IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
March 2024 Vol.:30, Issue:3

A Review on Mucoadhesive Oral Tablets

IJPPR
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An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 20 February 2024
Accepted: 25 February 2024
Published: 30 March 2024

Keywords: Orally bio adhesion, theories of mucoadhesion, important factors, and mechanism of mucoadhesion.

ABSTRACT

Drug bioavailability can be enhanced by Novel drug delivery system. Mucoadhesive drug delivery system interconnect with the mucus layer covered by the mucosal epithelial surface, and mucin molecules. It Extend the resistance time of the drug at the absorption or application site. mucoadhesion is described as the adhesion between two materials at least one of which is a mucosal surface. The mucosal drug delivery has a high in blood supply and permeability. These system helps to prevent the dosage form from Gastrointestinal secretion (Acid degradation) and avoid first pass metabolism. In this review briefly describes the Introduction to mucoadhesion drug delivery, Bio adhesion, mechanism and approaches in the Mucoadhesive drug delivery system.

INTRODUCTION

Extensive efforts have been made recently to target a drug delivery system in a particular region of the body for an extended period, not only for local targeting of drugs but also for the better control of systemic drug delivery. The concept of mucosal-adhesive or mucoadhesive was introduced into the controlled drug delivery in the early 1980‘s. Mucoadhesives are polymers, which interconnect with the mucus layer covering the mucosal epithelial surface and mucin molecule. Mucoadhesive systems render the treatment more effective and safer not only for topical disorders but also for systemic problems.

BIO ADHESION:

American society of testing and Materials has defined ‒Adhesion‖ as the state in which two surfaces are bound together by interfacial forces.

Good defined Bio adhesion as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. It is also defined as the ability of a material to adhere to a biological tissue for an extended period of time. In biological systems, four types of bio adhesion can be distinguished,

1) Adhesion of a normal cell on another cell,
2) Adhesion of a cell with a foreign substance,
3) Adhesion of a normal cell to a pathological cell,
4) Adhesion of an adhesive to a biological substrate.

For drug delivery purposes, the term bio adhesion implies the attachment of a drug carrier system to a specified biological surface. If adhesive attachment is to a mucus coat, the phenomenon is referred to as ‒Mucoadhesion. Leung and Robinson described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer.

A ‒bioadhesive is defined as a substance that is capable of interacting with biological materials and being retained on them or holding them together for extended period of time. Bioadhesives are classified into three types based on phenomenological observation, rather than on the mechanisms of bioadhesion.

Type I: Bioadhesion is characterized by adhesion occurring between biological objects

without involvement of artificial material. Eg: Cell fusion and Cell aggregation.

Type II: Bioadhesion can be represented by adhesion of a biological phase to an artificial substance. Eg: biological cell adhesion to culture.

Type III: Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues

The idea of muccoadhesive was derived from the need to localize drugs at a certain site in body. Extent of drug absorption can be enhanced by increasing the residence time of the drug at the absorption site. Eg. Ocular drug delivery of less than two minutes are available for drug absorption after instillation of drug into the eye. Since it is removed rapidly by solution drainage, the ability to extend contact time of an ocular drug delivery system in front of the eye would undoubtedly improve bioavailability of drugs. So also in GI tract, since many drugs are absorbed only from the upper part of small intestine. Localising oral drug delivery systems in the stomach or in the duodenum would significantly improve the extent of drug absorption.

Mucoadhesive dosage forms provide intimate contact between dosage form and the absorbing tissue, which may result in high localized drug concentration and hence high drug flux across the absorbing tissue. Furthermore, intimate contact is likely to increase the total permeability of high molecular weight drugs such as peptides and proteins. By incorporating a permeation enhancer, drug absorption through mucus membrane can be enhanced. Thus bioavailability of the drug increases. Drug absorption across nasal mucosa is comparable with drug administered by I.V. infusion. Polymers are used to control the release of drug from the formulation. Hence the release of drug from the formulation is sustained.

THEORIES OF MUCOADHESION (BIOADHESION):

For bioadhesion to occur, a succession of phenomena is required. In initial stage bioadhesion and a membrane get contact by moistening or swelling of biological surface.

In second stage, after contact is established, penetration of the bioadhesive into the crevice of tissue surface or interpenetration of the chains of the bioadhesive with those of the mucus takes place on a molecular level, mucoadhesion can be explained based on molecular interactions. The interactions between two molecules are composed of attraction and repulsion. Attraction interactions arise from Vander Walls forces, electrostatic attraction,

hydrogen bonding and hydrophobic interaction. Several theories have been proposed to explain the fundamental mechanisms of adhesion:

1) **Electronic Theory:** Electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in the electronic structures. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

2) **Absorption Theory:** According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces two types of chemical bonds resulting from these forces can be distinguished:

- Primary chemical bonds of covalent nature, are undesirable in bioadhesion because their strength many results in permanent bonds.
- Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Waals forces, hydrogen bonds and hydrophobic bonds.

3) **Wetting Theory:** Wetting theory is predominantly applicable to liquid bioadhesive systems. It measures the liquid phase, that are spread over the biological systems.

The work of adhesion (W_a) is defined as the energy per square centimeter released when an interface is formed and is expressed in terms of surface and interfacial tension (γ). The work of adhesion is given by,

$$(W_a)=\gamma A + \gamma B - \gamma AB$$

Where A is refer to the biological membrane and B is refer to bioadhesion formulation.

The work of cohesion is given by,

$$(W_c)=2\gamma A \text{ or } 2\gamma B$$

For B is spreading on A is given by,

$$S_{B/A}= \gamma A - \gamma B + \gamma AB$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane.

4) Diffusion Theory: According to diffusion theory, the polymer chains and the mucus

mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact.

5) Fracture Theory: Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion.

$$G = (E_{\varepsilon} \setminus L)^{1\setminus 2}$$

Where E is Young ‘s modulus of elasticity, ε is fracture energy and L is critical

crack length when two surfaces are separated.

FACTORS IMPORTANT TO MUCOADHESION [2,3]:

Bioadhesion power of polymers or polymers is mainly affected by two factors,

1) POLYMER RELATED FACTORS:

a) **Molecular Weight:** The interpenetration of polymer molecules is variable for low molecular weight polymers, whereas entanglements is favored for high molecular weight polymers.

b) **Concentration of Active polymer:** For solid dosage forms such as tablets, the higher the polymer concentration, the stronger the bioadhesion.

c) **Flexibility of polymer:** Flexibility is important for interpenetration and entanglement.

d) **Spatial Conformation**: Bioadhesive power also depends upon the conformation of polymers, i.e. helical or linear. The helical conformation may shield many adhesively active groups, primarily responsible for adhesion, which bind strongly in linear conformation in contrast to the polymer of similar molecular weight.

2) ENVIRONMENTAL-RELATED FACTORS:

a) pH: pH influences the charge on the surface of both mucus and polymers.

Mucus will have a different charge, and density depending on pH, because of differences in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone.

b) Applied Strength: To place a solid bioadhesive system, it is necessary to apply a defined strength. Whatever may be the polymer, the adhesion strength increases with the applied strength or with the duration of its application.

c) Initial Contact time: The initial contact time between the muccoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. The muccoadhesive strength increases as the initial contact time increases.

d) Selection of the Model Substrate Surface: The handling and treatment of biological substrates during the testing of muccoadhesive is an important factor. Physical and biological changes are likely to occur in the mucus gels or tissues under the experimental conditions.

e) Swelling: The swelling characteristic is related to the polymer itself, and also its environment, inter penetration of chains is easier as polymer chains are detangled and free of interactions.

f) Physiological Variables: Mucin turnover and disease states of the mucus layer are physiological variables.

Bioadhesive or Mucoadhesive Polymers:

Bioadhesive polymers are either water-soluble or water-insoluble which form swellable networks joined by cross-linking agents. The polymer should possess optimal polarity to make sure it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

An ideal polymer for a mucoadhesive drug delivery system should have the following characteristics,

 The polymer and its degradation products should be non-toxic and non- absorbable in the gastrointestinal tract.

 It should be non-irritant to the mucus membrane.

 It should preferably form a strong non-covalent bond with the mucin epithelial cell surfaces.

 It should adhere quickly to moist tissue and should possess some site specificity.

