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A REVIEW ARTICLE ON MUCOADHESIVE FORMULATIONS FOR BUCCAL MUCOSA

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ABSTRACT

Mucoadhesion could be a field of current interest within the style of drug delivery systems. Mucoadhesive drug delivery system prolongs the continuance of the indefinite quantity kind at the positioning of application or absorption associate degreed facilitates an intimate contact of the indefinite quantity kind with the underline absorption surface and so contributes to improved and higher therapeutic performance of the drug. In recent years several such mucoadhesive drug delivery systems are developed for oral, buccal, nasal, body part and canal routes for each general and native effects. Issues like high first-pass metabolism and drug degradation within the canal surroundings is circumvented by administering the drug via the buccal route. Moreover, speedy onset of action is achieved relative to the oral route and therefore the formulation is removed if medical care is needed to be out of print. It's additionally attainable to administer medication to patients UN agency unconscious and fewer co-operative. To forestall accidental swallowing of medicine adhesive tissue layer indefinite quantity forms were advised for oral delivery, including adhesive tablets, adhesive gels, adhesive patches and plenty of alternative indefinite quantity forms with numerous combos of polymers, absorption enhancers. Additionally to the current, studies are conducted on the event of controlled or slow unharness delivery systems for general and native medical care of diseases.

INTRODUCTION

The impact of a drug will currently be strengthened as a results of the event of recent unleash systems. Controlled release consists of techniques that build the active chemical agents on the market for a target, providing Associate in nursing adequate unleash rate and period to supply the specified impact. the most controlled drug delivery systems presently on the market embrace matrices, pellets, floating systems, liposomes, micro emulsions, liquid crystals, solid dispersions, Nano suspensions and percutaneous systems.[1,2]bioadhesion is outlined because the state during which 2 materials, a minimum of one among that is biological in nature, area unit maintained along for a protracted fundamental measure by suggests that of surface forces. Throughout the Nineteen Eighties, this idea began to be applied to drug delivery systems. It consists of the incorporation of adhesive molecules into some quite pharmaceutical formulation meant to remain in shut contact with the absorption tissue, cathartic the drug regarding the action web site, thereby increasing its bioavailability and promoting native or general effects.[3]

The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the continuance at the absorption web site, permitting intense contact with the cyclodextrins inclusion complexes, diffusion pumps and bioadepithelial barrier (Hagerstown, 2003). On the opposite hand, adhesion of preparations onto tissue layer is impaired by the mucociliary clearance system. This clearance, a natural defence mechanism of the body against the deposition of impurities onto the tissue layer, may also take away the preparation. Thus, by mistreatment bio adhesive molecules, it's doable to retain the preparation at the action and to direct the drug to a selected site or tissue. Alternative options related to the event of controlled drug delivery systems mistreatment bioadhesive molecules embrace a decrease in drug administration frequency and a rise in patient compliance to the medical care. Therefore, a bioadhesive system dominant drug unleash might improve the treatment of diseases, serving to keep up a good concentration of the drug at the action web site.[3,8]

Mucous membrane is that the main administration web site for bioadhesive systems, though the necessity for brand spanking new bioadhesive formulations for dermal administration has conjointly been according once prolonged body covering action is desired. A protracted impact upon the dermal administration of creams, solutions, and lotions is sudden, since such preparations is simply far from the skin by wet, temperature, and physical movement.[4]

Mucosal membranes of human organism area unit comparatively permeable and permit quick drug absorption. They're characterised by Associate in nursing animal tissue layer whosesurface is roofed by mucous secretion. The mucous secretion contains glycoproteins, lipids, inorganic salts and ninety fifth water by mass, creating it an extremely hydrous system. Glycoprotein is that the most significant conjugated protein of mucous secretion and is answerable for its structure. The most functions of mucous secretion area unit protective and lubricating the animal tissue and alternative further functions counting on the animal tissue coated. Mucus Site most used for drug administration and absorption is canal, however alternative routes, as well as nasal, ocular, buccal, vaginal, rectal, oral, and dental medicine have conjointly been studied. Bioadhesive systems applied to tissue layer area unit of times outlined as mucoadhesive, however the terms area unit interchangeable. It's possible to style a bio (muco) adhesive system in numerous dose forms, since the properties of adhesion mostly rely on the options of the fabric utilized in its preparation. Therefore, many typical drug delivery systems already in use will become bioadhesive when design by as well as bioadhesive substances in their formulation systems[5,8]

CONCEPT OF BIOADHESION[3,6,7,8]

Bioadhesion is that the state during which 2 materials, a minimum of one among that being of a biological nature, are control along for Associate in nursing extended amount of your time by surface force.

