Review Article

Buccoadhesive Drug Delivery System: A Review

Poonam K[1]*, Saurabh SS[1], Arpana Kumari[1], Rathore KS[2]
[1]Department of Pharmaceutics,
Lachoo Memorial College of Science and Technology, Pharmacy Wing,
Jodhpur, Rajasthan, India.
[2]BN Institute of Pharmaceutical Sciences, Udaipur, Rajasthan, India
*poonam28nov.pharm@gmail.com

ABSTRACT

The main aim for the oral delivery of most of the drugs as potential therapeutic agents is their extensive presystemic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Parenteral route of administration is the only established route that overcomes all these drawbacks associated with these orally inefficient drugs. But these formulations are costly, have least patient compliance, require repeated administration, in addition to the other hazardous effects associated with this route. Buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. Buccoadhesive drug delivery is relatively new drug delivery strategy; in this traditional polymers are replaced by novel bioadhesive polymers such as Thiomers and lectins etc. to overcome limitation of traditional polymer. Buccoadhesive characteristic are factor of both bioadhesive polymer and the medium in which the polymer reside. It is the objective of this article to review buccoadhesive drug delivery by discussing the structure, permeability of buccal mucosa, mechanism of buccoadhesion, novel bioadhesive polymers, buccoadhesive dosage form and their evaluation, recent advances in buccoadhesive drug delivery system.

Keywords: Buccoadhesive drug delivery, Bioadhesion, Bioadhesive polymer, Buccoadhesive dosage form

INTRODUCTION

Bioadhesion can be define as a phenomenon of interfacial molecular attractive forces in the surfaces of biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to biological surfaces for an extended period of time. Among the various routes of drug delivery the oral route is perhaps the most preferred by the patient and clinicians alike. [1] The oral route preferred route for the administration of therapeutic agent due to low cost, ease of administration and high level of patient compliance. However, significant barriers impose for the oral administration of drugs, such as hepatic first pass metabolism and drug degradation within the GI tract prohibiting the oral administration of certain classes of drugs especially biologics e.g. peptides and proteins. Consequently, other absorptive mucosae are being considered as potential sites for drug administration including the mucosal lining of the nasal, rectal, vaginal, ocular, and oral cavity. Amongst these, delivery of drugs to the oral cavity has attracted particular attention due to its potential for high patient compliance and unique physiological features. Within the oral mucosal cavity, the delivery of drugs is classified into two categories: (1) local delivery and (2) systemic delivery either via buccal or sublingual mucosa. [2]

BIOADHESIVE DELIVERY OF DRUG SYSTEM IN ORAL CAVITY

Sublingual delivery, which is systemic delivery of drugs through the mucosal membrane lining the floor of the mouth,

Buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and

Local delivery, which is drug delivery into the oral cavity.[1]

BUCCOADHESIVE DRUG DELIVERY SYSTEM

Other than the low surface area available for drug absorption in the buccal cavity, the retention of the dosage form at the site of absorption is another factor which determines the success or failure of buccoadhesive drug delivery system. The utilization of buccoadhesive system is essential to maintain an intimate and prolonged contact of the formulation with the oral mucosa allowing a longer duration for absorption. [2]

An ideal property of buccoadhesive drug delivery system:

- Should adhere to the site of attachment for a few hours,
- Should release the drug in a controlled fashion,
- Should provide drug release in an unidirectional way toward the mucosa,
- Should facilitate the rate and extent of drug absorption,
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking etc.

Advantages of buccal bioadhesive drug delivery system

- Termination of therapy is possible.
- Permits localization of drug to the oral cavity for extended period of time.
- Ease of administration, good patient compliance

- Avoids first pass metabolism.
- Reduction of dose can be achieved.
- Selective use of therapeutic agents like peptides, proteins, and ionized species can be achieved.
- Drugs which are unstable in acidic environment of stomach or destroyed by the alkaline environment of intestine can be given by this route.
- Administration of drug with poor bioavailability.
- It follows passive diffusion.
- Administration of drugs with short half life.
- Prolongation of contact time with mucosa.
- There is no requirement of medical practitioner to apply the dosage form.
- It not hinders the talking function of patient.
- The buccal mucosa is relatively permeable with a rich blood supply, as comparison to other mucosal tissue.
- Flexibility in shifting the position of the drug in buccal cavity (in case of buccal film).

