

FORMULATION AND EVALUATION OF BUCCOADHESIVE TABLETS OF BARICITINIB AN OVERVIEW

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Abstract: Buccal drug delivery has become one of the popular delivery systems due to its comparable and significant advantages over the conventional dosage form. The purpose of the present work was to prepare buccal adhesive tablets of Baricitinib Buccal drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. Buccal dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. This review covers the overview of oral mucosa, factors affecting bioadhesion and also various buccal dosage forms. The simplex experimental design was used to arrive at optimum ratio of carbopol 934, sodium cmc, Na alginate, HPMC K4 which will provide desired drug release and mucoadhesion, swelling index, mucoadhesive strength and invitro release of the prepared tablet was determined. The drug release and bioadhesion was dependent on the type and relative amounts of polymers.

Dissolution of baricitinib from tablets was sustained release 93% release of baricitinib during 24h period. Baricitinib blocks the activity of certain enzymes involved in activating inflammation in the body. Baricitinib is used to reduce pain, stiffness and swelling in adults with rheumatoid arthritis after other treatments have failed. Buccal delivery of drugs that undergo a first pass effect such as cardiovascular drugs, analgesics and peptides Buccal tablets were prepared by a direct compression method. This review covers the overview of oral mucosa, factors affecting bioadhesion. The results: the DSC, FTIR, analyses were determined. Further the formulations were evaluated for in vitro studies, stability studies.

Keywords: buccal, first pass effect, Bioadhesion, Buccal release, sustained release of tablets

INTRODUCTION

1. Amongst the various routes of drug delivery, oral route is mostly preferred by the patient. Based on our current understandings of biochemical and physiological aspects of absorption and metabolism many drugs, cannot be delivered effectively through the conventional oral route, because after administration are subjected to pre-systemic clearance extensively in liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability² Drug delivery via the buccal route using bioadhesive dosage forms offers a novel route of drug administration. This route has been used successfully for the systemic delivery of number of drug candidates. Administering the drug via the buccal route can avoid problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment¹. 3 Lower enzymatic activity of saliva, facile removal of formulation, better patient acceptance and compliance are some other prominent meritorious visages of buccoadhesive systems² buccal drug delivery offers a safe and easy method of drug utilization, because drug absorption can promptly be terminated in cases of toxicity by removing the dosage form from the buccal cavity.⁴ It is an alternative route to administer drugs to patients who are unable to be dosed orally³ adhesive mucosal dosage forms are suggested for buccal delivery, including adhesive tablets, adhesive gels and adhesive patches.

ADVANTAGES

- Prolongs the residence time of the dosage forms at the site of absorption, hence increases bioavailability.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good flow rates.
- Drug is protected from degradation in the acidic environment in the git.
- Improved patient compliance

DISADVANTAGES

- Occurance of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- Eating and drinking is prohibited.
- Patient acceptability in terms of taste and irritancy

CHARACTERISTICS OF AN IDEAL BUCCOADHESIVE SYSTEM

- Quick adherence to the buccal mucosa and sufficient mechanical strength.
- Drug release in a controlled fashion.

- Facilitates the rate and extent of drug absorption.
- Should have good patient compliance.
- Should not hinder normal functions such as talking, eating and drinking.
- Should accomplish unidirectional release of drug towards the mucosa.

STRUCTURAL FEATURES OF ORAL CAVITY

Oral cavity is the area of mouth delineated by the lips, cheeks, hard palate, soft palate, and floor of the mouth.

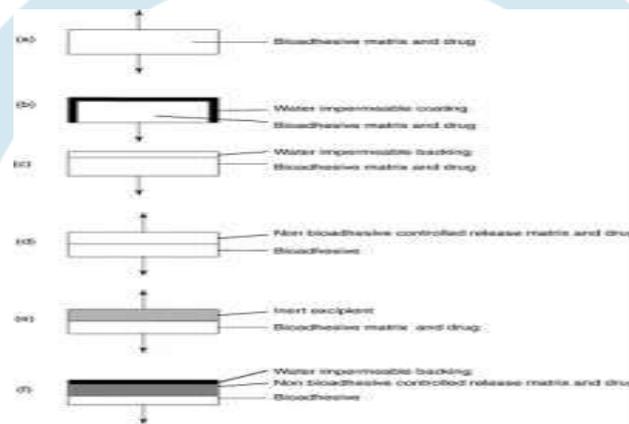
The oral cavity consists of two regions

Outer oral vestibule which is bounded by cheeks, lips, teeth, and gums.

Oral cavity proper which extends from teeth and gums back to the fauces with the roof comprising the hard and soft palate. The tongue projects from the roof of the cavity.

