5.1.1. Classification based on the interfacial forces

Noncovalent binding polymers. Noncovalent binding polymers entangled with the mucus glycoproteins either via hydrogen bonding or electrostatic interaction. All first-generation mucoadhesive polymers fall in this group. Based on their surface charge, they are divided into nonionic, anionic, cationic, and amphiphilic polymers.

Nonionic polymers. For anionic and cationic polymers, mucoadhesive properties are largely dependent on pH of the media. However, nonionic polymers show mucoadhesive properties independent of the pH. The major mechanism for the interaction of these polymers is through the formation of hydrogen bonding as in case of polyethylene oxide or through interpenetration at polymer mucus interface and their entanglement. Nonionic polymers are largely less adhesive than corresponding cationic and anionic polymers. Polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), HPMC, HEC, and HPC are some examples for nonionic polymers. Thiomers will be discussed in detail, later in this chapter.

Anionic polymers. Anionic polymers have negatively charged groups on their backbone. Most of the mucoadhesive anionic polymers have –COOH which ionize at basic pH. Sulfates and sulfonates are other anionic groups that are present in anionic polymers but they are of no practical importance. Some of the examples of anionic polymers include polyacrylates, alginates, carbomers, hyaluronic acids, and pectins in.

Polyacrylates are the most extensively studied polymers. Polyacrylates are insoluble or show very low-swelling behavior. However, at neutral pH and higher carboxylic groups are ionized and due to highly negative charge, a strong intramolecular repulsion is developed which results in the uncoiling of polymer chains and helps in the interpenetration of the polymer and mucus interfaces. Further presence of carbonyl oxygen, they form hydrogen bonds with glycoproteins of mucus which is mainly responsible for the mucoadhesion of anionic [51].

Cationic polymers. Cationic polymers adhere mucus by means of interacting with sialic acid substructure within the mucus gel layer. The negatively charged mucus interacts effectively with positively charged cationic polymers and develops an electrostatic binding. Among them, chitosan is a reasonably cheap and well-studied cationic polymer in the field of drug delivery. In contrast to anionic polymers, cationic polymers have better ability to swell and release entrapped drug at acidic pH comparatively to pH above 6.5. Some of the common examples include polylysine and trimethylated chitosan [52, 53].

Covalent binding polymers. First-generation mucoadhesive polymers interact with mucus either through the formation of electrostatically, mechanically (through chain entanglement), or through the formation of hydrogen bonds. However, these connections are reversible and do not render the polymer to bind with mucus for significantly longer period of time. The quest to find stronger and longer mucoadhesion led to second-generation mucoadhesive polymers which bind to mucus covalently and significantly enhance the residence time of drug delivery systems. One of the most-studied branches of covalently bonding polymers are thiolated polymers, generally known as thiomers which are developed by functionalizing the existing polymers with thiol moieties. They bind to cysteine rich domains in the mucus through oxidation or by disulfide exchange reaction, as shown in Fig. 5.

5.2. Classification Based on the Source of Polymer

5.2.1. Natural polymers and ligands

Polymers and the ligands from natural origin because of their biocompatibility are commonly used in mucoadhesive drug delivery systems and therefore are discussed in detail as follows:

Polysaccharides. Polysaccharides constitute the major chunk of excipients/polymers that are used in pharmaceuticals. They inherit the advantages of cost effectiveness, easy availability, low toxicity, biocompatibility, and biodegradability for their use as excipients in pharmaceuticals [54]. Polysaccharides play their role in plant and animal bodies as:

- Food storage polysaccharides that serve as energy storage such as starch, inulin, and glycogen.
- Structural polysaccharides which give structural support to plant and animal bodies such as cellulose and chitin.
- Slime-forming polysaccharides also termed as mucopolysaccharides or mucilages which play elastic and lubricating function in animal and plant bodies such as pectin, hemicellulose, chondroitin sulfate, hyaluronic acid, and agar.
- Pathological exudates of plants and are commonly known as gums such as gum arabica, gum tragacanth, and guar gum.

Some of the polysaccharides reported for their mucoadhesive properties in literature include agar, carrageenans, alginate, gum tragacanth, guar gum, locust bean