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Review Article

Nanoparticulate Mucoadhesive System: Innovative Approach in Drug Delivery

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A B S T R A C T

Hepatic first pass metabolism and enzymatic degradation of the numbers of drugs leads to low systemic bioavailability in systemic circulation. To avoid this issue in drug delivery systems various modified drug delivery devices has been developed by pharmaceutical research scientists. But in last decade much more attentiveness has been focused towards the formulation and development of modified drug delivery systems by oral route because oral route is main and mostly preferred route of drug administration to the patients, So Nanoparticulate mucoadhesive system is one of the most innovative and novel approach in drug delivery. This Nanoparticulate mucoadhesive system avoids the hepatic first pass metabolism and enzymatic degradation of the drugs which may leads to enhanced systemic bioavailability. Conventional buccal drug delivery devices having lots of demerits to overcome this buccal film are formulated by using different excipients. Solvent casting, solid dispersion, semisolid casting, melt extrusion and rolling methods are used for the formulation and development of this mucoadhesive drug delivery system. This review provides an updated and up to date information with respect to the mechanism of mucoadhesion, selection of excipients, methods of preparation, evaluation parameters and unique applications of buccal film as a drug delivery device in treatment of various life threating diseases. At the last this review concludes the current issues, possible future investigation and scope in the field of pharmaceuticals.

Keywords: Mucoadhesion, Buccal film, Nanoparticulate, Solvent Casting, Tensile strength, Drug Delivery System.

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INTRODUCTION:

The development of novel approaches in drug delivery system for the drug molecules which are already existed in market not only improves the performance of the drugs in terms of safety and efficacy but it also improves the patient compliance along with other therapeutic benefits to a greater extent. There are various routes of drug administration and each route has its own demerits. As compared to injectable and oral delivery of drugs the buccal delivery is mostly preferred routes of drug delivery. Because oral delivery of the drug is more convenient but it may cause the problems such as hepatic first pass metabolism, enzymatic degradation of drugs in gastro intestinal conditions and poor bioavailability problems so this routes may show inadequate absorption of drugs. Injectable routes of drug administration can avoid these problemsbut it may also have some drawbacks such as pain at site of administration, extravasation infection and anaphylaxis[3]. Since last 40 decades the concept of mucoadhesion has gained greater interest in the field of pharmaceutical technology [4]. Among the number of drug delivery systems buccal drug delivery systems is found to be the most promising approach because buccal mucosa itself provides a protective covering to the underlying tissues which may

act as physical barriers against various toxins and micro-organisms. In recent years various mucoadhesive dosage forms has been developed such as tablets, patches, strips, ointments, gels, disks and films. Mouth dissolving or mucoadhesive buccal film is formulated as a novel promising dosage form, which has some prominent advantages due to drug delivery through the buccal mucosa[57]. An ideal mucoadhesive buccal film must be soft, flexible, expandable and strong enough to withstand breakage because of stress from the various activities in the mouth and also it may possess excellent mucoadhesive strength so due to this films can be retained in mouth for the desired duration of time[44]. Size reduction improves solubility and bioavailability of various drugs with respects to reducing toxicity, increasing release rate and providing better formulation opportunities for drugs. Nanoparticulate mucoadhesion related to the nanometer size range enhance performance in a variety of dosage forms[26].

Overview of Oral Mucosa:

The oral cavity comprises of cheek, tongue, lip, soft and hard palate and mouth floor. The oral mucosa is differentiated into three distinctive layers which are outer epithelium, middlebasement and inner connective tissue[3].

In drug delivery oral mucosa acts as prominent routes of the drug delivery systems. Oral mucosa provides delivery of the various drugsby

