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Review on: Oral Mucoadhesive Drug Delivery System

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ABSTRACT

New drug delivery systems, such as mucoadhesive systems, can improve drug delivery. This system improves local and systemic effects by maintaining the relationship between tissue and mucosal absorption and release of the drug at the site of action. There are many ways to administer mucoadhesive drugs; most of them are oral, which is still the preferred route by patients due to its convenience. However, the oral route has many disadvantages such as liver front-pass metabolism and intestinal digestion, which affect the absorption of protein and peptide drugs. The oral mucosa provides a strong barrier to drug penetration; one way to improve drug delivery is to use adhesives, and the mucosa has an adequate blood supply and is relatively permeable. Buccal mucosa is a good bioadhesive system because it is a smooth, immobile surface and easy to use. Mucoadhesion can be achieved with mucoadhesive polymers. There are many types of mucoadhesive polymers. Laminate materials are designed to provide chemical release.

Keywords: Oral gel; Mucoadhesive gel; Buccal cavity; Mucoadhesion

INTRODUCTION

Mucoadhesive drug delivery system

Mucoadhesive drug delivery systems are delivery systems that utilize the bioadhesive properties of certain polymers that become sticky when hydrated and can therefore be used to target drugs to specific areas of the body for extended periods of time. Bioadhesion is an interaction phenomenon in which two substances, at least one of which is a biomaterial, are held together by interaction. This bond will be between a biofilm and a synthetic material. If the polymer adheres to the mucin layer of mucosal tissue, the term mucoadhesion is used [1-3].

Mucoadhesive drug delivery systems can be delivered by various routes:

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

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Mucoadhesive oral drug delivery systems

Oral route is the most preferred route for the delivery of any drug. Drug delivery via the membranes of the oral cavity can be subdivided as:

- **Sublingual delivery:** This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
- **Buccal delivery:** This is drug administration through the mucosal membranes lining the cheeks (buccal mucosa).
- **Topical delivery:** This is the administration of medication into the mouth. The buccal area in the oral mucosal cavity provides an attractive method of control to maintain systemic drug delivery. Buccal control is controlled through the mucosal membrane of the jaw. Although the sublingual mucosa is known to be more permeable than the buccal mucosa, the buccal mucosa is the preferred route of drug delivery. This is because the buccal mucosa consists of smooth muscle and inactive mucosa, making it an ideal site for storage. Therefore, the buccal mucosa is suitable for continuous drug delivery.

Advantages of oral mucoadhesive drug delivery systems

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

Disadvantages of mucoadhesive drug delivery systems

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for *in vitro* screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste and irritancy.
- Eating and Drinking is prohibited.

Ideal characteristics of mucoadhesive polymers

Mucoadhesion enhancers or polymers are added to formulations to increase the adhesion of active drug ingredients to the oral mucosa. The agent may have additional properties, such as swelling, to promote separation on contact with saliva.

- Polymer priority a high sub-atomic load up to 100.00 or more. This is important to advance the adhesiveness between the polymer and bodily fluid.
- Long chain polymers-chain length should be sufficiently long to advance the interpenetration and it ought not be too lengthy that dissemination turns into an issue.
- High consistency.
- Degree of cross connecting it impacts affix versatility and protection from disintegration. Profoundly cross connected polymers enlarge in presence of water and hold their construction. Expanding favors controlled arrival of the medication and builds the polymer/bodily fluid interpenetration
- Spatial adaptation.
- Flexibility of polymer chain-this advances the interpenetration of the polymer inside the bodily fluid organization.
- Concentration of the polymer-an ideal fixation is expected to advance the mucoadhesive strength. It depends be that as it may, on the measurement structure.
- Charge and Ionization-Bernkop-Schnurch and Freudl explained the impact of electric energy on mucosal attachment. Cationic chitosan hydrochloride showed huge bond contrasted with the benchmark group. Restricting of anionic gatherings of EDTA prompts solid mucosal bond. Because of lower cost, DTPA/chitosan framework showed lower mucoadhesion strength than cationic chitosan and anionic EDTA chitosan edifices. Accordingly, mucoadhesion strength can be connected as anionic>cationic>nonionic.
- Optimum hydration-extreme hydration prompts diminished mucoadhesive strength because of development of a dangerous adhesive.
- Optimum pH → Mucoadhesion is ideal at low pH, yet at higher pH the progress changes to a pole structure that permits more straightforward crosslinking and connection. At extremely high pH, electronic materials, for example, chitosan structure polyelectrolyte buildings with bodily fluid and show solid mucoadhesion.
- It ought to non-harmful, financial, biocompatible ideally biodegradableable.