ANATOMY AND NATURE OF ORAL CAVITY

The oral cavity may be divided into two regions, the outer oral vestibule, bound by the lips, cheeks, and the oral cavity itself borders being and formed by the hardened soft palates, the floor of the mouth and tonsils.



Anatomy of the oral mucosa

Physical Description of Oral Cavity:

The mucosa that lines the oral cavity may be divided into three types, classified according to their function as:-

1. Masticatory mucosa: Which includes the mucosa around the teeth and on the hard palate and these regions have keratinized epithelium
2. Lining mucosa: Which covers the lips, cheeks, base of the oral cavity, lower part of tongue, buccal mucosa and the soft palate and these regions have non keratinized epithelium
3. Specialized mucosa: Covering the dorsum of the tongue with highly keratinization.

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Specialized mucosa: Covering the dorsum of the tongue with highly keratinization. The oral mucosa is comprised of squamous stratified (layered) epithelium, basement membrane, the lamina propria and submucosa. It also contains many sensory receptors including the taste receptors of the tongue. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer.

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PERMEABILITY:

- The oral mucosa is somewhat leaky epithelia intermediate between that of epidermis and intestinal mucosa .it is estimated that the permeability of the buccal mucosa is 4-4000times greater than that of skin. There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:
 - Transcellular (intracellular, passing through the cell) and;
 - Paracellular (intercellular, passing around the cell).
- Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules.

MUCOSAL PENETRATION ENHANCERS AND MECHANISMS OF ACTION

Classification	Examples	Mechanism
Surfactants	Anionic: sodium lauryl sulfate, Sodium laurate Cationic: cetylpyridinium chloride Nonionic: poloxamer, Brij, Span, Myrj, Tween Bile salts: sodium glycodeoxy cholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate, Azone®	Perturbation of intercellular lipids, protein domain integrity
Fatty acids	Oleic acid, caprylic acid	Increase fluidity of phospholipids domains
Cyclodextrins	α -, β -, γ -cyclodextrin, methylated β -cyclodextrins	Inclusion of membrane compounds
Chelators	EDTA, sodium citrate Polyacrylates	Interfere with Ca^{2+}
Positively charged polymers, Cationic compounds	Chitosan, trimethyl chitosan, Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface

COMPOSITION OF MUCUS LAYER:

Mucus is a translucent and viscid secretion which forms a thin, contentious gel mean thickness of the layer varies from about 50-450micrometer in humans secreted by the goblet cells lining the epithelia. Its composition:

Water-95%

Glycoprotein and lipids -0.5-3.00%

Mineral salts -1%

Free proteins -0.5-1.0%

Functions of mucus layer:

Protective: resulting particularly from its hydrophobicity.

Barrier: the role of the mucus layer as a barrier in tissue absorption of the drugs and influence the bioavailability.

Adhesion: mucus has strong adhesion properties.

Lubrication: it is to keep the mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion bacterial degradation and solubilisation of mucin molecules.

Theories of mucoadhesion :

THEORIES OF MUCOADHESION

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion:-

The electronic theory suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. This is proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces.

The wetting theory is primarily applied to liquid systems and considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously onto a surface as a prerequisite for the development of adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle goniometry to measure the contact angle of the liquid on the surface, with the general rule being that the lower the contact angle, the greater the affinity of the liquid to the solid.

The adsorption theory describes the attachment of adhesives on the basis of hydrogen bonding and van der Waals' forces. It has been proposed that these forces are the main contributors to the adhesive interaction. A subsection of this, the chemisorptions theory, assumes an interaction across the interface occurs as a result of strong covalent bonding

The diffusion theory describes interdiffusion of polymers chains across an adhesive interface. This process is driven by concentration gradients and is affected by the available molecular chain lengths and their mobilities. The depth of interpenetration depends on the diffusion coefficient and the time of contact. Sufficient depth of penetration creates a semi-permanent adhesive bond. The mechanical theory assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.

The fracture theory differs a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion

FACTORS AFFECTING MUCOADHESION

[1] Based on the theories of the adhesion, it can be summarized

FACTORS PROPERTIES COMMENTS

a. Polymer related factors

1. Molecular weight The mucoadhesive force increases with molecular weight of polymer, up to 1, 0000 and beyond this level there is no much effect.
2. Concentration of active polymers For solid dosage forms such as tablets showed that the higher the polymer concentration the stronger the mucoadhesion. There is an optimum concentration of polymer corresponding to the best mucoadhesion.
3. Flexibility of polymer chain Flexibility is an important factor for interpenetration and enlargement.

b. Environment related factors

1.pH

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

2. Applied strength To place a solid mucoadhesive system, it is necessary to apply a defined strength.
3. Initial contact time The mucoadhesive strength increases as the initial contact time increases.
4. Swelling Swelling depends on both polymers concentration and on presence of water.

c. Physiological Variables 1.Mucin turn over a. The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layers.