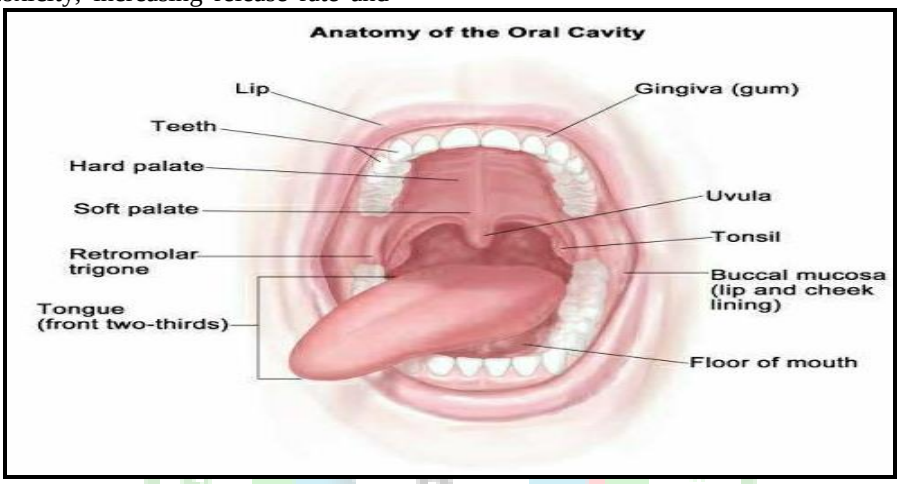

Figure 1: Oral mucosa

both mechanisms i.e. systemic as well as by local ways. Oral mucosa may contain large surface area of mucus membrane so it can provide rapid and complete absorption of drugs into body. The total surface area of the oral cavity is composed by mucus membrane is near about 100 [cm235]. Oral mucosal area is adhesive in nature and due to these properties it may acts as a lubricant, which may allow the movement of cell to another with less friction. The anatomic site for the administration of drugs between the cheeks and gingival is known as a buccal mucosa. Mucus layer presents on the surface of the cells which may plays key role in cell to cell adhesion, oral lubrication and mucoadhesion of mucoadhesive drug delivery systems. [50]. Oral mucosa acts as intermediates between that of the epidermis and intestinal mucosa due to leaky epithelial nature of oral mucosa. Permeability of oral mucosa is 4-4000 times greater than that of the skin. The capacity of permeability of the oral mucosal membrane decreases in the order of sublingual than greater than buccal and buccal greater than palatal, but this rank order is totally based on the relative thickness and degree of keratinization of this tissues[51].

Mechanism of Mucoadhesion:

Mechanism of mucoadhesion is divided into two steps,

1. Contact stage
2. Consolidation stage

The contact stage involves intimate contact between a mucoadhesive and a membrane by wetting and swelling phenomenon.

Consolidation stage requires penetration of the mucoadhesive into crevices of the tissue or into the surface of the mucus membrane. [55,15].

Various factors affecting on mucoadhesion they are as follows…

1. Polymer related factor: Properties of the active polymers used in preparation may play an important role in mucoadhesion such as molecular weight of polymers, concentration, swelling properties, flexibility and confirmation of polymers[68].
2. Physiological factors: Physiological factors like disease state and mucin turn overplays a key role in mucoadhesion[68].
3. Environmental related factors: Several environmental related factors such as pH of the polymer substrate interface, functional strength and contact time is able to influence process of mucoadhesion[68].

Theories of Mucoadhesion:

Following theories have been considered for the complete understanding of the mechanism of mucoadhesion or bio adhesion…. [61].

1. Wetting theory

2. Diffusion theory
3. Electronic theory
4. Fracture theory
5. Adsorption theory

Wetting theory: Wetting theory is one of the oldest theories of mucoadhesion. This theory is applied to liquid or low viscosity mucoadhesives. This theory explains process of adhesion whereby bio adhesive agents or polymers penetrates into the surface of the substrate and make it's hardened, producing many bio adhesive anchors. So free movement of this adhesive on the surface of the substrate means it may overcome any surface tension effects presents at interface. [46].

This theory calculates the contact angle and the thermodynamic work of adhesion. Wetting theory also states that the intimate molecular contact is a pre-requisite for the development of the strong adhesive bonds, which may require observation of the wetting equilibrium and dynamic behavior of the mucoadhesive candidate materials include…

a) A zero contact angle
b) A relatively low viscosity
c) An contact between that exclude air entrapment

The work of adhesion between mucoadhesive controlled release system and the tissue is equal to the sum of the two surface tensions and less than the interfacial tension [51].

Electronic Theory: Electronic theory of mucoadhesion states that there is likely to be electron transfer on contact of the mucoadhesive polymer and glycoproteinic network which have a differential electronic structure which will in turns leads to the formation of the double layer of electrical charge at mucoadhesive interface. A series of attractive forces responsible for stabilizing contact between the two layers [46].

Adsorption theory: Adsorption theory of mucoadhesion states that mucoadhesive systems adhere to the tissue due to Vander wall forces, Hydrogen bonding and Electrostatic attraction[51].

Diffusion theory: Diffusion theory states that mucoadhesive polymers may diffuses into mucus layer by breaking glycoprotein chain like framework. So this diffusion is time dependent and totally depends on diffusion coefficient and molecular weight of both the phases [11].

Fracture Theory: Fracture theory represents existing bonds of bio adhesion between the systems which are related to the force that is needed to detach the two surfaces means separation of two surfaces after adhesion[11, 53].

So fracture theory is somewhat equivalent to adhesive strength through the following equation also, also this theory is essential for the study of bio adhesion by using tensile apparatus[56].

$$\sigma = \left(E \times \frac{£}{L}\right) 1/2$$

Where,

σ = Fracture strength

£ = Fracture energy

E = Young modules of elasticity

L = Critical crack length

Mechanical Theory: Mechanical theory of mucoadhesion represents process of mucoadhesion starts from an interlocking of liquid adhesive into irregularities on the rough surface [69]. This rough surface must provide an improved surface area which is available for the interaction along with an increased viscoelastic and plastic dissipation of energy during joint failure, which is more essential in the bio adhesion process than mechanical effects[68].

Mucoadhesive drug delivery devices:

a) Buccal tablet
b) Buccal patches
c) Buccal films
d) Buccal gel
e) Buccal ointment [69].

