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A Review on Promising Novel Drug delivery System- Bioadhesive Drug Delivery System

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ABSTRACT

Bioadhesive drug delivery system has gained sufficient attention of researchers not only due to their enormous advantages but also feasibility of formulation and patient compliance. In this review an effort was made to describe aspects of bioadhesive films, their preparation methods, polymer used in the formulation of this type of drug delivery system, different mechanism of how plasticizer work in drug delivery films and different evaluation parameters of this type of formulation so that this can be further studied and formulated with wide spectrum drug by checking suitability of the formulation with the active pharmaceutical ingredient.

Key words: Bioadhesive formulations, polymers, plasticizers, evaluation.

1. INTRODUCTION

According to novel technologies for pediatrics, geriatrics, non-compliance patient bioadhesion mucosal dosage form are most preferred due to non-invasiveness, adaptability, ease of administration.

Bioadhesion is a biological phenomenon of interfacial molecular attractive force between the surface of biological substrate i.e. mucous membrane and natural or synthetic polymer which allows the system to adhere to the biological surface for a desired period and time. Among the various routes of drug delivery, mucoadhesive drug delivery system is the most desirable route and most preferred by patient and clinicians.¹

A mucoadhesive controlled release device can improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels.² In recent years mucoadhesion's pharmaceutical aspects has been gaining interest as it is present drug from destruction by gastrointestinal contents or hepatic first pass inactivation of drug. The mucoadhesive drug delivery system includes the following:

1. Buccal drug delivery systems
2. Sublingual drug delivery systems
3. Rectal drug delivery systems
4. Vaginal drug delivery systems
5. Ocular drug delivery systems
6. Nasal drug delivery systems²

Among all routes of administration, buccal drug delivery is considered to be potent to medicine associated with severe pain and discomfort.^{3,4}

Constant and prolonged drug delivery required for orthopedic patients suffering from disorder of joints, ligaments, skeleton system for effectively managing the therapeutic condition. Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drug.⁵ This drug delivery prevent medicament from GIT content or hepatic first pass inactivation and due to intimate contact of drug to the biological system for better absorption.^{6,7}

This drug delivery system deals with the drug which undergoes high first pass metabolism, improve bioavailability with dosing frequency to plasma peak levels. This makes it cost effective and minimizes adverse/ side effect. Because of small size and reduced thickness patient compliance of films have been improved compared to lozenges and tablets. Films as dosage forms are considered as novel, patient friendly, convenient product.⁸

1.1 Structure and Design of Buccal Dosage Form

Buccal Dosage form can be of matrix type or reservoir type.

1.1.1 Matrix type

Buccal patch consist of drug, adhesive and additives which are mixed together designed in matrix configuration.

1.1.2 Reservoir type

In reservoir system, patch contains a cavity for a drug and additives which are separated from the adhesives. In it impermeable backing layer is present to control the drug delivery. It prevent patch from deformation as well drug loss.⁹

1.1 Advantages of buccoadhesive drug delivery

Drug administration via the buccoadhesive drug delivery offers several advantages such as

- As oral rich in blood supply the drugs absorption from buccal cavity is fast.
- Due to its good assessibility to membranes makes application painless and comfort.
- Patients can control the period of administration or terminate delivery in case of emergencies¹⁰
- Drug is easily administered
- Extinction of therapy in emergency can be facilitated.
- Prolongation of drug release for a period of time.
- Drug can be administered in case of unconsciousness and trauma patient

- Drug's bioavailability is increased as it bypass the metabolism.
- Drugs which are unstable in acidic environment of stomach can be administered by this delivery.
- Flexibility can be achieved in physical state, shape, size and surface.¹¹

1.2 Limitations of buccoadhesive drug delivery system

- There are some limitations of buccal drug delivery system such as-
- Drugs cannot be administered which are unstable at buccal pH.
- Drugs cannot be formulated for buccal cavity which will cause allergic reactions, discoloration of teeth or contain antimicrobial agents which affects desired natural microbes.
- As compared to sublingual membrane buccal membrane has low permeability.
- Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa are not applicable for this route.¹²⁻¹⁴

1.3 Physiological factors affecting buccal bioavailability

1.3.1 Inherent permeability of the epithelium

The permeability of the oral mucosal epithelium is intermediate between that of the skin epithelium, which is highly specialized for barrier function and the gut, which is highly specialized for an adsorptive function. Within the oral cavity, the buccal mucosa is less permeable that the sublingual mucosa.