MATERIALS AND METHODS

Mechanisms of mucoadhesion

The mechanism of mucoadhesion is generally divided in two steps,

- Contact stage
- Consolidation stage

The chief stage is portrayed by the contact between the mucoadhesive and the mucousmembrane, with spreading and growing of the arrangement, beginning its significant contact with themucus layer. Now and again, for instance, for visual or vaginal subtleties, the movement structure ismechanically affixed over in various cases, the declaration is progressed by the ideal plan of the organ to the film, the system is directed, for instance, for the nasal course. In the hardening step, the mucoadhesive materials are authorized by the presence of sogginess. Sogginess plasticizes the structure, allowing the mucoadhesive particles to part free and to connect up by slight van der Waals and hydrogen bonds. Fundamentally, there are two hypotheses getting a handle on the association step:

- The diffusion theory
- The dehydration theory

As indicated by dispersion hypothesis, the mucoadhesive particles and the glycoproteins of the bodily fluid commonly communicate through interpenetration of their chains and the structure of auxiliary securities. For this to occur the mucoadhesive gadget has highlights leaning toward both substance and mechanical connections. As per lack of hydration hypothesis, materials that can promptly gelify in a fluid climate, when put in touch with the bodily fluid
can make its lack of hydration due the distinction of osmotic tension (Figures 1 and 2).

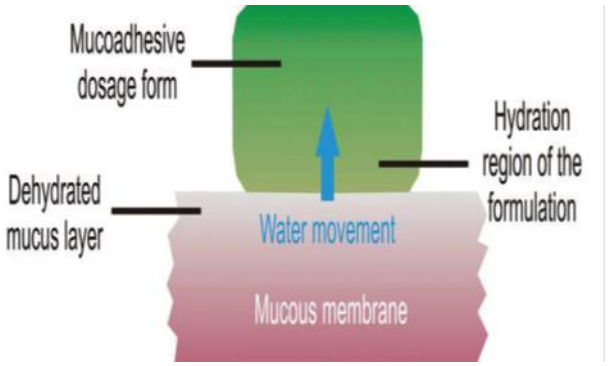

Figure 1: Two steps of mucoadhesion.

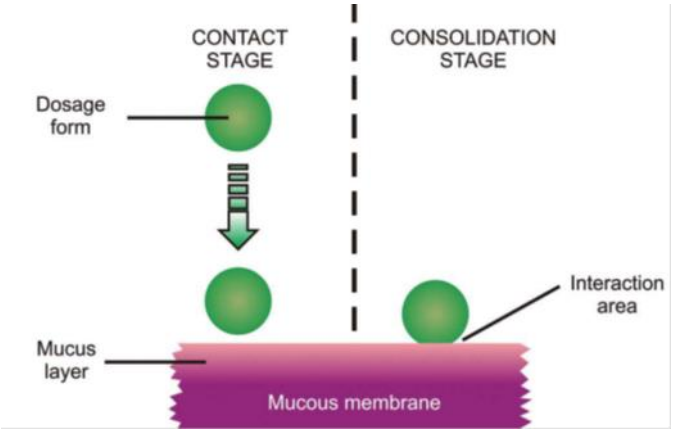

Figure 2: Dehydration theory of mucoadhesion.

