Structural and Dynamic Properties of Amorphous Solid Dispersions: The Role of Solid-State Nuclear Magnetic Resonance Spectroscopy and Relaxometry

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ABSTRACT: Amorphous solid dispersions (ASDs) are one of the frontier strategies to improve solubility and dissolution rate of poorly soluble drugs and hence tackling the growing challenges in oral bioavailability. Pharmaceutical performance, physicochemical stability, and downstream processability of ASD largely rely on the physical structure of the product. This necessitates in-depth characterization of ASD microstructure. Solid-state nuclear magnetic resonance (SS-NMR) techniques bear the ultimate analytical capabilities to provide the molecular level information on the dynamics and phase compositions of amorphous dispersions. SS-NMR spectroscopy/relaxometry, as a single and nondestructive technique, can reveal diverse and critical structural information of complex ASD formulations that are barely amenable from any other existing technique. The purpose of the current article is to review the recent most important studies on various sophisticated and information-rich one-dimensional and two-dimensional SS-NMR spectroscopy/relaxometry for the analysis of molecular mobility, miscibility, drug–carrier interactions, crystallinity, and crystallization in ASD. Some specific examples on microstructural elucidations of challenging ASD using multidimensional and multinuclear SS-NMR are presented. Additionally, some relevant examples on the utility of solution-NMR and NMR-imaging techniques for the investigation of the dissolution behavior of ASD are gathered. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2635–2662, 2014

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AMORPHOUS SOLID DISPERSION

The use of the amorphous state of poorly water-soluble active pharmaceutical ingredients (APIs) can provide remarkably higher aqueous solubility/dissolution rate compared with the crystalline counterpart.[1] Owing to the higher molecular mobility and energy state, this thermodynamic benefit of solubility is often negated by the inherent propensity of metastable amorphous form to undergo nucleation and crystal growth through solid-state or solution-mediated routes.[2,3] Therefore, the amorphous form of the pure API is seldom used in the drug product. Amorphous composite systems wherein amorphous API is dispersed, to the best, at molecular level in the hydrophilic polymer matrices constitutes amorphous solid dispersion (ASD).[4] Polymers used are generally amorphous and with high glass transition temperature (T_g). This leads to significant reduction in molecular mobility of API and hence stabilizes against crystallization. In addition, specific intermolecular interactions between API and polymer in ASD aid to inhibit nucleation and crystal growth. These benefits of ASD have been exploited as one of the key approaches of oral bioavailability improvement of poorly water soluble drugs.[5,6]

Despite distinct advantages, very few commercial formulations based on ASD have reached the market through more than four decades of academic and industrial research in this field.[6] The key hurdles associated with the development of ASD are poor understanding of the physical structures and the relationship of the latter with the pharmaceutical performance and physical stability of the product. ASD manufactured by industrial processes such as spray drying (SD), hot-melt extrusion (HME), milling, and so on generally consists of API dispersed in the polymer at the concentration level higher than solid-state solubility of API in the particular polymer.[7,8] As shown in Figure 1, the supersaturated ASD systems exhibit (partial) amorphous–amorphous demixing and/or nucleation and crystal growth of API upon exposure to elevated heat, humidity, or mechanical stress through downstream processing, *in vitro* or *in vivo* environment, or storage.[9–11] Generally, these stresses induce thermodynamic (binodal/spinodal) immiscibility, weakening of stabilizing interactions between API and carrier (e.g., ionic, H-bonding), enhanced molecular mobility (α, β processes), or combinations.[12] This eventually result into the loss of the claimed solubility advantages of these enabling formulations. It has been demonstrated through several researches that the physical stability of ASD can be markedly improved by generating molecularly mixed amorphous dispersions wherein API and polymer molecules are at the closest proximity and involved in stronger molecular interactions such as ionic, H-bonding, dipolar interactions, or electrostatic interactions.[13,14]

There are very few analytical techniques that offer spatial capability to probe the miscibility at molecular level in complex ASD.[5,15] This is one of the key hurdles in identifying, at nanoscopic level, whether API molecules are dispersed at molecular level (glass solution), present as amorphous clusters