Disadvantages of buccoadhesive drug delivery system

- Eating and drinking may become restricted.
- By mistake system can be swallowed (in case of buccal tablet, buccal film).
- Saliva takes some drug into GIT.
- Drug which irritate mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Only those drugs are absorbed by passive diffusion can be administered by this route. [3]

Buccal drug delivery and Buccoadhesivity

In the development of these buccal drug delivery systems, buccoadhesion of the device is a key element. The term 'buccoadhesive' is commonly used for material that binds to the mucin layer of a biological membrane. Buccoadhesive polymers have been utilized in many different dosage forms in efforts to

achieve systemic delivery of drugs through the different mucosae. [4]

Mechanism of Buccoadhesion

Buccoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Buccoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Buccoadhesion has the following mechanism-
- Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon)
- Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration). [5]

Theories of Bioadhesion or Buccoadhesion

The theories of polymer- polymer adhesion can be adapted to polymer-tissue adhesion or bioadhesion by recognizing that bioadhesion is different only because of the differing properties of the tissue as opposed to those of the polymer.

Electronic theory: According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface.

Absorption theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. There are two types of chemical bonds resulting from these forces. *Primary chemical bonds* are of covalent nature, which are undesirable in bioadhesion because their strength may result in permanent bonds. *Secondary chemical bonds* are having many different forces of attraction, including electrostatic forces, Vander Waal forces and hydrogen bonds.

Wetting theory: is predominantly applicable to liquid bioadhesive systems and analyses adhesive and contact behavior in terms of the ability of a liquid or a paste to spread over a biological system.

Diffusion theory: According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact.

Fracture theory: this theory attempts to relate the difficulty of separating of two surfaces after addition.

$$G = (E\varepsilon/L)^{1/2}$$

Where E is the Young's
ε is the fracture energy
L is the critical crack length. [6]

Buccoadhesive Polymer

Buccoadhesive polymers are water soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agent. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to replace. [7]

Ideal characteristics of buccoadhesive polymer

The buccoadhesive polymers should possess following characteristics.
- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- It should have good spread ability, wetting, swelling and solubility and biodegradability properties.
- It should have biocompatible pH and should possess good visco-elastic properties.
- It should be adhere quickly to buccal mucosa and should sufficient mechanical strength.

- It should possess peel, tensile and shear strengths at the bioadhesive range.
- It must be easily available and its cost should not be high.
- It should show bioadhesive properties in both dry and liquid state.
- It should demonstrate local enzyme inhibition and penetration enhancement properties.
- It should acceptable shelf life.
- It should have optimum molecular weight.
- It should possess adhesively active groups.
- It should have required spatial conformation.
- It should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- It should not aid in development of secondary infection such as dental caries.

Buccoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad categories i.e. first and second generation buccoadhesive polymers.

FIRST GENERATION BUCCOADHESIVE POLYMERS

The most widely investigated group of buccoadhesive is hydrophilic macromolecules containing numerous hydrogen bond forming groups, so called 'first generation' buccoadhesive polymers. First generation buccoadhesive polymers present significant formulation challenges, being hydrophilic, with limited solubility in other solvents while forming high viscosity, often pH sensitive, aqueous solution at low concentrations. These are non-specific traditional type of buccoadhesive polymers and divided into three main sub-sets. They are namely-
- Anionic polymer
- Cationic polymer
- Non-ionic polymer

Among these three sub types anionic and cationic polymers shows greatest buccoadhesive strength.

Anionic polymers

Anionic polymers are having high buccoadhesive functionality and low toxicity. So these are most widely used buccoadhesive polymers in the pharmaceutical formulations. These are having negative charge at pH values exceeding the pKa of the polymer due to the presence of carboxyl and sulphate functional groups and the examples includes poly (-acrylic acid) (PAA), sodium carboxy methyl cellulose (NaCMC). Both PAA and NaCMC possess excellent buccoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin. Polycarbophil is insoluble in aqueous media, permitting high level of entanglement within the mucus layer and it increases the mass 100 times in aqueous media at neutral pH. One clear distinction between Carbomer and Polycarbophil is the level of cross-linking and the cross-linking agent itself. Carbomers are cross-linked with allyl sucrose or allylpentaerythriotol, whereas Polycarbophil polymers are cross-linked with divinyl glycol. Both compounds have the same acrylic backbone but vary in their cross-link density that is often tailored to suit pharmaceutical or cosmetic performance.

