formats such as a dosage form where both drugs are present in the same solid (such as hot melt extrudates) or formulated as capsules with multiparticulates where the two drugs are present in different particles, or as bilayer tablets. Since a majority of the approved FDC products are solid oral dosage forms, this can result in two or more drugs entering the solution phase within the gastrointestinal tract at the same time. The same scenario can also occur when different drug products are ingested at the same time for unrelated disease conditions. Physicochemical drug–drug interactions have not been widely explored but could potentially impact the dissolution rate and even solubility of some compounds, which could in turn impact absorption. In a previous study, it was found that the amorphous solubility of a compound, as determined by measuring the liquid liquid phase separation behavior, was depressed by the presence of a second drug and *vice versa* (Trasi and Taylor, 2015). The purpose of the present work was to extend these studies to evaluate the dissolution behavior and maximum achievable solution concentrations of amorphous solid dispersions of co-formulated ritonavir and lopinavir. It was hypothesized that co-formulation or co-dissolution would lead to a reduction in the maximum achievable solution concentrations for dissolution under non-sink conditions, due to a mutual reduction in the amorphous solubility of each component. The hypothesis was tested by determining the solution concentration-time profiles produced by dissolving individual ritonavir and lopinavir amorphous solid dispersions, as well as a ternary dispersion containing both drugs, under non-sink conditions. Nanoparticle tracking analysis was used to characterize colloidal material formed during the dissolution process. Results from the dissolution study revealed that, although supersaturated solutions resulted following dissolution, the maximum achievable concentration of each drug, when present in combination, was dramatically lower than when the individual dispersions were dissolved.

2. Material and methods

2.1. Materials

Ritonavir and lopinavir were purchased from Attix Pharmaceuticals (Montreal, Canada). HPMCAS-MF was a gift from Shin-Etsu Chemicals (Niigata, Japan). Poly(vinylpyrrolidone) K-29/32 (PVP, Mw ~30,000 g/mol) was obtained from BASF Chemicals (New Jersey, USA). The structures of the compounds used are shown in Fig. 1.

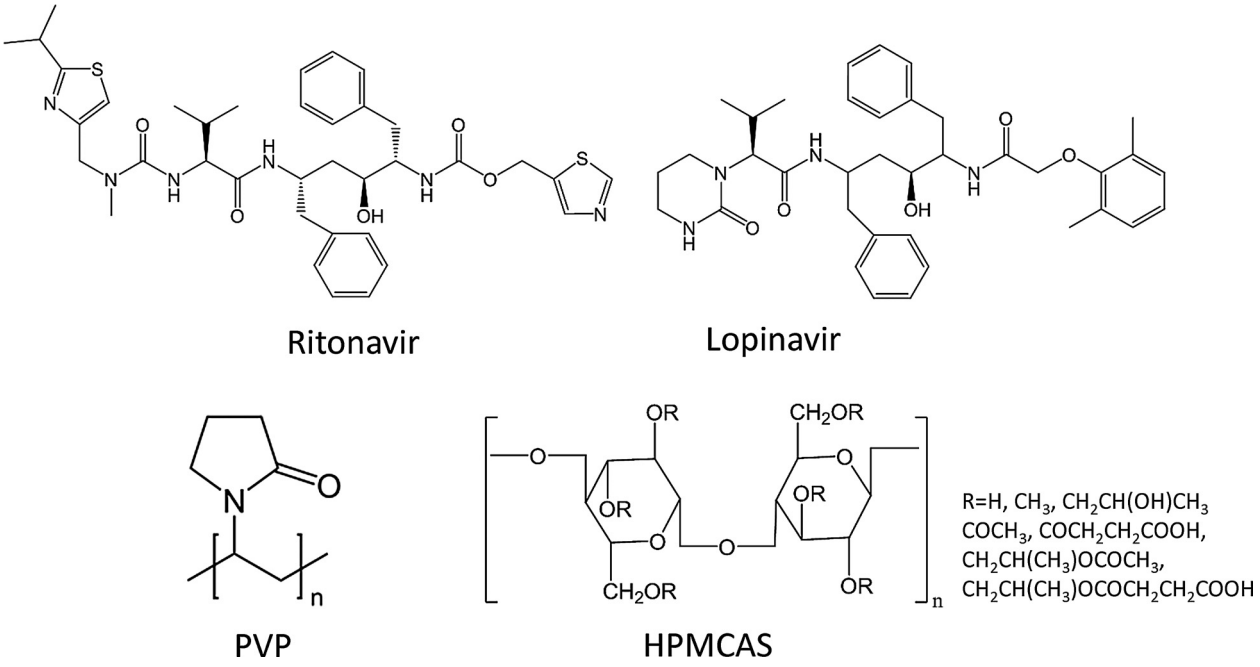

Fig. 1. Chemical structures of the drugs and the polymers used in this study.