WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 5, 233-248. Review Article ISSN 2277– 7105

BIOADHESIVE DRUG DELIVERY SYSTEM-A REVIEW

K. V. S. Varalakshmi*, M. Mohan Varma, Munikoti Lakshmi Kavya and Abbas Ali

Department of Pharmaceutics, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534202, Andhra Pradesh, India.

Article Received on
03 February 2023,

Revised on 24 Feb. 2023,
Accepted on 14 March 2023

DOI: 10.20959/wjpr20235-27412

***Corresponding Author**
K. V. S. Varalakshmi
Department of Pharmaceutics, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534202, Andhra Pradesh, India.

ABSTRACT

Mucoadhesive drug delivery system are delivery system which utilized the property of the polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. Bio adhesion is an interfacial phenomenon in which to materials, at least one of which is biological, are held together with the interfacial forces. The attachment could be between an artificial material and biological substrate, such adhesion between polymer and a biological membrane. In case of polymer attached to the mucin layer of a mucosal tissue, the term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the gastro intestinal tract, the urogenitial tract, the airways, the ear, nose and eye. These represents potentials sites for attachment of any bio adhesive system and hence, the mucoadhesive drug delivery system includes, buccal, oral, rectal, nasal and ocular delivery systems.

KEYWORDS: Bio adhesive dug delivery system (BADDS), Mucin, Bio adhesion, Mucoadhesion.

INTRODUCTION

The systemic availability of drugs taken orally may be limited by the g.i.t transit time of the drug delivery system. This is particularly so far drugs those are majorly absorbed from the intestine. their availability is limited by the residence time of the drugs in or upstream of the small intestine. So potential approach to extend the gastro intestinal residence time is the development of bio (muco) adhesive DDS. Basically the drugs is incorporated in a polymer that has the mucoadhesive properties.[1]

Definition of bio adhesion

In bio adhesive drug delivery systems, the term *bio adhesion* is used to describe the bonding or adhesion between a synthetic or natural polymer an soft tissues such as epithelial cells. The term *mucoadhesion* is used to describe adhesion interactions between polymers and mucus or mucosal surfaces.[2,3]

Advantages[3,4]

- These dosage forms are readilily localized in the region appilied to improve and enhance the bioavailibity of drugs.
- These dosage form facilitate intimate contact of the formulation with the underlying absorption surface. This allows modification of tissue permeability for absorption of macromolecules such as peptides and proteins. inclusion of penetration enhancers such as sodium glycocholate, sodium tauochaolate and L-Lysophos photidyl choline 9LPLO and protease inhibitors in the mucoadhesive dosage forms resulted in better absorption of peptides Mucoadhesive dosage form also prolong the residence time of the dosage form at the site of application and absorption to permit once or twice a day.

Types of bio adhesion can be distinguished as

- Adhesion of a normal cell on another normal cell.
- Adhesion of a cell with a foreign substance.
- Adhesion of normal cell to a pathological cell.
- Adhesion of an adhesive to a biological substrate.

Classification of bioadhesives

Based on phenomenological observation bio adhesives are divided into three types.[5,6]

TypeI: Bio adhesion is characterized by adhesion occurring between biological objects without involvement of artificial materials. Eg: cell fusion and cell aggregation.

Type II: Bio adhesion is characterized by cell adhesion on to culture dishes or adhesion to variety of substances including metals, woods and other synthetic materials.

Type III: Bio adhesion can be described as adhesion of artificial substrates such as adhesion of polymers to skin or other soft tissues.

Development Issues of Bio adhesive Drug Delivery Systems: Products and Clinical Trials

- Novel Formulation Approaches to Oral Mucoadhesive Drug Delivery Systems

- Bio adhesive Formulations for Nasal Peptide Delivery
- Development of Bio adhesive Buccal Patches
- Vaginal Delivery of Calcitonin by Hyaluronic Acid Formulations
- Ocular Bio adhesive Drug Delivery Systems
- Bio adhesive Preparations as Topical Dosage Forms

Novel Concepts and Strategies for Bio adhesive Drug Delivery Systems

- Multifunctional Polymers for the Peroral Delivery of Peptide Drugs
- Chitosan and Chitosan Derivatives as Absorption Enhancers for Peptide Drugs Across Mucosal Epithelia
- Plant Lectins for Oral Drug Delivery to Different Parts of the Gastrointestinal Tract
- Bacterial Invasion Factors and Lectins as Second-Generation Bio adhesives
- Novel PEG-Containing Acrylate Copolymers with Improved Mucoadhesive Properties
- Bio adhesive, Bio erodible Polymers for Increased Intestinal Uptake

Mechanisms of bio adhesion[7,8,9,10]

The mechanisms responsible in the formation of bio adhesive bonds are not fully known, however most research has described bio adhesive bond formation as a three step process.

