Patho-physiology of diseases that are currently among the leading causes of death now require much more than just a stethoscope for diagnosis and a pill for treatment. The developing generation of therapeutics needs to combine with a degree of intelligence; the ability to sense and respond to their environment at the desired site of action. Dosage forms, when combined with intelligent polymers (i.e. bioadhesive, pH responsive) have the ability to sense and respond to external stimulus and with the advent of nanotechnology; these polymers can be fabricated on microsize, nanosize and on the same size scale as cellular and sub-cellular processes.

Recently, the formulation scientists applied the bioadhesion phenomenon for the development of novel and smarter systems for the delivery of therapeutics in order to maximize the effectiveness with minimal or no adverse effects. When a bioadhesive drug delivery system come in contact of application/absorption site, an intimate interaction between the biological surface and bioadhesive delivery system has been established. This course of action prolongs the residence of therapeutic agent for better absorption and superior performance. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of drug administration. In carrier technology microspheres, nanospheres, liposomes, nanoparticles, etc., offers an intelligent approach for drug delivery by coupling the drug to a carrier particle which modulates the release and absorption of the drug from the carrier system. In recent years, types of such mucoadhesive drug delivery systems have been developed for both systemic as well as local effects by different routes i.e. oral, buccal, nasal, rectal and vaginal routes (Table 1.1).

Bioadhesion is relatively new and emerging opinion in drug delivery. It keeps the delivery system adhering to the underline absorption surface. This phenomenon is facilitated with the aid of bioadhesive polymers and these polymers lead to the possible
Bioadhesion: Approaches to Drug Delivery

development of novel drug delivery systems with modified drug release patterns. Bioadhesive drug delivery systems show various merits over conventional drug delivery systems. In the recent years the interest is growing to develop a drug delivery system with the use of a bioadhesive polymer. Such systems that are developed using bioadhesive polymers that will attach to related tissue or to the surface coating of the tissue for targeting various absorptive mucosal surfaces such as ocular, nasal, pulmonary, buccal, gastric, vaginal etc., are known as bioadhesive/mucoadhesive delivery systems.

Table 1.1 Some commercially available bioadhesive drug formulations

<table>
<thead>
<tr>
<th>Brand</th>
<th>Company</th>
<th>Bioadhesive polymer</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccastem®</td>
<td>Reckitt Benckiser</td>
<td>PVP, Xanthum gum and locust bean gum</td>
<td>Buccal tablet</td>
</tr>
<tr>
<td>Corlan pellets®</td>
<td>Cell Tech</td>
<td>Acacia gum</td>
<td>Oromucosal pellets</td>
</tr>
<tr>
<td>Suscard®</td>
<td>Forest</td>
<td>HPMC</td>
<td>Buccal tablet</td>
</tr>
<tr>
<td>Gaviscon liquid®</td>
<td>Reckitt Benckiser</td>
<td>Sodium Alginate</td>
<td>Oral liquid</td>
</tr>
<tr>
<td>Orabase*</td>
<td>ConvTech</td>
<td>Pectin, gelatin</td>
<td>Oral paste</td>
</tr>
<tr>
<td>Nyogel</td>
<td>Novartis</td>
<td>Carbomer and PVA</td>
<td>Ocular gel</td>
</tr>
<tr>
<td>Zidoval®</td>
<td>3-M</td>
<td>Carbomer</td>
<td>Vaginal gel</td>
</tr>
<tr>
<td>Corsodyl gel®</td>
<td>GalaxoSmithKline</td>
<td>HPMC</td>
<td>Oromucosal gel</td>
</tr>
</tbody>
</table>