1.3.2 Blood supply

Lamina propria are rich in blood supply and lymphatic network, thus drug moieties are readily absorbed in systemic circulation. Flow of blood in buccal cavity is 2.4ml/min⁻¹cm.

1.3.3 Metabolic activity

Drug moieties adsorbed via buccal mucosa is redilly delivered directly to the blood as it avoid first pass metabolism and null the effect of liver and gut wall. Thus it is more liable drug delivery route for enzymatically labile drugs such as therapeutic peptides and proteins.

1.3.4 Saliva and mucous

Salivary glands continuously washed the oral mucosa surface by stream of saliva, approx. 0.5-2L per day. Buccal mucosa

is constantly in contact with saliva which enhances drug dissolution and increase bioavailability.

1.3.5 Ability to retain delivery system

Buccal mucosa is ideal for retentive drug delivery as it is smooth and relatively immobile surface.¹⁵

2. CLASSIFICATION OF BUCCAL SYSTEMS

In place of conventional oral medication, recently new formulation has been studied i.e. buccal mucoadhesive formulation. It can retained for longer period of time and removed at any time. Various research groups studied buccal mucoadhesive drug delivery system - tablets, films, layered systems, discs, micro particles, ointments, wafers, lozenges and hydrogel systems.

2.1 Buccal tablets

Bucoadhesive buccal tablets can be prepared by direct compression or wet granulation method. It must be sufficiently hard because it will be inserted in the buccal pouch and may dissolve or erode.

Water impermeable material like ethyl cellulose, hydrogenated castor oil etc. are either coated by spraying method or compressed with it achieve unidirectional release of drug. It must be spray at every face of tablet except one which is in contact with buccal mucosa. Bilayered and multilayered tablet has been already formulated, further it can be formulated in certain physical state such as microspheres, prior to direct compression in order to attain some desired properties e.g. enhanced activity and prolonged drug release.

2.2 Buccal semisolid dosage forms

Semisolid dosage form can be easily dispersed out of the oral mucosa over other dosage form. To overcome problems of poor retention of formulation like gel, certain bioadhesive polymers for eg: sodium carboxy methyl cellulose which undergoes phase alteration from liquid to semisolid result in improving as well as enhancing the viscosity gives sustained or controlled release of drugs. For example, finely powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution like Arabase.

2.3 Buccal films

In recent years buccal films were developed as dosage form for delivery of drug via buccal route. These are prepared over discs and tablets for patient comfort and flexibility. Films ensure

longer residence time as well as precise drug dosing. It increase effectiveness by reducing pain by protecting wound surface.

2.4 Buccal powders

Buccal bioadhesive powders are sprayed onto the buccal mucosa are a mixture of drug and Bioadhesive polymers which are used in the reduction in diastolic B.P. after the administration of buccal tablet and buccal film of nifedipine.

2.5 Micro particle

Micro particles have more advantages than tablet site of adhesion but the success of these microspheres is limited due to their short residence time at site of absorption.

2.6 Wafer

Wafer is a novel periodontal drug delivery system, generally used for the treatment of microbial infection.¹⁶

3. FORMULATION CONSIDERATIONS

Formulation is decided by keeping in mind various parameter such as performance characteristics such as taste masking, fast dissolving, physical appearance, mouth feel *etc.* Fast dissolving film is a thin film incorporate with an active ingredient. Special matrix water-soluble polymers is responsible for immediate dissolution, in water or saliva respectively. The excipients used in formulation of fast dissolving buccal films are also discussed in detail and it must generally regarded as safe (*i.e.* GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

Drugs can be incorporated up to single dose of 15 mg.¹⁷ Mechanical properties of the films, such as shifting the glass transition temperature to lower temperature, formulation considerations have been reported as important factor.