Cationic polymers

Cationic polymer system also used in the formulation of buccoadhesive dosage forms and the main cationic polymer is chitosan, most extensively investigated within the current scientific literature. Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide in the world, next to cellulose. Among presently explored buccoadhesive polymers, chitosan is gaining increasing importance due to its good biocompatibility, biodegradability and due to their favorable toxicological properties and it has been reported to bind via ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures

of mucus. The major benefit of using chitosan within pharmaceutical applications has been the ease with which various chemical groups may be added, in particular to the C-2 position allowing for the formation of novel polymers with added functionality. Using such modifications, the properties of chitosan may be tailored to suit the requirements of specific pharmaceutical-technological challenges.

SECOND GENERATION BUCCOADHESIVE POLYMERS

These are novel promising strategy to improve the buccoadhesive properties of the formulations. The major disadvantage in using traditional non-specific buccoadhesive system (first generation) is that adhesion may occur at sites other than those intended. A scenario that is particularly true for platforms designed to adhere to a distal target such as those hypothesized in targeted mucoadhesion within the GI tract. Unlike first- generation non-specific platforms, certain second-generation polymer platforms are less susceptible to mucus turnover rates, with some species binding directly to mucosal surfaces; more accurately termed "cytoadhesive". Furthermore as surface carbohydrate and protein composition at potential target sites vary regionally, more accurate drug delivery may be achievable.

Lectins

Lectins are defined as proteins or glycoprotein capable of specific recognition of and reversible binding to carbohydrate moieties of complex glycol-conjugates, without altering the covalent structure of any of the recognized glycosyl ligands. After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptor-mediated adhesion possibly become internalized via a process of endocytosis. Lectin-based platform could not only allow targeted specific attachment but additionally offer a method of controlled drug

delivery of macromolecular pharmaceutical via active cell-mediated drug uptake.

Thiomers

Thiolated polymers (Thiomers) are a type of second-generation buccoadhesive derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. The presence of thiol groups allows the formation of covalent bonds with cysteine-rich sub domain of the mucus gel layer, leading to increased residence time and improved bioavailability. Current buccoadhesive polymers can improve buccoadhesive delivery of drug into the systemic circulation by molecularly modifying their chemical structures. [8]

Buccoadhesive dosage form

Buccoadhesive dosage forms can be categorized in to three types based on their geometry.

Type I: A single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II: An impermeable backing layer is superimposed on top of the drug-loaded bioadhesive layer, creating a double-layered device and preventing drug loss the top surface of the dosage form into the oral cavity.

Type III: A unidirectional release device, from which drug loss is minimal, since the drug is released only from the side adjacent of the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

Buccal tablets

Tablets have the most commonly investigated dosage form for buccal drug delivery date. Buccal tablets are small, flat, and oval, with a diameter of approximately 5-8mm. Unlike conventional tablets, buccoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution

and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as the lip and the gum. Successive tablets can be applied to alternate sides of the mouth. The major drawback of Buccoadhesive tablets is their ;ack of physical flexibility, leading to poor patient compliance for long-term and repeated use.

Buccal patches

Patches are laminates consisting of an impermeable backing layer, a drug-containing reservoir layer from which the drug is released in a controlled manner, and a bioadhesive surface for mucosal attachment. Buccal patch systems are similar to those used in transdermaldrug delivery. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogeneously mixed and compressed to the desired thickness, and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and distintegration of the device during the application period.

Buccal films

Films are the most recently developed dosage form for buccal administration. Buccal films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover, in case of local delivery for oral disease, the films also help protect the wound surface, thus helping to reduce pain and treat the disease more effectively. An ideal film should be flexible, elastic, and soft, ye t adequately strong to withstand breakage due to stress from mouth movements. It must also possess good bioadhesive strength in order to be retained in the mouth for the desired duration of action. Swelling of film, if it occurs, should not be too extensive in order to prevent discomfort.

Buccal gels and ointment

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention of the gel at the site of application has been overcome by using buccoadhesive formulations. Certain bioadhesive polymers, e.g. poloxamers 407, sodium carboxy methyl cellulose, Carbopol, hyaluronic acid, and xanthan gum, undergo a phase change from a liquid to a semisolid. This change enhances the viscosity, which results in sustained and controlled release of drugs. However, these polymers have been investigated for this purpose primarily in ocular drug delivery. [4]

Buccal chewing gums

Although medicated chewing gums pose difficulties in regulating the dose administered, they still have some advantages as drug delivery devices, particularly in the treatment of disease in the oral cavity and in nicotine replacement therapy. Some commercial products are available in the market. Caffeine chewing gum, Stay Alert®, was developed recently for alleviation of sleepiness.