Mucosal surfaces are highly permeable membranes allowing rapid absorption of drug into the systemic circulation with avoidance of first pass metabolism. The well-organized uptake offers several paybacks over other methods of drug delivery and allows active agents to avoid some of the body’s natural defense mechanism. The focal idea of bioadhesion was derived from the need to localize drugs at a definite site in the body. Habitually the extent of drug absorption is restricted by the residence time of the drug at the absorption spot. For e.g. in ocular drug delivery system, less than 2 min are available for drug absorption after instillation of a drug solution into the eye, since it is removed rapidly by the solution drainage and hence the ability to extend the contact time of an ocular delivery system in front of the eye would undoubtedly improve the bioavailability. In oral drug delivery, the drug absorption is restricted by the gastrointestinal transit time of the dosage form. In view of the fact that many drugs are absorbed only from the upper small intestine, localizing oral drug delivery system in the stomach or in the duodenum would extensively improve the drug absorption. To overcome the relatively short GI retention time and improve localization for oral controlled drug delivery system, bioadhesive polymers which adhere to the mucin or the epithelial surface are valuable and lead to significant improvement in oral drug delivery. By involving the bioadhesive polymers in novel drug delivery systems improvement is also expected for other mucus covered sites of drug administration.
In biological systems, four types of bioadhesion (Figure 1.1) could be speculated:

1. Normal cell-normal cell adhesion i.e. cell fusion or cell aggregation.
2. Cell (normal/pathological)-foreign substance adhesion i.e. cell adhesion onto culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.
3. Normal cell-pathological cell adhesion i.e. adhesion of pus cell to normal cell.
4. Biological surface-adhesive material adhesion i.e. adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues.

Bioadhesive drug delivery system implies attachment of a drug carrier system to a specific biological site or the surface and this biological surface may be epithelial tissue. If this attachment or adhesion is with a mucus layer, it is referred as mucoadhesion.

Bioadhesion/Mucoadhesion can be defined as an experience of interfacial molecular attractive forces amongst the two surfaces i.e. biological substrate and adhesive polymers of natural or synthetic origin. This interfacial interaction results into adherence of polymeric material to the biological surface and keep it at the site of adhesion for a longer duration. Practice of bioadhesive polymeric systems for biomedical purposes are not new; the utilization of adhesive bandages, surgical glues etc., witnessed the presence of

1.1 BIOADHESION AND MUCOADHESION

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bioadhesive products from a long time. The human gut housed several bacterial species, this bacterial adhesion results due the interaction between mucin (present in mucus lining of gut mucosa) and lectin resembling structures (present on bacterial cell surface). In common, a variety of biopolymers shows the bioadhesive property and has been utilized for a choice of therapeutic purposes in medicine. Broadly, bioadhesive polymers can be categorized under two groups i.e. specific and non-specific. The polymers with the capability to adhere to specific chemical structure of biological molecules comes under specific bioadhesive polymers e.g. Lectins, fimbrin. On the other side, non-specific bioadhesive polymers bind to both i.e. cellular and mucosal surfaces e.g. Poly-acrylic acid and Cyano-acrylates.

**Bioadhesion** is the course of action which explains the interaction between an adhesive polymer (natural/synthetic) with a biological substrate.

The interaction of adhesive polymers with mucosal layers instead of other cellular layers is acknowledged as **mucoadhesion** (Figure 1.2).

The substrate possessing bioadhesive assets can help in devising a delivery system proficient of delivering a bioactive agent for a prolonged period of time at a specific delivery location. The literature provided in this book gives a good insight on bioadhesive polymers, the phenomenon of bioadhesion and the factors which have the ability to affect the bioadhesive properties of a polymer.

### 1.2 HISTORY OF BIOADHESION

The utilization of bioadhesive polymers for the development of pharmaceutical formulations has been tried in 1947 to deliver penicillin to the oral mucosa. In that attempt, gum tragacanth and dental adhesive powders were incorporated in formulation to deliver bioactive agent to mucosal surface of oral cavity. Later on, carboxy methyl cellulose and petrolatum were reported for the development of bioadhesive preparations. With the advancement in bioadhesive drug delivery systems a mucoadhesive formulation Orahesive® was marketed which consists of sodium carboxy methyl cellulose (SCMC; finely ground), gelatin and pectin as bioadhesive component. Subsequently, another bioadhesive formulation Orabase® based on blend of poly methylene/mineral oil entered into the clinical trials. A newer bioadhesive system was also developed in which SCMC and poly-isobutylene were blended to coat a polyethylene leaf, this coating supplements
the shielding of bioadhesive layer by polyethylene backing film and minimizes the physical interference due to surrounding environment.

