WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 15, 203-213. Review Article ISSN 2277– 7105

A REVIEW ON MUCOADHESIVE AND BIOADHESION AS A NOVEL DRUG DELIVERY SYSYTEM

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Article Received on
04 June 2018,

Revised on 24 June 2018,
Accepted on 14 July 2018

DOI: 10.20959/wjpr201815-12952

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ABSTRACT

The current Review article has been focused on the mucoadhesive and Bioadhesion drug delivery system may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. Drug actions can be improved by new drug delivery system, such as mucoadhesive system. This system remains in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to improvement in both local and systemic effects. There are many routes of mucoadhesive drug delivery system, oral route is the most ancient as well as preferred by patient being convenient to take. However per oral route has avoiding such as hepatic first pass metabolism and enzymatic degradation in GIT which is a delay to the absorption of most proteins and peptides groups of drugs. Mucoadhesive 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. The administration of drugs by the buccal route has several advantages over per oral administration such as quick action, improved patient compliance particularly with peadiatric & geriatric patient. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation.

KEYWORDS: Muchoadhesion, Bioadhesion, Oral mucosa, buccal patch.

INTRODUCTION

The oral mucosa has many properties which make it an attractive site for drug delivery but also Provides several challenges for researchers investigating novel delivery techniques to

overcome many different formulations including sprays, tablets, mouthwashes, gels, pastes and patches are presently used for delivery into and/or across the oral mucosa. The concept of mucoadhesion has provided the great application in prolonging the residence time as well as controlled release effect of various bioadhesive dosage forms through different mucosal routes. The formulations based on the mucoadhesive drug delivery system have shown the enhanced bioavailability of many drugs. The use of various mucoadhesive polymers have achieved the significant interest in formulating the sustained release, extended release as well as prolonged release dosage forms.

The mucoadhesive drug delivery provides greater absorption and enhanced bioavailability of dosage forms due to the large surface area and higher blood flow in the mucosal cavities. The delivery across the mucus membrane provides various advantages over other drug delivery routes i.e., overcome the hepatic first pass metabolism as well as the degradation of drugs by various gastrointestinal enzymes as well as intestinal flora.[1]

Mucoadhesion and bioadhesion

Mucoadhesion system defined as a state in which two components, of which one is of biological source, are joined together for prolonged periods of time by the promote of interfacial forces. 'Bioadhesion' broadly includes adhesive interactions with any biological or biologically derived substance, whereas 'Mucoadhesion' is used when the bond is formed with a mucosal surface, while the term cytoadhesive means adhesion to cells. Mucoadhesive drug delivery systems are also a sub- type of gastro- retentive drug delivery systems. In the formulation of oral controlled-release dosage forms, significant benefits may follow from the use of mucoadhesive polymers providing brief adhesion between the drug delivery system and the mucous or epithelial cell surface of the alimentary canal. The bond between polymer and mucous membrane involves secondary forces, such as hydrogen bonds or Van der Waals forces. Mucoadhesives may, therefore, be regarded as a specific class of bioadhesives. Mucoadhesive/biodhesive drug delivery system can be applied to the following systems:

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system[2,3]

Advantages of Mucoadhesive Drug Delivery System

- Excellent quality being to be entered, rapid onset of action possible.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability andits therapeutic effect.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Reduced dosing frequency
- Maximum utilization of drug enabling reduction in total amount of drug administered
- Shorter treatment period.
- An alternative to oral route, whereby the drug is protected from degradation in the acidic environment of the GIT, E. g. Buccal patch
- Moreover, rapid cellular recovery and healing of the local site
- Rapid absorption because of enormous blood supply and good perfusion rates.
- Better patient compliance.
- Significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.
- It offers a passive system of drug absorption and does not require any activation.[4,5,6]

Disadvantages

- The formulation may irritate the sensitive nasal mucosa.
- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be administered by this route.
- Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers
- Drugs, which are unstable at buccal pH, cannot be administered by this route.
- The vaginal formulation may be contraindicated in case of pregnancy
- Only drugs with small dose requirements can be administered.
- The vaginal formulation may leak and cause disorderlines.
- Drugs may be swallowed along with the saliva and lose the advantages of buccal route.
- Eating and drinking may become restricted.[4,5,6]

Theories of Mucoadhesion

The process of mucoadhesion is mainly based on formation of two types of bond between bio adhesive system and mucus membrane and they are:

1. Chemical bond

It may include covalent bonds, Weak secondary bonds, ionic bond and hydrogen bond etc.