It is absorbed at a significantly faster rate and its bioavailability was comparable to that in capsule formulation. Nicotine chewing gums (e.g. Nicorette® and Nicotinell®) have been marketed for smoking cessation. The

permeability of nicotine across the buccal mucosa is faster than across the skin. However, chewing gum slowly generates a steady plasma level of nicotine rather than a sharp peak as experienced when smoking. Possible swallowing of considerable amount of nicotine during chewing may lead to decreased effectiveness of the chewing gum due to first-pass metabolism and gastrointestinal discomfort. It is a major challenge to optimize the dose-response relationship of nicotine administered in a chewing gum. [6]

Hydrogel
Hydrogels are also a promising dosage form, which are formed polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion. Buccoadhesive hydrogel are able to interact with the mucus and attach mucosal surface, resulting in a prolonged residence time of buccoadhesive drug release device in a body. These dosage forms provide an extended retention time, adequate drug penetration, as well as high efficacy and patient acceptability. Normally, hydrogel are cross linked so that they would not dissolve in the medium and absorb water. When drugs are loaded into these hydrogel, as water is absorbed into matrix, chain relaxation occurs and drug molecules are released through the spaces or channel within the hydrogel network. Drug release would then occur through the spaces or channels within the network as well as through the dissolution and/or the disintegration of the matrix. The use of hydrogel as adhesive preparation for buccoadhesive drug delivery has acquired considerable attention in recent years. [8]

Fibers
Hollow fibers
The reservoirs without rate control delivery include devices such as hollow fibers filled with a therapeutic agent in which the agent is released simply by diffusion through the reservoir wall. Goodson's first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline. These fibers released tetracycline at a first order rate with 95% of the drug released in the first 2 hr. hollow fiber system that have been used in periodontal pockets have been shown to release the drug so rapidly that they would be qualified only marginally as sustained-release devices.

Ethylene vinyl acetate fiber
After noting the poor control of drug release from hollow fibers, Goodson evaluated the delivery of tetracycline incorporated into different polymers such as polyethylene, cellulose acetate propionate and ethylene vinyl acetate (EVA).EVA was found to be flexible and allow drug delivery for up to 9 days in vitro. The EVA fibers containing 25% tetracycline hydrochloride commercialized under the trademark Actisite® (Alza Corporation, Palo Alto, CA, USA) were placed circumferentially into the pockets with an applicator, and secured with cyanoacrylate adhesive. The EVA fibers maintained constant drug level in GCF of periodontal pockets above 600μg/ml throughout day 10.

Strip and Compacts
Larsen studied *in vitro* release of doxycycline from different bioabsorbable material and acrylic strips. Doxycycline loading was 40% (w/w) for all the formulation. Surgical produced very high concentrations, above 250μg/ml, throughout the study. Strips containing 25% tetracycline hydrochloride or Metronidazole in poly (hydroxybutyric acid) (PHBA) as a biodegradable polymer matrix showed sustained release over 4-5 days with a significant burst effect at day 1. A controlled release strip coded PT-01 and made of poly (methacrylic acid) and hydroxypropyl-cellulose containing 10% ofloxacin has been reported by Kimura et al. the controlled release strips that

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gave the most interesting and long-term clinical improvement were chlorhexidine strips.

Injectable systems

Injectable systems are particularly attractive for the delivery of antibiotic agent into the periodontal pocket. The application can be easily and rapidly carried out, without pain, by using a syringe. Thus, the cost of the therapy is considerably reduced compared to devices that need time to be placed and secured. Moreover, an injectable delivery system should be able to fill the pocket, thus reaching a large proportion of pathogens. Two types of injectable delivery systems have been assessed in the treatment of periodontal disease, biodegradable microparticles a gel. [9]

EVALUATION OF BUCCOADHESIVE DRUG DELIVERY SYSTEM

In addition of weight variation, thickness, content uniformity, bioadhesive strength, dissolution tests some specific tests for patches/film, tablets, gels.