Solid mucoadhesive dosage forms:

a) Tablet
b) Micro patches
c) Wafers
d) Lozenges

Semisolid dosage forms:

1) Gel
2) Patches
3) Films

Liquid dosage forms:

1) Viscous liquid

Nanoparticulate Mucoadhesive System: The addition of mucoadhesive properties to the Nanoparticulate systems like nanoparticles, microspheres have a greater importance in development of novel drug delivery systems. Nanoparticulate mucoadhesive dosage forms are spherical, free flowing and discrete. This system encloses drugs with mucoadhesive polymers. This system releases the drugs by prolonging residence time at the site of drug absorption[47].In recent years various mucoadhesive dosage forms for buccal drug delivery systems have been developed with great attention such as tablet, lozenges, patches, discs but mucoadhesive buccal films are innovative approach over other dosage forms in terms of patient compliance, flexibility, accuracy of dosing and longer residence time. Ideal mucoadhesive buccal films should be flexible, elastic, soft, strong and enough to withstand breakage due to stress from activities in the mouth. Films should pass good mucoadhesive strength so it can be retained in the mouth for the desired duration [69].

Nanoparticulate mucoadhesive buccal films can be defined as a dosage form that employs a water dissolving polymer, which allows the dosage forms to rapidly hydrate, adhere and attach and dissolve when placed on the oral cavity which may leads to systemic drug delivery. A film having large surface area so due to this property it allows fast wetting of the films which may accelerates absorption of the drug rapidly as compared to the other dosage forms[50]. Films are fabricate to cause a systemic and local action since mucoadhesion implies

attachment to the buccal mucosa most of the mucoadhesive buccal films have been developed in order to treat some fungal infection in buccal or oral cavity[55].

Nanoparticulate mucoadhesive films is made by using hydrophilic polymers which having ability to rapidly dissolves on the surface of tongue or with the buccal cavity and releases the drug to the systemic circulation via dissolution when it comes in contact with liquid phase. Mucoadhesive buccal films as a dosage forms have much more importance in the pharmaceutical fields as novel approach, better patient compliance and convenient products. Friability of the films is less as compared to other the dosage forms and usually needs special packaging. These films are small in size and thickness. When dry buccal films come in contact with surface of the thin mucus layer, two steps are required to form mucoadhesive bond i.e. contact and consolidation stage. Process of mucoadhesion is defined as the ability of synthetic or biological macromolecules attach to mucosal tissues such as mucosa of eyes, nose, oral cavity, intestine, vagina and rectum. This process is considered to occur in three major stages i.e. wetting, interpenetration and mechanical interlocking between the polymer and mucus[33,44].

Buccal films have direct access to the systemic circulation via the internal jugular vein which bypasses the drug formulation from the hepatic first pass metabolism then films may leads to the improved bioavailability. Mucoadhesivebuccal films are pharmacoeconmic, self-administrable and superior patient compliance[50].

Advantages of Nanoparticulate Mucoadhesive Buccal Films:

1. Nanoparticulate mucoadhesive buccal films may provide greater surface area that leads to rapid disintegration and dissolution in the oral cavity so due to this it promotes or enhances the systemic absorption of drug candidates.
2. No need of chewing and swallowing.
3. It provides protection of drugs from degradation by GIT enzymes and acidic environment.
4. Possibility of taste masking is higher.
5. Provides good mouth feel and good stability.
6. Provides rapid onset of action and low risk of side effects.
7. Self-administration is possible.
8. Avoids or bypasses hepatic first pass metabolism so it increases the systemic availability of drugs that leads to improved bioavailability of drugs.
9. Provides accuracy of dosing as compared to other dosage forms.
10. Ease of administration to pediatric, geriatric patient and also to the patient who are mentally unstable and non-cooperative.
11. Ease of transportation, storage, customer handling and improved patient compliance.
12. It requires less excipient.
13. More economical [50.]

Disadvantages of Nanoparticulate Mucoadhesive Buccal Films:

1. High dose cannot be incorporated into films[50].
2. Provides limited absorption area[69].
3. Swallowing of saliva leads to the loss of dissolved or suspended drug and it again leads to removal of the dosage forms.
4. Drugs which are unstable at buccal pH cannot be administered[55].
5. Drug candidate which may cause allergic reactions and discoloration of teeth cannot be formulated as films.
6. Buccal mucosa has low permeability as compared to sublingual mucosa.

Excipients Involved In Formulation of Nanoparticulate Mucoadhesive Buccal Film:

Active pharmaceutical ingredients: Normally 5 to 3% W/W of active pharmaceutical ingredients (API) can be used in the formulation of film. Water miscible API presents in the dissolved state in buccal film or in the solution form. The water immiscible drugs are dispersed continuously in the buccal film**.** This involves the solubility of API's can be improved by complexation with cyclohexatriene.[50]. API can also use in the form of milled, micronized, nanocrystals or particles which may leads to improve the texture of the film, better dissolution and uniformity in the buccal film [33,40].

Polymers: Polymer used in the formulation of mucoadhesive buccal film is either water miscible or immiscible. Polymers used in the formulation of film may be derived from natural and synthetic sources. These polymers have an ability to form a several hydrogen bonds due to the presence of carboxyl or hydroxyl functional groups[55].

