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Supersaturating drug delivery systems: The potential of co-amorphous drug formulations

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ABSTRACT

Amorphous solid dispersions (ASDs) are probably the most common and important supersaturating drug delivery systems for the formulation of poorly water-soluble compounds. These delivery systems are able to achieve and maintain a sustained drug supersaturation which enables improvement of the bioavailability of poorly water-soluble drugs by increasing the driving force for drug absorption. However, ASDs often require a high weight percentage of carrier (usually a hydrophilic polymer) to ensure molecular mixing of the drug in the carrier and stabilization of the supersaturated state, often leading to high dosage volumes and thereby challenges in the formulation of the final dosage form. As a response to the shortcomings of the ASDs, the so-called co-amorphous formulations, which are amorphous combinations of two or more low molecular weight components, have emerged as an alternative formulation strategy for poorly-soluble drugs. While the current research on co-amorphous formulations is focused on preparation and characterization of these systems, more detailed research on their supersaturation and precipitation behavior and the effect of co-formers on nucleation and crystal growth inhibition is needed. The current status of this research is reviewed in this paper. Furthermore, the potential of novel preparation methods for co-amorphous systems with respect to the current preparation methods are discussed.

1. Introduction

Efficient drug discovery tools used in the pharmaceutical industry today produce numerous drug development candidates. These drug candidates however, often face serious challenges in their later development into medicines and subsequent market launch (Kalepu and Nekkanti, 2015). Oral formulations of these problematic drugs may fail to deliver the drug to the biological target in the body in a sufficient quantity due to poor biopharmaceutical properties, most often due to poor solubility and slow dissolution of the drug in biological fluids of the gastrointestinal tract (Williams et al., 2013). An estimated 40% of approved drugs and nearly 90% of drug candidates in the development pipeline are poorly water soluble molecules (Loftsson and Brewster, 2010).

Several established and emerging strategies exist to address the poor water solubility problem (Aungst, 2017; Williams et al., 2013). Among these, the so-called enabling, *i.e.* supersaturating drug delivery systems (SDDS) have attracted increased attention as an effective bioavailability enhancing approach (Fong et al., 2017; Taylor and Chang, 2016). These delivery systems are able to maintain an elevated and sustained level of drug supersaturation in the gastrointestinal fluids which enables improvement of the bioavailability of poorly water-soluble drugs by increasing the driving force for absorption (Sun and Lee, 2013). Amorphous solid dispersions (ASDs) are probably the most common and important SDDS for the formulation of poorly water-soluble drugs (He and Ho, 2015). In an ASD, the drug is ideally molecularly dispersed in

Abbreviations: AFM, atomic force microscopy; ASD, amorphous solid dispersion; AUC, area under curve; C, concentration; C_S, solubility of crystalline drug; DS, degree of supersaturation; DSC, differential scanning calorimetry; EGF, excipient gain factor; FaSSIF, fasted-state simulated intestinal fluid; FeSSIF, fed-state simulated intestinal fluid; FTIR, Fourier-transform infrared spectroscopy; HIF, human intestinal fluid; HPMC, hydroxypropylmethylcellulose; HPMCAS, hydroxypropylmethylcellulose acetate succinate; LLPS, liquid–liquid phase separation; Na–CMC, sodium carboxy methyl cellulose; PG, propylene glycol; PEG, polyethylene glycol; PO, propylene oxide; PVP, polyvinylpyrrolidone; SDDS, supersaturating drug delivery system; SEM, scanning electron microscopy; SI, sink index; SLS, sodium lauryl sulfate; T_g, glass transition temperature; V, volume; USP, Unites states pharmacopea; UV, ultraviolet

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an amorphous polymeric carrier to form a glass solution (Grohganz et al., 2014; Vasconcelos et al., 2016). Despite their obvious benefits, the number of commercially available ASDs is relatively low. ASDs often require a high weight percentage of carrier (polymer) to ensure molecular mixing of the drug in the carrier, leading to high dosage volumes and thereby problems in the formulation of the final dosage form (tablet or capsule). In addition, the common carrier polymers are often hygroscopic, which again leads to problems in manufacturing and stability (plasticization by absorbed moisture) (Janssens and van den Mooter, 2009; Srinarong et al., 2011; Vasconcelos et al., 2016).

As a response to the shortcomings of ASDs, the so-called co-amorphous formulations have emerged as alternative formulations for poorly-soluble drugs (Chieng et al., 2009; Dengale et al., 2016; Grohganz et al., 2014; Laitinen et al., 2013). These formulations are a combination of two or more low molecular weight components that form a homogeneous amorphous single-phase system. They are classified as a solid-dispersion subtype of glass solutions, with the other forms of glass solutions being polymer- or mesoporous silica-based (Dengale et al., 2016). Combinations of either an active molecule and an excipient (*e.g.* an amino acid) or two active drug compounds have been shown to enhance the dissolution properties of poorly-soluble drugs and stabilize the amorphous form of both components (Löbmann et al., 2013a; Korhonen et al., 2017). Our review article "Emerging trends in the stabilization of amorphous drugs", covering the literature before 2013, was the first review presenting achievements of the co-amorphous approach by that time, with future prospects also being discussed (Laitinen et al., 2013). In that review, the research in this field was anticipated to grow and this indeed has happened as reflected by the number of co-amorphous combinations reported today (~50 different drug-excipient combinations in various molar ratios, Korhonen et al., 2017) and review articles about this topic (five according to PubMed search: Chavan et al., 2016; Dengale et al., 2016; Grohganz et al., 2014; Korhonen et al., 2017; Laitinen et al., 2013). In a recent review by Chavan et al. (2016), formulation perspectives and different aspects in the development of co-amorphous formulations as drug products were reviewed. It was stated that while the current research on co-amorphous formulations is focused on preparation and characterization of amorphous systems, more detailed research on the formation mechanism of co-amorphous systems, stabilization and their dissolution benefits is needed. In particular, the precipitation behavior of co-amorphous systems in the solution state and the effect of co-formers on nucleation and crystal growth inhibition, required for a stabilized supersaturated system, need to be investigated. In addition, the need for novel preparation methods, especially those capable of production at an industrial scale, was highlighted.

