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Recent advances in co-amorphous drug formulations☆

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ABSTRACT

Co-amorphous drug delivery systems have recently gained considerable interest in the pharmaceutical field because of their potential to improve oral bioavailability of poorly water-soluble drugs through drug dissolution enhancement as a result of the amorphous nature of the material. A co-amorphous system is characterized by the use of only low molecular weight components that are mixed into a homogeneous single-phase co-amorphous blend. The use of only low molecular weight co-formers makes this approach very attractive, as the amount of amorphous stabilizer can be significantly reduced compared with other amorphous stabilization techniques. Because of this, several research groups started to investigate the co-amorphous formulation approach, resulting in an increasing amount of scientific publications over the last few years. This study provides an overview of the co-amorphous field and its recent findings. In particular, we investigate co-amorphous formulations from the viewpoint of solid dispersions, describe their formation and mechanism of stabilization, study their impact on dissolution and *in vivo* performance and briefly outline the future potentials.

Contents

1. Introduction

The development of amorphous drug delivery systems has been widely investigated in academia and by the pharmaceutical industry to overcome the poor aqueous solubility of many drugs. Briefly, the same solid material can be crystalline or amorphous, where amorphous drugs exhibit a significantly higher solubility and dissolution rate than their crystalline counterpart [1]. The main drawback of using pure amorphous highly soluble drugs is their physical instability with respect to their inherent tendency to recrystallize into the poorly soluble crystalline form as they are thermodynamically unstable [2].

As only pure amorphous drugs often appear non-feasible in drug delivery systems, a major focus within amorphous research and development is the stability of the amorphous form through the use of excipients. Several approaches have been introduced in previous studies, including polymer-based glass solutions, mesoporous silica and co-amorphous formulations. Of them, the co-amorphous strategy has recently gained considerable interest in the pharmaceutical field as it provides opportunities to overcome shortcomings associated with the

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other two approaches. The objective of this study is to provide an overview on the state of the art of co-amorphous drug formulations.

2. What are co-amorphous formulations?

Polymer-based glass solutions, mesoporous silica and co-amorphous formulations all come under the term glass solutions, which itself is a subcategory of solid dispersions. The use of this expression is very inconsistent in the pharmaceutical field; therefore, this section provides a short guidance to the complex classification of solid dispersions.

The term solid dispersion was defined by Chiou and Riegelman [3] in 1971 as "a dispersion of one or more active ingredients in an inert carrier at the solid state prepared by the melting (fusion), solvent, or melting-solvent method." According to this definition, solid dispersions can be classified according to their number of solid-state phases and the physical state of these phases. As presented in Table 1, solid dispersions can be very diverse, including eutectic mixtures, solid solutions, glass solutions and glass suspensions. A more detailed description of the different types of solid dispersions is provided by Chiou and Riegelman [3] and Laitinen et al. [4]

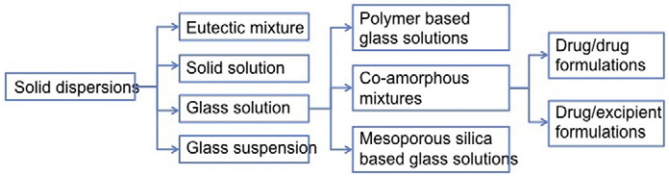
Glass solutions, that is, single amorphous phase systems, are often referred to as amorphous solid dispersions (ASD) and can further be subdivided according to the excipients that stabilize the amorphous drug. Vaka et al. differentiated them into polymeric and non-polymeric excipients, where the former can further be classified into ionic and non-ionic polymers [5]. The group of non-polymeric excipients can further be divided into mesoporous silica-based glass solutions and those containing only low molecular weight components, the so-called co-amorphous formulations (Scheme 1).

To date, polymer-based ASDs are by far the most investigated ASDs. Thus, the term solid dispersion is highly connected to the use of polymers in stabilizing amorphous drugs. This is misleading as solid dispersions are a rather large group of different types of solid mixtures (Table 1). Thus, for a clearer differentiation, ASDs with polymeric excipients are called polymer-based glass solutions in this study.