Specific tests for Patches/Films

Folding Endurance: folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300times manually, which was considered satisfactory to reveal good patch properties. The numbers of time of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on three patches.

Swelling study: swell on the surface of agar plate kept in an incubator maintained at 37^{0C}. Increase in the weight and diameter of the patches (n=3) was determined at preset time interval (1-5h). The percent swelling, %S, was calculate using the following equation:

$$\%S = (Xt-Xo/Xo)x100$$

Where Xt is the weight or diameter of the swollen patch after time t,

And Xo is the original patch weight or diameter at zero time.

Tensile strength of the film tensile strength of the film is total weight, which is necessary to break or rupture the films and this was done by a device has rectangular frame with two plates made up of Plexiglas.

The one plate is in the front and is the movable part of the device and can be pulled by loading weights on the string, which is connected to the movable part. The required diameter of films containing dose were fixed between the stationary and movable plate. The force needed to fracture the films was determined by measuring the total weight loaded in the string. Tensile strength = Breaking load (N) / Cross sectional area of the film.

Viscosity of the vehicle: this test is mainly done to check the Spreadability on the flat surface. From the viscosity, the vehicle is proper or not can be checked. Viscosity was measured by dial gauge at 50°C, RT of 29.9°C, RPM 20, Dial-8, off vam 10.7% viscometer.

Thickness of film: the thickness of film is important for the brittleness of film. Thickness is of each film was measured at five different locations (center and four corners) using a micrometer screw gauge and a mean value of five locations was used as a film thickness. Generally it should be less than 200μm.

***Ex-vivo* buccoadhesion time:** the *ex-vivo* buccoadhesion time was performed (n=3) after application of the films on freshly cut goat buccal mucosa. The goat buccal tissues were fixed on the internal side of a beaker with cyanoacrylate glue. Each film was divided in portions of 4 cm^2 and cut, a side of each film was wetted with 0.1 ml of simulated saliva fluid and was pasted to the goat buccal tissue by applying a light force with the finger tip for 20s. The beaker was filled with 800ml of the

simulated saliva fluid and was kept at 37°C. After 2 min, a 150rpm stirring rate was applied to simulate the buccal cavity environment and film adhesion was monitored during 8h.

***Ex-vivo* buccoadhesion force:** Ex-vivo adhesion strength was assessed by a simple modification in the weighing balance using goat buccal mucosa. For buccoadhesive measurements, films were cut in portion of 4cm^2 and pasted on a support, connected to the one part of weighing balance with cyanoacrylate glue and the balanced with a preload. Apiece of goat buccal mucosa was glued on a support and kept in a vessel. The free side of the film was pasted to the goat buccal tissue by applying a light force with the finger tip for 20 s. the vessel was filled with simulated saliva fluid at 37°Cand the measurement was started after 2min. the maximum adhesive force is the average of three measurements (n=3). [10]

Specific tests for Tablets:

$$\text{Drug loading efficiency} = \frac{Amount\ of\ drug\ in\ known\ amount\ of\ formulation}{Initial\ drug\ load} \times 100$$

Gelation and gel melting temperature: gelation and gel melting were evaluated using a modified Miller and Donavan technique. 5ml aliquot of gel was transferred to the test tubes and sealed with aluminum foil. The tubes were immersed in a water bath at 4°C. The temperatures of the water bath was augmented by increment of 1°C and were allow equilibrating to 1 minute at each new setting. The samples were then examined for gelation, which was said to have occurred when the meniscus no longer moved upon slanting the tube through 90°C. The gel melting temperature, the temperature, at which a gel starts flowing upon tilting through 90°C,was recorded. [11]

Friability: five tablets were weighed and placed in the Roche friabilator and apparatus was rotated 25 rpm for 4 minutes. After revolutions of the tablets were dusted and weighed again. The % friability was measured using the formula.

%F = $[1 - \frac{W}{Wo}]$ x 100

Where, %F = friability in percentage
Wo = Initial weight of tablet
W = weight of tablets after revolution

Hardness: hardness was measured using Monsanto hardness tester. For each batch two tablets were tested. [6]

Specific tests for Gels:
Drug loading efficiency: 50ml gel was dissolved in 100ml phosphate buffer (pH 6.8). After dilution the solution was spectroscopically analyzed. The Drug loading efficiency as determined by following formula-

Determination of pH: 1g of gel were weighed and diluted 10 times with isopropyl alcohol. Then, pH of gels was measured with pH-meter.