Table 1: Composition of oral thin film

S. No.	Name of excipient	Quantity in %
1	Drug	5-30
2	Film forming agent	40-50
3	Plasticizers	0-20
4	Saliva stimulating agent	2-6
5	Sweetning agent	Q.S
6	Surfactant	Q.S
7	Flavouring agent	Q.S
8	Colouring agent	Q.S

3.1 Active pharmaceutical agents

From any class of pharmacology drugs, active pharmaceutically active substance can be used for administration but it must be compatible to the buccal environment. According to previous literature drug can be added from 5%-25% w/w of total weight of polymer. Dose of drug in mgs (less than 20mg/day) is required for effective formulation.

Various drugs like: Pediatrics (antitussive, expectorants, antiasthmatics), Geriatrics (antiepileptic, expectorants), Gastrointestinal diseases, Nausea (*e.g.* due to cytostatic therapy), Pain (*e.g.* migraine), CNS (*e.g.* antiparkinsonism therapy) grasp attention of researcher for the development of fast dissolving films. Following are the preferred active agents include chlorpheniramine maleate, brompheniramine maleate, dexchlorpheniramine, triprolidine hydrochloride, acrivastine, azatadine maleate loratidine, phenylephrine hydrochloride, dextromethorphan hydrochloride, ketoprofen, sumatriptan succinate, zolmitriptan, loperamide, famotidine, nicotine, caffeine, diphenhydramine hydrochloride, and pseudophedrine hydrochloride, and their amounts per strip can be well known.

3.2 Polymers

For the desired properties of buccal films various polymer used either alone or in combination. It provide toughness to the strip enough to avoid damage while handling or during transport. Types of polymer and its amount decides film robustness

Following are the polymers used make fast dissolving films: cellulose or cellulose derivatives, pullulan, gelatin, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, xanthine gum, tragacanth gum, guar gum, acacia gum, methyl methacrylate copolymer and hypromellose.

Modified starches are also used for preparation. Due to low cost of this excipient it is used in combination of pullulan to decrease the overall cost of the product. To formulate fast dissolving films combination of microcrystalline cellulose and maltodextrin has also been used. Different polymers *viz.*, HPMC E15, HPMC K4M, HPMC E5, PVP, PVA, gelatin, eudragit RL100 and pullulan were used to formulate fast dissolving buccal films by solvent casting method.¹⁸

3.3 Plasticizers

The extensive use of polymers in medical and pharmaceutical applications including particularly packaging, medical devices, drug carriers and coatings has caused a substantial

demand for the proper plasticizers. It is a vital ingredient of the fast dissolving buccal films formulation.^{19,21}

Generally the plasticizers used in the concentration of 0-20% w/w of the dry polymer weight.²²

A chemical added to a polymer to increase its flexibility is known as plasticizers. It reduces the forces of attraction between the polymer chain and keeps them further apart by getting in between them which makes the material more flexible. Although polymer's strength and stiffness is reduced, but more useful where flexibility is required. Among all plasticizer which are used in chemical industries has been approved for the pharmaceutical application. It affects the absorption of drug, while its inappropriate use will result into cracking, splitting, peeling of the strip.

Low volatile substances with molecular weights between 200 and 400 such as diesters derived from dicarboxylic acids (*e.g.* sebacic acid, azelaic acid) or from ethylene glycol and propyleneglycol, or glycerol (triacetin, tributyrin) citric acid (tributylcitrate, triethylcitrate) are used as Plasticizer. Liquid drugs or liquids with a potential pharmacodynamic effect can serve as plasticizers.²³

3.3.1 Mechanism of Action of Plasticizer

Better plasticizing effect, can be typically obtained by heating and mixing until either the resin dissolves in the plasticizer or the plasticizer dissolves in the resin. The resulting solution is then poured into mould of desired shape and thickness and cooled down. Different plasticizers will show different characters in both circumstance, the ease of forming plasticized material and mechanical as well as physical properties of flexible product.²⁴

The mechanism of action of can be explained in such way that plasticizers act as interpose between every individual strand of polymer chain causing breakdown of polymer polymer interaction. Modified structure of tertiary structured polymer is obtained with more porous, flexible and less cohesive structure. Polymer overcome resistance to deformation as it was made soft and swell by plasticizer. So it will require lower tensile strength to deform polymer with plasticizers as compared to with plasticizer. Plasticizers will enhance elongation time.

All the polymers have glass transition temperature, the temperature at which hard glassy material convert to flexible rubber material. On interaction with plasticizers its glass transition temperature is reduced.²⁵

Some theories have been proposed to explain the mechanisms of plasticization process as follows:

The lubrication theory postulates that plasticizers act as internal lubricants by interspersing themselves and reducing frictional forces between polymer chains.

