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Pharmaceutical Nanoparticles and the Mucin Biopolymer Barrier

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SUMMARY

Mucus in the gastrointestinal tract remains a tenacious barrier that restricts the passage of many orally administered compounds into the GIT's epithelial layer and consequently into the systemic circulation. This results in significant decreases in the oral bioavailability of many therapeutic molecules. Nanoparticles offer an avenue to surpass this mucus barrier. They can be used as drug carriers to improve the bioavailability of many compounds that are restricted by mucus. Nanoparticles achieve penetration of the mucus barrier through a multitude of properties that they possess as their size, charge density, and surface functional groups which can all be tailored to achieve optimal penetration of the thick and fibrous mucus barrier. This article offers a quick review about the use of nanoparticles as drug carriers to increase mucus penetration in the gastro intestinal tract.

Mucus is a visoelastic hydrogel composed of a 2-5% wt/v mucin fiber dispersion in biological fluids. These mucin fibers are naturally found as a sequence of hydrophilic and hydrophobic regions; the hydrophilic regions are compactly covered by glycans which contain negatively charged sulfate or carboxylic groups. The hydrophilic glycosylated regions are separated by lipophilic naked proteins that are folded into lipophilic globules. In the gastrointestinal tract (GIT), there are structurally 2 types of mucin: secreted mucin and cell attached mucin. Secreted mucins are composed of two layers, the outer loosely and the inner tightly adherent layers. The cell attached mucin on the other hand is extended for 700 nm into the intestinal lumen and is characterized by having a cytoplasmic component. Both the tightly adherent layer of the secreted mucin and the cell attached mucin form a significant part of the most tightly packed layer in the intestinal mucosa, namely, the glyocalyx (Ensign *et al*. 2012).

The function of mucus is to allow the exchange of nutrients, water, gases and hormones while preventing permeation of bacteria and pathogens. The defensive mechanism of mucin is based on its lipo- and hydrophilic regions which form low affinity bonds with any particulates that come in contact with it (Cone 2009). Mucin fibers also form a network with a mesh spacing size of 30-100nm which can physically entrap any foreign particulates that exceed this low spacing cut-off (Knowles and Boucher 2002). The mucus barrier however poses a serious obstacle that prevents the penetration of therapeutic xenobiotics across epithelial lining of the gut to the systemic circulation. Hence, overcoming this barrier is an important goal that will improve the bioavailability of many drugs whose use is hindered by the effects of this tenacious barrier.

Nanoparticles offer an avenue through which the mucus barrier can be surpassed. Hence, nanoparticles can be used as drug carriers which have the potential of increasing the bioavailability therapeutic molecules (Lai *et al*. 2009). This is due to the ease at which these nanoparticulate structures can be altered and tailored to fit custom needs in drug delivery. This includes the ability to form nanoparticles with multiple functional groups with several functionalities such as increased drug loading, modulated release, targeting, protection and modulation of kinetics in different environments (Jain *et al*. 2011) such as mucus itself.

The first evidence that macromolecules such as nanoparticles have the ability to traverse the mucus barrier was shown by Saltzman's group. The group reported that particulates as small as 30-60nm can diffuse across mucus matrices (Saltzman *et al*. 1994). However, several studies have shown that particles above 100nm in size exhibit retarded diffusivity in mucus (Amsden 1998, 1999). Low particle size viruses like polio (28 nm) and hepatitis (43 nm) show rapid diffusivity in mucus. Similarly, CTB-fluorescein isothiocyanate NPs of 6.4 nm could cross the mucus barrier and bind enterocytes (Frey *et al*. 1996).

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The use of nanoparticles as vehicles to increase the absorption of drugs across mucus can be achieved by: 1. Increasing the residence time of a drug in the tightly packed immobile layer of mucus to delay its intestinal clearance; and/or 2. Acting as a carrier with improved diffusion across the mucus barrier.

Increasing the residence time of the drug-nanoparticle complex in the tightly packed layer of mucus consequently increases the chances of the drug/nanoparticle complex to cross the mucus matrix (Woodley 2001). Several groups attempted to achieve this goal through the use of mucoadhesive nanoparticles that are specifically engineered to adhere to tightly packed layer of mucus. This could be achieved through electrostatic interactions, hydrogen bonding or simple van der Waal's forces (Ponchel and Irache 1998) or through specific ligand-receptor interactions in the intestinal epithelium. The use of mucoadhesive nanoparticles as drug carriers has been shown to increase the oral bioavailability of many drugs such as indomethacin (Lele and Hoffman 2000).

For a nanoparticle to be successful in penetrating the mucus barrier, it needs to avoid adherence to the lipophilic or negatively charged parts of the loosely packed mucin matrix. Nanoparticles have to be also small enough to permeate across the spaces in the fiber mesh (Lai *et al*. 2007). The surface chemistry of the nanoparticle plays a crucial role since mucus could bind various surfaces that come in contact with it by either lipophilic or hydrophilic interactions (Brayshaw *et al*. 2003). Consequently, nanoparticles with cationic termini are more likely to adhere to the mucus layer retarding its diffusion. Negatively charged nanoparticles however can also be problematic as they can be electrostatically repelled by the anionic barrier which could explain the retarded diffusion of some negatively charged nanoparticles (Kas 1997). Uncharged or neutral nanoparticles on the other hand could be highly hydrophobic, which causes considerable hydrophobic interactions and retardation in the mucus in the same fashion as with different bacteria (Mantle *et al*. 1989). Some viruses have evolved to solve this electrical interaction dilemma. Capsid viruses for example are densely charged with opposing charges, affording a neutral net charge (i.e. they will not get trapped or repelled by the mucus) while avoiding hydrophobic interactions with the mucus due to their hydrophilicity (Olmsted *et al*. 2001).

Although viruses beyond the size of 100nm showed drastic retardation in mucus diffusion, nanoparticles of larger sizes can act differently. The work of Lai *et al*. (2007) showed that PEG based nanoparticles with the size range of 200-500nm can rapidly traverse mucosal barriers. This comes as a result of their design where the non-charged hydrophilic nature of PEG reduces its interaction with mucin to a bare minimum.

A radical intervention that can increase nanoparticle diffusion across the mucus would be disrupting mucus itself through the use of mucolytic agents (Broughton-Head *et al*. 2007). Similarly, large cationic nanoparticles (e.g. chitosan coated) can tightly bind to mucus gels. The use of such cationic nanoparticles at high concentrations can collapse the gel upon the vigorous electrostatic interactions, forming large channels that can increase the bioavailability of target drugs (Wang *et al*. 2011).

Competing interests

Authors declared no competing interests.

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