Ideal Characteristics of Mucoadhesive Polymer:

- Good bioavailability [55.]
- High spreadability.
- Good wetting.
- High solubility.
- Good swelling properties.
- Must be economical or cost effective.
- Biocompatible.
- Must have high molecular weight. [46].
- High viscosity
- Must have spatial confirmation.
- High applied strength and initial contact time.
- Should be non-toxic.

Natural polymers: Various naturally occurring polymers are used alone or in the combination they are as follows….

- **Polysaccharides:** e.g. Starch, Cellulose, Alginate, Cyclohexatriene, Chitosan, Agarose and Dextran etc.
- **Protein based polymers:**e.g. Gelatin, Collagen, Albumin etc. [55.]

Synthetic polymers: Polymers obtained from synthetic reaction may be classified into following two types...

1) **Biodegradable polymers:**
   a) Polyadipic acid, Polysebacic acid, Polyterpthalicacid.
   b) Polyamides: Poly amino acid, Polyiminocarbonates.
   c) Polyesters: Polyacetic acid, Polyglycolic acid, Polyacetic acid, Polyhydroxyl butyrate, Polycaprolactone, Polydoxanones.

d) Phosphorus based polymers: Polyphosphates, Polyphosphazanes.
e) Other Polymers: Polyorthoesters, Polyacetals, Poly urethanes Poly cyanoacrylates.

2) **Non-Biodegradablepolymers: -**
a) Silicones: Colloidal silica, Polymethacrylates, Polydimethylsiloxane.
b) Cellulose derivatives: Carboxyl methyl cellulose, Ethyl cellulose, Cellulose acetate, HPMC.
c) Others: Polyvinyl pyrolidine, EVA, Poloxamines[55].

Novel second generation polymers:

Advantages:

- More site specific hence called as cytoadhesives.
- Less effected by mucus.
- Site specific drug delivery[46].

1. **Lectins:**Lectins are naturally occurring protein that plays a key role in biological recognition phenomenon containing cells and proteins. Lectins are structurally diverse group of protein and glycoprotein that binds reversibly to specific carbohydrate residue. After binding to the cells Lectins may remain on the cell surface or may be removed inside the cell surface through endocytosis process but these Lectins are immunogenic in nature [55, 46].
2. **Thiolated polymers:** Thiolated polymers are thiomers which may have obtained from hydrophilic polymer such as Polyacrylates, Chitosan and Gallan gum. In the presence of thiol group improves the residence period by promoting covalent bond with the cysteine residues in mucus. [46]
   E.g.Poly (acrylic acid) cysteine, Chitosan thioglycolic acid, Sodium carboxymethyl cellulose- cysteine, Poly (acrylic acid) homocysteine, Chitosan-iminothiolane etc.
3. **Poloxomers:**This polymer used on a wide scale in the pharmaceutical field due to their high viscous nature. It may also offer choice of vehicles for controlled release drug delivery. Due to its thermo reversible polymeric characters used in formulation development of film[53].Phase transition is exhibited by this polymer from liquid to mucoadhesive gels at body temperature and it will allow in-situ gelation at the site of target [55].
4. **Pluronics and combination:** To produce a system with improved adhesion and retention in the nasal cavity this pluronicsare combined chemically with polyacrylic acid. E.g. Dihydroxyphenylalanine (DOPA) and amino acid found in mucosal adhesive protein combined with pluronics to improve their adhesion[55.]

5. **Plasticizers:** Plasticizers are the key ingredients of the mucoadhesive buccal film which may enhance the flexibility of the buccal film and also reduces the bitterness of the film by reducing the glass transition temperature of the film. The Plasticizers are used in the concentration of 0-20% w/w of dry polymer. Selection of the polymer depends on compatibility with the polymer and types of solvent [50].

1. **Surfactant:** Surfactantused as wetting agent, dispersing agent, and solubilizing agent in film formulation. Primary role of surfactants in formulation of film is due to surfactant film gets rapidly dissolved within few seconds and that may lead to the release of API immediately. Surfactant also enhances the solubility of poorly soluble drugs in fast dissolving buccal film [50].

E.g. Tweens and Spans, Benzalkonium chloride, Sodium lauryl sulfate, Polaxomer 407 etc.

2. **Penetration Enhancer:** Permeation enhancers areagent that facilitates the permeation via buccal mucosal membrane is drug specific. Permeation enhancer should be non-toxic and non-irritant in nature[55, 50]. Selection of proper permeation enhancer and its efficiency totally depends on the various parameters like its physiochemical properties, site of administration, nature of excipients and vehicles [70].

1. Chelating agent: EDTA, Sodium salicylate, Citric acid and Methoxy salicylate.
2. Fatty acids: Lauric acid, Capric acid, Oleic acid, Methyl oleate, Phosphatidylcholine.
3. Bile salts: Sodium taurocholate, Sodium glycodeoxycholate and Sodium deoxycholate etc.
4. Inclusion complex: Cyclohexatriene
5. Surfactant: Sodium lauryl sulfate, Benzalkonium chloride, Polyoxyethylene-9- lauryl ether, Polyoxyethylene-20- cetylether, Polyoxyethylene 23 – lauryl ether etc.
6. Non surfactant: Unsaturated cyclic ureas.
7. Others: Dextran sulfate, Methanol, Azone, Polysorbate 80, Aprotinin. [55.]