Mucoadhesion theories

Six speculations have been introduced to make sense of mucoadhesion peculiarity. Mucoadhesion is characterized as the connection between a mucoadhesive polymer and mucosal layer, and these hypotheses portray different strides of the collaboration between two substrates. In the accompanying, these speculations are introduced:

Wetting theory

This hypothesis expects the infiltration of a mucoadhesive polymer into the inconsistencies of the engrossing surface, which becomes solidified and prompts mucoadhesion. The proclivity toward the surface not set in stone by estimating the contact point.

Absorption theory

According to this speculation, grasp is the eventual outcome of association between the concrete polymer and natural liquid substrate through two extraordinary kinds of compound holding, including H-holding and Van der Waals powers. After a fundamental contact, the hold of the two surfaces is a direct result of the power between the particles of the two surfaces.

Electronic theory

This hypothesis makes sense of that distinctions in the electronic designs of two surfaces assume a significant part in their associations. The development of bonds happens through the exchange of electrons between the polymer and the mucous film. The advancement of alluring power among polymer and mucous surface happens by an electronic twofold layer.

Mechanical theory

In this hypothesis the grip of two surfaces happens, in light of the fact that the harsh surface is filled by a mucoadhesive liquid. This step is a persuasive in mucoadhestion processes, despite the fact that abnormalities increment the region of the connection point.

Fracture theory

As indicated by this hypothesis, the power that causes the obligation of bond between two surfaces and the power which is expected to withdraw them are connected. This supposition decides how much power expected to isolate the polymer from the bodily fluid, through following condition: $\sigma=\sqrt{(E^{*}\varepsilon)}/L$ where σ is the break strength, E is Youthful's modulus of J flexibility, ε is the energy of crack, and L is the basic length of break.

Diffusion theory

The dissemination hypothesis is put together both with respect to the fixation angle and the hour of entrance of the polymer chain in the glycoprotein organization of the bodily fluid. The dispersion is a two-way process. One is the development of a layer of interpenetration, and the other one is the accomplishment of a successful grip, which happens when the interprenetration layer thickness comes to around 0.2-0.5 μm. The arrangement of this layer relies upon factors like focus inclination, atomic load of cement macromolecules, hydrodynamic size, portability, adaptability, and the length of the polymer chains [3-7].

RESULTS AND DISCUSSION

Factors affecting mucoadhesive drug delivery systems

- **Polymer related factors:** A couple of properties or characteristics of the powerful polymer expect a central part in mucoadhesion. Among them, polymer nuclear weight, center, broadening, of polymer chains flexibility, and explicit confirmation which could impact the mucoadhesion.
- **Environment related factors:** pH of the polymer substrate interface, utilitarian strength and first contact time can affect the mucoadhesion.
- **Physiological components:** Disease state and mucine turn over are the critical physiological factors, which can moreover impact mucoadhesion (Figures 3-5).

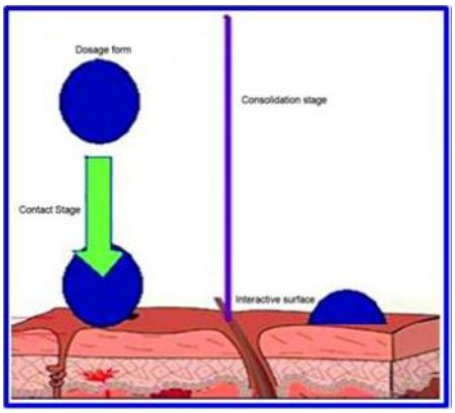

Figure 3: The process of contact and consolidation.

