



Cover Story

Different phase behaviors of enzalutamide amorphous solid dispersions



Many existing and developmental drugs exhibit poor aqueous solubility necessitating the implementation of enabling formulations, some of which rely on solid state modification including amorphous solid dispersions (ASDs), co-crystals, and salts. In recent years, several new products based on ASD technology have reached patients and there has been an intense research effort to better understand under what circumstances these formulations improve bioavailability. ASDs are difficult to characterize *in vitro* because of their complex and time-dependent phase behavior. The dissolution behavior is particularly convoluted, whereby the supersaturated solutions that generate under non-sink conditions can exhibit a variety of phase transformations, including crystallization and glass liquid (or liquid liquid) phase separation with the formation of colloidal drug-rich species. The formation of colloidal species in supersaturated solution first attracted attention in the area of *in vitro* screening assays to determine biological activity of candidate drugs [1]. In this context, the phenomenon has been termed promiscuous aggregation and is considered an unwanted interference. More recently, it was found that certain ASD formulations dissolve and produce colloidal aggregates [2], with suggestions, based on *in vitro* studies, that these may actually be beneficial for oral drug delivery [3].

The paper by Professor Lynne Taylor and her coworkers in this issue [4] presents an approach to move toward testing the hypothesis that drug-rich aggregates improve bioavailability. By varying the drug loading and type of polymer used in the ASD, the phase behavior and types of species formed following dissolution could be modified. One ASD crystallized rapidly, showing the expected poor performance when dosed to rats. Two of the ASDs dissolved to produce solutions with a concentration equivalent to the amorphous solubility of the drug, and these supersaturated systems provided enhanced absorption. However, one dispersion dissolved to produce a supersaturated solution containing colloidal drug-rich species, and this system showed the highest area under the curve (AUC) and the maximum systemic concentration (C_{max}) following oral administration to rats. The amount of colloidal drug generated following ASD dissolution was quantitated using an innovative approach, whereby a fluorescence probe was used to discriminate between molecularly dissolved and aggregated drug. In-

terestingly, although dissolution testing of the various formulations did not correlate particularly well with the *in vivo* observations, flux measurements in a side-by-side diffusion cell were able to rank order the formulation performance.

Drug-rich colloidal species are unlikely to be a panacea to enhance the delivery of all poorly water-soluble compounds. However, these species could be beneficial for some drugs, namely where there is a need to increase biological exposure beyond that already achieved with an enabling formulation. These preliminary studies by Taylor and coworkers suggest that drug-rich aggregates with nano-dimension play an important role in improving oral absorption, and further studies are warranted for better understanding of their formation leading to beneficial results.

The study by the Taylor team is important, as it highlights the importance of understanding the mechanisms by which the pharmacokinetics of ASDs vary. The ability to discriminate between crystallization and glass liquid phase separation forming nanosized amorphous aggregates allows better formulations of biopharmaceutics classification system (BCS) Class II drugs (having high permeation and low solubility) such as enzalutamide. The study is also important, as the Taylor team sought out thorough understanding of the phase behavior of the amorphous formulations following dissolution to find a beneficial effect of nanosized amorphous drug aggregates as compared with supersaturated solutions. The drug aggregates in nano-dimension outperformed due to their ability to sustain the flux at a maximum value through rapid dissolution and replenishment of dissolved drug removed by absorption. Without such mechanistic understanding, this could easily lead to a false conclusion that nanoparticles can be absorbed from the gastrointestinal tract. The Taylor team shows how good research is done by focusing on their theoretical analysis to explain the data, instead of finding evidence to fit a preconceived conclusion.

References

- [1] S.L. McGovern, E. Caselli, N. Grigorieff, B.K. Shoichet, Aggregation: a common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening, *Biochemistry* 41 (2002) 8967–8967.
- [2] G.A. Ilevbare, L.S. Taylor, Liquid-Liquid Phase Separation in Highly Supersaturated Aqueous Solutions of Poorly Water-Soluble, Drugs: Implications for Solubility

- Enhancing Formulations, *Crys. Growth Des.* 13 (2013) 1497–1509.
- [3] A.S. Indulkar, Y. Gao, S.A. Raina, G.G.Z. Zhang, L.S. Taylor, Exploiting the Phenomenon of Liquid–Liquid Phase Separation for Enhanced and Sustained Membrane Transport of a Poorly Water-Soluble Drug, *Mol. Pharmaceutics* 13 (2016) 2059–2069.
- [4] V. Wilson, X. Lou, D.J. Osterling, D.F. Stolarik, G. Jenkins, W. Gao, G.G.Z. Zhang, L.S. Taylor, Relationship between amorphous solid dispersion in vivo absorption and in vitro dissolution: phase behavior during dissolution, speciation, and membrane mass transport, *J. Control. Release* (2018).

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