Advanced Drug Delivery Reviews 100 (2016) 85–101

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Amorphous solid dispersions: Rational selection of a manufacturing process☆

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ARTICLE INFO

Article history:
Received 15 October 2015
Received in revised form 21 December 2015
Accepted 19 January 2016
Available online 27 January 2016

Keywords:
Amorphous products
Solid dispersions
Solvent evaporation process
Melting process
Laboratorial scale
Industrial scale
Drug delivery

ABSTRACT

Amorphous products and particularly amorphous solid dispersions are currently one of the most exciting areas in the pharmaceutical field. This approach presents huge potential and advantageous features concerning the overall improvement of drug bioavailability.
Currently, different manufacturing processes are being developed to produce amorphous solid dispersions with suitable robustness and reproducibility, ranging from solvent evaporation to melting processes. In the present paper, laboratorial and industrial scale processes were reviewed, and guidelines for a rationale selection of manufacturing processes were proposed. This would ensure an adequate development (laboratorial scale) and production according to the good manufacturing practices (GMP) (industrial scale) of amorphous solid dispersions, with further implications on the process validations and drug development pipeline.
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Abbreviations: ASES, Aerosol solvent extraction system; BCS, Biopharmaceutical classification system; DMSO, Dimethyl sulfoxide; DSC, Differential Scanning Calorimetry; EMA, European Medicines Agency; EU, European Union;; FDA, Food and Drug Administration; GAS, Gaseous antisolvent; GMP, Good manufacturing practices; HME, Hot melt extrusion; HPC, hydroxypropylcellulose; HPMC, Hydroxypropyl methylcellulose; HPMCAS, Hydroxypropyl methylcellulose acetate succinate; ICH, International Conference Harmonization; N.A., Not available.; PCA, Particles by compressed antisolvent; PEG, Polyethyleneglycol; PEO, Polyethylene oxide; PGSS, Particles from gas saturated solutions; PVOH, Polyvinyl alcohol; PVP, Povidone; PVP-VA, Povidone-vinyl acetate; RESS, Rapid expansion of a supercritical solution; SAS, Supercritical antisolvent; SCFs, Supercritical fluids; SEDS, Solution enhanced dispersion by supercritical fluids; SEM, Scanning Electron Microscopy; SLS, Sodium Lauryl Sulphate; TPGS, d-alpha Tocopheryl Polyethylene Glycol 1000 Succinate; XRPD, X-ray Powder Diffraction; US, United States of America.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Amorphous pharmaceutical solids".

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http://dx.doi.org/10.1016/j.addr.2016.01.012
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1. Introduction

The majority of drugs molecules developed by the pharmaceutical industry during the last decades of the 20th century were classified according to the biopharmaceutical classification system (BCS) as class I drugs [1,2]. This means that most of the drugs presented high permeability and high solubility. If a molecule failed to meet these criteria, it would most probably be discarded from the industry development pipeline due to concerns about low bioavailability and/or troublesome formulation process [1].

In the 1990s, with the advent of Computer Science and its application to the pharmaceutical field, a new paradigm was raised in the Pharmaceutical Industry regarding drug candidate selection, introducing target-modulation candidate selection [3–5]. This new tool provided the Pharmaceutical Industry with the ability to produce more potent and specific drugs. However, these more potent drugs generally present poor water solubility, and consequently, fit BCS classes II or IV [6,7]. This change in drug candidate properties brought new challenges since most of the new molecules resulted in poor *in vivo* dissolution and consequently poor and/or highly variable bioavailability [8]. Additionally, most of them present small absorption windows, generally located in the upper small intestine [6,9]. In addition, and emphasizing the current challenges faced by the Pharmaceutical Industry, several of these drugs present poor permeability or are substrates of efflux transporters [10,11].