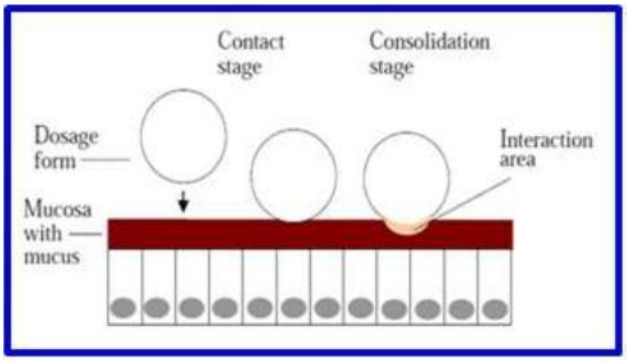

Figure 4: The two stages in mucoadhesion.

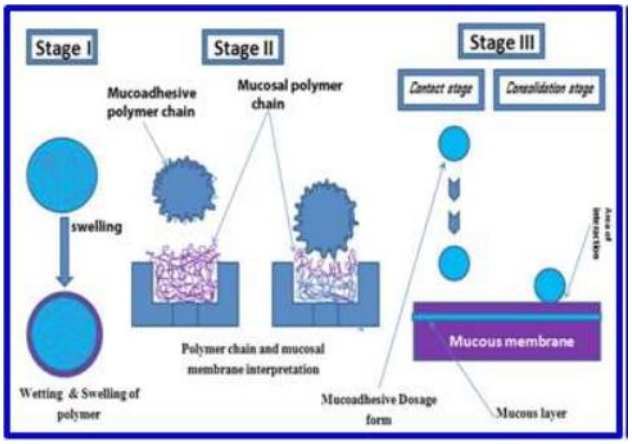

Figure 5: Steps involved in mechanism of mucoadhesion.

Evaluation studies of mucoadhesive drug delivery system

- *In vitro*/*ex vivo* tests
- Strategies deciding rigidity
- Strategies deciding shear pressure
- Grip weight strategy
- Fluorescent test strategy
- Stream channel strategy
- Mechanical spectroscopic strategy
- Falling fluid film strategy
- Colloidal gold staining strategy
- Viscometer strategy

- Thumb strategy
- Bond number
- Electrical conductance
- Expanding properties
- In vitro drug discharge studies
- Mucoretentability studies

***In vivo* methods**

- Use of radioisotopes
- Use of gamma scintigraphy
- Use of pharmacoscintigraphy
- Use of Electron Paramagnetic Resonance (EPR) oximetry
- X - ray studies
- Isolated loop technique

Explain procedure for various tests

Methods determining tensile strength: In malleable and shear explores, the pressure is consistently conveyed over the cement joint, while in the strip strength stress is engaged at the edge of the joint. Accordingly, pliable and shear measure the mechanical properties of the framework, though strip strength estimates the stripping force [8].

Surface profile analyzer is a business instrument which is utilized to quantify the power expected to eliminate bioadhesive movies from extracted tissue in vitro. For this test, a piece of creature mucous layer was taken and tried for the power expected to remove the formulation from a model film which comprises of plate made out of mucin. The surface analyzer, working in elastic test mode and combined with a sliding lower stage, was likewise used to decide strip strength of comparable definitions. On a versatile stage the creature skin was put and on top of it the bioadhesive film was set, which was later on pulled upward to determine the strip strength. Figures 6 and 7 are outlines of surface profile analyzer and assurance of strip strength [9].

Methods determining shear stress: The assessment of the shear pressure fortifies a quick correlation to the bond. In a direct shear pressure assessment based method two smooth, cleaned plexi glass boxes are picked; one block is fixed with adhesive Araldite on a glass plate, which is fixed on leveled out table. The level is changed with the spirit level. To the upper block, a string is tied and the string is gone down through a pulley, the length of the string from the pulley to the holder was 12 cm. Close to the completion of the string a compartment of fixed is joined. More loads can be added to it. Another procedure incorporates the assessment of mucoadhesion by use of a treated steel turning cylinder which is covered with recently separated porcine intestinal mucosa to which polymer plates were associated. The chamber is placed in a crumbling contraption and turned at 125 RPM. It is bankrupt down every 30 mins for the annexment of the polymers plates [10].