In the development wave of bioadhesive polymers, a range of other bioadhesive polymers from natural or synthetic resources were reported with their applications in pharmaceutical delivery systems. Sodium alginate, guar gum, hydroxy ethyl cellulose (HEC), karya gum, methyl cellulose (MC), retene, tragacanth and polyethylene glycol (PEG) etc., demonstrated their potential for bioadhesive application for drug delivery purpose. The period of 1980s witnessed the exhaustive use of hydroxy propyl cellulose (HPC) and SCMC as a bioadhesive component in pharmaceutical formulations. From that time, the use of acrylated polymers in the formulations intended for bioadhesive delivery, increases many-fold. The effect of molecular level structure modification of these polymers on bioadhesive properties has also been investigated by several researchers in order to develop more effective bioadhesive polymers for therapeutic delivery.

### 1.3 MERITS OF BIOADHESION/MUCOADHESION

Bioadhesion promotes the residence time of dosage form in addition to improved intimacy of contact between the delivery system and biological surfaces. These attributes of bioadhesive systems attracted the scientific community to utilize them for enhanced effects with localization of therapeutic agents at the site of absorption/application. These delivery systems are also capable to control the rate and extent of drug release, that’s why there is a possibility to be utilized as a platform for the development of sustained release systems.

1. Prolongs the residence time of the dosage form at the site of absorption. Due to an amplified residence time it enhances absorption and hence the therapeutic efficiency of the drug.
2. Surface characteristics can be easily manipulated to accomplish both passive and active drug targeting after parenteral administration. Drug is protected from degradation due to acidic surroundings in the GIT and drug bioavailability is increased due to the avoidance of first pass metabolism.
3. The controlled and sustained release pattern of the drug during the transportation and at the site of localization altering organ allocation of the drug and succeeding clearance of the drug so as to attain enhanced drug therapeutic efficacy and diminution in side effects.
4. Controlled release pattern and particle degradation characteristics can readily modulated by the choice of matrix constituents. Drug loading is comparatively high and drug can be integrated into the system without any chemical reaction; this is a vital factor for preserving the drug activity.
5. Site specific targeting can be achieved by attaching targeting ligands to exterior of particles or make use of magnetic guidance.
6. The system can be used for various routes of administration including oral, nasal, parenteral and intraocular etc.
7. Tremendous accessibility and reduced dosing due to lengthen residence time of the dosage form at the intended site and absorption to allow once or twice a day dosing.
8. Superior patient compliance due to ease of drug administration.
9. Quicker onset of action is achieved as the mucosal surface offers rapid absorption due to enormous blood supply and good blood flow rates.
10. These dosage forms smooth the progress of intimate contact of the formulation with the underlying absorption surface. This allows adaptation of tissue permeability for absorption of macromolecules, such as peptides and proteins. Addition of penetration enhancers such as Sodium glyco-cholate, Sodium taurocholate and L-lysophosphatidyl choline and protease inhibitors in the mucoadhesive dosage forms resulted in healthier absorption of peptides and proteins.

1.4 DEMERITS OF BIOADHESION/MUCOADHESION

Based upon the therapeutic requirement i.e. local or systemic action, several demerits are associated with the drug delivery through bioadhesive systems.
1. In case of local delivery, the bioadhesive system may possibly flush-off by biological fluids (saliva/lacrimal fluid) or ingested food stuffs resulting into rapid elimination or termination of local effect. In that condition frequent dosing is required, this nullifies the advantage of prolonged residence associated with bioadhesive systems.
2. As the majority of bioadhesive systems for local delivery are available in solid or semisolid form, they lack the uniform distribution over the intended biological surface. There may be possibility that some area of intended biological surface may remain deficient in terms of effective therapeutic levels.
3. Patient compliance is compromised in some cases e.g. application of bioadhesive system for buccal delivery may be irritable due to the ‘mouth feel’ effect as it resembles a foreign stuff over buccal mucosa.
4. For systemic delivery the relative impermeability of biological surface with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

