Journal of Pharmaceutical Sciences xxx (2016) 1–18

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Review

Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs

Shrawan Baghel, Helen Cathcart, Niall J. O'Reilly*

Pharmaceutical and Molecular Biotechnology Research Centre (PMBRC), Waterford Institute of Technology, Waterford, Ireland

ARTICLE INFO

Article history:

Keywords:
solid dispersion
biopharmaceutics classification system
crystallization
dissolution
drug-excipient interaction
formulation
in silico modeling
oral drug delivery
polymeric drug delivery systems
supersaturation

ABSTRACT

Poor water solubility of many drugs has emerged as one of the major challenges in the pharmaceutical world. Polymer-based amorphous solid dispersions have been considered as the major advancement in overcoming limited aqueous solubility and oral absorption issues. The principle drawback of this approach is that they can lack necessary stability and revert to the crystalline form on storage. Significant upfront development is, therefore, required to generate stable amorphous formulations. A thorough understanding of the processes occurring at a molecular level is imperative for the rational design of amorphous solid dispersion products. This review attempts to address the critical molecular and thermodynamic aspects governing the physicochemical properties of such systems. A brief introduction to Biopharmaceutical Classification System, solid dispersions, glass transition, and solubility advantage of amorphous drugs is provided. The objective of this review is to weigh the current understanding of solid dispersion chemistry and to critically review the theoretical, technical, and molecular aspects of solid dispersions (amorphization and crystallization) and potential advantage of polymers (stabilization and solubilization) as inert, hydrophilic, pharmaceutical carrier matrices. In addition, different preformulation tools for the rational selection of polymers, state-of-the-art techniques for preparation and characterization of polymeric amorphous solid dispersions, and drug supersaturation in gastric media are also discussed.

Introduction

Oral drug delivery is the most commonly used route due to its ease of administration, high patient compliance, cost effectiveness, reduced sterility constraints, and flexibility of dosage form design.[1] When a drug is administered orally, it has to cross certain checkpoints (varies from drug to drug) within the biological system including dissolution in gastrointestinal fluids, permeation across the gut membrane, and first pass metabolism to finally reach its site of action via systemic circulation. Every checkpoint presents a potential bottleneck, of which dissolution in gastric fluid is of prime importance. Indeed, for most drugs, it is the main requirement to enable systemic circulation which determines the bioavailability. Taking into account the conceivable rate-constraining steps, Amidon et al. (1995) classified active pharmaceutical ingredients (APIs) into 4 groups on the basis of their solubility and permeability known as the Biopharmaceutical Classification System (BCS) as shown in Figure 1.[2] BCS involves mathematical analysis to experimentally determine solubility and permeability of drugs under specified conditions.[3] According to the US Food and Drug Administration, a drug is considered to be highly soluble when its highest clinical dose strength is soluble in ≤250 mL of aqueous media over a pH range of 1-7.5 at 37.5°C, and it is considered to be highly permeable if the absorption of an orally administered dose in humans is >90% when determined using mass balance or in comparison to an intravenous reference dose.[4] A biowaver (permission to skip *in vivo* bioequivalence studies) may be applied for certain drugs that pass specific *in vitro* solubility and permeability requirements. The following discussion is limited to BCS class II drugs (low solubility and high permeability).

* *Correspondence to:* Niall J. O'Reilly (Telephone: +353-51-306167; Fax: +353-51-302150).
E-mail address: noreilly@wit.ie (N.J. O'Reilly).

http://dx.doi.org/10.1016/j.xphs.2015.10.008
0022-3549/

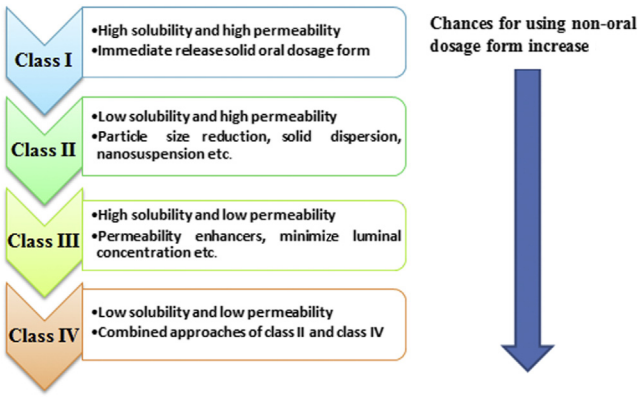

Figure 1. Biopharmaceutics classification system and formulation approaches for different classes of drugs.