The gel theory postulates Polymer poses three dimensional structure which provides him rigidity and plasticizers break polymer-polymer interaction.

The free volume theory states that plasticizers work by lowering the T_g (glass transition temperature) as well it increase free volume. Free volume defined as difference between volume of glass, liquid etc. at absolute zero and volume measured at given temperature. Thus when specific volume of material increase results mater becomes rubbery or fluid.

When temperature above T_g, molecule will freely move, can be bend or rotate and produce greater amount of free volume.

Free volume comes from three principal sources:

- The motion of chain ends
- The motion of side chains
- The motion of the main chain.²⁶

Criteria of the plasticizer selection in medicine and pharmacy.

Different parameter are focused for making a selection of plasticizers for polymeric dosage form. Pharmaceutically used plasticizers need following criteria to be studied before use:

- biocompatibility
- compatibility of a plasticizer with a given polymer
- effect of plasticizer on drug release
- effect of plasticizer on mechanical properties
- processing characteristics
- cost-benefit analysis.

3.3.2 Effect of Plasticizers on other component of Formulation

Several factors influence consumption of plasticizers by fillers. These include:

- Particle size distribution – less plasticizer is required to fill this space if combination of small and large particle sizes are there thus leaves less free space between filler particles.
- Particle shape – Spherical shape are best for better packing as it leave less free space between particle. Particle shape is measured on basis of aspect ratio for

major fillers. It must be within 1 to 3, but for flaky filler(10-100) and largest for fibre (above 100). particle size distribution and particle shape both contribute to packing volume of filler which is a fraction of total volume occupied by fillers.

- Surface roughness and pore volume and size affect the plasticizer uptake by filler. Small pores (e.g., molecular sieves) do not permit plasticizer to enter them because plasticizer molecule is too bulky to fit small diameters of pores. Many physical and chemical interactions reduce or increase plasticizer uptake: interactions between filler particles, formation of agglomerates and aggregates, flocculation, zeta potential, acid/base interactions, surface energy, chemical interactions between filler and plasticizer.²⁷

3.3.3 Drug Release Enhanced by Plasticizers

For the desired drug release from the polymer made delivery system is modified by changing method of preparation or by altering the ingredients such as plasticizers. Modified release includes delayed release, extended release (prolonged, sustained), and pulsatile release Dosage forms based on polymeric carriers can be classified according to the mechanism of drug release into the following categories:

- Diffusion-controlled drug release either from anoporous polymer drug delivery system or
- from a porous polymer drug delivery system, and
- disintegration controlled systems.

Diffusion of a drug within a non-porous polymer drug delivery system occurs through the void spaces between polymer chains, and in the case plasticizers reduce polymer-polymer chain secondary bonding, and provide more mobility for the drug will automatically affect its release. Burst release occur if plasticizer leached out of the polymer results in pore formation. Subsequent release stage of drug is based on diffusion through the dense polymer phase²⁸⁻²⁹

3.4 Surfactants

Surfactants are used as wetting or dispersing agents so that the film gets dissolved within seconds and release active agent immediately. Surfactants also improve the solubility of poorly soluble drugs in fast dissolving buccal film's other excipient. Eg: polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, tweens and spans etc.³⁰

3.5 Sweetening agents

Sweeteners have become important in the pharmaceutical preparation intended to be disintegrated or dissolved in the oral cavity. The classical source of sweetener is sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose. Fructose is used widely in industries as sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose and while it is sweeter than sorbitol and mannitol and. Polyhydric alcohols such as sorbitol, mannitol. Polyhydric alcohols are less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. Recently artificial sweeteners have gained more popularity in pharmaceutical preparations such as saccharin, cyclamate and aspartame comes under first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame. Acesulfame-K and sucralose have more than 200 and 600 time sweetness.³¹

3.6 Saliva stimulating agents

Saliva stimulating agents increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid³² are the few salivary stimulants, among them citric acid being the most preferred.