2. Mechanical bond

This bond can be arising from the physical connection between two surfaces. It is similar to that of the interlocking system. On the basis of nature and strength of these two kinds of bonds, there are following five theories of mucoadhesion that are been discussed.[7]

3. Electronic theory

According to the electronic theory, there is difference in the electronic structure of mucin surfaces and bio adhesive system which results in attaining a electronic gradient. Due to presence this electronic structure difference, the transfer of electrons occurs in these two systems (mucin surface and bioadhesive system) when they come in contact with each. As a result of this electron transfer there is the formation of an electronic bi-layer at the interface of the two surfaces. This interfacial bi-layer exerts an attractive force in the interface of two surfaces that may produce an effective mucoadhesion.[7]

4. Adsorption theory

This theory describes the involvement of both type of chemical bond, that is, primary and secondary bond in the bio adhesion mechanism. Both the surface that is mucin and drug delivery system has their own surface energy. When they come in contact, the adhesion occurs due to the surface energy and results in the formation of two types of chemical bond. Primary chemical bond such as covalent bond, which is strong in nature, thus produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and hydrogen bonding, which are weak in nature, thus produces a semi-permanent bond.[7]

5. Wetting theory

This theory is based on the mechanism of spreadability of drug dosage form across the biological layer. This theory is mainly applicable to liquids or low viscous mucoadhesive

system. According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion.[8]

6. Diffusion interlocking theory

This theory describes the involvement of a mechanical bond between the polymeric chain of drug delivery system and polymeric chain of mucus membrane, that is, glycol proteins. When two surfaces are in intimate contact, the polymeric chain of drug delivery system penetrates in to the glycoprotein network. According to this theory, the bioadhesion basically depends on the diffusion coefficient of both polymeric chains. The other factors that may influence the inter movement of polymeric chain are molecular weight, cross linking density, chain flexibility, and temperature in order to achieve a good bio adhesion, the bio adhesive medium should have a similar solubility with glycoprotein resulting in effective mucoadhesion.[8]

Mucoadhesive Polymers[9,10]

Mucoadhesive polymers can be classified as following:

Synthetic polymers

Cellulose derivatives (methylcellulose, ethyl cellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxyl propyl methylcellulose, sodium carboxy methylcellulose, Poly (acrylic acid) polymers (carbomers, polycarbophil), Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol), Natural polymers, Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, Lectin, Soluble starch, Gelatin, Pectin, Chitosan.

2. Hydrophilic Polymers

These are the water-soluble polymers that swell indefinitely in contact with water and eventually undergo complete dissolution, e.g. Methyl Cellulose, Hydroxyl Ethyl Cellulose, Hydroxyl Propyl Methyl Cellulose, Sodium Carboxy Methyl Cellulose, Carbomers, Chitosan and Plant gums.

3. Hydrogels

These are water swellable materials, usually a cross-link polymer with limited swelling capacity, E.g. poly (acrylic acid co acrylamide) copolymers, carrageenan, sodium alginate, guar gum and Modified guar gum etc.

4. Thermoplastic Polymers

These polymers include the non-erodible neutral polystyrene and semi-crystalline bio-erodible polymers, which generate the carboxylic acid groups as they degrade, e.g. polyanhydrides and polylactic acid. Various synthetic polymers used in mucoadhesive formulations include polyvinyl alcohol, polyamides, polycarbonates, polyalkylene glycols, polyvinyl ethers, esters and halides.

Mucoadhesive Agents[11,12,13]

Plasticizers

Plasticizer is a vital ingredient of the film formulation. It helps to improve the flexibility of the film and reduces the brittleness of the film. Plasticizer significantly improves the film properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in thecasting of film. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0–20% w/w of dry polymer weight.