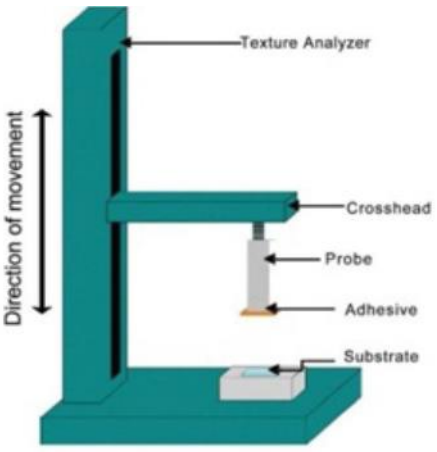

Figure 6: Texture profile analyzer in bioadhesion test mode.

Falling liquid film method: In this strategy the mucous layer is set in a hardened steel round and hollow cylinder, which has been longitudinally cut. This help is put leaned in a round and hollow cell with a temperature controlled at 37º. An isotonic arrangement is siphoned through the mucous film and gathered in a measuring glass. Consequently, on account of particulate frameworks, the sum staying on the mucous layer can be counted with the guide of a coulter counter. For semi-strong frameworks, the non-stuck

mucoadhesive can be measured by superior execution fluid chromatography [11].

This philosophy permits the representation of arrangement of fluid glasslike mesophase on the mucous film after the streaming of the liquids and through examination through enraptured light microscopy.

Fluorescent probe method: In this technique the layer lipid bilayer and membrane proteins are marked with pyrene and fluorescein isothiocyanate, separately. The cells are blended in with the mucoadhesive specialists and changes in fluorescence spectra were observed. This gives a sign of polymer restricting and its effect on polymer attachment.

Flow channel method: The procedure was coordinated attempting to understand essential requirements for bioadhesion to setup improved bioadhesives polymers for oral use. The film lipid bilayer and layer proteins were set apart with pyrene and fluorescence isothiocyanate, separately. The cells were then mixed in with candidate bioadhesives and the change of brightness spectra was noticed. This offered a hint of polymer limiting and its impact on polymer hold.

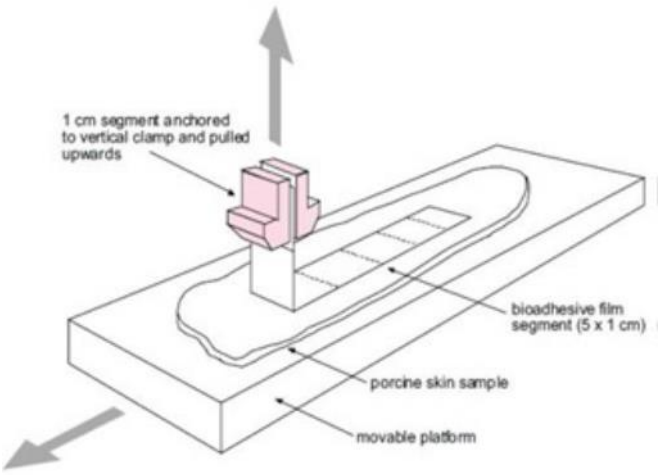

Figure 7: Determines peel strength of bioadhesive films.

Swelling index: The extent of swelling can be measured in terms of % weight gain by the dosage form. The swelling index is calculated using following formula.

Where,

S.I=Swelling Index

Wt=Weight of tablet at time t

Wo=Weight of tablet before placing in the beaker

Colloidal gold staining method: Colloidal gold staining strategy is proposed for the investigation of bioadhesion. The method utilizes red colloidal gold particles, which are adsorbed on mucin molecules to shape mucin-gold forms, which upon collaboration with bioadhesives hydrogels fosters a red variety on a superficial level. This can be evaluated by measuring either the power on the hydrogel surface or the forms at 525 nm [12].