Step 1: Wetting and swelling of polymer.

Step 2: Interpenetration between the polymer chains and the mucosal membrane.

Step 3: Formation of chemical bonds between the entangled chains.

Step 1

The wetting and swelling step occurs when the polymer spreads over the surface of the biological substrate or mucosal membrane in order to develop an intimate contact with the substrate. This can be readily achieved for example by placing a bio adhesive formulation such as a tablet or paste within the oral cavity or vagina. Bio adhesives are able to adhere to or bond with biological tissues by the help of the surface tension and forces that exist at the site of adsorption or contact. Swelling of polymers occur because the components within the polymers have an affinity for water.

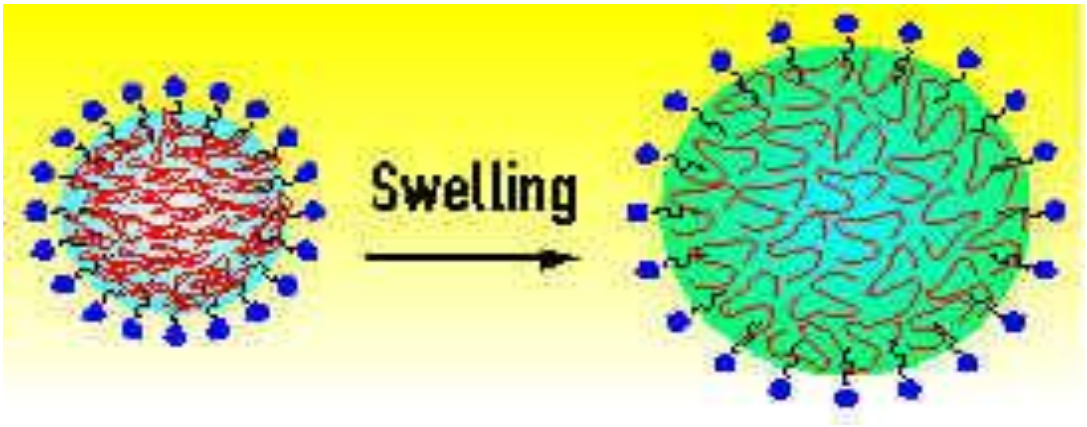


Fig: 1- swelling of a polymer.

Step 2

The surface of mucosal membranes are composed of high molecular weight polymers known as glycoproteins. In step 2 of the bio adhesive bond formation, the bio adhesive polymer chains and the mucosal polymer chains intermingle and entangle to form semi permeable adhesive bonds. The strength of these bonds depends on the degree of penetration between the two polymer groups. In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure.

Step 3

This step involves the formation of weak chemical bonds between the entangled polymer chains. The types of bonding formed between the chains include primar bonds such as covalent bonds and weaker secondary interactions such as van der Waals Interactions and hydrogen bonds. Both primary and secondary bonds are exploited in the manufacture of bio adhesive formulations in which strong adhesions between polymers are formed.

Factors affecting muco/Bio adhesion

The Bio adhesive power of polymer is affected by the nature of polymer and also by the nature of surrounding media.[11,12] They are.

1. **Polymer related factors**

- Molecular weight
- Concentration of active polymer
- Flexibility of polymer chains
- Special conformation
- Swelling

2. **Environmental related factors**

- P^H of polymer substrate interface
- Applied strength
- Initial contact time

3. Physiological factors

- Mucin turnover
- Disease state

Polymer related factors

i) Molecular weight: Numerous studies have indicated that there is a certain molecular weight at which bio adhesion is at a maximum. The *interpenetration* of polymer molecule is favorable for low molecular weight polymers whereas *enlargements* are favoured for high molecular weight polymers.

ii) Flexibility of Polymer chains: As water soluble polymers become cross-linked, the mobility of the individual polymer chain decreases. As the cross-linking density increases, the *effective length* of the chain which can penetrate into the mucus layer decreases even further and mucoadhesive strength is reduced.

iii) Spatial conformation: Besides molecular weight or chain length, spatial conformation of a molecule is also important. The helical confirmation of dextran may shield many adhesively active groups primarily responsible for adhesion, unlike PEG polymers which have a linear confirmation.