• It is that the ability of fabric to stick to a biological tissue for Associate in Nursing extended amount of your time.

• In biological systems four kinds of bioadhesion are often distinguished as:

(a) Adhesion of a traditional a standard cell on another normal cell,

(b) Adhesion of a cell with a remote substance,

(c) Adhesion of a traditional cell to a pathological cell,

(d) Adhesion of Associate in nursing adhesive to a biological substrate**.**

The drug are often incorporated into a cross joined chemical compound device that may adhere to tissue layer membrane within the body. The drug will diffuse from device directly within the tissue.

- Adhesion, anchoring of chemical compound device end in increase continuance, bioavailability & web site
- Specificity.
- Decrease in frequency of administration with low dose, rate of elimination.

Buccal route of drug delivery may be a sensible different, amongst the varied routes of drug delivery. Oral route is maybe the foremost most popular for the patients. Among the oral tissue layer cavity, the buccal region offers a lovely route of administration for general drug delivery. However, oral administration of medication has disadvantages like viscous initial pass metabolism and accelerator degradation among the canal, that compel oral administration of bound categories of medication particularly peptides and proteins.

Buccal routes of drug delivery supply distinct benefits over oral administration for general drug delivery. These benefits embrace attainable bypass of initial pass impact, turning away of pre-systemic elimination among the canal, these factors build the oral tissue layer cavity a really engaging and possible website for general drug delivery. Considering the low patient compliance of body part, vaginal, articulator and nasal drug delivery for controlled unharness, the buccal membrane has wealthy blood offer and it's comparatively pervious.

The buccal membrane lines the inner cheek and buccal formulations area unit placed within the mouth between the higher animal tissue (gums) and cheek to treat native and general conditions. The buccal route provides one amongst the potential routes for generally giant, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, in addition as standard tiny drug molecules.[7]

ORAL TISSUE LAYER SITES[8,9]

Within the oral tissue layer cavity, delivery of medication is classed into 3 classes,

1) Sublingual delivery: is that the administration of the drug via the articulator membrane (the membrane of the ventral surface of the tongue and also the floor of the mouth) to the circulation.

2) Buccal delivery: is that the administration of drug via the buccal membrane (the lining of the cheek) to the circulation.

3) Local delivery:for the treatment of conditions of the oral fissure, mainly ulcers, plant conditions and periodontitis.

These oral tissue layer sites disagree greatly from each other in terms of anatomy, porosity to Associate in Nursing applied drug and their ability to retain a delivery system for a desired length of your time.

OVERVIEW OF BUCCAL MUCOSA[11,13,18,21]

• The oral mucous membrane is anatomically divided into

1) Epithelial tissue

2) Basement membrane and Connective tissues

1) Epithelium:

The epithelial tissue consists of roughly 40–50 layers of stratified squamous animal tissue cells having thickness 500-800µm. The epithelial tissue of the oral mucous membrane is a protecting covering for the tissues and a barrier to the entry of foreign materials. These functions are mirrored within the organization of the epithelial tissue during which individual animal tissue cells are closely opposed and stratified thus there are variety of layers that show a sequence of differentiation. The topmost layers type a surface that's proof against physical insult and to penetration by foreign substances. Membrane Coating Granules (MCG) are spherical or oval organelles

(100–300 nm in diameter). MCGs discharge their contents into the animate thing house and therefore type the porosity barrier. Major metric weight unit lipoid parts are sterol esters, sterol, and glycosphingolipids.

Cells increase in size and become planate as they increasingly mature and migrate from the basal layer towards the animal tissue surface, showing increasing levels of macromolecule tonofilaments and declining levels of some living substance organelles.