Saliva Stimulating Agent: Acids which are used in film preparation can be used as saliva stimulants. The main purpose of this agent is to enhance the rate of production of saliva which may leads to rapid disintegration of fast dissolving buccal film formulation [50]. Saliva stimulating agents are used alone or in combination between 2-6% w/w of the film [40].

E.g. Malic acid, Citric acid, Lactic acid, Ascorbic acid and Tartaric acid etc[50.]

Sweeteners: Main purpose of this agent is to improve the patient compliance by masking the bitter taste and unpleasant odor of the drug. Both naturally occurring and artificial sweeteners are included in the formulation of buccal film. Sweeteners are used alone or in combination between 2-6% w/w[40].

1. Natural sweeteners: Sucrose, Dextrose, Glucose, Fructose and Maltose etc.
2. Artificial sweeteners: Saccharin sodium, Aspartame, Sucralose.

Flavoring Agents: Acceptance and palatability of any pharmaceuticals formulation mainly depends on quality of flavor which is identified within few seconds after the administration of the dosage form. [50, 40]. Preferably up to 5-10 % w/w concentration of flavor added in mucoadhesive buccal

film formulation. There are three types of flavor such as natural flavor, natural identical flavor and artificial flavors.[11.]

E.g. Cinnamon oil, Peppermint oil, Spearmint oil, Vanilla, Coccoa, Coffee, Chocolate, Citrus, Apple, Cherry, Raspberry and Pineapple etc[40].

Coloring Agents: Coloring agents used in the formulation of mucoadhesive buccal film is not more than 1 % w/w. FD&C approved color and dyes are used as coloring agents in formulation of the film.[11] Coloring agents used to improve the appearance of the film formulation[50,40].

E.g. Titanium dioxide

Method of Preparation of Nanoparticulate Mucoadhesive Buccal Film:

The manufacturing methods involved in the mucoadhesive buccal films are as follows….

a) Solvent casting methods
b) Hot melt extrusion
c) Semisolid casting
d) Solid dispersion
e) Rolling methods

Solvent casting method: In this methods drug and film forming polymers such as plasticizer, permeability enhancer, taste masker and preservatives is added into volatile solvents such as ethanol and acetone to form a homogeneous mixture[39]. Then this formed solution are stirred continuously and then at lastly casted into petri plate or into molds. [55.] The casted solution is the dried and remaining film is removed from molds. Drying of film is crucial step so performed in an oven or in a convection chamber. This method is suitable for heat sensitive drugs and other materials [39]. Hydroxyl propyl methyl cellulose (HPMC), sodium alginate, pullutan and pectin as water soluble hydrocolloids used to formulate films[55.]

Hot- melt extrusion method: Researcher Rebekah et.al. has been used this method for the preparation of mucoadhesive buccal film. [55.] In this method firstly a mixture of all pharmaceutical ingredients is heated to molten and then molten mass is forced through a vent or die due to this homogeneous material is produced such as tablets, films and granules. This method used to formulate controlled released formulation such as pellets, tablets, granules and orally disintegrating films [33].

Semisolid casting method: In this method a solution of water miscible film forming polymer is prepared. Then this formed solution is added to solution of acid insoluble polymers such as cellulose acetate phthalate and cellulose acetate butyrate which was prepared in sodium and ammonium hydroxide. Then in the next step appropriate amount of plasticizer is added into above solution then final gel mass is casted into the films or ribbons by using heat controlled drums. The thickness of formed film is about 0.015-0.05 inches. The ratio of the acid insoluble polymers to film forming polymers should be 1:4[44].

Solid dispersion technique: In solid dispersion technique insoluble material are extrude with drug molecules and then solid dispersion are prepared. Then finally formulated solid dispersion is shaped into films by means of appropriate size dies [44].

Rolling method: In rolling method the solution containing drug is firstly rolled on a carrier. Solvent used for this method is mainly water and alcohol. Then film is mainly dry on the roller and cutter used to cut formed films into proper shape and size. Other material such as active agent dissolved in small amount of aqueous solvent using high shear processor. Water soluble hydrochloride is dissolve in water to form homogeneous solution[44].

Mucoadhesion testing: Mucoadhesion testing of the formulated mucoadhesive buccal film can be done by following three methods…

1. A Direct staining method
2. A lectin binding inhibition method
3. Atomic force microscopy

A direct staining method: A direct staining method was used to evaluate or to determine the Mucoadhesion of the polymeric aqueous dispersion on buccal cell by binding alcian blue to anionic polymers or also eosin to the amine groups in polymer. Then unbounded dye or color was removed by giving washing it with 0.25 M sucrose solution. But method is only useful for liquid dosage form which is used to improve the oral hygiene and to treat local disease condition of the oral cavity such as oral candidiasis, dental carries and tooth decay[55.]

A lectin binding inhibition method: This method involves the binding of various mucoadhesive polymers to the mucous or buccal epithelial cells without disturbing their physiochemical characteristics with the addition of 'Marker' entities. Then lectin from Canavaliaensiformis has been found to sugar groups which are presents on the surface of buccal cells[55.]