 It should allow easy incorporation of the drug and offer no hindrance to its release.

 The polymer must not decompose on storage or during the shelf life of the dosage form.

 The cost of the polymer should not be too high, so that the prepared dosage form remains competitive. Many mucoadhesive polymers are made of either synthetic or natural polymers. Most of the current synthetic muccoadhesive polymers are either Polyacrylic acid or cellulose derivatives. Examples of Polyacrylic acid-based polymers are Carbopol, Polycarbophil, Polyacrylic acid and Polyacrylates. Cellulosic include Carboxy Methylcellulose Hydroxypropyl Methylcellulose, Methylcellulose and Methyl hydroxy ethyl cellulose. In addition, natural muccoadhesive polymers include Chitosan and various gums as Guar, Xanthan, Carragenan, Pectin and Alginates.

DIFFERENT APPROACHES:

The goal of the development of bioadhesive is to duplicate, mimic or improve biological adhesives. Muccoadhesive drug delivery systems utilise the property of bioadhesion of certain water-soluble polymers, which become adhesive on hydration and hence can be used for targeting a drug to a prolonged action. The potential sites for attachment of any bioadhesive system and hence the mucoadhesion drug delivery system may include the following,

i) Buccal Drug Delivery System,

ii) Sublingual Drug Delivery System,

iii) Vaginal Drug Delivery System,

iv) Rectal Drug Delivery System,

v) Nasal Drug Delivery System,

vi) Ocular Drug Delivery System,

vii) Gastrointestinal Drug Delivery System.

ORAL CAVITY:

The oral cavity drug delivery system can be divided as follows,

1) Sublingual Drug Delivery,

2) Buccal Drug Delivery,

3) Local Drug Delivery for the treatment of conditions of the oral cavity, principally Apthous Ulcers, fungal conditions and Periodontal diseases.

ANATOMY OF THE ORAL CAVITY:

The oral cavity is lined by a relatively thick, dense and multilayered mucous membrane of a highly vascularised nature. Drugs penetrating into the membrane can find access to the systemic circulation via a network of capillaries and arteries lying underneath.

The epithelium of the oral cavity is in principle similar to that of the skin, with differences being sited about keratinisation and the protective and lubricant mucus spread across its surface.

It can be divided into three functional zones:

1. The mucus secreting region which consist of the soft palate, the floor of the mouth, the underside of the tongue, and the labial and buccal mucosa, which have a normally non-keratinised epithelium.

2. The hard palate and the gingiva are the regions of the masticatory mucosa, which have a normally keratinized epidermis.

3. Specialized zone consisting of the borders of the lips and the dorsal surface of the tongue with its highly selective keratinization.

As the stratum corneum may be a potential barrier to mucosal penetrations, drugs are traditionally placed at the non-keratinised sites like the buccal and sublingual regions.

Mucus Layer:

The target for interactions of most bioadhesive polymers is the mucus. In higher organisms epithelia are covered by a protective gel layer defined as mucus. Mucus is mixture of large glycoproteins (mucins), water, electrolytes, sloughed epithelial cells, enzymes, bacteria and bacterial products and various other materials, depending on the source and location of the mucus. Mucins are synthesized either by global cells lining the mucus epithelium or by special exocrine glands with mucus cell acini. The main component of mucus secretion is the

glycoprotein fraction, which is responsible for its gel-like characteristics.

Based on the structure of mucin, there are four characteristics of the mucus layer related to mucoadhesion:

 Mucus is a network of linear, flexible and random coil macromolecules.

 Mucin is negatively charged due to sialic acid and sulphate residues.

 Mucus is a cross linked network connected by disulfide bonds between mucin molecules.

 Mucin is heavily hydrated.

MECHANISM OF PERMEATION VIA BUCCAL MUCOSA:

There are two routes potentially involved in drug permeation across epithelial membranes.

➢ **The transcellular route (lipoidal Pathway)**: Permeation is mainly by partitioning and depends on the lipophilicity of the drugs.