2. Environment Related Factors

i) pH: pH was also found to have a significant effect on mucoadhesion as observed in studies of polyacrylic polymers cross-linked with -COOH groups. pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density, depending on pH, because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone. Maximum adhesion was observed at pH 5 and 6 and minimum at pH 7.

ii) Applied Strength: To place a solid bioadhesive system, it is necessary to apply a defined strength. The *adhesion strength* increases with the *applied strength* or with the duration of its application, upto an optimum. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with mucin.

iii) **Initial contact time:** The initial contact time between mucoadhesives and the mucus layer determines the extent of *swelling* and the *interpenetrations* of polymer chains. Along with the initial pressure, the initial contact time can dramatically effect the performance of a system. The mucoadhesive strength increases as the initial contact time increases.

iv) **Degree of hydration:** Depending on the degree of hydration adhesion properties will be different. It is maximum at a certain degree of hydration. When the degree of hydration is high, *adhesiveness* is lost probably due to formation of slippery, non-adhesive mucilage in an environment of large amount of water at or near the interface.

THEORIES OF BIOADHESION[13,14,15]

- ✓ Electronic Theory
- ✓ Wetting Theory
- ✓ Diffusion Theory
- ✓ Adsorption Theory
- ✓ Fraction Theory

Electronic Theory

This theory depends on the assumption that the bio adhesion material and the target biological material have different electronic structures. On this assumption when the two material come and contact with each other, the electron transfer will occur. These electron transfer results in the formation of double layer of electrical charge at bio adhesive – biological adhesive interface. Hence these interface can be treated as a capacitor. The system is charged when the adhesive and substrate are in contact and discharged when they are separated.

Wetting theory

The ability of the adhesive layer to spread spontaneously on mucin influences development of intimate contact between the mucoadhesive and mucin and consequently influences the mucoadhesion strength. The thermodynamic work of adhesion is a function of surface tension of surface in contact as well as interfacial tension. A small value interfacial tension would be a more intimate contact between the two surfaces.

Adsorption theory

This theory states that bio adhesion bond formed between an adhesive substrate and tissue as a mucus is due to vanderwall interactions, hydrogen bonds and related forces. Although these forces individually weak, the sheer number of interactions a whole produce intense adhesive strength.

Diffusion theory

The concept that interpenetrations and entanglement of bio adhesive polymer chains and mucus polymer chains produced semi permeable adhesive bonds and is separated by diffusion theory.

It is believed that the bond strength increases with degree of penetration of the polymer chains in to the mucus layer. Penetration of polymer chains into the mucus network and vice versa is depends upon the concentration gradients and diffusion coefficients. Interpretation is required to produce an effective bio adhesion bond, it has not been determined exactly, but it is believed to be in the range of 0.2-0.5µm.

The penetration of depth (l) = $(t\text{-}Db)^{1/2}$

where, t = time of contact; Db= diffusion coefficient of the bio adhesive material in mucus.

Fracture theory

This theory analysis the force required to separate two surfaces after adhesion. The maximuim tensile stess produced during detachment can be determined by dividing the maximium force detachment(Fm) by total surface area (A_0) involved in the adhesive interaction.

$Sm = Fm/A_0$

In a uniform single component system, fracture strength (S_f), which is equal to maximium stress of detachment (Sm)is proportional to fracture energy (g_c), youngs modulus of elasticity (E) and the critical crack length (C) of fracture site as described.

$S_f \sim (g_c E/C)$

Fracture enery g_c can be obtained from sum of reversible work of adhesion.

$G_c = Wr + Wi$

Where, Wr = energy required to produce new fracture surface ; Wi = plastic deformation at the tip of growing.

The elastic modules of system (E) is stress(s) and strain(c) through Hook's law.