Penetration Enhancers

Penetration enhancers are also required when a drug has to reach the systemic circulation to improve its action. These must be non-irritant and have a reversible effect and also improve absorption. The most common classes of buccal penetration enhancers include fatty acids, surfactants and, among these, bile salts, azone and alcohols. Recently, chitosan and its derivatives, polymers already known for their mucoadhesive properties, have been shown to be the potential penetration enhancers for transmucosal (intestinal, nasal, buccal and vaginal) absorption of drugs. Although the penetration enhancement properties of chitosan through mucosae (intestinal and nasal) are mainly owing to a transient widening of the tight junctions between the cells, the mechanism of penetration enhancement through the mucosa of the oral cavity has still to be clarified.

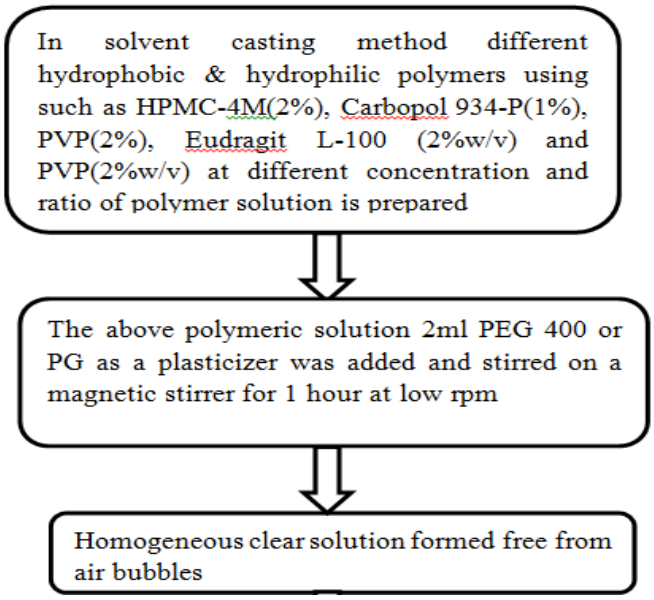
Examples of some penetration enhancers

Aprotinin, Cetyl Pyridinium Chloride, Azone, Benzalkonium Chloride, 2,3-lauryl ether, Cyclodextrin, Glycol, Lauric Acid, Polysorbate-80, Sodium Salicylate, Phosphatidyl choline etc.

Ideal Properties of Patch[14]

- It has been estimated that the total amount of drug that can be delivered across the buccal mucosa from a 2-cm2 system in 1 day is approximately 10–20 mg.
- Physiology of mucus membrane under disease condition need to be accounted (for e.g.: Cancer patients suffer from oral candidosis).
- Size of the flexible buccal patch may be as large as 10–15cm2 in area.
- Shape of the delivery system may also vary, although for buccal drug administration, an ellipsoid shape appears to be most acceptable
- Mucoadhesive buccal patches with a surface area of 1–3 cm2 are most acceptable
- Thickness of the delivery device is usually restricted to only a few millimeters. The location of delivery device also needs to be considered
- Maximal duration of buccal drug retention and absorption is approximately 4-6 h because food and liquid intake may require removal of delivery device.

Methodsof Preparationof Buccal Patches[15]



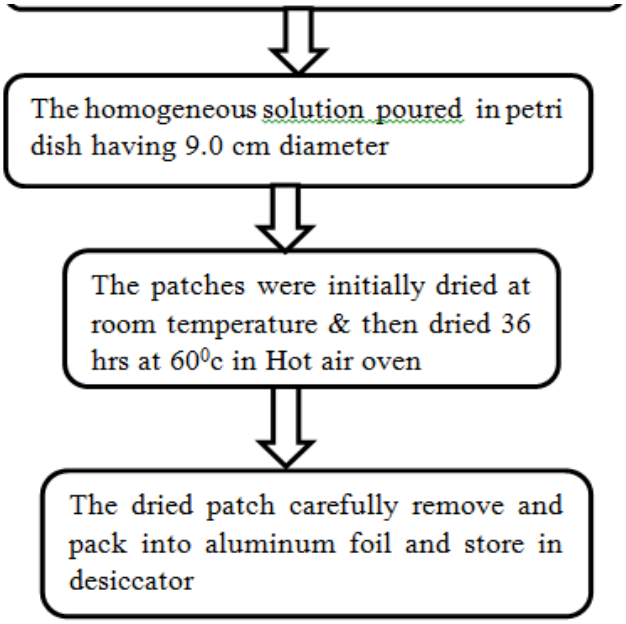


Fig: Solvent casting method.