Viscometric method: A basic viscometric technique is utilized to evaluate mucin-polymer bioadhesive bond strength. Viscosities of 15% w/v porcine gastric mucin scattering in 0.1 M HCl (pH 1) or 0.1M acetic acid derivation cushion (pH 5.5) is estimated with a Brookfield viscometer in the nonappearance or presence of chosen unbiased, anionic, and cationic polymers. Thickness components and the powers of bioadhesion are determined.

Thumb method: This is an extremely basic test utilized for the subjective determination of strip cement strength of the polymer and is valuable instrument in the improvement of buccal glue conveyance frameworks. The adhesiveness is estimated by the trouble of pulling the thumb from the cement as an element of the strain and the contact time.

Adhesion number: Bond number for mucoadhesive not entirely set in stone as the proportion of the quantity of particles connected to the substrate to the complete number of applied particles, communicated as a rate. The grip strength increments with an expansion in the attachment number [13].

Electrical conductance: The rotational viscometer was adjusted to decide electrical conductance of different semi-strong mucoadhesive treatments and observed that the electrical conductance was low within the sight of sticky material.

Mucoadhesive strength: Mucoadhesive strength of the piece design can be measured on the changed genuine balance. The contraption incorporates a changed twofold bar veritable congruity wherein the right holder is evacuated by a glass slide with copper

wire and additional weight, to make the right side weight vague with left side dish. A Teflon block of fixed evaluation and level is made with an upward piece of 2 cm level and 1.5 cm width on one side. This is kept in surveying utencil stacked up with help media 0.1 N HCl pH 1.2, which is then organized under right 50% of the balance. Goat or rat stomach mucosa can be used as a model film and pad media 0.1 N HCl pH 1.2 can be used as hosing fluid. The one side of the evaluation structure is joined to the glass slide of the right arm of the congruity and a short period of time later the recepticle is raised gradually until contact between goat mucosa and mucoadhesive piece structure is spread out. A preload of 10 g is placed on the slide for 5 min (preload time) to spread out adhesion holding between mucoadhesive part improvement and goat or rat stomach mucosa. The preload and preload time are kept consistent. After the satisfaction of preload time, preload is taken out from the glass slide and water is then reviewed the plastic holder for left side arm by peristaltic guide at a reliable speed of 100 drops for every min. The extension of water is ended when mucoadhesive appraisal structure is separated from the goat or rat stomach mucosa. The liberality of water expected to pull out mucoadhesive fragment structure from stomach mucosa is noted as mucoadhesive strength in grams. Figure 7 is mucoadhesion test get together [14-17].

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive Strength} \times 9.81}{1000}$$

$$\text{Bond strength (N/m}^2\text{)} = \frac{\text{Force of Adhesion (N)}}{\text{Surface area of tablet (m}^2\text{)}}$$

Stability Studies: The progress of a viable definition can be assessed exclusively through strength studies. The motivation behind solidness testing is to get a steady item which guarantees its wellbeing and viability up to the furthest limit of timeframe of realistic usability at characterized capacity conditions and pinnacle profile. ICH rules can be continued in such manner.

Measurement of the Residence Time/*In Vivo* Techniques: Assessments of the home time of mucoadhesive at the application site give quantitative information on their mucoadhesive properties. The GI travel times of various mucoadhesive game plans have been examined using radioisotopes and the fluorescent checking techniques.

Oral mucoadhesive dosage forms

Tablets: Tablets are pretty much nothing, level, and oval, with a width of around 5-8 mm. Not by any stretch like the customary tablets, mucoadhesive tablets think about drinking and talking without critical pain. They unwind, adhere to the mucosa, and are held prepared until deterioration or possibly release is done. Mucoadhesive tablets, generally speaking, might potentially be used for controlled release drug transport, yet coupling of mucoadhesive properties to tablet appreciates additional advantages, for example, it offers compelling ingestion and redesigned bioavailability of the prescriptions in light of a high surface to volume extent and works with an impressively more confidential contact with the organic liquid layer. Mucoadhesive tablets can be modified to adhere to any mucosal tissue recalling those found for stomach, thusly offering the expected results of confined as well as crucial controlled appearance of drugs.