$E= [\sigma/\varepsilon]_{\varepsilon \rightarrow 0} = [F/A_0/\delta l/t_0]$

Types of Bio adhesive Formulations[16,17]

1. Solid Bio adhesive Formulations: Examples of such formulations are given below.

Tablets: Dry formulations such as tablets are able to form strong interactions with mucosal surfaces by attracting water from the mucosal surface. **Inserts:** These include ocular inserts such as eye drops and eye gels. **Lozenges:** Bioadhesive lozenges containing antibiotics and local anaesthetics can be used topically to treat conditions affecting the mouth.

2. Semi-solid bio adhesive Formulations Gels: Bio adhesive polymers that are able to form gels include *polyacrylic acid* which adheres to mucosal surfaces in a cross-linked form. **Films:** Bio adhesive films that are flexible in nature can be used to directly deliver drugs to specific mucosal membranes.

3. Liquid Bio adhesive Formulations

Viscous liquids: Viscous liquids containing bioadhesive polymers such as carboxymethyl cellulose may be used to protect mucosal membranes from damage and irritation. **Gel-forming liquids:** These formulations are administered as liquids but undergo a change in their form in response to conditions such as temperature and pH. Such formulations are used for the controlled-release of drugs into the eye.

POLYMERS

Definition

A polymer is a substance formed by the linkage of a large number of small molecules known as monomers. A bio adhesive polymer is a synthetic or natural polymer which binds to biological substrates such as mucosal membranes.[18,19,20]

Three categories of bio adhesive polymers

- Polymers that become sticky when placed in water and owe their bioadhesion to stickiness.
- Polymers that adhere through non-specific, non-covalent interactions which are primarily electrostatic in nature.
- Polymers that bind to specific receptors sites on the cell surfaces.

Characteristics of bio adhesive polymers

- In order for polymers to adhere to mucosal surfaces or epithelial cell they must ideally possess certain characteristics:
- **Flexibility**- The flexibility of bio adhesive polymers is important because it controls the extent of the interpenetration between the polymers and mucosal/epithelial surfaces.
- **Hydrophilicity** – Polymers that are hydrophilic in nature are able to form strong adhesive bonds with mucosal membranes because the mucus layer contains large amounts of water.
- **Hydrogen bonding** – Hydrogen bonding between the entangled polymer chains forms strong adhesive bonds, therefore the presence of hydrogen bond – forming groups such as OH and COOH groups are vital in large quantities.
- **High molecular weight** – Polymers with a high molecular weight are desirable because they provide more available bonding sites.
- **Surface tensions** – Surface tensions are needed to spread the bioadhesive polymer into the mucosal layer epithelial surface.

Examples

Bioadhesive polymers come from both natural and synthetic sources, some common examples are highlighted below.

- **Acacia gum** - This natural polymer is a dried gum obtained from the stem and branches of the tree *Acacia Senegal.* It is used as a thickener in pharmaceuticals.
- **Alginic acid** – Is a natural polymer found in the cell walls of brown algae. It is widely used in the manufacture of alginate salts such as sodium alginate which is a constituent of Gaviscon liquid®.
- **Carbomers** – Are polyacrylic acid polymers widely used in the pharmaceutical and cosmetic industries as thickening agents.
- **Hydroxypropyl methylcellulose (HPMC)** – This polymer is included in preparations used to moisten contact lenses and in oral gels.
- **Sodium hyaluronate -** A high molecular weight biological polymer made of repeating disaccharide units of glucuronic acid and N-acetyl-D - glucosamine.
- **Other examples of polymers include**: Pectin, Polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Tragacanth.

Different Types of Bio adhesive Formulations

- OCCULAR BIOADHESIVE DRUG DELIVERY
- VAGINAL BIOADHESIVE DRUG DELIVERY SYATEM
- BUCCAL BIOADHESIVE DRUG DELIVERY SYSTEM
- NASAL BIOADHESIVE DRUG DELIVERY SYSTEM

EVALUTION OF BIO ADHESIVE DRUG DELIVERY SYSTEM[21,22,23,24]

❖ **In vitro / ex vivo methods**

- Methods based on measurement of tensile strength
- Methods based on measurement of shear strength
- Methods based on detachment of stress
- Other methods in vitro methods
  - Adhesive weight method
  - Fluorescent probe method
  - Flow channel method
  - Analytical ultracentrifuge criteria for muco adhesion
  - Falling liquid film method
  - Colloidal gold staining method
  - Direct staining method.
  - Visco metric method
  - Thumb test
  - Adhesion number
  - Electrical conductance
  - Atomic force microscopy
  - Determination of peel strength

❖ **In vivo methods**

- Use of radio isotopes
- Use of gamma scintigraphy

Determination of tensile strength

Tensile strength can be defined as the strength of material expressed as the greatest longitudinal stress it can bear without tearing apart. As it is the maximum load applied in breaking a tensile test piece divided by the original cross-sectional area of the test piece, it is

measured as Newton's/sq.m. Specifically, the tensile strength of a material is the maximum amount of tensile stress that it can be subjected to before failure. The definition of failure can vary according to material type and design methodology.

There are three typical definitions of tensile strength:

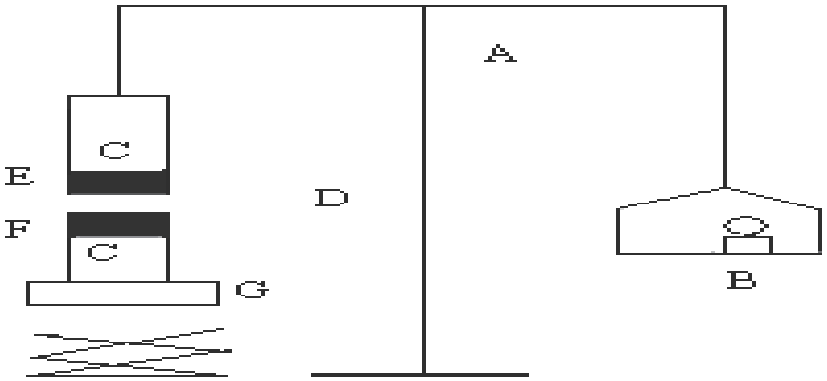
- **Yield Strength** — The stress a material can withstand without permanent deformation.
- **Ultimate Strength** — The maximum stress a material can withstand.
- **Breaking Strength** — The stress coordinate on the stress strain curve at the point of rupture.

Determination of shear strength:. Shear stress, τ is the force acting tangentially to a surface divided by the area of the surface. It is the force per unit area required to sustain a constant rate of fluid movement. Mathematically, shear stress can be defined as:

$\tau = F/A$ Where, τ shear stress; F force; A area of the surface subjected to the force.

Detachment stress

The mucoadhesive forces of the bilayer tablets were determined by the measuring device shown in Fig. 2.



*A, modified balance; B, weights; C, glass vial; D, Bioadhesive Bilayer tablet; E, Intestine tissue; F, supportive adhesive tape; G, height adjustable pan .

Fig: 2- Determination of tensile strength.

OTHER INVITRO METHODS[25-27]

Adhesion weight method

Smart & kellaway developed a test system where suspension of ion –exchange resin particle flowed over the inner mucosal surface of a section of guinea-pig intestine and the weight of the adhered particles determined. Although the method was of limited value due to poor data

reproducibility results, from fairly rapid degeneration and biological variation of the tissue, it was possible from to determine the effect of particle size and charge on the adhesion after five minutes contact with everted intestine.

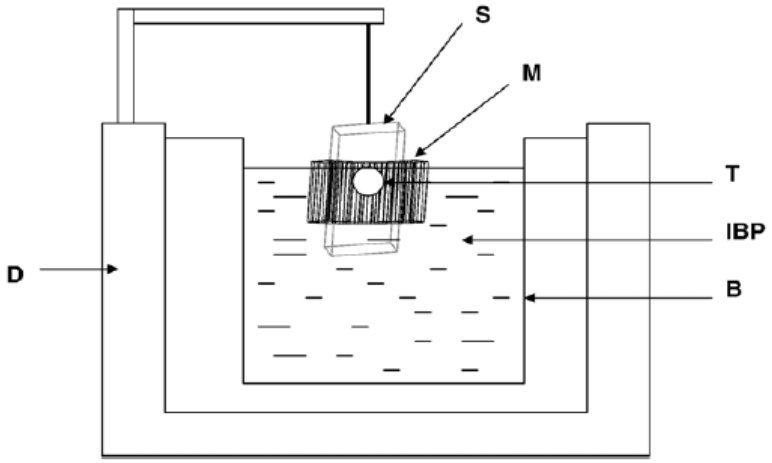


Figure 3: Schematic diagram of the apparatus used for the determination of a adhhesion time. S: glass slab; D: disintegration apparatus; B: glass beaker; M: mucosal membrane; T: mucoadhesive tablet; IBP: Isotonic phosphate buffer.

Fluorescent probe method

In this method the membrane lipid bilayered and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were mixed with the mucoadhesive agents and changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

Flow channel method

They study was done in an attempt to understand structural requirements for bioadhesion in order to design improved bioadhesive polymers for oral use. The membrane lipid bilayer and membrane proteins were labeled with pyrene and fluorescence isothiocyanate, respectively. The cells were then mixed with candidate bioadhesives and the change in florescence spectra was monitored. This gave and indication of polymer binding and its influence on polymer adhesion.

Analytical ultracentrifuge criteria for mucoadhesion

These methods are useful in identifying the material that is able to form complexes with the mucin. The assay can be done for change in molecular mass using sedimentation equilibrium,

but this has an upper limit of less than 50MDa. Where mucin is available in only miniscule amounts, a special procedure known as Sedimentation Fingerprinting can be used for assay of the effect on the mucoadhesive. UV absorption optics is used as the optical detection system. However, in this case the mucoadhesive is invisible, but the pig gastric mucin at the concentrations normally employed is visible.

Falling liquid film method

Small intestine segments from rats were placed at inclination of a tygon tube flute. The adhesion of particles to this surface was monitored by passing the particles suspension over the surface. By comparing the fraction of particles adhere to the tissue the adhesion strength of different polymers can be determined.

Colloidal gold staining method

Park proposed the colloidal gold staining technique for the study of bioadhesion. The technique employs red colloidal gold particles, which were adsorbed on mucin molecules to form mucin–gold conjugates, which upon interaction with bioadhesive hydrogels develops a red color on the surface. This can be quantified by measuring at 525 nm either the intensity on the hydrogel surface or the conjugates.

Viscometric method

Katarina Edsman has studied the dynamic rheological measurements on gels containing four different carbopol polymers and the corresponding mixtures with porcine gastric mucin and bovine submaxillary mucin. The method does not give the same ranking order when two different comparison strategies were used.

Thumb test

This is a very simple test used for the qualitative determination of peel adhesive strength of the polymer and is useful tool in the development of buccal adhesive delivery systems. The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time.

Electrical conductance. Bremakar used modified rotational viscometer to determine electrical conductance of various semi-solid mucoadhesive ointments and found that the electrical conductance was low in the presence of adhesive material.

Determination of peel strength

The peel adhesion tests are mainly used for buccal and transdermal patches. The test is based on the calculation of energy required to detach the dosage form from the substrate material (usually excised buccal mucosa) attached through the bioadhesive material in the direction as shown in Fig.

Fracture Energy (G)

$$G = \frac{P(1-Cos\ \theta)}{w} = W\phi(1+k)$$

Where P is the peel force; w is the peel width; W° is the intrinsic work of adhesion and k is the proportionality constant that accounts for hysteretic losses. Peel work is the sum of the following components.

CONCLUSION

However, the exploitation of specific structural or chemical features for the development of drug delivery platforms has only started. A good balance between excellent adherence, prolonged residence time, controlled drug release and low irritation potential, tolerability and acceptance by the patients must be achieved. In liquid dosage forms, such as viscous eye drops where polymer solutions are fully hydrated before instillation, the mucoadhesive performance is limited. Mucoadhesion is based on entanglement or non-covalent bonds between polymers and mucus. Increased polymer concentration in semi-solid dosage forms enhances the possibility for interactions and entanglement with mucus. In highly concentrated dispersions however, chain flexibility and the length available for interpenetration decrease. A controlled release from microspheres or nanospheres could enhance drug bioavailability. Small, mucoadhesive solid dosage forms, in particular gel-forming mini tablets and erodible inserts, show interesting in vivo performances and allow for therapeutic levels to be obtained over an extended period of time in the tear film and anterior chamber. Sustained release can be modulated by the composition and manufacturing procedure. Mucoadhesive polymers are very promising candidates for systemic and local vaginal drug delivery. There is still ongoing research dealing with muco (bio)adhesive vaginal formulations that are capable of delivering the active agent for an extended period at a predictable rate. To date most of the existing dosage forms are based on the synthetic polyacrylates but in the near future natural compounds such as chitosan or carrageenan and new derivatives will gain more significance.

