6.1.3. Crosslinking

Along with molecular mass, the cross-link density of polymers also affects mucoadhesion that is inversely proportional to the degree of swelling [128]. Lower cross-link density provides higher chain flexibility and hydration exposing large surface areas of the polymers ultimately resulting in higher mucoadhesion. Addition to molecular mass, the spatial conformation of a polymer is also important. It can be explained with an example of dextran having average molecular mass of 19,500,000 Da have adhesive strength similar to that of PEG with a molecular mass of 200,000 Da. It is because of the helical conformation of dextran that shielded many adhesive active groups unlike PEG polymers, which have a linear conformation [129, 130].

Generally, the mucoadhesive properties of a polymer increase with molecular mass. Various studies conclude that an optimum molecular weight is necessary for a maximum mucoadhesion. This optimum molecular mass depends upon the type of polymer. Gurny et al. explained that the degree of mucoadhesion increases with the increase in molecular mass up to 100 kDa and a further increase in the molecular mass does not show any significant effect in case of branched or cross-linked polymers [126]. However, in case polymers having linear chains such as polyethylene oxide the mucoadhesive strength increase even up to 4 M Da due to higher interpenetration [131].

6.1.4. Concentration

The optimum concentration of polymer is also a key factor in corresponding mucoadhesion [131]. In case of higher concentration, the adhesive strength drops significantly due to the change in conformation on one hand from linear to coiled molecules and decreases the surface area and fewer groups available for interaction. This result seems to be of interest only for liquid mucoadhesive formulations while on the other hand for solid dosage forms such as tablets, higher polymer concentration provides stronger mucoadhesion.

6.2. Physiological Factors

The nature of mucosal surface presented to the mucoadhesive formulation can vary significantly depending on the body site and the presence of local or systemic disease [132]. Various physiological factors can play a vital role in determining the degree of mucoadhesion.

6.2.1. pH at the site of action

Adhesion of the polymers having ionizable groups is highly influenced by the pH and ionic strength at polymer–mucus interface. If the pH at the interface is above or below the pKa of the polymer, it will ionize the surface groups results in increased electrostatic interaction between polymer and mucoadhesion [133]. On the other hand, charge in the mucus also depends on the pH due to the difference in pKa values of functional groups on glycoproteins. For example, in case of polyacrylic acids protonated carboxylic groups at low pH are more mucoadhesive may be due to hydrogen bonding. At higher pH, the polymeric chains are highly extended due to electrostatic repulsion of carboxyl anions which are also repelled due to negatively charge mucus.

Moreover, the pressure applied initially at the contact site increases the degree of interpenetration of molecular chains. On the other hand, contact time is also an equally important factor. Longer the contact time, higher will be interpenetration of the chains. Even if the two surfaces held for a longer period together, the nonmucoadhesive shows mucoadhesive properties. For swellable materials, the mucoadhesive strength decreases with increasing degree of swelling. In some routes of administration, it can be controlled physically as in case of buccal, nasal, and vaginal routes. But in case of gastrointestinal tract, pressure and contact time depend on the physiology of intestine.

6.2.2. Availability of water

As the swelling of the polymer depends on availability of water at the site of administration, hence an optimum amount of water at mucosal surface is needed. A higher than optimum amount of water, increases the swelling and if this phenomenon occurs too quickly without giving a sufficient time for mucoadhesion to mucosal layer, the dosage form is detached easily and is washed off without complete release of the API.

6.2.3. Mucus turnover

The mucus from the surface of the mucus gel layer is continuously washed away and is readily replaced by the freshly prepared mucus from goblet cells of the mucosal cell layer to maintain a certain thickness and consistency of the gel layer. This continuous replenishment of the mucus is called mucus turnover which varies in different parts of the body. Even if a dosage form is highly mucoadhesive, it cannot last more than the turnover time of the mucus as it is also washed away along