The utilization of mucoadhesive tablets to the mucosal tissues of gastric epithelium is used for association of meds for restricted movement. Mucoadhesive tablets are extensively used considering the way that they release the drug for a postponed period, lessen repeat of prescription association and work on the patient consistence. The critical disadvantage of mucoadhesive tablets is their shortfall of genuine versatility, inciting sad patient consistence for long stretch and repeated use.

Films: Mucoadhesive movies might be liked over glue tablets with regards to adaptability and solace. What's more, they can evade the moderately short home season of oral gels on the mucosa, which are handily washed away and taken out by spit. Besides, on account of nearby conveyance for oral illnesses, the movies additionally assist with safeguarding the injury surface, in this manner assisting with lessening agony, and treat the sickness all the more actually. An ideal film ought to be adaptable, flexible, and delicate, yet sufficiently solid to endure breakage because of stress from mouth developments. It should likewise have great mucoadhesive strength to be held in the mouth for the ideal length of activity. Enlarging of film, assuming it happens, ought not be too broad to forestall inconvenience.

Patches: Patches are overlays containing an impermeable sponsorship layer, a prescription containing vault layer from which the medicine is conveyed in a controlled manner, and a mucoadhesive surface for mucosal association. Fix systems resemble those used in transdermal drug transport. Two procedures used to design stick patches integrate dissolvable anticipating and direct handling. In the dissolvable projecting methodology, the moderate sheet from which patches are punched is prepared by extending the game plan of the medicine and polymer(s) onto a help layer sheet, and in this way allowing the solvent(s) to disseminate. In the quick handling procedure, plan constituents are homogeneously mixed and stuffed to the best thickness, and patches of destined size and shape are

then taken out or punched. An impermeable help layer may in like manner be applied to control the course of prescription release, thwart drug setback, and breaking point winding and disintegrating of the device during the application time span.

Gels and ointments: Semisolid measurements structures, like gels and treatments, enjoy the benefit of simple scattering all through the oral mucosa. Be that as it may, drug dosing from semisolid measurements structures may not be basically as precise as from tablets, fixes, or movies. Unfortunate maintenance of the gels at the site of use has been overwhelmed by utilizing mucoadhesive details.

Certain mucoadhesive polymers, for instance, sodium carboxymethylcellulose, carbopol, hyaluronic corrosive, and thickener, go through a stage change from fluid to semisolid. This change upgrades the thickness, which brings about maintained and controlled arrival of medications. Hydrogels are likewise a promising measurements structure for buccal medication conveyance. They are shaped from polymers that are hydrated in a watery climate and genuinely entangle drug atoms for resulting slow delivery by dissemination or disintegration. The use of mucoadhesive gels gives a drawn out maintenance time in the oral pit, sufficient medication entrance, as well as high adequacy and patient agreeableness. A significant use of glue gels is the nearby conveyance of restorative specialists for the treatment of periodontitis, which is an incendiary and irresistible infection that causes development of pockets between the gum and the tooth, and can ultimately cause loss of teeth. It has been recommended that mucoadhesive polymers may be helpful for periodontitis treatment when consolidated in antimicrobial-containing definitions that are handily brought into the periodontal pocket with a needle. HPMC has been utilized as a cement salve fixing. Moreover, an exceptionally gooey gel was created from carbopal and hydroxypropylcellulose for treatment measurements shapes that could be kept up with on the tissue for as long as 8 hours.

CONCLUSION

The peculiarity of mucoadhesion can be utilized as a model for the controlled medication conveyance approaches for various medication up-and-comers. There is no question that the oral course is the most preferred and presumably most complex course of medication conveyance. The buccal mucosa offers a few benefits for controlled drug conveyance for expanded timeframes. The mucosa is very much provided with both vascular and lymphatic waste and first-pass digestion in the liver and pre-foundational disposal in the gastrointestinal lot are kept away from.

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