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editorial

Amorphous Pharmaceutical Solids: Characterization, Stabilization, and Development of Marketable Formulations of Poorly Soluble Drugs with Improved Oral Absorption

In the past decade, there has been a high level of interest and investigation on the use of amorphous solids of small molecule active pharmaceutical ingredients (APIs) (MW $\lesssim$ 1000 Da) as attractive means of improving the oral bioavailability of poorly soluble drugs.

When prepared in their glassy, higher free-energy (amorphous) forms, many poorly soluble drugs exhibit significantly higher solubility and faster dissolution than their crystalline form. It has been widely demonstrated that when amorphous compounds are appropriately prepared and delivered orally, their advantage of enhanced dissolution rate and solubility can result in improved bioavailability when the solubility or dissolution rate of the drug in the gastrointestinal tract is the limiting step for absorption.

Given the inherent instability of amorphous solids with respect to crystallization, the current general strategy employs appropriate polymeric matrices to stabilize the amorphous state by inhibiting crystallization of the drug. A critically important factor toward the successful development of formulations containing amorphous drugs involves kinetic stabilization of the amorphous state of the drug below the glass transition temperature (T_g). The impact of different polymers on the crystallization tendency of amorphous APIs has been well demonstrated with a variety of pharmaceutically acceptable polymers including povidone, crospovidone, poloxamer, hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose (HPMC), polymethacrylates, and so forth.

The preparation of solid dispersions is now routinely achieved through the advances in the development of novel manufacturing process technologies, such as hot-melt extrusion, spray-drying, and freeze-drying technologies, that typically employ the poorly soluble API in admixture with polymeric materials as stabilizing agent. The successful application of hot-melt extrusion technology in the commercial scale production of drug products such as Kaletra tablet (a combo product containing ritonavir and lopinavir for AIDS therapy) is based on solid dispersion. This is a noteworthy and important breakthrough in that the oral bioavailability of both ritonavir and lopinavir are markedly improved by the novel formulation.

There is considerable interest among academic researchers and industrial scientists in characterizing the amorphous solid state and in maximizing the benefit of improved oral bioavailability of such systems for the delivery of poorly soluble drugs. The development and application of appropriate analytical methodologies are widely reported in the investigation of the properties of the amorphous solid state with the aim of experimentally elucidating the mechanism and crystallization kinetics, the nature of the drug−polymer interactions, and the mechanism(s) responsible for improving intestinal absorption of amorphous poorly soluble drugs.

Because amorphous drug solids are characterized by an absence of long-range order of the constituent molecules, the resulting solid dispersion systems usually favor heterogeneity. The structural heterogeneity of amorphous solids arises from nonuniformity in structure and possible changes in the composition of samples during preparation, subsequent handling, and/or storage. Obviously, both intra- and intermolecular interactions are present in these systems, and this results in a highly complex system for characterization. Given the diversity of the solid dispersions and their complexity, many analytical techniques are used to characterize the solid dispersion system. These methods include thermal analysis (e.g., DSC, modulated-DSC, TGA, microcalorimetric, etc.), thermodynamic, X-ray diffraction, spectroscopic (IR, Raman, solid state NMR), microscopic (optical microscopy, scanning electron microscopy), dissolution rate, and solubility methods. Usually, a combination of methods is required in order to obtain a complete characterization of the solid dispersion system.

In this special issue of *Molecular Pharmaceutics*, we have assembled manuscripts authored by a number of highly respected and experienced scientists, from both academia and the pharmaceutical industry with active programs dealing with poorly soluble drugs. The topics in this issue of *Molecular Pharmaceutics* do not cover all aspects of amorphous pharmaceutical solids; however, this collection provides an excellent broad assessment of the current knowledge base and the state-of-the-art techniques involved in the characterization of amorphous solids and solid dispersions and their application in drug product development.