The presented challenges forced the Pharmaceutical Industry to pursuit approaches to improve dug solubility, exploring chemical, physical or formulation approaches [6]. Chemical approaches comprise molecular modification of drug structure, such as the inclusion of polar groups, resulting in the formation of new chemical entities that may present different potency and pharmacokinetics [12]. Other examples of chemical approaches include the formation of salts [12–18] and co-crystals [19], but their application is very restricted. Salts are only feasible for weak acid or basic drugs and co-crystals generally do not sufficiently enhance *in vivo* drug solubility. Additionally, both salts and co-crystals tend to precipitate *in vivo* [20,21]. The basic principle behind all physical approaches is that increasing the contact surface area enhances solubility [15]. This is accomplished by particle size reduction, resulting in crystals in the micro- or nano-size range [22,23]. The feasibility and simplicity of this approach is adequate in some cases. However, tends to be inadequate for drugs presenting water solubility below 50 μm/mL [22]. Formulation approaches consist in the production of liquid systems based on lipid vehicles and/or surfactants [24–26], or solid formulations that generally resembles in using carrier(s) [15]. From the later, amorphous solid dispersions depict one of the most interesting approaches, since drug presents a reduced particle size, improved wettability, high porosity and enhanced solubility [6]. A wide range of manufacturing processes to obtain amorphous products are currently available and will be further explored in this review, as well as, a rational approach for the selection of the manufacturing process.

2. Amorphous products

Amorphous products are pharmaceutical materials characterized by its solid-state nature and lack of distinct intermolecular arrangement, without crystalline structure and, consequently, with poor thermodynamically stability [6,7]. In a standard crystalline structure, the solubility/dissolution process firstly needs to break the crystal structure in order to occur molecular dissolution. In the case of amorphous products, the first step is abbreviated and lower energy is required to promote dissolution [7,27]. Amorphous materials also present broad background signal patterns in X-ray Powder Diffraction (XRPD) analysis, absence of enthalpy energy related to melting processes, and irregular surface structures, among other typical thermal, microscopic and spectroscopic properties, such as dynamic mechanical properties, particle porosity or Infra-red spectrum, respectively [28].

Amorphous products may be classified in two types: (i) molecularly pure and (ii) solid dispersions. Main features of different amorphous products are presented in Table 1.

2.1. Molecularly pure amorphous products

Molecularly pure amorphous products are only composed by the pure drug, which due to the specific manufacturing process results in amorphous products. Generally, processes to obtain molecularly pure amorphous products require a fast solvent evaporation process. It can be achieved by using rotary evaporator evaporation, spray-drying or freeze-drying. Fast removal of the solvent prevents the formation of crystal structures and, thus, random amorphous materials are formed [29]. Traditionally, pure amorphous products are obtained in a laboratorial scale and are undesirable because they are difficult to scale up due to their high instability, a consequence of their high-energy state [29]. Hence, pure amorphous products are rapidly converted into crystalline structures [29,30]. Zafirlukast (Accolate®, Astra Zeneca) is one of the very few commercially available molecularly pure amorphous drugs. This amorphous neutral drug is known to convert to a monohydrate form in the presence of water, with decreased bioavailability compared to the amorphous form [31,32]. Another example is cefuroxime axetil (Ceftin®, GlaxoSmithKline) [33,34], an amorphous drug that crystallizes in the presence of water [30].

2.2. Amorphous solid dispersions

Amorphous solid dispersions can be defined as molecular mixtures of poor water soluble drugs with hydrophilic carriers, responsible for modulate drug release profile, and characterized by the reduction of drug particle size to a molecular level solubilizing or co-dissolving the drug in the soluble carriers. Overall, they provide better wettability and dispersibility as the drug is in its supersaturated state due to forced solubilisation in the hydrophilic carriers [6,35–40]. Solid dispersions can be classified as first, second or third generation [6]. Briefly, first generation originates crystalline solid dispersions where a molecule of a crystalline carrier replaces one drug molecule in its crystalline structure. Second generation originates amorphous solid dispersions and uses polymeric carriers. The third generation comprises amorphous solid dispersion composed by a combination of amorphous carriers and most preferably a combination of amorphous carriers and surfactants, presenting enhanced drug release, long term stability and higher bioavailability [6].

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