Overcoming gastrointestinal barriers to nanoparticle delivery

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ABSTRACT SUMMARY
Nanoparticles used for drug delivery to the gastrointestinal (GI) tract must overcome numerous hurdles, including the degradative environment and continuous mucus secretion that protects the GI tract. Nanoparticle carriers can shield drugs from degradation, deliver cargo to intended sites within the GI tract, and provide sustained drug delivery. However, many types of nanoparticles are efficiently trapped and removed by mucus. The importance of the mucus barrier in the GI tract and the limitations of animal models used to study nanoparticle delivery in the GI tract will be discussed.

INTRODUCTION
The surface area of the GI tract of an average adult human is 300-400 m² (1). The GI tract is constantly exposed to foreign particulates and bacteria from ingested material, requiring effective protection and clearance mechanisms to maintain homeostasis within the gut. The mucus barrier in the GI tract serves to lubricate the epithelium, as well as trap and clear indigested material, as depicted in Figure 1 (2). The mucus barrier can also limit the effectiveness of nanoparticle formulations designed for improved local or systemic drug delivery via the GI tract (2). Overcoming the mucus barrier may provide increased distribution and retention, leading to improved drug delivery and efficacy, as has been demonstrated in the mouse vagina (3).

Animal models, particularly rodents like mice, rats, and rabbits, have limitations in studying the impact of the mucus barrier on nanoparticle-based drug delivery. Reduced mucin production, increased numbers of Peyer’s patches, and reduced acidity compared to humans may contribute to inflated systemic bioavailability observed for nanoparticle systems in these animals (4, 5). Certain techniques, including oral gavage of large volumes of fluid and studying uptake using intestinal loops, may also impact drug delivery efficacy observed in animal models (6).

EXPERIMENTAL METHODS
Using multiple particle tracking (MPT) (7), the motions of conventional nanoparticles (CP) that adhere to mucus and nanoparticles formulated with non-adhesive surface coatings (mucus-penetrating particles, or MPP) were tracked in mucus on freshly excised epithelial tissue (8). CP and MPP distribution throughout the GI tract was assessed in vivo by both qualitative and quantitative measures after intrarectal and oral administration.

RESULTS AND DISCUSSION
We found that CP are adhesively immobilized in mucus coating freshly excised mouse and rat small intestine and colon tissue, and do not penetrate efficiently toward the underlying epithelium. This finding is contrary to reports of CP diffusion through purified reconstituted gastric mucin gels in vitro. It is likely that techniques for purifying mucins remove components, such as lipids and cells, that contribute to the hydrophobic barrier properties of gastrointestinal mucus. Compared to CP, we found that MPP provided improved distribution over the mouse rectal epithelium following intrarectal administration, and improved distribution over the small intestine epithelium following oral administration. When administered to intestinal loops ex vivo, nanoparticle distribution was not different for...
MPP compared to CP, likely due to intestinal distension and mucus dilution induced by filling the intestine with fluid.

CONCLUSION
Overcoming the mucus barrier in the GI tract may lead to improved drug delivery with nanoparticle systems.

REFERENCES