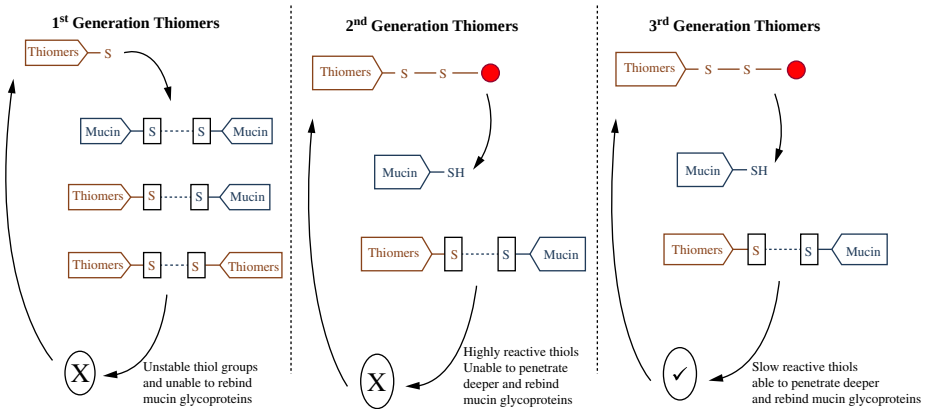

FIG. 6 Mucoadhesive mechanism of first-, second- and third-generation thiomers.

compared to first scheme where all the thiol groups were not protected.

Third-generation thiomers. The previous first and second generations of thiomers showed substantially higher mucoadhesion as compared to non-covalently binding polymers. However, these generations react extensively with thiols on the surface of the mucus gel layer and are hindered to penetrate the deeper mucus regions. That is why, their residence time is limited to mucus turnover. The solution to this issue has led to the development of third-generation thiomers which show lower reactivity, giving enough time to the formulation for deeper penetration into mucus. Therefore, third-generation thiomers are designed with S-protection of less reactive thiols such as cysteine or *N*-acetyl cysteine. As it is an endogenous substructure that can be regarded as safe. These cys-cys substructure is a less reactive disulfide ligand that makes third-generation thiomers, penetrate deeper into the mucus providing enhanced mucoadhesion. This crosslinking of even less reactive S-protected thiomers in the presence of a low number of free thiols, is highly beneficial for various applications. In case of nasal sprays, eye drops or vaginal gels, third-generation thiomers can be administered at low viscosity strongly increasing their viscosity in the presence of endogenous thiols and avoiding subsequently unintended rapid elimination via an outflow.

6. FACTORS AFFECTING MUCOADHESION

Mucoadhesion is a complex process depending on many factors that can affect the degree of polymer attachment to the mucosal membrane. Therefore, these factors such as physiological conditions on the mucosal site significantly influence the degree of mucoadhesion. These factors can include the folowing.

6.1. Polymer Backbone

6.1.1. Solubility

The extent to which polymers are soluble in an aqueous medium also has an impact on their mucoadhesive nature. The presence of numerous hydrophilic functional groups, such as hydroxyl and carboxyl, enhances the solubility of the polymers providing more intensive interactions with the mucus gel layer leading to increased mucoadhesion. The soluble polymers have more surface area to interact with the mucosal surface and result in a higher degree of mucoadhesion.

6.1.2. Swellability

When a hydrophilic polymer comes in contact with the aqueous medium, it swells up and retains water within the cross-linked chain structure of the polymer. However, this swelled-up structure provides maximum distance between the polymer chains within the structure, leading to increased chain flexibility and efficient penetration of the mucus chains into it. Polymer swelling also depends on their molecular mass resulting in entanglements that are usually favored at higher molecular mass resulting in enhanced mucoadhesion as compared to low molecular mass polymers [126]. A general rule can be set in a way that if drug–polymer interaction results in less water holding capacity than it could lead to enhanced mucoadhesion and vice versa [127].