



Cover Story

Transport of nanostructured lipid carriers across the intestinal barrier

Currently, there are a wide variety of nanocarriers that are used and investigated to enhance the solubility and the oral bioavailability of poorly soluble drugs. Of these, solid lipid nanoparticles (SLNs) present many advantages compared with other colloidal systems. They can be prepared without an organic solvent and their production can easily be scaled up. Toxicity problems can be minimized by the use of biocompatible/physiological lipids. Nanostructured lipid carriers (NLCs), the second generation of SLNs, have a solid matrix blended with a liquid lipid to form a nanosized unstructured matrix. Many NLCs have shown higher drug loading capacity and reduced drug expulsion. Oral absorption and bioavailability of several drugs (e.g., curcumin, simvastatin and vinpocetine) were enhanced after formulating into NLCs for oral administration.

Before reaching the bloodstream NLCs have to cross the gastrointestinal (GI) fluid, the mucus layer, and the intestinal epithelium. Little work has been done to understand the fate of NLCs in the GI tract and in the body. In particular, the mechanisms by which NLCs enhance oral absorption have not been clearly understood. In this issue, Professor Véronique Pr at and her team present the underlying mechanisms of the enhanced intestinal transport of NLCs loaded with a poorly soluble drug [1]. They used *in vitro* models mimicking the intestinal barrier. In the study they chose as a model drug saquinavir (SQV), a class IV drug in the Biopharmaceutics Classification System and a P-glycoprotein (P-gp) substrate. The transport of SQV across Caco-2 cell monolayers was enhanced by up to 3.5-fold by NLCs as compared with SQV suspension. The transport was influenced by the size of the NLCs and the amount of surfactant used for their formulation. Using a co-culture of Caco-2 cells and Raji cells to mimic the follicle-associated epithelium of the Peyer's patches, Professor V eronique Pr at and her group showed that, in contrast to polymeric nanoparticles and drug suspension, the transport of SQV-loaded NLCs was not enhanced by the M cells.

Professor V eronique Pr at's team studied the transport mechanisms of SQV across Caco-2 cell monolayers by comparing three different NLC formulations. Specific inhibition of different endocytosis pathways indicated that one formulation was transported by both caveolae- and clathrin-mediated transcytosis, while the other NLC formulations used only caveolae-mediated transcytosis. This formulation circumvented the P-gp efflux. Thus, it appears that the physicochemical parameters of the NLC formulation alter the transcytosis mechanism of the nanoparticles and modify the P-gp drug efflux. By

studying the mechanisms of transport of different NLCs, Professor V eronique Pr at and her colleagues demonstrated that the size and amount of surfactant in the NLCs influenced SQV permeability, the transcytosis pathway and the efflux of SQV by P-gp. These data again highlight the importance of not only the composition of the nanocarriers designed for oral drug delivery but also their physicochemical properties [2,3], in particular, their size and surface properties. The data also suggest that the formulation of NLCs should be optimized by investigating both the pharmaceutical properties (e.g., drug solubility and NLC stability during storage) and the biopharmaceutical properties (e.g., stability in the gastrointestinal tract, mechanisms of transepithelial transport, effect on efflux pumps).

There is no doubt that more in-depth mechanistic studies are necessary to unravel the mechanisms of transport of the orally delivered nanocarriers, including NLCs. Furthermore, the *in vitro* studies need to be validated in the *in vivo* animal studies, and ultimately in human studies. Nevertheless, the findings in this study clearly demonstrate that NLCs can be used for oral delivery of poorly water-soluble P-gp substrates. This is a very promising first step towards the right direction of translating the still illusive nanotechnology to clinically useful formulations.

References

- [1] A. Beloqui, M.A. Solin s, A.R. Gasc n, A. Del Pozo-Rodr guez, A. des Rieux, V. Pr at, Mechanism of transport of saquinavir-loaded nanostructured lipid carriers across the intestinal barrier, *J. Control. Release* 166 (2013) 115–123.
- [2] L. Plapied, N. Duhem, A. des Rieux, V. Pr at, Fate of polymeric nanocarriers for oral drug delivery, *Curr. Opin. Colloid Interface Sci.* 16 (2011) 228–237.
- [3] A. des Rieux, V. Fievez, M. Garinot, Y.J. Schneider, V. Pr at, Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach, *J. Control. Release* 116 (2006) 1–27.

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