2) Basement Membrane and animal tissue

The basement membrane (BM) could be a continuous layer of extracellular materials and forms a boundary between the basal layer of epithelial tissue and therefore the connective tissues. This basal advanced anchors the epithelial tissue to the animal tissue and supplements. The barrier functions of the superficial layers of the epithelial tissue to forestall some massive molecules from passing the oral mucous membrane.

The bulk of animal tissue consists of analbuminoidal fibre network, the organization of that determines mechanical stability, resistance to deformation, and extendibility of the tissue. Possibly, the animal tissue, together with the basement membrane, isn't thought of to influence

the diffusion of most compounds of medicine interest though these 2 regions could limit the movement of some macromolecules and complexes.

Environment

The oral fissure is marked by the presence of secretion made by the secretion glands and secretion that is secreted by the key and minor secretion glands as a part of secretion.

Role of secretion

• Protective fluid for all tissues of the oral fissure.

• Continuous mineralization / demineralization of the enamel.

• To hydrate oral membrane indefinite quantity forms.

Role of secretion

• Made of proteins and carbohydrates.

• Cell-cell adhesion

• Lubrication

• Bio adhesion of mucoadhesive drug delivery

ROUTES OF DRUG TRANSPORT

A=Transcellular route, B= Paracellular route

There ar 2 potential routes of drug absorption through the squamous stratified animal tissue of the oral mucous membrane.

1. Trans cellular (intracellular, passing through the cell) and

2. Para cellular (intercellular, passing round the cell).

Permeation across the buccal mucous membrane has been reported to be chiefly by the paracellular route through the animate thing lipids made by membrane granules.

Although passive diffusion is that the main mechanism of drug absorption, specialised transport mechanisms are reported to exist in alternative oral mucous membrane (that of the tongue) for many medicine and nutrients; aldohexose and Mefoxin were shown to be absorbed during this means. The buccal mucous membrane may be a potential website for the controlled delivery of deliquescent molecule therapeutic agents (biopharmaceuticals) like peptides, oligonucleotides and polysaccharides. However, these high relative molecular mass medicine sometimes have low porosity resulting in an occasional bioavailability, and absorption enhancers is also needed to beat this. The buccal mucous membrane conjointly contains proteases which will degrade amide secretion enzymes may cut back stability.

THEORIES OF MUCOADHESION[13,15,19,21,22]

Although the chemical and physical basis of mucoadhesion don't seem to be nevertheless well understood, there ar seven classi¬cal theories tailored from studies on the performance of many materials and polymer-polymer adhesion that justify the development.

1. Electronic theory

Electronic theory is predicated on the premise that each mucoadhesive and biological materials possess opposing electrical charges. Thus, once each materials get contact, they transfer electrons resulting in the building of a double electronic layer at the interface, wherever the engaging forces inside this electronic double layer determines the mucoadhesive strength.

2. surface assimilation theory

According to the surface assimilation theory, the mucoadhesive device adheres to the mucous secretion by secondary chemical interactions, like in Vander-Waals and gas bonds, static attraction or hydrophobic interactions. as an example, gas bonds ar the prevailing surface forces in polymers containing carboxyl teams. Such forces are thought of the foremost necessary within the adhesive interaction development as a result of, though they're one by one weak, a good range of interactions may result in AN intense world adhesion.

3. Wetting theory

The wetting theory applies to liquid systems that gift affinity to the surface so as to meet it. This affinity are often found by mistreatment measurement techniques like the contact angle. the final rule states that the lower the contact angle then the larger the affinity. The contact angle ought to be equal or near zero to produce adequate spreadability.

MECHANISMS OF MUCOADHESION[21,22,2325]

The mechanisms responsible in the formation of bioadhesive bonds are not fully known, however most research has described bioadhesive 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

1. Process of bioadhesion can be classified,
1. Chemical (electronic and adsorption theories)
2. Physical (wetting, Diffusion and cohesive theory)

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.

Bioadhesive 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 occurs because the components within the polymers have an affinity for water.

