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Spray drying formulation of amorphous solid dispersions☆

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ABSTRACT

Spray drying is a well-established manufacturing technique which can be used to formulate amorphous solid dispersions (ASDs) which is an effective strategy to deliver poorly water soluble drugs (PWSDs). However, the inherently complex nature of the spray drying process coupled with specific characteristics of ASDs makes it an interesting area to explore. Numerous diverse factors interact in an inter-dependent manner to determine the final product properties. This review discusses the basic background of ASDs, various formulation and process variables influencing the critical quality attributes (CQAs) of the ASDs and aspects of downstream processing. Also various aspects of spray drying such as instrumentation, thermodynamics, drying kinetics, particle formation process and scale-up challenges are included. Recent advances in the spray-based drying techniques are mentioned along with some future avenues where major research thrust is needed.

Contents

Abbreviations: AGU, anhydro-D-glucopyranose unit; API, active pharmaceutical ingredient; ASD, amorphous solid dispersion; ATR-FTIR, attenuated total reflectance Fourier transform infrared spectroscopy; BCS, Biopharmaceutics Classification System; CAP, cellulose acetate phthalate; CAAdP, cellulose acetate adipate propionate; CMC, carboxymethyl cellulose; CMCAB, carboxymethylcellulose acetate butyrate; Compritol 888 ATO, glyceryl dibehenate; CQA, critical quality attribute; DCM, dichloromethane; DMA- N, N-dimethylacrylamide; DOE, design of experiments; EC, ethylcellulose; EHEC, ethylhydroxyethyl cellulose; Gelucire, lauroyl polyoxyl-32 glyceride; GI, gastrointestinal; Inutec SP1, inulin lauryl carbamate; HEC, hydroxyethyl cellulose; HME, hot melt extrusion; HPC, hydroxypropyl cellulose; HPCDS, hypulcon pulse combustion dryer system; HPMC, hydroxypropyl methylcellulose; HPMC-AS, hydroxypropyl methylcellulose acetate succinate; HPMC-P, hydroxypropyl methylcellulose phthalate; Kollicoat IR, polyvinyl alcohol-polyethylene glycol graft copolymer; MC, methylcellulose; MCC, microcrystalline cellulose; Myrj 52, polyoxyl 40 stearate; NaCMC, sodium carboxymethyl cellulose; NIR, near infra-red; PAT, process analytical tool; PCSD, pulse combustion spray dryer; PDMA, poly-dimethylacrylamide; P(DMA-grad-MAG), poly(N,N,-dimethylacrylamide-grad-methacrylamido glucopyranose); PEG, polyethylene glycol; PEP, poly(ethylene-alt-propylene); PEP-PDMA, diblock copolymer of DMA and PEP; PHPMA, poly[N-(2-hydroxypropyl)methacrylate]; Poloxamer, poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol); PVP, poly(vinylpyrrolidone); PVP VA64, poly(1-vinylpyrrolidone-co-vinyl acetate); PWSD, poorly water soluble drug; QbD, quality by design; QTPP, quality target product profile; SCM, supercritical method; SLS, sodium lauryl sulphate; Soluplus, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer; Sucroester 15, sucrose monopalmitate; THF, tetrahydrofuran; T_g, glass transition temperature; Vitamin E TPGS, D-α-Tocopheryl polyethylene glycol 1000 succinate.

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1. Introduction

As we enter into the latter half of the current decade, the paradigm of solubility challenges faced by formulation scientists remains largely unchanged. Many of the drug molecules can be categorized under Biopharmaceutics classification system (BCS) class 2 or 4 (Fig. 1) [1]. The problem is a difficult one to overcome because of multifaceted factors driving it. The use of non-aqueous (or solvent mixture) based media for screening and purification purposes in high throughput screening tend to give hits with higher molecular weight and lipophilicity [2,3]. The quest for identification and targeting of kinase pathways, ion channels, nuclear receptors and protein–protein interactions with potent and selective agents is also motivating the choice towards lipophilic compounds [4,5]. The presence of many low solubility compounds in the drug discovery pipeline is not good for any stakeholder of the drug development process due to high fall-out rate and associated development costs. Apart from chemistry based strategies to improve solubility, onus is on formulation scientists to provide enabling drug delivery strategies for such candidates.