2.Diseased state

b. Mucin turnover results in substantial amounts of soluble mucin molecules.

Physicochemical properties of mucus are known to change during diseased states, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of

the female reproductive tract and inflammatory conditions of the eye.

Mechanism of Mucoadhesion⁴⁰: The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and hence increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered.

Thus, the mechanism of mucoadhesion is generally divided in two steps:

- The contact stage, and
- The consolidation stage

The first stage or the contact stage (Figure 4) is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In the consolidation step the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds.

MUCOADHESIVE POLYMERS

Mucoadhesive drug delivery systems are based on the adhesion of a drug/ carrier to the mucous membrane.

To promote this adherence a suitable carrier is required

An ideal polymer for buccal drug delivery systems should have following Characteristics

It should be 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 possess 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 economical.

Criteria followed in polymer selection

It should form a strong non covalent bond with the mucin/epithelial surface.

- It must have high molecular weight and narrow distribution.
- It should be compatible with the biological membrane.

The polymers that are commonly used as bioadhesive in pharmaceutical applications are: •

Natural polymers, Ex: Gelatin, sodium alginate. • Synthetic and semi synthetic polymers, Ex: PVA, PEG, HPMC, PVP, Carbomers etc.

Pharmaceutical applications of mucoadhesive polymers 33

Polymer Pharmaceutical applications

Sodium alginate : Suspending agent, gelation for dental films, stabilizer, sustained release agent, tablet coating, mucoadhesive microspheres

Pectin: Thickening agent, suspending agent, protective agents, colon drug delivery, transdermal drug delivery

Carbomer :Suspending agent , emulsifier, bioadhesive for cervical patches, used in cosmetic preparations Chitosan : Controlled drug delivery, peptide drug delivery, colonic drug delivery

Hydroxy propyl methyl cellulose : Viscosity modifier, film forming, gelling and binding agent

Sodium carboxy methyl cellulose :Produce thixotropic gels as suspending vehicles in pharmaceutical and cosmetic preparations

Hydroxy propyl cellulose :Binder in tableting, film coating, used in extended release matrix former

Hydroxy ethyl cellulose: Thickening agent in ophthalmic preparations, film coating agent for tableting

Delivery through Buccal Mucosa:

Administration of a drug via the buccal mucosa to the systemic circulation is defined as buccal delivery.

The buccal mucosa is significantly less permeable than the sublingual mucosa and usually not able to provide rapid drug absorption, it is relatively more permeable than the skin so it is more desirable site for sustained drug delivery.

Physiology of the Oral Mucosa:

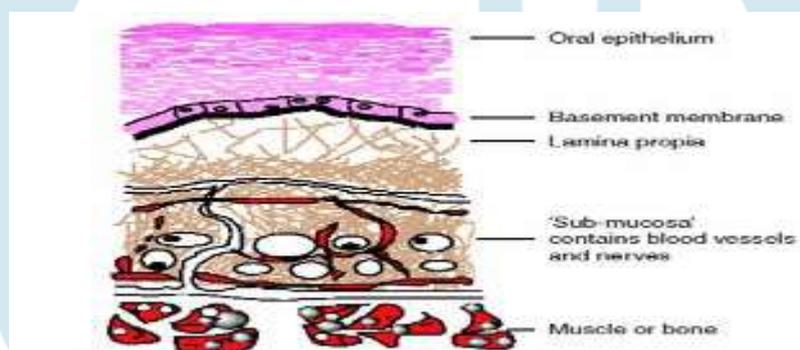
The oral mucosa is consisted of an outermost layer of stratified squamous epithelium, which is covered with mucous and consists of stratum distendum, stratum filamentosum, stratum suprabasale and a stratum basale.

The area below the basal lamina, covered with lamina propia and sub mucosa

The epithelium serves as the mechanical barrier that protects underlying tissues, where as the lamina propia provides a mechanical support and also carries the blood vessels and nerves.

Some regions of the oral mucosa are keratinized.

The non-keratinized regions, such as buccal mucosa is more permeable than the keratinized regions.



Cross section of oral mucosa

The tissue layer responsible for the formation of the adhesive interface is mucous. Mucous is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent mucosal epithelial surface. The mean thickness of this layer varies from about 50-450 μm in humans. The role of the mucous is to protect and lubricate the epithelial tissue beneath it. Mucous is primarily composed of approximately 95% water, 1% electrolytes, 0.5-1% proteins and 0.5-1% lipids and glycoproteins.

The placement of an adhesive polymer device on the buccal mucosal surfaces decreases the rate of mucin turnover, which can result in the buccoadhesion remaining on the mucous for up to 15hrs

CONCLUSION

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. There is no doubt that the oral route is the most favoured and probably most complex route of drug delivery. The buccal

mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided.

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