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A REVIEW – MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Now days, drug action may be improved by developing innovative drug delivery system to improve safety, efficacy, and patient compliance. One such delivery system is mucoadhesive buccal drug delivery system. Mucoadhesive buccal drug delivery has many advantages over conventional drug delivery system. The phenomenon of mucoadhesion in drug delivery was introduced in the early 1980s. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for extended periods of time by the help of interfacial forces. This review focus on theories and properties of mucoadhesion, factors affecting mucoadhesion, evaluation method, types of dosage form permeation enhancer.

INTRODUCTION

The concept of bioadhesion refers to any bond formed between two biological surfaces or bond between a biological and synthetic surface. The administration of drugs by transdarmal or transmucosal routes offers the advantage of being relatively painless [1, 2].The term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In other words mucoadhesion drug delivery system may be defines as drug delivery system that utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to particular region of body for extended period of time.Mucoadhesion is used when the bond is formed with the mucosal surface. Mucosalmembranes of human organism are relatively permeable and allow fast drug absorption. Mucin is important glycoprotein of mucus and is responsible for its structure. Protecting and lubricating the epithelium is main function of mucus.

Mucosal drug delivery systems include the following;

- Buccal drug delivery system
- Oral drug delivery system
- Vaginal drug delivery system
- Rectal drug delivery system
- Nasal drug delivery system
- Ocular drug delivery system

Amongst the various route, buccal route of drug delivery is a good alternative. However oral administration of drugs has demerits such as hepatic first pass metabolism and enzymatic degradation within GI tract, that prohibit oral administration of certain classes of drug especially peptides and proteins. The buccal mucosa lines the inner cheek and buccal formulations are placed in the mouth between the upper gingival (gums) and cheek to treat local and systemic conditions.

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM [3]

- Improve Patient compliance due to elimination of pain occurring from injection.
- Ease of drug administration.
- Sustained drug delivery.
- Can be administered to unconscious patients.
- Termination of therapy is easy.

- Drugs with poor bioavailability, via the oral route can be administered conventionally.
- Provides reduction in dose and side effects.
- Drug is protected from degradation in the acidic environment in gut.
- Rapid onset of action.
- Extent of perfusion is more therefore quick and effective absorption.
- Nausea and vomiting are avoided.

LIMITATION OF BUCCAL DRUG DELIVERY SYSTEM[4,5]

- Drugs that irritate the mucosa or have a bitter or unpleasant test or cause allergic reaction cannot be administered.
- If formulation contains antimicrobial agents, affects the natural microbes in the buccal cavity.
- Administered only small dose requirement of drug.
- Drugs which absorbed by passive diffusion can be administered.
- Eating and drinking become restricted.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Less surface area is available for absorption.
- Buccal mucosa is relatively less permeable than small intestine, rectum etc.

COMPOSITION OF MUCUS LAYER[6]

General composition:

1. Water 95%
2. Glycoprotein and lipids ..... 0.5 to 5%
3. Mineral salts 1%
4. Free proteins ..... 0.5 to 1%

MECHANISM OF MUCOADHESION/ BIOADHESION[7,8]

The mechanism responsible for formation of bond is not completely clear. Inorder to develop idea mucoadhesivebuccal drug delivery system, it's important to describe and understand the forces that are responsible for adhesive bond formation.

Bond formation describe in 3 steps, mentioned below;

- Wetting and swelling of polymer to permit intimate contact with biological tissue,
- Interpretation of bioadhesive polymer chains and entanglement of polymer and Mucin chains,
- Formation of weak chemical bonds between entangled chain.

Adhesion of polymers to tissues may be achieved by;

a. Primary ionic or covalent chemical bonds
b. Secondary chemical bonds
c. Physical or mechanical bonds

FACTORS AFFECTING MUCOADHESION[9,10,11,12]

- **Polymer based factors.**

i. Molecular weight of polymer
ii. Concentration of polymer used
iii. Flexibility of polymer chain
iv. Swelling factors steriochemistry of polymer.

- **Physical factors substrate interface.**

1. pH at polymer
2. Applied strength
3. Contact time

- **Physiological factors rate**

I. Mucin turn over
II. Diseased state

- **THEORIES OF MUCOADHETION**

There are six theories of mucoadhesion are mentioned below;

I. Fracture theory
II. Electronic theory
III. Diffusion theory
IV. Adsorption theory.
V. Wetting theory.

1) FRACTURE THEORY[19,20]

This theory analyzes the forces required to separate two surfaces after adhesion. The maximum tensile strength (α_m) produced during detachment can be determined by dividing the maximum force of detachment ,F_m, by the total surface area (A_0) involved in the adhesion interaction.

$$\alpha_m = F_m/A_0$$

In a uniform single component system, fracture strength (sm) , is proportional to fracture energy(gc), Young's modules of elasticity (E) and critical crack length © of the fracture site, as described in the following equation (Kammer , 1983),

$$\alpha_f \_ (\gamma c\ E/C)^{1/2}$$

The fracture theory can be obtained by the sum of the reversible work of adhesion, W_r(work done to produce new fracture surfaces) and the irreversible work of adhesion , W_i (work of plastic deformation),

$$gc = W_r + W_i$$

2) ELECTRONIC THEORY[15,16]

The electronic theory depends on the assumption that the bioadhesive material and the target biological material have different electronic surface characteristics. Thus, when two surfaces come In contact with each other, electron transfer occurs in an attempt to balance the Fermi levels, resulting in the formation of double layer of electrical charges at the interface of the bioadhesive and the biologic surface. The bioadhesive force is believed to be present due to the attractive forces across this double layer.

3) DIFFUSION THEORY[17]

Diffusion theory describes the interpenetration of both polymers and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. In this, with the degree of penetration of polymer chains the adhesion force increases (Mathiowitz, Chickering.Lehr.1999). This penetration rate depends on the diffusion coefficient, flexibility and nature of mucoadhesive chains, motility and contact time (Hagerstrom, 2003; Huang et al., 2000; Lee Park, Robinson; Smart, 2005). It is believed that interpretation in the range of 0.2-0.5µm is required to produce effective bond strength. The penetration depth (I) can be estimated by,

$$I = (tD_b)^{1/2}$$

Where, t = time of contact and

D_b = diffusion coefficient of the bio adhesive material in the mucus.

4) ADSORPTION THEORY:-

In this theory, mucoadhesive device adheres to the mucus by secondary chemical interaction, such as in van der Waals and hydrogen bonds, electrostatic or hydrophobic interactions.

5) WETTING THEORY[13,14,18]

The ability to spread spontaneously on mucin influences development of intimate contact between the mucoadhesive and mucin and consequently influences the mucoadhesive strength. The thermodynamic work of adhesion is a function of the surface tension of the surface in contact as well as the interfacial tension. A small value of interfacial tension would mean a more intimate contact between the two surfaces (Helfand and Tegami, 1971).

- **Basic components of buccal drug delivery system:-**
  1) **Drug substance**
  2) **Bioadhesive polymers**
  3) **Backing membrane**
  4) **Permeation enhancers**[21,22]

1. **Drug substance:**[26]

The selection of suitable drug for the design of buccoadhesive drug delivery systems should be based on pharmacokinetic properties.

The drug should have following characteristics:

- The conventional single dose of the drug should be small
- The drug having biological half life between 2-8 hours is good candidates for controlled drug delivery.
- T_{max} of the drug shows wider-fluctuations or higher values when given orally.
- Through oral route drug may exhibit first pass effect or presystematic drug elimination
- The drug absorption should be passive when given orally.

1) BIOADHESIVE POLYMER[23]

Polymers are also in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of releases of drug. An ideal polymer for buccoadhesive drug delivery systems should have following characteristics.

- It should inert and compatible with the environment.
- The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
- It should adhere quickly to moist tissue surface and should posses'some site specificity.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and the economical.
- It should allow easy incorporation of drug in to the formulation.

Criteria followed in polymer selection:-

- It should form a strong non covalent bond with the mucin/epithelium surface.
- It must have high molecular weight and narrow distribution.
- It should be compatible with the biological membrane.

2) BACKING MEMBRANE[27]

Backing membrane is important in attachment of bioadhesive devices to the mucus membrane .The material should be inert, and impermeable to the drug and permeation enhancer.This prevent drug loss and gives patient compliance.

Ex., carbopol, magnesium stearate, HPMC, HPC, CMC, Polycarbophil etc.

3) PERMEATION ENHANCER:-

Substrates that facilitate the permeation through buccal mucosa are referred as permeation enhancers. It increases the membrane permeation rate or absorption rate of a co-administered drug. They improve bioavailability without causing toxicity. Enhancer efficacy depends on the physiochemical properties of drug, administration site, nature of vehicle, and whether enhancer is used alone or in combination.

MECHANISM OF ACTION OF PERMEATION:-

1) Changing mucus rheology:

- By reducing the viscosity of the mucus and overcomes this barrier.

2) Increasing the fluidity of lipid bilayer membrane:-

- Disturb the intracellular lipid packing interaction with either lipid packing by interaction with either lipid or protein components.

3) Acting on the component at tight junctions:-

- By inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier.
- In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

4) Increasing the thermodynamic activity of drugs:-

- Some enhancers' increase the solubility of drug there by alters the partition coefficient.

Examples of permeation enhancers;

1) **Surfactant and Bile salts** :- Sodium glycodeoxycholate
   Sodium dodecyl sulphate
   Sodium lauryl sulphate
   Polysorbate 80
2) **Fatty acids** :- Oleic acid
   Cod liver oil
   Capric acid
   Lauric acid

3) **Polymers and polymer** :-Chitosan

DerivativesTrimethylChitosan

Chitosan-4-thiobutylamide

4) **Others** :- Ethanol

Azone

Octisalate

Padimate

Menthol

- **BUCCAL FORMULATIONS:-**

The buccal formulations are mentioned below;

1) Buccal patches and films
2) Buccal semisolids (Ointments and gels)
3) Buccal powders
4) Buccal tablet

1) BUCCAL PATCHES AND FILMS[25]

Buccal patches consist of two poly laminates or multilayered thin film round or oval as consisting of bioadhesive polymeric layer and permeable backing layer. Flexible films/patches have been prepared either by solvent casting or hot melt extrusion techniques to deliver drugs directly to a mucosal membrane.

Ex.buccoadhesive film of clindamycin used pyorrhea treatment.

2) BUCCAL SEMISOLID DOSAGE FORMS[24]

A buccal semisolid dosage form consists of fine powder natural or synthetic polymer dispersed in polyethylene or in aqueous solution.

EX. Gels, Ointment, or a base.

3) BUCCAL POWDER DOSAGE FORMS:-

Buccal bioadhesive powder dosage forms are the mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa.

4) BUCCAL TABLET:-

- Adhesive tablets are held between gum and cheek.
- Generally flat, elliptical or capsule shaped.
- Troches & lozenges are two other types of tablets used in oral cavity where they are intended to expert a local effect in the mouth or throat.
- Buccoadhesive tablet may be monolithic or bilaminated system.

- Monolithic is multidirectional release
- Bilayer containing core layer and backing layer.
- Backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated castor oil or may be polymeric coating layer.
- Backing layer avoids sticking of the tablet to the finger during application

- **EVALUATION OF BUCCAL TABLETS[28]**
  - In vitro swelling rate and bioadhesion studies
  - In vitro surface pH studies
  - In vitro drug release studies
  - In vitro permeation studies
  - In vitro mucoadhesion strength
  - In vitro residence time
  - In vitro release studies
  - Stability studies in human saliva
  - Ex viva release studies
  - Ex vivo mucoadhesion time
  - Ex vivo transmucosal permeation studies.

- **Evaluation of Mucoadhesive Buccal Drug DeliverySystems**

A. In Vivo Methods:

In vivo methods were firstoriginated by Beckett and Triggs[35] with the socalled*buccal absorption test.* Using this method, thekinetics of drug absorption were measured. The methodologyinvolves the swirling of a 25 mL sample ofthe test solution for up to 15 min by human volunteersfollowed by the expulsion of the solution. The amountof drug remaining in the expelled volume is thendetermined in order to assess the amount of drugabsorbed. The drawbacks of this method include salivarydilution of the drug, accidental swallowing of aportion of the sample solution, and the inability tolocalize the drug solution within a specific site (buccal,sublingual, or gingival) of the oral cavity. Variousmodifications of the buccal absorption test have beencarried out correcting for salivary dilution and accidentalswallowing, but these modifications also sufferfrom the inability of site localization. A feasible approachto achieve absorption site localization is toretain the drug on the buccal mucosa using a bioadhesivesystem [36,37]. Pharmacokinetic parameterssuch as bioavailability can then be calculated from theplasma concentration vs time profile. Other in vivomethods include those carried out using a small perfusionchamber attached to the upper

lip of anesthetizeddogs. The perfusion chamber is attached to thetissue by cynoacrylate cement. The drug solution iscirculated through the device for a predetermined periodof time, and sample fractions are then collectedfrom the perfusion chamber (to determine the amountof drug remaining in the chamber) and blood samplesare drawn after 0 and 30 min (to determine amount ofdrug absorbed across the mucosa) [36,37].