For a compound to reach to its target site, it should first be dissolved in the gastrointestinal (GI) fluid (in most of the cases) [7]. The rate at which this happens is given by the Nernst Brunner equation [8].

$$\frac{dC}{dt} = \frac{SD(C_s - C_t)}{Vh} \quad (1)$$

Here, dC/dt — dissolution rate of the drug, S — surface area of the dissolving surface, D — diffusion coefficient of the drug, C_s — saturation solubility, C_t — concentration at time t, V — volume of dissolution medium and h is the thickness of the diffusion layer surrounding the dissolving particle. Diffusion coefficients of the drug and dissolution medium volume are the factors which cannot be significantly modified in vivo. Thus, the enabling strategies focus on altering solubility and/or surface area.

Amorphization is an approach wherein the solid state form of the drug is changed from crystalline to amorphous. The rationale behind this approach can be understood by the following equation [9].

$$\Delta G_T^{\circ\,\text{Amorphous,Crystalline}} = -RT \ln\left(\frac{\sigma_T^{\text{Amorphous}}}{\sigma_T^{\text{Crystalline}}}\right). \quad (2)$$

Here, $\Delta G_T^{\circ\,\text{Amorphous,Crystalline}}$ is the energy difference between the crystalline and the amorphous state, R is the gas constant, T is the absolute temperature of concern and $\frac{\sigma_T^{\text{Amorphous}}}{\sigma_T^{\text{Crystalline}}}$ is the solubility ratio of the two forms. It follows from Eq. (2) that the amorphous form has a higher theoretical solubility as compared to the crystalline form due to its excess thermodynamic properties (Fig. 2). In simple terms, in the amorphous state there is no energy requirement to break the crystal lattice structure so that the drug molecules can interact with solvent molecules through intermolecular interactions and become solubilized. But the excess thermodynamic properties of amorphous forms also result in their tendency to crystallize thereby negating the solubility advantage. ASD can be considered as a potential solution to this issue.

2. Amorphous solid dispersions (ASDs)

ASDs consist of drug molecules dispersed in amorphous polymeric carriers. The drug stabilization is a consequence of factors such as intermolecular interactions, anti-plasticization effect exerted by the polymer, physical barriers to the crystallization process (local viscosity) and the reduction in chemical potential of the drug [11]. The role of the polymeric carrier is not limited to the stabilization but also mechanisms responsible for improved dissolution rate and absorption. Hydrophilic carriers such as poly(vinylpyrrolidone) (PVP), poly(1-vinylpyrrolidone-co-vinyl acetate) (PVP VA64) and hydroxypropyl methylcellulose (HPMC) are highly water-soluble and enhance water uptake into the solid dispersion matrix. Carriers also play a crucial role in maintaining supersaturation and precipitation inhibition in vivo which is widely accepted as critical in improving solubility in the GI tract [12]. Other mechanisms responsible for improved solubility are reduced particle size resulting in increased surface area [13,14]. In ideal case, i.e., molecular dispersion, the surface area available for dissolution is the maximum since the drug size is reduced to (almost) a single molecule. On several occasions this is not the case and the active pharmaceutical ingredient (API) distribution within the carrier matrix becomes inhomogeneous leading to drug-rich and polymer-rich regions. Since drug polymer miscibility is crucial for solid dispersion stabilization, phase separation can promote API crystallization [15–17]. Therefore, every effort should be made to produce miscible solid dispersion systems and protect them from drivers of phase separation such as high temperature, humidity and mechanical stress [13,18,19].

Amorphous to crystalline transition is a thermodynamically driven phenomenon due to lower free energy of the crystalline state and is bound to happen at a certain point of time (the time-scales involved can be really long in absence of external stimuli). But for crystalline to amorphous transition, external energy needs to be imparted to the system. Mechanical activation such as milling can generate amorphous forms [20]. Another way is to either dissolve in a solvent or melt the