Atomic free microscopy: This method was used to determine the mucoadhesion strength of the various polymers onto the buccal cell surface[55.]

Evaluation Parameters of Nanoparticulate Mucoadhesive Buccal Film:

Formulated nanoparticulate mucoadhesive buccal film evaluated for the following evaluation parameters…

Film weight and Thickness: Formulated nanoparticulate mucoadhesive buccal film was evaluated for uniformity of weight by using a digital balance. Three films of every formulation batch was taken and weighed. Then average weight of the film was calculated[55, 44].

Similarly thickness of the each formulated fast dissolving mucoadhesive buccal film was determined by using a micrometer screw gauge at the different points of the films and average was calculated[40,11].

Folding endurance: Folding endurance of the formulated film was determined by repeatedly folding one film at the same point till the film broken or folded up to 300 times manually. Then number of times the film could be folded at

the same place without breaking this gives the value of the folding endurance [55, 44,50].

Surface pH: Measurement of the surface pH of the formulated film is necessary to assess the any side effects which may be produced inside the body [40]. Surface pH of the film can be measured by allowing three formulated film of each batch to swell for two hours on agar plate. Then pH of the film was measured by using pH paper and mean value is calculated. [55.] Acidic or Basic films may cause irritation to the mucosal membrane. Surface pH is also measure with the pH meter by using glass electrode [40].

Swelling index: Swelling index or Swelability of the formulated films was measured by placing the portion of the film into agar plate. Then this plate was kept in incubator for 37 +−2^{0}C. Then observe the increase in weight and diameter of the film. Swelling index of the film is calculated at different time intervals i.e. for 1 – 5 hours[55,40].

Swelling index of the formulated film is calculated by using following formula…

% Swelling index = (Xt – Xo /Xo) × 100

Where, Xt = weight of the swollen film after time 't'.

Xo = Initial weight of the film.

Moisture content: Amount of moisture presents in the film may affect the friability and brittleness of the mucoadhesive buccal film. Also the moisture presents in the film formulation is determined by moisture content testing apparatus, Karl fisher titration method. The moisture content in the ideal mucoadhesive buccal film should be less than 5% [70]. The formulated film are weighed separately and kept this film in a desiccator containing calcium chloride at room temperature for at least 24 hrs. Then after this specified period the film are to be weighed again until the film show no variation in weight[55,50].

Finally, the moisture content was calculated by using following formula…

% Moisture content (% M.C.) = W1 - W2/ W2 ×100

Where, W1 = Initial weight of the film

W2 = Final weight of the film

Water vapor transmission rate: To determine the water vapor transmission rate minimum 1 gm of calcium chloride was taken in the empty vial which is used as transmission cell. Then polymeric films measuring 2cm^{2}areas were fixed over the brim by using adhesive. The Initial weight of the transmission cell was note down by weighing them accurately. After that cells are placed in desiccator which may contain saturated solution of potassium chloride and subsequently weighed at standard intervals. Then finally water vapor transmission rate was calculated by using following formula[50].

WVTR = WL/S

Where, W = water vapor transmitted in mg

L = thickness of film in mm

S = exposed surface area in cm2

Tensile strength: Tensile strength of the nanoparticulate mucoadhesive film is measure to determine the mechanical strength of the film during formulation optimization. The film sample under test is stretched until it tears and that stress needed to it represents the tensile strength. [70,53.]

Tensile strength of the formulated film was calculated by using following formula…

Tensile strength = (N/ Cross sectional area of the film)

Where, N = Force at failure

Drug content uniformity: Drug content uniformity of film was measured by dissolving in 10 mm size of buccal film from each batch of formulation using homogenization in 100 ml of phosphate buffer having pH 6 for 5-6 hours under the occasional stirring. Then from this 5 ml solution was pipette out and diluted with the isotonic solution of phosphate buffer having pH 6.8 up to 20 ml and this solution was filtered through 0.45mm whatman filter paper. Then drug content was determined after preparing proper dilution at appropriate Ymax using UV spectrophotometer. Average of the drug content of three films is taken to get final reading[44,50,53].

***In-vitro* release study:** *In-vitro* drug release study or dissolution studies of the film is determined in a USP dissolution apparatus by using 900 ml of dissolution medium at temperature 37 +- 0.5^{0}C rotated at constant speed of 50 RPM. Samplealiquot is withdrawn periodically at suitable time intervals and the volume replaced with fresh dissolution medium. Then finally sample is analyzed at proper Ymax nm by UV visible spectrometer and amount of drug release was calculated. [55.] Most of the dissolution studies are carried out using paddle over disc method[70].

Moisture uptake: To measure moisture uptake films are place in desiccator at room temperature for 24 hrs. Then films are removed from desiccator and exposed to 84% of relative humidity by using saturated solution of potassium chloride in desiccator until the constant weight is achieved[50,40,11].

% Moisture uptake = [Final weight – Initial weight / Initial weight] × 100

Surface morphological study: To determine the size, shape and number of pores presents on the surface of the film various techniques are used such as Scanning electron microscopy (SEM), electron microscopy, scanning tunneling microscopy, but SEM is mostly used to determine size and shape of the film[40,11].

