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The molecular basis of bioadhesion

CLAUS-MICHAEL LEHR

Department of Biopharmaceutics and Pharmaceutical Technology, University des Saarlandes, 66123 Saarbrücken, Germany

Bioadhesion refers to adhesion phenomena where at least either the adhesive or the substrate is biological. As a remarkable difference compared with other adhesion phenomena, bioadhesion therefore usually occurs in the presence of water, which is a common subverter of adhesive joints in many technical applications. Bioadhesive drug delivery systems (BDDS) are designed to adhere to epithelial tissues, which—except for the particular case of skin adhesion in (trans)dermal delivery systems—mostly are mucosal epithelia. Therefore, the term mucoadhesion is sometimes used as a synonym for bioadhesion.

Bioadhesion was introduced to the pharmaceutical sciences in the 1980s. The original idea was probably to create a 'platform' for controlled-release formulations. For example, after oral administration, bioadhesion should prolong the residence time at the site of drug absorption, and thus improve bioavailabilty and dosing interval. Moreover, bioadhesion was expected to create an intensified contact between the drug delivery system and the absorbing biological membrane, resulting in a locally increased drug concentration and a steeper concentration gradient across the biological barrier concerned. The latter aspect made bioadhesion particularly attractive for other mucosal routes (e.g. ocular, nasal, buccal, vaginal) and for the non-parenteral delivery of peptide and protein drugs.

The first generation of BDDSs preferentially used some known pharmaceutical polymers. In particular polyacrylic acid, cellulose derivatives and, more recently, chitosan are distinguished by their capability to adhere to mucosal tissue surfaces under certain conditions. It must, however, be distinguished whether the tissue surface and body cavity is just humid or entirely wet, and whether the mucoadhesive polymer is applied in dry or in swollen state. The exact mechanisms of mucoadhesion are still not completely understood, but most researchers agree that interfacial energy effects, polymer interpenetration, and the movement of water, along with some rheological changes in the polymeric hydrogels involved, are important components of this remarkable phenomenon.

Some bioadhesive formulations have meanwhile reached clinical studies or are even on the market for topical mucosal applications. However, for the gastrointestinal (GI) route, this concept has encountered difficulties. First, GI mucus undergoes a relatively rapid turnover. This prevents long-term adhesion to the tissue, although the polymers may still stick to the mucus. Second, mucoadhesive polymers adhere by non-specific physicochemical mechanisms and therefore also bind to shed mucus and cells or to other gut contents.

Therefore, the idea to control GI transit of dosage forms by means of mucoadhesive polymers has mostly been abandoned. Nevertheless, it has been found that the same polymers can increase the absorption of usually poorly absorbed peptide drugs across various mucosal epithelia, including oral delivery. Further studies have revealed that some mucoadhesive polymers act as penetration enhancers by temporarily opening epithelial tight junctions, and are also potent inhibitors of proteolytic enzymes. As these mucoadhesive polymers can be regarded as safe excipients, this concept is now ready for clinical evaluation.

Still, breaking a biological barrier by opening epithelial tight junctions is not without concerns. Although probably more difficult to realize, it appears desirable to identify novel and specific transport pathways to overcome epithelial barriers. A new generation of bioadhesive molecules is designed to specifically recognize appropriate receptors at the epithelial cell surface. This type of bioadhesion no longer involves mucus, but provides direct contact with the apical cell membrane and should therefore be referred to as cytoadhesion. Here, interactions of lectins and lectin-like molecules with their corresponding glyco-ligands hold much promise. Moreover, such binding is not restricted to mere surface adhesion, but may deliver drugs or drug carrier systems into and through epithelial cells by active transport via membrane-derived vesicles (endo-/transcytosis). Bioadhesion phenomena of this type can therefore be refered to as bioinvasion.