In polymer-based glass solutions, polymeric carriers are used to stabilize the amorphous drug and improve its solubility and dissolution rate [6]. In these systems, stabilization of the drug in its amorphous form is achieved by several factors. One key aspect is the solubility of the drug in the amorphous polymer [7,8]. Below its limit of solubility, the drug is molecularly dispersed in the amorphous polymer and stabilized by physical separation of the molecules between the polymer chains. Most polymeric carriers have a high glass transition temperature (Tg), and thus increase the Tg (while reducing the molecular mobility) of the drug in the glass solution compared to that in its pure amorphous form [9]. Furthermore, intermolecular interactions between the drug and functional groups of the polymer have been found to play a role in the stabilization mechanism [10]. However, limited drug solubility in large polymeric excipients often increases the dosage and does not necessarily make the formulation very stable against recrystallization [11–13]. Another drawback is the hygroscopic nature of many polymeric carriers, which results in absorption of moisture. The absorbed moisture acts as a plasticizer, thus reducing the Tg and increasing mobility, which in turn can result in phase separation and recrystallization [13]. Thus, despite an active research interest, polymer-based glass solutions have led to only a few marketed products [5,14].

Table 1
Classification of solid dispersions (reproduced from ref. [4]).

Solid dispersion	Number of phases	Physical state of phase(s)
Eutectic mixture	2	C/C
Solid solution	1	C
Glass solution	1	A
Glass suspension	2	A/A or A/C



Scheme 1. Classification of co-amorphous mixtures within glass solutions based on the choice of the stabilizing agent.

In mesoporous silica-based glass solutions, the drugs are amorphized by adsorption onto the surface of the silica particles, which consists of a matrix of pores with diameter between 2 and 50 nm [15]. On the one hand, stabilization of the amorphous drug is achieved through molecular interactions between the drug and the functional groups of the silica matrix [16,17]. On the other hand, crystallization is inhibited physically by the pore diameter of the materials, which may be smaller than the size of a crystal nucleus of the drug [18]. However, the main drawbacks of mesoporous silica-based glass solutions are their production, which predominantly involves the use of organic solvents for drug loading [18], and often a limited loading capacity of only 20%–30% [19].

The co-amorphous drug formulation approach is characterized by the combination of two or more low molecular weight components that form a homogeneous amorphous single-phase system [20,21]. In order to differentiate glass solutions comprising only small molecules from those with stabilizing polymers or mesoporous silica matrices, Chieng et al. coined the term 'co-amorphous' in 2009 [22]. Using this approach, it was proposed that the amount of stabilizing excipient (if used) can be drastically reduced due to the low molecular weight of the co-amorphous co-former. Two types of co-amorphous principles have been proposed so far, namely drug–drug combinations and drug–excipient mixtures [21]. In the first type, two pharmacologically relevant drugs intended for multidrug therapies are combined, where both drugs stabilize each other in the amorphous form. Thus, both drugs act as an active component and stabilizing excipient at the same time. As a result of the stable amorphous system, both of the poorly soluble drugs achieve a higher solubility and dissolution rate. In the second type, low molecular weight excipients such as amino acids are used to prepare stable and quick-dissolving co-amorphous drug–excipient blends.

3. Technologies for the preparation of co-amorphous systems

Several techniques for the production of amorphous drugs have been described in the literature. Depending on the mechanism involved, these techniques can be divided into two types as including thermodynamic and kinetic disordering processes [23,24]. The thermodynamic pathway has a thermodynamically stable non-crystalline form as a starting point, that is, the drug as a melt or in solution. In order to obtain the amorphous drug, the melt needs to be subsequently vitrified by rapid cooling, a process called quenching, or the drug needs to be precipitated from the solution, followed by solvent removal. The kinetic pathway involves direct solid-state conversion of the crystalline drug into its amorphous form. This can be achieved by continuously introducing crystal defects and disorders through shear forces, crushing and impact during a milling process [2,25]. In general, both mechanisms have been described for the preparation of amorphous blends [26].

The co-amorphous drug formulation approach is still in its early stage of development, hence majority of studies focused on the basic understanding of these systems using laboratory-scale preparative techniques such as quenching [11,27–37], solvent evaporation [38–47] and ball milling [28,43,47–57]. All of these techniques are attractive as they represent fast and easy ways of (co-)amorphization, and are ideal for screening purposes as only small sample sizes are required. In addition, quenching offers the possibility to quickly assess the critical