➢ **The paracellular route (aqueous pore pathway)**: In this the drug is transported through the aqueous pores of mucus layer. Lesser molecular weight compounds are transported through this route like sugar, salts and vitamins etc. Transmucosal permeation of polar molecules such as peptide, based pharmaceuticals may occur by way of paracellular route; however, several barriers like basal lamina, keratin layer are encountered during the course of paracellular permeation.

KINETICS:

The oral mucosal absorption of drugs could be adequately described by first-order rate processes. Several potential barriers to oral mucosal drug absorption have been identified. These include the mucus layer, keratinised layer and intercellular lipid of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply, blood lymph drainage, cell renewal, and enzyme contact will all contribute to reducing the rate and amount of drug entering the systemic circulation. Salivary secretions alter the buccal absorption kinetics from drug solution by changing the concentration of the drug in the mouth. A linear relationship is proposed between salivary secretion and time.

Thus,

$$-dm / dt = KC/ (V_i + V_t)$$

Where _m 'and _C 'are the mass and concentration of drug in the mouth at time_t', V_i is the volume of solution put into mouth cavity and V_t is salivary secretion rate.

Tsuzuki et al designed a new perfusion system to study oral mucosal absorption of drug using salicylic acid as model drug in oral perfusion medium.

He proposed a three –compartment model

ADVANTAGES OF BUCCO-MUCCOADHESIVE SYSTEMS:

Drug administration via the oral mucosa offers several advantages:

- Ease of administration.
- Termination of therapy is easy.
- Permits localization of the drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients.
- Offers an excellent route for the systemic delivery of drugs with high first pass metabolism, there by offering a greater bioavailability.
- A significant reduction in dose can be achieved, thereby reducing dose-dependent side effects.
- It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective use of therapeutic agents like peptides, proteins and ionized species can achieved.
- Drugs which are unstable in the acidic environment of the stomach and destroyed by the enzymatic or alkaline environment of the intestine can be administered by this route.
- Drugs, that show poor bioavailability via the oral route, can be administered conveniently.
- It offers a passive system for drug absorption and does not require any activation.
- The oral mucosa lacks prominent mucus-secreting globet cells and therefore there is no problem of a diffusion-limited mucous build up, beneath the applied dosage form.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike rectal and transdermal routes.
- Oral mucosal delivery may be of great help to patients suffering from nausea and

vomiting if the patient is unconscious and in patients who have difficulty in swallowing peroral medication as in case of very young or elderly persons.

- Sterile techniques are not required for manufacturing or administration.

LIMITATIONS OF MUCOADHESIVE BUCCAL DELIVERY:

Drug administration via this route has certain limitations:

- Drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour, cannot be administered by this route.
- Drugs, that are unstable at buccal pH, cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drug contained in the swallowed saliva follows the peroral route and advantages of buccal route are lost.
- Excessive hydration may lead to formation of slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration effect of the bioadhesive polymers.
- The permeability of the oral mucosa is not great when compared to other mucosal membranes.
- Conventional types of buccal delivery systems do not allow the patient to concurrently eat, drink or in some cases talk.

FORMULATION:

An ideal drug delivery system is that which possesses two main properties:

a) Spatial placement (Targeting a drug to specific organs/tissues)

b) Temporal delivery (Controlling the rate of drug delivery to the targeted tissues).

Unfortunately, such ideal systems which fulfill all the necessities are not available till today. This led to the development of sustained/ controlled release delivery systems. Still, sustained/ controlled delivery lacks in preventing the drug loss by either hepatic first pass metabolism or presystemic elimination like gastric, intestinal or colonal degradation. So several approaches have been tried out to form a suitable dosage form for the above said conditions. Oral mucosal drug delivery, one of the physiological approaches was reported to be a method to formulate these drugs into suitable dosage forms with good therapeutic effects. Oral mucosal drug delivery of different drugs can be achieved by bioadhesive

polymer systems.

ORAL DOSAGE FORMS:

With a better understanding of the mechanism of adhesion, several bioadhesive dosage forms have been reported. Because of the presence of a smooth and relatively immobile surface for placement of a bioadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using a bioadhesive system. Relevant bioadhesive dosage forms in the buccal cavity include adhesive tablets, adhesive patches, and adhesive ointments.