Poor aqueous solubility is a matter of serious concern if the clinical dose of drug cannot dissolve in the available volume of gastrointestinal fluids. A well-known example is danazol which has an aqueous solubility of ~1 μg/mL at gastric pH and a dose of 200-600 mg/d.[5,6] To completely dissolve the lowest clinical dose of danazol at gastric pH, approximately 200 L of aqueous media would be required, which is obviously impossible *in vivo*. Furthermore, poorly water-soluble drugs will typically exhibit dissolution rate-limited absorption as they may pass their absorption site before complete dissolution. Therefore, there is great interest among formulation scientists to develop reliable, efficient, cost effective, and scalable methods to increase the aqueous solubility of BCS class II drugs. Common formulation strategies to tackle this challenge include pH adjustment, self-emulsifying drug delivery systems, particle size reduction, supercritical fluid (SCF) processing, inclusion complexes, cosolvency, micellar solubilization, hydrotrophy, solid dispersions, nanosuspensions, cocrystals, and nanocrystallization.[7-9] The choice of a particular method depends mainly on the physicochemical characteristics of drugs, carrier properties, and their expected use.[10]

The crystalline form of a drug offers the advantage of high purity and physical or chemical stability. However, the lattice energy barrier is a major constraint in the dissolution of crystalline drug molecules.[11] The amorphous state, on the other hand, exhibits a disordered structure in comparison to crystalline form and possesses higher free energy (thermodynamic driving force) leading to higher apparent water solubility, dissolution rate, and oral absorption.[12] Pure amorphous drugs are rarely used in formulation development because of their inherent physical or chemical instability. The solubility advantage of these systems can be retained by devising effective strategies to "kinetically stabilize" amorphous APIs. This has encouraged the development of amorphous solid dispersions (ASDs) products.

The concept of solid dispersions was first proposed by Sekiguchi and Obi in 1961.[13] On the basis of the distribution of the drug molecules in the carrier matrix, solid dispersions can be divided into 3 types: (1) Eutectic systems are mixtures of 2 compounds in a specific ratio and have a single melting point which is lower than the melting points of the individual components; (2) Solid solutions which are further divided into substitutional solid solutions (solute molecule replaces a solvent molecule), interstitial solid solutions (solute molecule is present in the interstices), and amorphous solid solutions having solute randomly distributed in an amorphous carriers; and (3) Microfine crystalline dispersions are crystalline dispersion of drugs in the carrier matrix.[14] The concept of solid dispersion has been successfully applied to oral formulations containing drugs with a high crystallization tendency (such as ivacaftor in Kalydeco) and also with a high drug loading (375 mg per tablet in Incivek; Table 1).[15] A wide range of pharmaceutical excipients such as carbohydrates, lipids, proteins, sugars (sucrose, xylitol), organic acids (succinic acid), surfactants (Spans®, Renex®), urea, pentaerythritol, and polymers have been investigated and used to kinetically stabilize the amorphous APIs.[16] Taking into consideration its most used form as shown in Table 1, solid dispersion can now be more narrowly defined as the dispersion of amorphous drug in a polymeric carrier matrix.[17] The following discussion is limited to a system that fits this more concise definition, that is, polymeric amorphous solid dispersions (PASDs). Information related to eutectic mixture or microfine crystalline dispersion can be found elsewhere.[18]

The main focus of the further discussion will be on how to engineer the thermodynamic properties of BCS class II drugs, different factors affecting the stability, and physicochemical properties of amorphous drug in solid dispersion; how different mechanisms are involved in stabilizing the amorphous form in polymer matrices; what should be considered for the rational selection of polymers and preparation techniques and latest characterization methods to develop a multidisciplinary approach toward the molecular level understanding of PASDs.

Amorphous State

To have a better understanding of the differences in the thermodynamic properties of crystalline and amorphous forms, consider a crystalline drug which, when heated, undergoes melting at temperature (T_m) as shown in Figure 2. On cooling the molten drug slowly, formation of an orderly system takes place as the molecules have sufficient time to move from their current location to a thermodynamically stable point on crystal lattice.[20] The molecules arrange themselves in a definite order, regenerating a crystalline structure. However, if the molten drug is cooled suddenly, then it may attain a supercooled liquid state (without undergoing crystallization), having a temperature lower than its T_m, which is in equilibrium with the molten drug.[21] On further cooling, the system remains in equilibrium until a glass transition temperature (T_g) is reached, below which it enters a nonequilibrium state (supercooled liquid state or lower viscosity rubbery state) and converts into the "frozen" glassy state of the drug.

A material in a glassy state behaves like a brittle solid, but without crystalline structure and having only short range order.[22] This transition is necessary because if the supercooled liquid state exists below the glass transition temperature, then a point comes whereby the crystals would have higher entropy compared to the supercooled liquid. The total entropy of the system would become negative before reaching absolute zero temperature, violating the third law of thermodynamics (entropy of perfect crystal is zero at 0 K).[23] The glass transition is a second order thermodynamic transition characterized by a step change in the heat capacity which is also associated with change in derivative of extensive thermodynamic properties such as volume, enthalpy, and entropy.[24] The amorphous state of a drug has a higher enthalpy, entropy, free energy, and volume as compared with the crystalline form which is responsible for its higher apparent solubility (as shown in Fig. 2). The relative increase in solubility of the amorphous form as compared with the crystalline form can be estimated by using the following equations (Eq. 1 and 2)[25]: