



Cover Story

Shape-dependent bioavailability of lovastatin nanocrystals



Development of oral formulations of poorly soluble drugs has been challenging, and various formulations have been made to improve their solubility, and thus, bioavailability. Reducing the particle size to increase the surface area has been one of the practical approaches. In particular, formulations of nanosized, crystalline drug particles (drug nanocrystals) have been successfully developed and marketed. Since the approval of the first nanocrystal formulation Gris-PEG® by the U.S. Food and Drug Administration (FDA) in 1975, only a small number of nanosuspension formulations have been introduced for clinical use [1,2].

One way to further improve the bioavailability of nanocrystal formulations is to examine different properties of nanocrystals, such as the particle shape. The cellular uptake of nano/micro particles has been shown to be shape-dependent [3,4]. In addition, the particle shape is known to affect the *in vivo* degradation, systemic absorption and excretion, especially lower liver distribution and urinal excretion [5]. Thus, understanding the impact of the particle shape on the bioavailability of nanocrystals may provide insights for further improvement of oral nanosuspension formulations.

The paper by Professor Qiang Fu and his coworkers in this issue investigated the impacts of three different particle shapes (rod-shaped, spherical, and flaky) on oral bioavailability of lovastatin nanocrystals [6]. They have found that the particle shape of nanocrystals has influences on the mucus permeation, cellular uptake, intracellular transport, and transmembrane transport. Of the three shapes tested, the rod-shaped lovastatin nanocrystal formulation has shown better mucus permeability and transepithelial transport. The rod-shaped, spherical, and flaky nanocrystals resulted in AUC_{0-24h} of 1632 ± 335 , 1138 ± 151 , and 905 ± 308 ng·min/mL, respectively, as compared with 1356 ± 308 ng·min/mL for the lovastatin solution formulation prepared with a 1:1 mixture of ethanol and Cremophor EL. The improved bioavailability of rod-shaped nanocrystal formulation over the ethanol/Cremophor formulation is impressive, considering the simplicity of nanocrystal formulation without undesirable excipients.

Currently, only a small number of studies are available on the impacts of particle shapes on the oral bioavailability of nanocrystals. The

research conducted by the Fu team at Shenyang Pharmaceutical University provides an understanding of the shape effects on the drug bioavailability. Although the improvement of the rod-shaped lovastatin nanocrystals is only by about 20% over the ethanol/Cremophor formulation, such improvement may be critical enough to make a poorly-soluble drug clinically effective. Further systematic studies are necessary on the shape-dependent dissolution kinetics of nanocrystals, permeation of the mucus layer and endothelial cells, and blood circulation. More important is to understand whether the shape effect is universal or drug-dependent. It is likely that drug nanocrystal formulations require the use of surfactants or polymeric excipients to stabilize the nanocrystals, and this, in turn, adds another variable in the formulation. Only after a mechanistic understanding, nanocrystal formulations can be developed for various poorly soluble drugs. The Fu team's work provides a rationale why we need to study the impact of the shape of drug nanocrystals.

References

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