Viscosity study: A Brookfield viscometer digital viscometer DVLV-II was used to measure the viscosity of gel formulation at 25°C. Spindle number 1 was rotated at 100 rpm. [13]

Estimation of drug content in formulated gels: formulation containing 1mg of drug was taken in 10ml volumetric flask, dissolved in 0.1 N sodium hydroxide made up the volume to 10ml with 0.1N NaOH and then filtered. Absorbance values were measured at respective λmax (319nm) for drug. Concentration of drug were calculated from the standard calibrations of drug were prepared in 0.1N NaOH.

Syringe ability study: Syringe ability study was carried out by using a 22 gauze needle. [13]

Spreadability: Spreadability was determined by an apparatus suggested by Muttimer et al., which was suitability modified in the laboratory and used for the study. It consisted of a wooden block which was provided by a pulley at one end. A rectangular ground glass plate was fixed on this block. An excess of gel (3gm) under study was placed on this ground plate. The gel was then sandwiched between this plate and another glass plate having the dimensions of the fixed ground plate and provided with the hook. A 1kg weight was place on the top of the two plates for 5 minute to expel air and to provide a uniform film of the gel between the plates. Excess of the gel was scrapped off from the edges. The top plate was then subjected to a pull of 50 gm, with the help of string attached to the hook and the time (in seconds) required by the top plate to cover the distance of 10 cm is noted. A shorter interval indicates better Spreadability.
The Spreadability can be calculated using the formula:

$$S = \frac{m.l}{t}$$

Where, S = Spreadability
m = weight tied to the upper slide
l = length of the glass slide
t = time

Extrudability: the formulation under study was filled in a clean, lacquered aluminum collapsible one-ounce tube with a nasal tip of 5 mm opening, extrudability was then determined by measuring the amount of gel/cream/ointment extruded through the tip when a constant load of 1 kg was placed on the pan were collected and weighed. The % of gel/cream/ointment extruded was calculated.

Drug polymer interaction studies: the studies were carried out using IR method with the help of Perkin-Elmer 1615 spectrophotometer to check the possible drug interaction. [14]

Adhesion strength measurement: the adhesion force of gel were determined by means of adhesive force measuring device showing in fig 1, using tissue cut from mucosal area of rat hairless abdomen. The pieces of tissue stored frozen in phosphate buffer pH 7.4, and thawed to RT before use. At the time of testing, a section of rat skin secured to the upper glass vial (C) using a cyanoacrylate adhesive (E). The diameter of each exposed mucosal membrane was 1.5cm. The vials were equilibrated and maintained at 37°C for 10 min. Next, one vial with the section of the tissue (E) was connected to the balance (A) and other vial was the fixed on height adjustable pan (F). To expose tissue on this vial, a constant amount of 0.1 g gel (D) was applied. The height of vial was adjusted so that the gel could adhere to the mucosal tissue of both vials. Immediately, a constant force of 1N is applied for 10 min to ensure intimate contact between tissues and the sample. The vial was then moved upwards at constant speed, and was connected to the balance. Weights were added at a constant rate to the other side of the modified balance of the used device until the two part vials were separated.
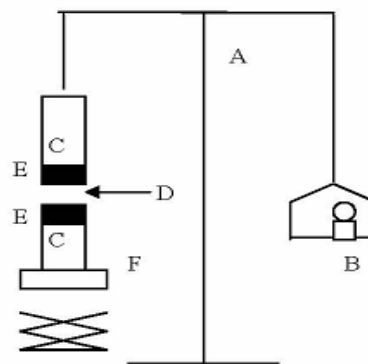

Fig. 1: Bioadhesive force measuring device: (A) modified balance; (B) Weights; (C) glass vial; (D) SA gel; (E) rat tissue; (F) height-adjustable pan.
The buccoadhesive force, expressed as the detachment stress in dyne/cm^2, was

determined from the surface of each formulation using the following equation

Detachment stress (dyne/ cm^2) = m.g/A

Where, m is the weight added to the balance in gm

g is the acceleration due to gravity taken as 980cm.s^2 and

A is the area of tissue exposed. [15]

RECENT ADVANCES IN BUCCOADHESIVE DRUG DELIVERY SYSTEMS

Recently buccoadhesive formulation may provide to be an alternative to the conventional oral medication as they can readily attached to the buccal cavity retained for longer period of time and removed at any time. Buccoadhesive drug delivery system using matrix tablets, lms, layered systems, discs, microspheres, ointment and hydrogel system has been studied and reported by several research groups.