B. **In Vitro Release Study** [38,39]:

A number ofin vitro release methods have been developed forsimulating in vivo conditions for buccal formulations.However, no standard in vitro method has yet beendeveloped. Different workers have used apparatuswith varying designs and different conditions, dependingon the shape and application of the dosage formdeveloped. They are as follows:

- Beaker method
- Interface diffusion system
- Modified KesharyChien cell
- Dissolution apparatus

CONCLUSION

The concept of mucoadhesion is a novel drug delivery system. It has many advantages over the other routes of administration like prolongation of the residence time of the drug which in turn increasethe absorption of the drug are important in oral bioavailability of many drugs. . Mechanism of mucoadhesion is backed up by ionic bond, covalent bond, Vander Waal bond and hydrogen bond. Ionic and covalent bonds results in very strong mucoadhesive property. Mucoadhesion commence with wetting which is described as contact stage.

REFERENCES

1. Robinson, D. H.; Mauger, J. W. Drug delivery systems. Am. J. Hosp. Pharm. 1991, 48, S14 –S23.
2. Ullyot, S. C. Paediatric premedication. Can. J. Anaesth.1992, 39, 533–536.
3. G.S. Asane, mucoadhesive gastro intestinal drug delivery system: an overview, vol. 5 issue 6,(2007).
4. Khanna, R.; Agarwal, S. P.; Alka, A. Mucoadhesivebuccal drug delivery: a potential alternative to conventional therapy. Indian J. Pharm.Sci. 1998, 60 (l), 1–11.
5. Vyas, S. P.; Khar, R. K. Controlled Drug Delivery—Concepts and Advances, 1st ed.; VallabhPrakashan: New Delhi, 2002
6. Lehr, C. M. Lectin-mediated drug delivery, generation of bioadhesives. J. ControlledRelease 2000, 65 (1–2), 19 –29.
7. Longer, M. A.; Robinson, J. R. Fundamental aspects of bioadhesion. Pharm. Int. 1986, 7, 114 –117.
8.. Gandhi, R. B.; Robinson J. R. Oral cavity as a site for bioadhesive drug delivery. Adv. DrugDeliv. Rev. 1994, 13 (1–2), 43–74.
9. Tiwari, D.; Goldman, D.; Sause, R.; Madan, P. L. Evaluation of polyoxyethylenehomopolymers for buccal bioadhesive drug delivery device formulations. AAPS PharmSci1999, 1 (3), 50 –57.
10. Lee, J. W.; Park, J. H.; Robinson, J. R. Bioadhesive- based dosage forms: the next generation. J. Pharm. Sci. 2000, 89 (7), 850 – 866.
11. Huang, Y.; Leobandung, W.; Foss, A.; Peppas, N. A. Molecular aspects of muco- and bioadhesion: tethered structures and site-specific surfaces. J. Controlled Release 2000, 65 (1–2), 63–71.

