Diving into the mucus – PEG micelles for oral delivery

Swallowing a pill of paracetamol for headache is fast and easy. The drug can be administrated at a desired time and location without any pain or assistance. Such is not the case for biological drugs like insulin, a peptide hormone that gets degraded by the proteolytic enzymes of the gastro-intestinal track and lacks means of transport across the intestinal epithelium. Oral delivery is also problematic for drugs with poor water-solubility, limiting their absorption. Despite the efforts of modern biotechnology and nanoscience finding an oral route for hydrophobic and peptide/protein-based therapeutics remains a long-standing challenge. The nature of the problem is complex. Successful oral delivery requires protection from the low pH and enzymes but must allow the cellular uptake and release of the therapeutics. To make the matters more problematic, the intestinal epithelium is covered by a viscous and sticky mucus layer, which is designed to clear the foreign particles away from the body, preventing the approach of drug delivery vehicles.

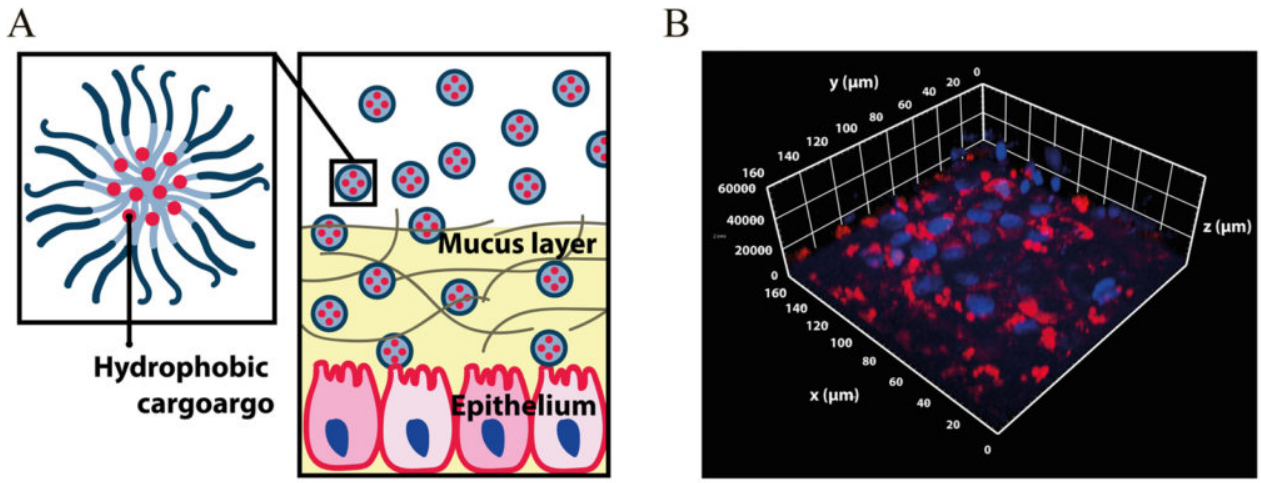

Fig. 1. A. A schematic presentation of mucopenetrating block copolymer micelles loaded with hydrophobic cargo,
B. Confocal laser scanning microscope image of cargo-loaded micelles in a Caco-2/HT29-MTX-E12 cell co-culture (blue = cell nuclei, red = cargo).

The mucus layer consist of glycopeptides called mucins. The mesh of these large branched polymers trap particles by entanglement, hydrophobic interactions and electrostatic interactions. An approach to address the challenge of mucopenetration is the assembly of nanoparticles capable of avoiding above-mentioned interactions. The nanoparticles were formed by utilizing the self-assembly of amphiphilic block copolymers, where a part of the polymer chain is hydrophilic and the other is hydrophobic. In aqueous media, the hydrophobic tails prefer to avoid the aqueous environment by facing one another, leading to a formation of spherical micelles. As a key element,

the hydrophilic block was chosen to be poly(ethylene glycol) (PEG). This neutral hydrophilic polymer provides the micelles with a “slippery” corona that allows no interaction with the components of the mucus. In addition, the core of the micelles, consisting of poly(caprolactone) or poly(cholesterol methacrylate) tails, allows the loading of hydrophobic cargo.

It is one matter to find a structure to avoid interactions with the mucus and another to assess the mucopenetration in practice. The use of animal (e.g., rat, pig) models requires time, money and ethical considerations. Furthermore, the complexity of an animal model makes it challenging to quantify and compare results between different nanomaterials. In the study by Taipaleenmäki *et al*., a fast and easy assessment method for mucopenetration was realized by using a microfluidic set-up, where the micelles were interacting with a mucus-filled channel, in which their penetration behavior could be observed and recorded. The microfluidic set-up mimics the intestinal flow but lacks the epithelium itself including features such as mucus secretion by the cells. The intestinal epithelium consist of four major cell types but is often mimicked by using Caco-2 cell line and HT29-MTX-E12 cells. The latter cells are capable to secrete mucus. Confocal laser scanning microscopy was utilized to create 3D images of the cell cultures to confirm the location of the micelles inside of the cells.

Taken together, PEG-based micelles were successfully employed to deliver model cargo across the mucus layer and have the potential to be develop into carriers for the oral delivery of hydrophobic therapeutics.

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