Evaluation of patches

Mass uniformity and thickness of patches

Mass uniformity and thickness was done for randomly selected ten individual patches. The thickness and mass uniformity is measured by using screw gauge and digital weighing balance carefully.

Folding endurance

The folding endurance of randomly selected patches (without backing membrane) was determined by repeatedly folding one patch at the same place till it break or folded maximum 250 times.[16]

Drug content uniformity

Buccal patches are allowed dissolve in 10 mL of simulated saliva pH (6.2), under continuous shaking for 3 hr, withdraw 2 mL sample solution filter with filter paper after that suitable dilutions was made and amount of drug present in per patch was determined by using UV spectrometer at 272nm.[17]

Measurement of surface pH

Buccal patches were placed on the surface of agar plate (the agar plate is prepared by dissolving agar 2% w / v in warmed phosphate buffer pH 6.2 under stirring then poured to Petridish to solidify at room temperature) allow to swell for some time. The surface pH is

measured bringing a glass electrode in contact with surface of the patch and allow to equilibrate for 1 min. Averages of three readings are recorded.[18]

Swelling studies

The weight of the patch, without backing membrane was determined by digital electronic weighing balance. Patches are placed on the surface of an agar plate and allowed to swell by keeping it an incubator at 37 ºC and the diameter is measured at predetermined time intervals for 90 minutes. Swelling index was calculated from following equation.

Swelling index = (W2- W1 / W1) ×100

Where,

SI (%) is percent swelling, W2 is the swollen patch weight, W1 is the initial weight of the patch.[19]

Ex vivo residence time

The in vitro residence time was determined using a locally modified USP disintegration apparatus the disintegration medium was composed of 500 mL simulated saliva pH 6.2 maintained at 37ºC. A segment of pig buccal mucosa (3 cm long), was attached by using thread to the surface of a glass slide, vertically attached to the apparatus and allowed to move up and down so that the patch was completely immersed in and out buffer solution The time taken by the patch to detach from the mucosal surface was recorded and the averages of three readings were recorded.[20]

In vitro drug release

The amount of drug release from buccal patches was studied using the USP type II dissolution test apparatus 100 mL simulated saliva pH (6.2) at 37 ± 5ºC stirred at 50 rpm, patch having 2 cm diameter was fixed to square shaped glass disk by using instant adhesive glass disk is placed inside a dissolution beaker contains simulated saliva pH (6.2).[19]

2 mL of samples are withdrawn at predetermined intervals of 240 min and replaced with fresh buffer solution. Collected samples are filtered through 0.45 µm filter paper and diluted with buffer solution pH (6.2) and the amount of drug release is assayed by UV spectrophotometer at 272 nm. Drug release mechanism was determined by Higuchi and Korsmeyer-Peppas plots.[21,22]

In vitro permeation

The in vitro buccal permeation study of buccal patches through the pig buccal mucosa was performed using Franz diffusion cell at 37ºC ± 0.2ºC. Pig buccal mucosa was obtained from a local animal place and used within 2 hours of slaughter. Freshly obtained pig buccal mucosa was mounted between the donor and receptor compartments. The patch was placed on the mucosa so the smooth surface of the mucosa placed towards receptor compartment and the compartments were clamped together. The donor compartment was wetted phosphate buffer (pH 6.2). The receptor compartment was filled with isotonic phosphate buffer (pH 7.4) stirred with a magnetic bead at 50 rpm. 1 mL sample was withdrawn at predetermined intervals and replaced with fresh buffer solution and assayed by UV spectrophotometer at 272nm.[23]

Stability studies

Buccal patches were packed in an aluminium foil and stored in an amber coloured glass bottles. These bottles were subjected to stability testing using stability chambers maintained at 37 ± 0.5ºC and 75 ± 5% RH for 6 months. Stability of selected patches is also carried out in human natural saliva. Patches are examined for changes in weight variation, thickness and drug content.[24]

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