

## Mucoadhesion to Improve Slipperiness of Mucin Layers

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### Abstract

Mucus gels are viscous slimes that are found from the surfaces of various internal organs, such as cervical, gastrointestinal, oculi, and reproductive tracts. A primary role of mucus gels in biological systems is known to be the protection against pathogens and mechanical insult as well as the lubrication of biological tissues. Mucins, the major macromolecular constituent of the mucus gels, not only serve as a building block of mucus gels, but also display unique slipperiness at the interface between engineering materials by forming lubricating films. Mucins and mucus gels have received particular interest in the areas of drug delivery [1-4] and biolubrication [5-9]. In the former case, the major interest lies in the mucoadhesive interaction between mucin/mucus and polymers that may be used as drug carriers so as to achieve better control in the delivery and release of drug molecules across the mucus gel on gastrointestinal organs. On the contrary, the latter case is primarily interested in understanding unique slipperiness of mucin/mucus layer at the interfaces of between biological tissues, biological tissue-biomaterials, or between engineering materials. As such, mucoadhesion and slipperiness of mucin and mucus layers appear to be two contradicting characteristics of mucins.

In this study, we demonstrate that mucoadhesion can be rather exploited to enhance the slippery nature of mucins layers. Firstly, the interaction between porcine gastric mucin (PGM) and chitosan were studied at low pH (about 3), where PGM and chitosan are negatively and positively charged, respectively. By varying the ratio of PGM to chitosan, a synergetic lubricating effect between PGM and chitosan based on their mucoadhesive interaction is observed at a hydrophobic interface comprised of self-mated polydimethylsiloxane (PDMS) surfaces. With increasing ratio of chitosan in PGM/chitosan mixture, the interaction of PGM with chitosan led to surface recharge (from negative to positive) and size shrinkage of the aggregates. This resulted in higher mass adsorption on the PDMS surface with increasing weight ratio of [chitosan]/[PGM + chitosan] up to 0.50. While neither PGM nor chitosan exhibited slippery characteristics, coefficient of friction being close to 1, their mixture improved considerably the lubricating efficiency (coefficient of friction 0.011 at optimum mixing ratio) and wear resistance of the adsorbed layers (See Figure 1 below). A primary driving force of this synergy can be ascribed to the reduction of charges of PGM by the formation of aggregates with oppositely charged chitosan, and consequent suppression of the electrostatic repulsion between PGM on nonpolar PDMS surface, which tends to weaken the stability of the lubricating layer. Similarly, PGM, as well as bovine submaxillary mucin (BSM), showed improved lubricity by forming aggregates with polycations, such as poly(L-lysine) (PLL) or poly(allyl amine) (PAAm) at neutral pH (PBS).

Interestingly, the interaction of PGM with poly(acrylic acid) (PAA) also provided a similar synergic lubricating efficacy at neutral pH (7.4); while neither PGM nor PAA showed any effective lubrication of the sliding contacts of PDMS-PDMS, the mixture of them effectively reduced the coefficient of friction by more than an order of magnitude. This is fairly surprising because, as with PGM, PAA is also negatively charged at this pH, and thus electrostatic repulsion between them is expected. The overall charge of the aggregates, as estimated by zeta potential measurements, also remained negative, in the entire range of aggregates. This observation suggests that the synergetic improvement of lubricating properties of mucins from the interaction with mucoadhesive polymers cannot be ascribed to the reduced charges of mucin-polymer aggregates alone. Instead, it can be concluded that the mucoadhesive interaction between PGM and PAA as achieved via non-electrostatic interactions, such as hydrogen bonding or hydrophobic interaction, is strong enough to overcome electrostatic repulsion and form the aggregates to assist the formation of network structure between mucins and polymer. Mucoadhesive polymers act as a physical crosslinker, and the cohesion within the lubricating layer is increased, and finally, chain interpenetration/bridging across the sliding interface bearing polymer layers can be minimized.

Nanoscale sliding contacts of the PGM-chitosan aggregate layers, as studied by atomic force microscopy, also showed lower friction forces in comparison to the reference buffer, primarily due to lower adhesion forces. However, the nanoscale tribological properties of the samples are in clear contrast to their macroscale properties. Firstly, both PGM and chitosan exhibit the lowest friction forces, whereas all the mixtures show higher frictional properties with the 0.50 [chitosan]/[biopolymer] weight

ratio displaying the highest friction. Secondly, their frictional differences are much less pronounced at the scale studied by FFM. Integrated probes have a very low radius (~ 30 nm), and thus can penetrate the biopolymer layer under loading conditions. Hence, the friction experienced by the tip is due to its interaction with the substrate, and also due to the resistance applied to it by the adsorbed layer as it plows through it. At the nanoscale the tip and the PDMS are in mechanical contact due to the loading force, and, consequently, the tip has to plow through the adsorbed layer. A higher mass density, such as the film obtained from the [chitosan]/[PGM] at the ratio of 0.33 or 0.50 w/w, means higher number of chains and bonds encountered by the tip per unit length of sliding. Therefore, higher energy is dissipated per unit length of sliding by the tip in breaking/disrupting these bonds (chitosan-PGM electrostatic bridges, PGM-PDMS hydrophobic bonds, chain entanglements) as it plows its way through the layer. Moreover, a higher degree of entanglement within the layer may result in a stiffer layer which could also explain a higher force needed by the tip to slide through it. The films formed from neat PGM or chitosan reveal the smallest friction forces, due to the lack of crosslinked bridges between the molecules on the same surface.

## References

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**Figure 1.** Coefficient of friction obtained from the sliding contacts between PDMS surfaces as lubricated by the aqueous solutions of PGM (0.1 mg/mL), chitosan (0.1 mg/mL), and their mixtures (1:1, 0.1 mg/mL in total biopolymer concentration) (Left panel),