Scanning electron photomicrograph of the film is taken at 600 X magnification power. Finally, photomicrograph of the film is compared with the drug and blank film from that we examine whether the drug is distributed uniformly throughout the film in amorphous forms[50].

Organoleptic evaluation: The formulated nanoparticulate mucoadhesive buccal film system was evaluated for sweetness and flavor[50]. Controlled human taste panels are used for psychophysical evaluation of the product and electronic tongue measurement device can be used for this purpose[40].

Flatness study: The formulated nanoparticulate mucoadhesive buccal film of size 1cm^2 is put against a plane surface. Then this film cut vertically into number of pieces and length of that truncated prices is measured. Then the percent constriction is calculated using following formula….

Constriction (%) = {(L1 - L2) / L1} × 100

Where, L1 = Initial length of the film.

L2 = Final length of the film.

A constriction of zero % infers 100 % flatness

Flatness (%) = 100 – constriction

Transparency: Transparency of the nanoparticulate mucoadhesive buccal film determines the transmission of the fast dissolving mucoadhesive buccal film by using UV spectrophotometer by following formula…. [11]

Transparency = (logT600) / b = -€C

Where, T699 = transmittance at 600 nm

b = film thickness in mm

c = concentration

Contact angle study: Measurement of contact angle is useful to predict wetting property, disintegration and dissolution time of the film. Apparatus used to measure contact angle attached with the digital camera that takes the photograph of drop of double distilled water placed on the surface of the dry buccal film within 10 second and then analyze using software to measure the exact contact angle. [11]

Drug Polymer interaction study: Drug - Polymer and drug – excipient interaction study was carried out using FTIR spectrum & Differential scanning calorimetry (DSC) thermogram is important to develop effective fast dissolving mucoadhesive buccal film. [70,11].

***Ex-vivo* permeation study:** To carry out the permeation study Franz diffusion cell is used. Franz diffusion cell consists of two compartments, one is donor and another one is receptor compartment which is having 18 ml capacity and 0.785 cm2 effective diffusion areas, second one receptor compartment was covered with water jacket to maintain temperature at 37^{0}C[50].

To carry out this study artificial mucosal membrane or mucosal membrane of rabbit is used. This membrane is placed between two chambers. Phosphate buffer solution having pH 7.4 is used to fill the second compartment. Then after that membrane is stabilized for 1 hour after stabilization of membrane the film is placed and samples are taken to carry out study. Removed volume of sample is replaced again with fresh medium. Finally, prepared aliquots are analyzed by using UV spectrophotometer[40].

***In-vitro* residence time:** To measure the *In vitro* residence time of the film IP disintegration test apparatus is used. The apparatus maintained at a temperature of 37 +- 2^{0}C using 800 to 900 ml of the disintegration medium[55,44]. Then goat or rat intestinal mucosa having 3 cm length is glued to the glass piece surface, which is then attached vertically to the apparatus. Then the film of each formulation batch are wetted or hydrated on one surface and upon contact with the mucosal layer the film is fully dipped into the buffer solution having pH 6.8. Then finally the time required for the complete detachment of the film from the mucosal surface is note down[50,63].

***Ex-vivo* mucoadhesive strength:** To measure mucoadhesive strength modified balance technique was used. Mucoadhesive strength is force required to detach the attachment of buccal film from the mucosal surface. To carry out this study the porcine buccal mucosa was used and the mucosal membrane was separated by removing the underlying fat tissue. Then this collected mucosa was attached to the dry petri plate surface and this plate again wetted with few drops of simulated saliva. The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. Then weight of the left pan i.e. (w1) 5 gm was brought in contact with pre wetted mucosa for 5 minutes. The weight of the left pan increases lightly until attachment breaks (w2).

The variation in weight (w1 - w2) was taken as mucoadhesive strength…. [55,44].

Mucoadhesive strength = force at break (N) / Cross sectional area of the film (mm2)

Percentage elongation break: The percentage elongation at break is defined as determination of the maximum deformation of the film can undergo before leaving apart. [55.]

Percentage elongation at break is calculated by following formula….

Elongation at break = increase in length of break / initial film length × 100

Chemical stability studies:

1. Stability study in human Saliva: The formulated nanoparticulate mucoadhesive buccal film was placed in natural human saliva containing petri plate. Then this film was regularly observed for its appearance, shape, size, color and physical stability. The result indicates if there is no change in the film considers it as more stable during administration. The stability study of the formulated fast dissolving mucoadhesive buccal film was performed with natural human saliva. Sample required to carry out this were collected from 10 humans having an age in between 18 – 40 years, collected sample were filtered and then this filtered sample placed in petri plate which may containing 5 ml of human saliva and put in a temperature controlled oven at 37 +- 0.5^{0}C for 5 – 6 hrs. Finally,film examined for any changes in their morphology and physical stability at definite time periods. [11]

2. Stability as per ICH guidelines: To perform the stability study of the nanoparticulatemucoadhesive formulation various guidelines and discipline provided or given by International council for harmonization (ICH) must be used. As per ICH guidelines well packed films should be stored for period of 3 months at a different storage condition of relative humidity, temperature. Then finally after this periods film evaluated for all possible parameters such as drug content, disintegration time and various physical properties. [11]

Packaging of Nanoparticulate Mucoadhesive Buccal Film:

Formulated nanoparticulatemucoadhesivebuccal film should be packed in proper packaging material to maintain its stability. Various options are available for buccal film packaging like single pouch, blister card with multiple units, multiple unit dispenser and continuous roller dispenser. But single packaging is mandatory for film formulation. Aluminum pouch is the most commonly used packaging material for film[33,50].