The review article by Descamps and Willart describes possible routes for converting a crystalline compound into the amorphous state and the resulting nature of the amorphous state obtained by various nonconventional methods along with scientific insight based on nonequilibrium physics.

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The article by Yu et al. reports that crystal growth at the surface of amorphous nifedipine was at least 1 order of magnitude faster than that of the bulk nifedipine below the glass transition temperature T_g (42 °C). In addition, they reported a higher mobility for the surface molecules, and the resulting fast crystal growth was suppressed by an ultrathin surface coating with gold.

The crystallization kinetics of amorphous griseofulvin solid was studied by Schmitt et al. They found a poor correlation between the rate of crystallization and molecular mobility below the T_g value with diminishing activation energy for crystallization, suggesting a change in the mechanism of crystallization.

Differences in the intermolecular interactions in amorphous and crystalline phases in a series of structurally related compounds including celecoxib, valdecoxib, rofecoxib, and etoricoxib were revealed by Bansal et al. based on FTIR evaluation. This work suggests that molecular interactions can critically impact the physical stability and the stabilization strategy with amorphous pharmaceuticals.

Taylor et al. examined several salts of nicardipine and propranolol with respect to glass transition temperature, crystallization tendency, and moisture sorption behavior. They revealed the impact of different counterions on the properties of amorphous drug salts.

Precipitation of ritonavir from a supersaturated state due to pH adjustment in aqueous media was examined by Rodríguez-Hornedo and her colleagues. Examination by polarized optical microscopy, small-angle X-ray scattering, and synchrotron X-ray diffraction suggests the formation of lyotropic liquid crystalline ordered assemblies.

DiNunzio et al. reported the incorporation of amorphous itraconazole (ITZ) in dispersions made with cellulose acetate phthalate (CAP) and polyvinyl acetate phthalate (PVAP) and demonstrated that amorphous compositions of ITZ with these polymers provided improved bioavailability due to the increased period of time in the supersaturated state of ITZ in rat small intestine.

Kennedy et al. reported the investigation of the solid dispersion approach for a poorly soluble compound, AMG 517, using a spray-drying process. The solid dispersion containing AMG517 and HPMCAS showed good physical stability with greatly improved oral exposure in monkeys.

The article by Serajuddin and his colleagues describes their studies with solid dispersions of poorly soluble drugs prepared by a solvent evaporation process and by a hot melt extrusion process with addition of appropriate polymers and surfactants. Enhanced oral bioavailability and good physical stability was achieved with the solid dispersions.

It is noteworthy that the article by Friesen et al. describes the application of a number of solid dispersions of amorphous NCEs that were prepared with HPMCAS using a spray-drying process. In vitro characterization of these solid dispersions indicated that a supersaturated state of drug was generated and maintained in aqueous test media, and this resulted in significantly improved bioavailability. The general applicability of the HPMCAS based solid dispersions was discussed with a perspective on appropriate formulation strategies for low-solubility drugs with various physicochemical properties.

In conclusion, the articles in this special issue of *Molecular Pharmaceutics* illustrate that amorphous APIs and their solid dispersion systems differ significantly from the crystalline state at the molecular level. It is anticipated that these drug−drug and drug−polymer interactions are not only important in determining the properties of the pure amorphous phase, but they also provide an opportunity to develop optimally stabilized amorphous systems based on manipulating intra- and intermolecular interactions and, thereby, achieving improved exposure of water insoluble drugs.

The insight presented by the authors of these publications will hopefully inspire further research and development of amorphous pharmaceutical solids. With the collective effort of multidisciplinary experts, including chemists, engineers, and pharmaceutical scientists, it is now possible to fully take advantage of amorphous solid dispersions for enhancing oral bioavailability of poorly soluble drugs by overcoming technical challenges such as physical stability and large scale manufacturing process. Ultimately, this will lead to a widespread, and confident, use of amorphous pharmaceutical solids with more efficacious drug products available for patients.

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