The image below shows swelling of a polymer

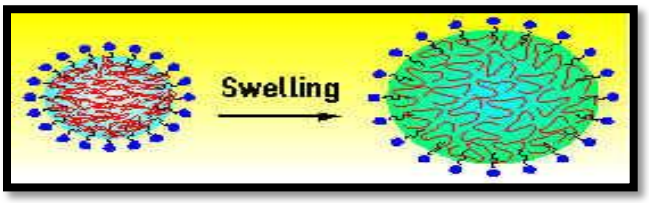

Fig. 3 Swelling of polymer

STEP-2

1. The surface of mucosal membranes is composed of high molecular weight polymers known as **glycoproteins.**
2. In step 2 of the bioadhesive bond formation, the bioadhesive 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.
3. 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 structures.

The interpenetration of polymer chains

STEP-3

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

Mechanisms of Mucoadhesion

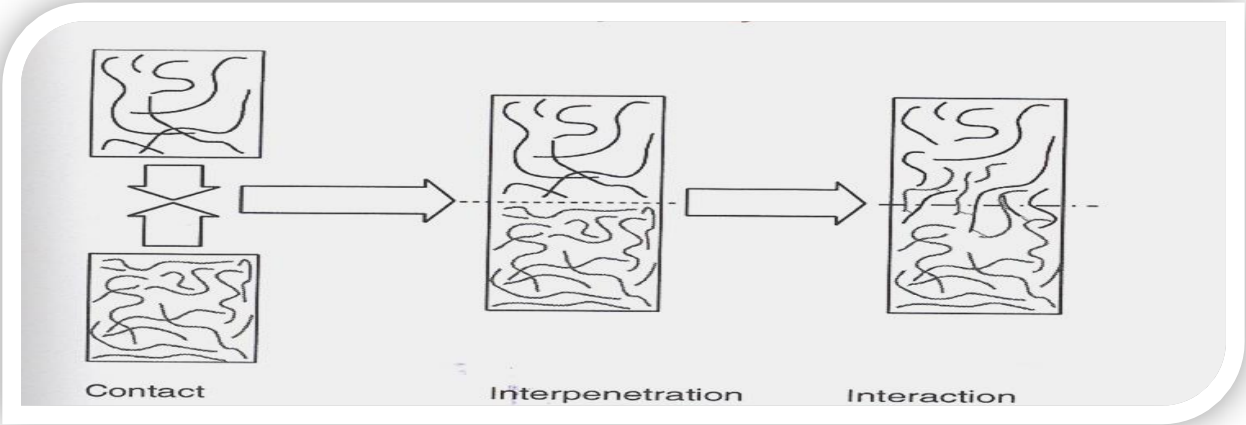

Fig.5 Mechanisms of Mucoadhesion

ADVANTAGES OF BUCCAL DRUG DELIVERY[23,28,29,30]

1. Bypass of the alimentary canal and viscous vascular system, increasing the bioavailability of orally administered medication that otherwise endure viscous first-pass metabolism.
2. Improved patient compliance as a result of the elimination of associated pain with injections.
3. Sustained drug delivery.
4. a comparatively fast onset of action will be achieved relative to the oral route and therefore the formulation will be removed if medical aid is needed to be out of print.
5. Exaggerated simple drug administration
6. The big contact surface of the mouth contributes to fast and in depth drug absorption.
7. Extent of insertion is a lot of so fast and effective absorption.

8. Nausea and expulsion are greatly avoided.

9. Utilized in case of unconscious and fewer cooperative patients.

10. Drugs, that show poor bioavailability via the oral route, will be administered handily.

Example: - medication, that are unstable within the acidic setting of the abdomen or are destroyed by the protein or alkali setting of the viscous.

LIMITATIONS OF BUCCAL DRUG DELIVERY[23,29]

1. Medication that irritate oral membrane or have bitter style, or cause hypersensitive reactions, discoloration of teeth can't be developed.

2. If formulation contains antimicrobial agents, affects the natural microbes within the cavum.

3. The patient cannot eat/drink/speak.

4. Solely those medication that are absorbed by passive diffusion will be administered by this route.

5. Medication that are unstable at buccal pH scale can't be administered by this route.

6. Swallowing of spittle may also probably result in the loss of dissolved or suspended drug

7. Low porosity of the buccal membrane, specifically when put next to the organ membrane.

METHODS TO EXTENDED DRUG DELIVERY VIA BUCCAL ROUTE[13,23,28,34,37]

1) Absorption Enhancers

Absorption enhancers have incontestable their effectiveness in delivering high relative molecular mass compounds, like peptides, that usually exhibit low buccal absorption rates.