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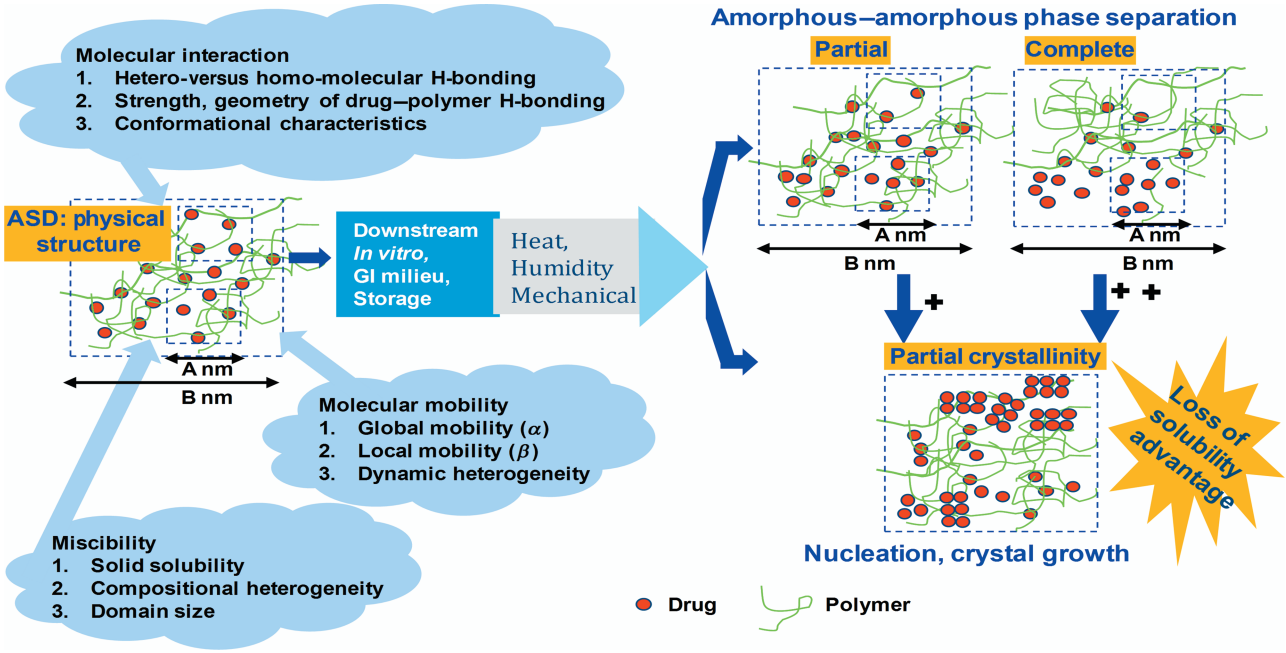

Figure 1. Schematic representation of physicochemical manifestations of ASD upon exposure to elevated heat, humidity, or mechanical stress (dashed box represents the scale of miscibility, A and B are hypothetical domain sizes A ≪ B).

(amorphous solid suspension) in carrier matrices or present spatial heterogeneity of composition.[16] For example, differential scanning calorimetry (DSC), the most commonly used technique for miscibility studies, can demonstrate immiscibility through multiple glass transitions only if the minimum size of phase-separated domains is approximately 30 nm or higher.[17–20] Likewise, often used vibrational spectroscopy can only provide qualitative information on the molecular interactions for most of the ASD.[21,22] Otherwise, it cannot provide direct quantitative information on the intermolecular proximity, molecular conformations, H-bonding geometries, and so on for most of the complex multicomponent systems. Furthermore, generally used techniques for molecular mobility studies such as dielectric spectroscopy (DES) lack the ability of speciation of the dynamic heterogeneity and probing the exact molecular origin of the primary and different secondary molecular relaxation processes.[23] Apart from confirming amorphicity, no direct and model-free information on the structural features can be extracted from the diffuse X-ray halo patterns conventionally obtained for amorphous powders.[17,20] Analytical limits of the existing tools often hinder the assessment on the level of disorder and heterogeneity at the nanoscopic or mesoscopic structure in partially crystalline systems. Moreover, subtle alterations on these structural attributes of ASD originated from different manufacturing processes, process parameters, or other formulation variables, for the same system can prove deleterious to the physical stability and other quality attributes of the final product.[24] Probing such delicate structural variation at molecular level needs strong analytical techniques.[4]

Solid-state nuclear magnetic resonance (SS-NMR) techniques can be broadly divided into three categories, namely, relaxometry, spectroscopy, and imaging. In this review, the use of the term "spectroscopy" will be used to the measurements intended to yield the spectral properties (experimental observables that can be determined from spectra), whereas "relaxometry" will be referred to all the techniques concerning the measurement of nuclear relaxation times. These techniques have been proven as one of the supreme tools for elucidating the physical structure of ASD with the maximum details among the existing techniques.[25,26] Expeditious application of SS-NMR techniques for the identification, characterization, and quantification of various solid forms of drug candidates (polymorphs, hydrate, solvate, salt, cocrystal, amorphous, mesomorphous, etc.) during drug development is eminent.[21,26–30] Beyond the applicability as "a solid-state-meter," SS-NMR techniques can yield comprehensive structural information of multicomponent amorphous systems ranging from molecular dynamics, associations, intra- and intermolecular interactions, molecular miscibility, crystallinity, and so on.[31,32] This analytical superiority has recently increased the utilization of SS-NMR in mechanistically understanding the structural features of a variety of complex drug delivery systems including ASD and in relating the same to the physical stability of the products.[33,34] Very recently, Skorupska et al.[35] published a compilation of case studies reflecting the application of SS-NMR for the characterization of a wide diversity of enabling drug delivery systems, namely, mesoporous silica-based systems, polymeric dispersions, cyclodextrin complexes, and so on. This review covers different SS-NMR methodologies with several case studies that provide readers with general insights on the utility of these techniques for the in-depth elucidation of the phase structures and dynamics of ASD.

SS-NMR: BASIC CONCEPTS

Nuclear magnetic resonance spectroscopy is a top-tier characterization tool in chemistry for structural elucidation, chemical identification, quantification of concentration/composition, and study of diverse molecular dynamics (molecular rotations,