In this review, our focus is on the evaluation of the supersaturation-ability of co-amorphous formulations. The general concepts and features of SDDS are presented first, after which the dissolution properties of co-amorphous systems and their dosage forms, such as tablets, are reviewed. Finally, we discuss the potential of novel preparation methods for co-amorphous systems with respect to the currently used preparation methods.

2. Supersaturating drug delivery systems

As a consequence of the lack of an ordered crystal lattice, amorphous solids possess enhanced apparent solubility and dissolution properties. This typically leads to drug concentrations in solution that are supersaturated with respect to the thermodynamic equilibrium solubility of the stable crystal form of the respective drug under those particular conditions (Fig. 1). This is referred to the spring effect of dissolution (Brouwers et al., 2009; Williams et al., 2013). This supersaturated state can provide a bioavailability advantage for the drug if it is maintained for a sufficiently long period in the fluids of the gastrointestinal tract. Nucleation and crystal growth of the drug may lead to fast precipitation, unless the rates of these processes are reduced by

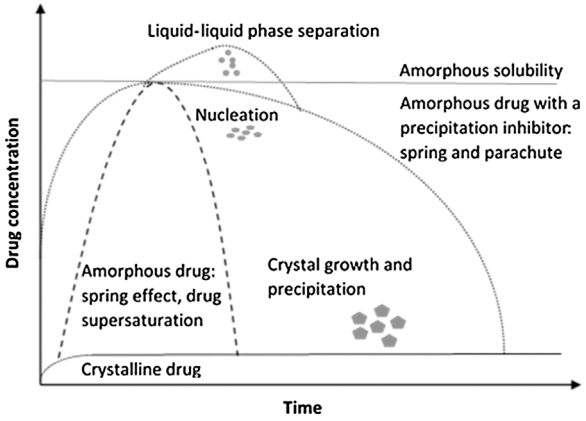

Fig. 1. Schematic showing a hypothetical dissolution profile of a crystalline drug and its amorphous counterpart with fast increase of drug concentration above the equilibrium solubility of the respective crystalline form (spring), and relatively fast formation of crystal nuclei, precipitation and drug concentrations reverting back to the level of crystalline solubility. For the spring and parachute case, a precipitation inhibitor effectively delays nucleation and crystal growth and allows the supersaturated state to prevail for longer. If the kinetics of crystallization are slow relative to the dissolution process, the drug concentration can exceed its amorphous solubility and undergo a liquid–liquid phase separation and subsequent crystallization.

precipitation inhibitors, such as polymers, or other substances (*e.g.* cyclodextrins) (Lainé et al., 2016; Palmelund et al., 2016; Williams et al., 2013). The stabilizing effect of precipitation inhibitors is called the parachute-effect (Fig. 1) (Brouwers et al., 2009; Williams et al., 2009). However, if the drug concentration exceeds the amorphous solubility in stabilized supersaturated conditions, *i.e.* the maximum achievable free drug concentration, and the kinetics of crystallization is slow relative to the dissolution process, a phenomenon called liquid–liquid phase separation (LLPS) may occur (Fig. 1). During LLPS, two phases (a water-rich and an amorphous drug-rich phase) existing in a metastable equilibrium are formed (Ilevbare et al., 2013a; Sun et al., 2016). The drug concentration of the water-rich phase corresponds to the amorphous solubility of the drug while the excess drug precipitates forming a dispersed, colloidal (nano-droplets) amorphous drug-rich phase (Indulkar et al., 2016; Sun et al., 2016). LLPS thus typically occurs under the following conditions: (i) in the presence of precipitation inhibitors, (ii) with weakly basic compounds when the pH of the solution is increased and (iii) upon dissolution of salts (Almeida e Sousa et al., 2016; Indulkar et al., 2015). After LLPS, the solution is still supersaturated with respect to the equilibrium solubility of the stable crystal form and crystallization will eventually occur at some time point (Fig. 1). Occurrence and duration of LLPS is dependent on formulation-related factors, such as drug loading and polymer type (precipitation inhibitor); intrinsic drug properties, such as amorphous-to-crystalline solubility ratio and crystallization tendency; particle size of the dispersion, and the medium composition and volume (Ilevbare et al., 2013a,b). The formation of a new phase following LLPS results in changes in the appearance and light scattering properties of the solutions (Taylor and Zhang, 2016). This can be utilized in characterization of the LLPS, *e.g.* detecting the light scattering that arises from the presence of a colloidal phase using ultraviolet (UV)/visible spectroscopy at a non-absorbing wavelength, fluorescence spectroscopy or dynamic light scattering. Specifically, the drug-rich phase can be characterized with cryo-transmission electron microscopy and scanning electron microscopy (SEM) (Ilevbare et al., 2013b; Taylor and Zhang, 2016). The glass transition temperature (T_g) of the amorphous material can be measured by differential scanning calorimetry (DSC) to determine if the drug-rich phase is a supercooled liquid or a glass at the temperature of interest (Ilevbare et al., 2013b). For example, the colloidal phase of ritonavir formed upon the dissolution of a ritonavir/PVP (polyvinylpyrrolidone) amorphous solid dispersion was examined by