2) Prodrugs

Nalbuphine and Narcan bitter medication once administered to dogs via the buccal membrane, the caused excess secretion and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and Narcan in prodrug type caused no adverse effects, with bioavailability starting from thirty five to five hundredth showing marked improvement over the oral bioavailability of those compounds that is generally5% or less.

3) pH

Permeability of Zovirax at pH scale ranges of three.3 to 8.8and within the presence of the absorption attention, Na glycholate. The in vitro porosity of Zovirax was found to be pH scale dependent with a rise in flux and porosity constant at each pH scale extremes (pH three.3 and 8.8), as compared to the mid-range values (pH four.1, 5.8, and 7.0).

4) Patch style

Several in vitro studies are conducted concerning on the kind and quantity of backing materials and therefore the drug unleash profile and it showed that each arereticulate. Also, the drug unleash pattern was completely different between single-layered and multi-layered patches

TYPES OF DOSAGE FORMS

1. TABLETS

Tablets are dry dosage forms that may have to moisten prior to placing in contact with the buccal mucosa. The size of the tablet is restricted to that which can be comfortably retained in place for prolonged time. There are two buccal adhesive tablet preparations currently commercially available in the UK: Bucastem mfg. By Reckitt and Colman, this contains prochlorpromazine maleat in a matrix containing ceratonia and xanthum gum; and Suscard buccal mfg. By Pharma, this contains glycerol trinitrate in a modified hydroxypropylmethyl cellulose matrix. The nature of matrix was probably decided by the requirement to produce the desired drug release profile, and as would be addicted from their constituents, these are both weekly mucosal adhesive.

2. PATCHES, TAPES, FILMS

• Buccal adhesive patches could also be upto 10-15 cm2 in size, however area unit a lot of typically 1-3 cm2 therefore on be convenient and cozy for the patient. they need to even be versatile and will be ellipsoid in form to suit well on to the centre of the buccal mucous membrane. Laminated patches to deliver medicine through the oral mucous membrane are delineated by Anders and Merkle. They developed patches consisting of 2 poly laminates with associate degree solution of the adhesive compound being solid onto associate degree imperviable backing sheet that was then move needed oval form.

• Nagai associate degreed Konishi has delineated an sticking plaster, consisting of a membrane adhesive drug reservoir formulation connected to associate degree inert backing ,which achieved a sustained delivery of associate degree autacoid to the animal tissue mucous membrane of associate degree animal model for eight hrs. with none sign of irritation.

• A bioadhesive multi-layered extruded film (containing hydroxypropylcellulose, synthetic resin compound, ethyl radical polysaccharide, or another water-insoluble compound, a plasticizer and a drug) has conjointly been investigated with a read to achieving native medical care within the oral fissure.

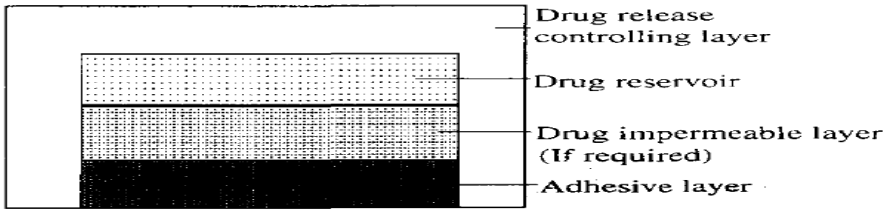

Fig.6 Mucoadhesive Sustained Drug Release

CONCLUSION

The use of buccal adhesive indefinite quantity forms offers a chance for optimizing the delivery of medication each regionally and consistently, and lots of differing types of formulations are developed. The presence of secretion among the oral fissure is vital in providing the wet to permit adhesion to occur, and to permit a medium for drug dissolution before absorption. though the mucosa gift as a formidable barrier to the penetration of enormous molecules, tiny lipotropic molecules of medication for native medical care would seem to be appropriate for delivery by this route. For the delivery of enormous molecules, the utilization of a buccal-adhesive indefinite quantity kind in conjunction with an acceptable safe however effective penetration attention would seem to produce the optimum conditions for drug absorption if different routes of drug delivery area unit found to be inappropriate.

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