Adhesive tablets: Unlike conventional tablets, bioadhesive tablets allow drinking and speaking without major discomfort. Triamcinolone acetonide has been formulated as a bioadhesive tablet for the treatment of Apthous stomatitis. This is a small, thin and double layer tablet, currently marketed in Japan under the trade name Afatch. Schor developed the Nitro-glycerine bioadhesive tablet- Susadrin for angina pectoris.

Adhesive gels: Bioadhesive Patches may range from simple erodible and non- erodible adhesive discs to laminated systems in the size range of 1-16cm^2. These can be designed to provide either unidirectional or bi-directional release of the drug.

Ointments: Ointment-type oral mucosal dosage form of Prednisolone for the treatment of Aphthae in 1982. It contained Carbopol-934 and white petrolatum from the ointment containing 30% Carbopol was better than the original base.

Some reported mucoadhesive buccal drug delivery systems:

DRUG	DOSAGE FORM	ACTION	MUCCOADHESIVE POLYMERS USED
Insulin	Tablet	Systemic	Carbopol-934, HPC
Lidocaine	Multilayered tablet	Local	Carbopol- 934, HPC
Metronidazole	Tablet	----------	Carbopol- 934, HPC
Betamethasone	Tablet	Systemic	Sodium CMC
Propranolol	Discs	Systemic	Carbopol- 940, HPC
Triamcinolon acetonide	Bilayered tablet	Local	Carbopol- 934, HPC
Nystatin	Slow-release tablet	Local	Chitosan
Tetracaine	Film	Local	HPC

EVALUATION OF BULK BEFORE COMPRESSION:

The angle of repose:

The method was used to determine the bulk flowability

It is the angle between the surface of a pile of blend and horizontal plane

$$Tan\theta = h/r$$

h- height of heap
r- radius of horizontal plane of blend

bulk density:

The method was used to determine the quantity of blend that can fit in a hopper on the tablet process

$$Pb=m/v$$

Pb- bulk density
m- weight of blend
v- volume of blend

Tapped density:

Used to determine the compressibility and flow property

Increased bulk attained after mechanical tapping a measuring cylinder (container) containing the blend

$$Pt= m/vt$$

Pt- Tapped density
m- The weight of blend
vt-minimum volume occupied after tapping

Carr's compressibility index:

An amount of blend is loaded into a measuring cylinder and the volume is recorded. then the cylinder is tapped for known period. Then the final volume after tapping was measured.

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

EVALUATION OF TABLETS:

Weight variation: The test is performed by weighing 20 tablets individually calculating the average weights. it helps to determine the amount of drug contained the tablets**.**

For example

The tablet weight is N= 500mg

$$N_1 = 500\text{mg}, N_2 = 499\text{mg} \ldots\ldots N_{20} = 501\text{ mg}$$

$$\textbf{Average weight} = \frac{N_1+N_2+\ldots.+N_{20}}{20}$$

Hardness:

It indicates the mechanical strength of the tablets. tablet was placed between the two movable jaws. The jaw moves towards the tablets and pressure applied; the point the tablet is breakdown is recorded

$$\text{Hardness} = \text{kg/cm}^2$$

Friability:

The percentage loss of the tablet due to mechanical strength during test, in this method 20 tablets was placed into the friabilator, and allow 100 rotation (4 minutes, 25RPM). the friability percentage is calculated by

$$\text{friability \%} = \frac{\text{initial wt} - \text{final wt}}{\text{initial wt}} \times 100$$

Tablet Thickness and Size:

Diameter and thickness of the tablets are main for uniformity of tablet size. Using digital vernier caliper the diameter and thickness was measured.

Disintegration test:

The disintegration test was performed by USP type 2 paddle apparatus. Basket contains 6

glass tubes the bottom covered with #10 mesh. the basket was placed into the beaker contains 1 litre of purified water 37℃ ±2℃.

In each glass tube put 6 tablet and perform the test, the basket moves upwards and downward position, the tablet will dissolve into fine particles, the time is recorded.

CONCLUTION:

The study of mucoadhesive delivery system provides, a wide range of advantages like prolonged duration of action, enhanced bioavailability and avoid first pass metabolism. The mucoadhesive drug delivery system helps to formulate a different dosage form to increase the patient complains and low gastric degradation.

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