The recent improvement in the area of targeted drug delivery holds great promise. Unfortunately, only a few studies have been conducted with new generation mucoadhesive

polymers for buccal drug delivery. With advantages such as an increase in the residence time of the polymer, site-specific adhesion, penetration enhancement, and enzymatic inhibition, site-specific mucoadhesive polymers will undoubtedly be utilized for the buccal delivery of a wide variety of therapeutic compounds. This class of polymers has enormous potential for the delivery of therapeutic macromolecules. There are a lot of exciting developments in the field of NDD including mucoadhesion. Newly marketed products based on existing polymers are on the increase, while new polymers and administration devices are still being developed. There is a lot of ground for optimism with respect to benefits derivable from more fundamental research and application leading to better understanding of the subject and eventually more marketed products.

REFERENCES

1. K.P.R.Chowdary A Review on current status on Mucoadhesive Drug Delivery System Indian Drugs, September 2000; 37(9): 400-404.
2. S.P.Vyas And Roop K.Khar Controlled Drug Delivery Concepts And Advances, 257-314.
3. Nagai T, Konishi R, Buccal/gingival Drug Delivery Systems. J Control Release, 1987; 6: 353-60.
4. Duchene D, Touchard F, Pappas NA. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev Ind Pharm, 1988; 14: 283-318.
5. S. B. Patil, R. S. R. Murthy, H. S. Mahajan, R. D. Wagh, S. G. Gattani, *Pharm Times*, 2006; 38(4): 25-28.
6. J Swarbrick, JC. Boylon, "Encyclopedia of Pharmaceutical Technology" Marcel Dekker, Volume-10, 458-460.
7. A Semalty, M Semalty. Pharmainfonet, 2006.
8. N. Vivien, R. Gaurl, Parshoen, M. Madan, *Euro J Pharm Biopharm*, 2002; *50*: 109-
9. B Jasti, X Li, *Pharmatech*, 2003; 53-58.
10. Smart J.D, The basics and underlying mechanisms of mucoadhesion, Adv. Drug Deliv. Rev, 2005; 57: 1556-1568.
11. R. Khanna, S. P. Agrawal and Alka Ahuja, *Indian J pharm sc*, 1998; 1: 1-11.
12. Toress D., Cunna, M., Alonso M.J, *Euro J Pharm Biopharm*, 2001; *51*: 199-205.
13. AK. Shingla, M Chawla, A Singh. *Drug Devel Indust Pharm*, 2000; 9: 913-914.
14. R.Bala Rane sha Chary and Y. Madhusudan Rao, *Drug Dev and Ind Pharm*, 26(8).
15. K.P.R.Chowdary A Review on current status on Mucoadhesive Drug Delivery System Indian Drugs, September 2000; 37(9): No.400-404.

16. Ghandhi R.B.etal 591-594. Drug Delivery Systems. J Control Release, 1987;
17. D Tivari, R Sause and PL. Madan; *AAPS Pharmscitech*, 1999; 1(3): 13.
18. NA Naffee, FA Ismail, NA. Boraje, *Drug Devel. Indust. Pharmacy*, 2004; 30(9): 995-1004.
19. K.P.R. Chowdary and G.Balatripura Sundari, *Indian J. pharm. Sci*, 2003; 65(6).
20. Chowdary K.P.R, and Kamlkara reddy G, *Indian Drugs*, 2002; 39(4): 225-229.
21. Lalla J.K and Gurnancy R.A., Indian Drug, 2002; 39(5): 270-276.
22. Collins E.M, Deasy P.B, MacCarthy D.J, Shanley D.B, Evaluation of a controlledrelease compact containing tetracycline hydrochloride bonded to tooth for the treatment of periodontal disease, Int. J. Pharm, 1989; 51: 103-114.
23. Samaranayake L.P, Ferguson M.M, Delivery of antifungal agents to the oral cavity, Adv. Drug Deliv. Rev, 1994; 13: 161-179.