Applications of Nanoparticulate mucoadhesive buccal film:

Vaccines: Nanoparticulate mucoadhesive buccal film is novel approach of the drug delivery for the vaccine delivery which is stable at room temperature, so due to this it is rapidly dissolved in mouth and in saliva. In USA rotavirus vaccine was prepared which is stable at room temperature and used as a vaccine that will make the vaccination as simpler as freshing your breath. This delivery may exhibit various advantages such as improved patient compliance, enhanced oral bioavailability, reduction in the cost associated with the storage, distribution, handling and administration [33].

Sustained and Controlled release film: Sustained release (SR) and Controlled release (CR) film formulation is useful in hospital preparation and different types of polymer such as Chitin and Chitosan derivatives are used as adjuvants. This SR and CR film formulation useful for various purposes such as decreases in toxicity, wound dressing, oral mucoadhesive and water resisting adhesive and adhesion[33].

Taste masking approach: Taste masking is necessary for the each and every formulation of pharmaceutical products, because drug which is having bitter taste and unpleasant odor may influence on acceptance of the formulation and patient compliance. So to increase patient compliance taste masking is one of the better approaches in formulation and development.

Nanoparticulate mucoadhesive buccal film dissolves or disintegrates rapidly patient mouth or in oral cavity, thus releases the drug which comes in contact with the taste buds and this is critical problems in patient compliance. In taste masking approach drug having bitter taste and unpleasant odor can be covered or microencapsulated with the pH sensitive acrylic polymers by solvent extraction and solvent evaporation methods[33].

Cardio vascular disease: Cardio vascular diseases such as hypertension, hypotension, and angina pectoris required lifelong therapy to control these conditions. Numbers of Cardio vascular drugs such as nifedipine, carvedilol, metoprolol succinate having low bioavailability and low half-life due to poor aqueous solubility and high hepatic first pass metabolism. The fast dissolving mucoadhesive buccal film provides direct access of the drugs into systemic circulation through the internal jugular vein by avoiding hepatic first pass metabolism which may leads to improved bioavailability and increasing patient compliance[52].

Migraine: Various anti migraine drugs such as Sumatriptan, Zolmitriptan and rizatripatanused in migraine condition. After the administration of this Drug numbers of patient may suffer from severe nausea and vomiting during their migraine attack and also having low oral bioavailability (15%) due to the high hepatic first pass metabolism. So to avoid this limitation it is necessary to develop an effective formulation approach which may allow the drug directly enters into the systemic circulation by avoiding hepatic first pass metabolism, so for this fast dissolving mucoadhesive buccal film is one of the promising approaches of the drug delivery[52].

Nausea and Vomiting: Drugs like Ondensetron HCL as model drug for treatment of nausea and Vomiting associated with emetogenic cancer chemotherapy. But to improve the oral bioavailability and patient compliance it is needed to formulate as buccal film[52].

FUTURE PROSPECTIVE:

Nanoparticulate mucoadhesive drug delivery systems offers number of advantages over other systems in terms of accessibility, administration, economy, withdrawal and patient compliance. Research scientists are now globally looking out for the traditional polymers for novel drug transport systems. In last decades'pharmaceutical researcher are finding various methods to develop fast dissolving mucoadhesive buccal film as novel dosage form and to enhance the bioavailability of less orally bioavailable drugs. Nanoparticulate mucoadhesive principle combined to develop a formulation for the poorly soluble drugs such as BCS class II drugs.

From various literature review it is found that the novel second generation mucoadhesive polymers having great potential. So in upcoming decade the global pharmaceutical experts will looking for modification in this dosage form for the treatment of various life threating diseases such as cardiac heart failure, Asthma, Nausea and Vomiting, Hyperacidity, Decongestant and Migraine etc.

CONCLUSION:

The present review concludes that nanoparticulate mucoadhesive buccal drug delivery system is one of the most promising and innovative approach of drug delivery. As compared to other dosage form buccal dosage is more accurate and acceptable dosage form, which avoids the hepatic first pass effect and shows improved bioavailability. This is useful for people of all ages, specifically for pediatric patient, geriatric patient and also for those patient who suffering from swallowing difficulties. Now a day'swidespread research work is going on this approach to improve the patient safety, effectiveness and patient compliance regarding drug. Buccal film is prepared by reducing the frequency of administration and achieve better therapeutic efficacy. Nanoparticulate mucoadhesive based formulations are being developed for potential improvements in drug delivery. The release of a drug from these types of formulations depends on variety of factors such as types of polymers or carriers and amount of drug contained in it.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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