1.5 RECENT DEVELOPMENTS IN BIOADHESIVE DRUG DELIVERY SYSTEMS

The scope of bioadhesive polymers in pharmaceutical arena covers a wide range of applications (Table 1.2). The expansion of bioadhesive drug delivery systems for oral,
topical, nasal, ocular, vaginal and rectal delivery, itself witnessed the potential of these systems. The basic principles involved in bioadhesion process can be applied for the development of drug delivery systems with controlled release of medicaments. Advantages associated with oral mucoadhesive drug delivery systems e.g. prolonged residence time for enhanced absorption of incorporated drug, lower dosing frequency etc., markedly influences the oral bioavailability. The successful implementation of bioadhesive systems for therapeutic purpose depends on the physicochemical properties of the polymers which contribute towards the bioadhesion phenomenon. The physiological factors such as mucin flow, mucin turnover rate and the pathological condition of biological surface at the site of application/absorption are also considered for the development of bioadhesive drug delivery systems. In the current scenario, several in-vitro and in-vivo techniques are available to evaluate the bioadhesive properties of such delivery systems. Hydrophilic, anionic molecules with high molecular weight e.g. carboomers are choice of bioadhesive polymers which are commonly studied for the development of bioadhesive systems. In recent years, the rise of second generation bioadhesive polymers grabs the attention for the development of bioadhesive system with better control over the bioadhesive properties for effective therapeutic delivery.

Table 1.2 Scope of bioadhesive drug delivery systems

- Novel formulation approaches to oral mucoadhesive drug delivery systems
- Bioadhesive formulations for nasal delivery
- Development of bioadhesive buccal patches
- Bioadhesive formulations for vaginal delivery
- Ocular bioadhesive drug delivery systems
- Bioadhesive preparations as topical dosage forms

1.5.1 Developments in Bioadhesive Nanoparticulate Drug Delivery Systems

In the previous 35 years, the expansion of nanotechnology has opened a number of innovative vistas in medical sciences, particularly in the field of drug delivery. New multifunctional moieties are approaching for treating diseases. The biotechnology has also produced several powerful drugs, but numerous of these drugs encounter problems delivering them in biological systems. Their therapeutic effectiveness is significantly spoiled owing to their incompatibilities and specific chemical structure. The input of today’s nanotechnology is that it allows genuine advancement to accomplish sequential and spatial site-specific delivery. The market of nanotechnology and drug delivery systems based on this technology will be extensively felt by the pharmaceutical industry. In recent years, the figure of patents and products in this field is escalating appreciably. The most straight advance application is in cancer treatment with quite a few products in market such as Caelyx®, Doxil®, Transdrug® and Abraxane®.
Paul Ehrlich (1854–1915), working on immunologist, summarized the lectures delivered by Herter at Johns Hopkins University and published few articles in 1904 in Boston Medical and Surgical Journal, the immediate predecessor of New England Journal of Medicine. These publications brighten the view of immunochemistry and explain the side-chain theory of antibody development. He also explains the in-vitro mechanism of immune hemolysis. However, later findings of other researches challenged those publications and remained controversial in the view of a clinical journal. Beside of all, Ehrlich’s contributions and findings related to infectious diseases and his concept of ‘magic bullet’ revolutionized the delivery of chemotherapeutic agents. The theory of Paul’s magic bullet has turned out to be veracity with the authorization of several forms of drug-targeting systems for the treatment of certain cancer and infectious diseases. Nanoparticulate drug delivery systems with the concept of bioadhesion may produce fruitful outcome in this direction.

Even though the mammoth amount of work has been done on this drug delivery platform, the center of attention has been primarily on the formulation of gastro-retentive dosage forms; hence, work must be done to take advantage of this drug delivery system for various other approaches like drug targeting and site specific drug delivery systems. Bioadhesive drug delivery systems is one of the most significant novel drug delivery systems with its collection of advantages and it has a lot of prospective in formulating dosage forms for a choice of chronic diseases.