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Cover Story

Drug release mechanisms from amorphous solid dispersions

Oral delivery of poorly water-soluble drugs has been a challenge, and various formulations have been developed to increase their bioavailability. Amorphous solid dispersions (ASDs) have been used as an important solubilization approach for the formulation of poorly soluble drugs for oral drug delivery. Traditionally, ASD formulations have been based on hydrophilic polymers that dissolve in dissolution medium rapidly to enhance the dissolution rate of amorphous pharmaceuticals. Naturally, commercially available ASD drug products have utilized exclusively water-soluble polymers. The dissolution profiles of these ASD systems under nonsink conditions have typically been characterized by an initial surge of supersaturation followed by a decline in drug concentration due to precipitation, and the extent of precipitation depends on the type of dissolved polymer carrier. Despite the apparent advantage of generating highly supersaturated drug solution, ASD formulations based on water-soluble polymers have not always been successful in achieving adequate oral bioavailability due to the precipitation of released drugs in the gastrointestinal tract which may not present a sink condition [1]. A study on the *in vitro-in vivo* relationship in the traditional ASD design approach has shown that fast dissolving supersaturating formulations actually lead to a suboptimal *in vivo* pharmacokinetic performance [2]. Many ASD formulations have demonstrated the improved *in vitro* dissolution behaviors and the concomitant enhancement of *in vivo* bioavailability. The mechanisms underpinning the observed kinetic solubility enhancement during ASD dissolution, however, are not well understood.

In this issue, the paper by Professor Ping Lee and his group uses a simple but clever experimental design to mechanistically differentiate the dissolution and supersaturation behaviors of ASDs in medium-soluble (i.e., hydrophilic) versus medium-insoluble (i.e., hydrophobic) polymer carriers under nonsink conditions [3]. The carriers used to prepare ASD systems included pH-dependent water-soluble polymers, such as enteric and reverse-enteric polymers. The pH-dependent polymers provide easy means of controlling the polymer solubility, and thus, the drug release mechanisms, by simply changing a solution pH. The study by the Lee group describes impact of the aqueous polymer solubility on the drug dissolution profiles, which in turn affect the rate of supersaturation generation and the evolution of supersaturation in ASD systems. The supersaturation profiles produced by ASDs based on medium-insoluble carriers are distinctively different from those based on conventional medium-soluble carriers. The ASDs based on medium-insoluble carriers lack the initial surge of supersaturation and are sustained for an extended period of time in the absence of any crystallization inhibitor. From the study on the supersaturation kinetics using various modes of concentration buildup, the Lee group made an important discovery that the rate of supersaturation generation is a critical factor impacting the overall kinetic solubility profiles [4]. In the present study, dissolution (or supersaturation generation) of ASDs based on medium-insoluble carriers is more gradual as drug release is controlled by a matrix diffusion-regulated mechanism that prevents the rapid buildup of supersaturation above the critical supersaturation. This avoids the typical "spring-and-parachute" release behavior characteristic to ASDs based on soluble carriers, and maintains an extended supersaturation.

The *in vivo* performance of ASD systems is already complicated enough by the intertwined kinetics of *in vivo* drug supersaturation (i.e., dissolution), precipitation and absorption. Without more mechanistic understanding of the release mechanisms from ASDs, however, it will be difficult to select an appropriate polymer carrier (or a combination of carriers) for optimized performance of ASD systems. This paper by the Lee team is important as it demonstrates that the characteristic sustained supersaturation behavior can be obtained in ASDs using medium-insoluble carriers. It also shows that the same ASDs can exhibit different supersaturation profiles when the same pH-dependent carrier polymers are rendered soluble or insoluble by changing the pH of the medium. The mechanistic insights gained here should open new avenues for improving the *in vivo* supersaturation behaviors of poorly water-soluble drugs through selecting appropriate medium-soluble and/or medium-insoluble ASD carriers. Many drug candidates for oral administration are poorly water-soluble and require suitable formulations for enhancing the solubility, and thus bioavailability. The study by the Lee group provides additional tools in formulation of poorly soluble drugs.

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