11. Hagerstrom, H.; Paulsson, M.; Edsman, K. Evaluation of mucoadhesion for two polyelectrolyte gels in simulated physiological conditions using a rheological method. Eur. J. Pharm. Sci. 2000,9 (3), 301–309.
12. Hagerstrom, H.; Paulsson, M.; Edsman, K. Evaluation of mucoadhesion for two polyelectrolyte gels in simulated physiological conditions using a rheological method. *Eur. J. Pharm. Sci.* 2000,*9* (3), 301–309.
13. Ugwoke, M. I.; Agu, R. U.; Verbeke, N.; Kinget, R. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. *Adv. Drug Deliv.Rev.* 2005, *57* (11), 1640 –1665.
14. van Wachem, P. B.; Bantjes, A.; Detmers, J. P.; van Aken, W. G. Interaction of cultured human endothelial cells with polymeric surfaces of different wettabilities. *Biomaterials* 1985, *6* (6), 403-408.
15. Dodou, P.; Breedveld, P.; Wieringa, P. A. Mucoadhesivesin the gastrointestinal tract: revisiting the literature for novel applications. *Eur.J. Pharm. Biopharm.* 2005, *60* (1), 1–16.
16. Derjaguin, B. V.; Smilga, V. P. The electronictheory of adhesion. In: *Adhesion: Fundamentalsand Practice;*University of Notingham, EnglandandGordon& Breach: New York, 1996.
17. Andrews, G. P.; Laverty, T. P.; Jones, D. S.Mucoadhesive polymeric platforms for controlleddrug delivery.*Eur. J. Pharm. Biopharm.*2009, *71* (3), 505–518.
18. Peppas, N. A. Surface, interfacial and molecularaspects of polymer bioadhesion on soft tissues.J. Controlled Release1985, *2,257.*
19. Gupta, A.; Garg, S.; Khar, R. K: Mucoadhesivebuccal drug delivery systems: areview. *IndianDrugs* 1992, *29* (13), 586 –593.
20. Khar, K.; Ahuja, A.; Javed, A. MucoadhesiveDrug Delivery. In Controlled and Novel DrugDelivery, 1st ed.; Jain, N. K., Ed.; CBS Publishersand Distributors, New Delhi, 1997.
21. Pramod Kumar, T. M.; Desai, K. G.; Shivkumar, H. G. Mechanism of buccal permeation enhancers.Indian J. Pharm. Educ. 2002, *36* (3), 147– 151.
22. McElnay, A. C.; Swarbrick, J.; Boyloan, J. C. Encyclopedia of Pharmaceutical Technology*;* Marcel Dekker: New York; 1988, Vol. 2; p 189.
23. Sudhakar, Y.; Kuotsu, K.; Bandyopadhyay, A. K. Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs. *Release J. Controlled* 2006, *114* (1), 15– 40.
24. Batchelor, H. Novel bioadhesive formulations in drug delivery. The Drug Delivery CompaniesReport 2004, Pharma. Ventures Ltd., Autumn/ Winter.
25. Reddy, P. C.; Rao, Y. M. A review on bioadhesivebuccal drug delivery systems: current status of formulation and evaluation methods. DARUJournal of Pharmaceutical Sciences2011, *19* (6), 385– 403.
26. Wise Donald L, Handbook of Pharmaceutical controlled release technology: 255-265.
27. www.controlled drugdelivery.com
28. Tayal Shivam and Jain Nishiprakash, buccal control drug delivery system: a review, ijpsr, 2011; 2(1): 27-38.
29. Jug, M.; Becirevic-Lacan, M. Influence of hydroxypropyl- B-cyclodextrincomplexation on piroxicamrelease from buccoadhesive tablets. *Eur. J. Pharm. Sci.* 2004, *21,* 251–260.
30. Dowty, M. E.; Knuth, K. E.; Irons, B. K.; Robinson, J. R. Transport of thyrotropin releasing hormone in rabbit buccal mucosa in vitro. *Pharm. Res.* 1992, *9,* 1113–1122.
31. Hosny, E. A.; Elkheshen, S. A.; Saleh, S. I. Buccoadhesive tablets for insulin delivery: invitro and in-vivo studies. *Boll.Chim.Farm.*2002, *141,* 210 –217.
32. Nakane, S.; Kakumoto, M.; Yukimatsu, K.; Chien, Y. W. Oramucosal delivery of LHRH: pharmacokinetic studies of controlled and enhanced transmucosal permeation. *Pharm. Dev.Technol.* 1996, *20* (3), 251–259.
33. Taylan, B.; Capan, Y.; Guven, O.; Kes, S.; Hincal, A. A. Design and evaluation of sustained release and buccal adhesive propronolol hydrochloride tablets. J. Controlled Release1996, *38* (1), 11–20.
34. Lesch, C. A.; Squier, C. A.; Cruchley, A.; Williams, D. M.; Speight, P. The permeability of human oral mucosa and skin to water.J. Dent. Res.1989, *68,* 1345–1349.
35. Beckett, A. H.; Triggs, E. J. Buccal absorption of basic drugs and its application as an in vivo model of passive drug transfer through lipid membranes. J. Pharm. Pharmacol. 1967, *19,* 31S– 41S.
36. Benes, L.; Claustrat, B.; Horriere F. Transmucosal, oral controlled-release, transdermal drug administration in human subjects: A crossover study with melatonin. J. Pharm. Sci. 1997, *86,* 1115–1119.
37. McQuinn, R. L.; Miller, A. L.; Oliver, A. Sustained oral mucosal delivery in human volunteers of buprenorphine from thin non-erodingmucoadhesive polymeric disks. J. Controlled Release1995, *34,* 243–250.
38. Jain, N. K. Controlled Release and Novel Drug Delivery,1st ed.; CBS Publishers and Distributors:New Delhi, 1997; pp 353–370.
39. Sonani, N. G.; Hiremath, S. P.; Dasankoppa, F. S.; Jamakandi, V. G.; Steenivas, S. A. Design and evaluation of gastroretentivemucoadhesive cephalexin tablets. *Pharm. Dev. Technol.* 2010,*15* (2), 178 –183.
40. Ch'ng, H. S.; Park, K.; Kelly, P.; Robinson, J. R. Bioadhesive polymers as platform for oral controlled drug delivery. II. Synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. *J. Pharm Sci.* 1985, *74* (4), 399 – 404.
41. Collins, P.; Squier, C. A. Comparative study of porcine oral epithelium. *J. Dent.Res.* 1981, *60,* 543.