3.7 Flavoring agents

Flavoring agents can be obtained from the synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Any flavor can be added such as essential oils or water soluble extracts of menthol, intense mints such as peppermint, sweetmint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary flavors⁴¹ such as vanillin, chocolate or fruit essence like apple, raspberry, cherry, pineapple. For masking taste depends on the flavor type and its strength and it will decide its amount. Flavors can be used alone or in the combination.

3.8 Coloring agents

A full range of colours is available including FD & C colors, EU colours, natural colouring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc dioxide and custom pantone-matched colours. These all coloring agents should not exceed concentration levels of 1% w/w.

3.9 Methods of manufacture of films

- Solvent casting
- Hot-melt extrusion

3.9.1 Solvent Casting^{33,34}

Buccal films are preferably formulated using the solvent casting method.

- Here water soluble ingredients are dissolved to form a clear viscous solution.
- The drug along with other excipients is dissolved in suitable solvent.
- Both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

Water soluble hydrocolloids used to prepare films are HPMC, HPC, SA, CMC, Pullulan and Pectin.

3.9.2 Hot-melt extrusion³⁵⁻³⁷

In hot-melt extrusion, A blend of pharmaceutical ingredients is molten.

Then forced through an orifice (the die) to yield a more homogeneous material in different shapes, such as granules tablets, or films.

Hot metal extrusion is commonly used to prepare granules, sustained release tablets, transdermal and transmucosal drug delivery systems. However, only a handful of articles have reported the use of hot-melt extrusion for manufacturing mucoadhesive buccal films.

3.10 Evaluation of Buccal Patches

3.10.1 Surface pH

Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.⁴⁸

3.10.2 Thickness measurements

The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer or Dial Thickness gauge.³⁸

3.10.3 Swelling study

Buccal patches are weighed individually (designated as W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1-hour time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter

paper.⁴⁶ The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated using the following formula.

$$SI = \frac{W2 - W1}{W1} \times 100$$

3.10.4 Folding endurance

The folding endurance of patches is determined by repeatedly folding 1 patch at the same place until it breaks or is folded up to 200 times without breaking³⁹

3.10.5 Water absorption capacity test

Circular Patches, with a surface area of 2.3 cm² are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na₂HPO₄, 0.19 g KH₂PO₄, and 8 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccator over anhydrous calcium chloride at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation.

$$SI = \frac{Ww - Wf}{Wf} \times 100$$

Where, Ww is the wet weight and W_f is the final weight.

The swelling of each film is measured^{40,45}

3.10.6 Ex vivo bioadhesion test

The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa was tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial was tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch was stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance were balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance has been kept in this position for 5 minutes of contact time. The water was added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength

3.10.7 In vitro drug release

The United States Pharmacopeia (USP) XXIII-B rotating paddle method was used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed for drug content after appropriate dilution. The *in vitro* buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at 37°C ± 0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with buffer

3.10.7 Permeation study of buccal patch

The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content⁴⁶

3.10.8 Ex vivo mucoadhesion time

The *ex vivo* mucoadhesion time can be determined by application of the buccal patch on freshly cut buccal mucosa. The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted on the buccal mucosa with the application of a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, and is kept at 37°C ± 1°C. After 2 minutes, stirring rate of 50-rpm is applied to simulate the buccal cavity environment, and adhesion of patch is monitored for 12 hours. The time for changes in colour, shape, collapsing of the patch, and drug content is noted.

3.10.9 Measurement of mechanical properties

Mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip break. The force and elongation of the film at the point when the strip break is recorded. The tensile strength and elongation at break values are calculated using the formula.

$$TS = \frac{m \times g}{b \times t} \times 100$$

Where, M is the mass in gm, g is the acceleration due to gravity 980 cm/sec^2 , B is the breadth of the specimen in cm and T is the thickness of specimen in cm. Tensile strength (kg/mm^2) is the force at break (kg) per initial cross-sectional area of the specimen (mm^2)

3.10.10 Stability study in human saliva

Bilayered and multilayered patches stability study can be performed in human saliva. Saliva is collected from humans of age group 18-50 years. Buccal patches are placed in petridishes separately containing 5ml of human saliva and placed in Oven at $37^\circ\text{C} \pm 0.2^\circ\text{C}$ for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), the dose formulations with better bioavailability are needed. Dosage forms such as liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides.⁴⁷⁻⁵⁰

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