Garala K. *et al* developed and optimized in situ gel for the treatment of periodontal disease. Temperature-sensitive in situ gel containing 0.1%w/v Chlorhexidine hydrochloride was formulated by cold method using different polymers. Result of evaluation parameters revealed that the drug release, gelation temperature was considerably decrease with increasing t_{50}% as the concentration of each polymer was increased. [16]

Suresh P. K. *et al* described the formulation of ciprofloxacin loaded cubic phase gels, a biodegradable, bioadhesive, biocompatible delivery system and their characterization for drug content, drug loading efficiency, gelation temp, gel melting temp, ph, bioadhesive force, viscosity, gel strength, swelling and drug release profile. The drug release kinetics revealed best fit with Higuchi's equation for all the formulations, indicating the drug release by diffusion.[11]

Vijaybhaskar D. *et al* prepared mucoadhesive gels for the treatment of oral submucous fibrosis, which provide effect for the extended periods of time. Stress was given for improvised local action of the drug with the addition of mucoadhesive polymer in the formulation. Curcumin was taken as a model drug as it exhibits profound anti-turmeric and anti-mutagenic activity. The formulation containing equal mixture of NaCMC and HEC as base showed good in-vitro release and good adhesion to oral mucosa. The *In-Vivo* studies were carried out into two phases using 18 mice, in first phase OSF was induced in mice using marketed Gutkha preparation and formulation into a mucoadhesive gel form and applying to mice oral mucosa with the help of cotton buds for a period of six months and in second phase, treatment was carried out following the above method using Curcumin formulation. Histopathological observation reported that there was considerable induction of OSF and excellent treatment results on Curcumin usage.[14]

Fini A., Bergamante V., Ceschel C.G. studied *in vitro/ex vivo* buccal release of Chlorhexidine (CHX) from nine mucoadhesive aqueous gels, as well as their physiochemical and mucoadhesive properties. The combination of HPMC or HPC with CMC showed slower drug release when compared to each of the individual polymers. An accurate selection and combination of the materials allow the design of different pharmaceutical forms suitable for different purposes, by simply modifying the formulation composition. [17]

Ramadan E. *et al* incorporatedMetronidazole (MTZ) (anaerobic antibacterial agent) into different bioadhesive matrices including gels and films using Carbopol 934p(4%), chitosan(3%), and HPMC(3%). The effects of selected MTZ formulations on the healing rate of experimentally induced periodontitis in

guinea pigs were estimated and histological compared between treated and control groups (Metronidazole gel). [18]

Yellanki S.K., Singh J. and Manvi F.V. prepared six batches of MTZ gels using natural biodegradable polymers chitosan, guar gum and locust bean gum in variable concentrations. The results revealed that the surface pH was within the range of neutral pH. The best formulation in terms of cumulative percent drug release along with bioadhesion was formulation F_3 (Chitosan 3%w/v) with 78.23% drug release. [13]

Shah D. *et al* developed a mucoadhesive film for the treatment of Leukoplakia (pre stage of oral cancer) by using Lycopene as a model drug, so that higher concentration was achieved in buccal cavity. As the film was intended for local effect, no drug release was performed. Solvent casting method was selected for film preparation. Lycopene is completely water insoluble, while other excipient are completely water soluble, so uniform film formulation is a major challenge. Viscosity of vehicle, thickness of the film, tensile strength, bending strength, film swelling, erosion properties and ex vivo mucoadhesion time and forces were the criteria to optimize the film formulation using propylene glycol as plasticizer. [10]

Jelvehdari M. *et al* investigated the properties of Carbopol 934P polymeric system in water miscible co-solvents such as glycerin and alcohol. Benzocaine mucosal gel formulation is prepared by Carbopol as a gelling agent was applied in the treatment of dental pain. Neutralization of pH in various concentrations of Carbopol gels resulted in increased viscosity. A relationship between the viscosity and bioadhesive strength was show in the neutralized Carbopol gels. On the other hand, the result indicated that increasing the amount of water, elasticity and release rate was increased. The result showed that diffusion of benzocaine from oromucosal gel and commercial sample followed Higuchi's law. [15]

Perioli L. *et al* prepared mucoadhesive tablets using different mixture of cellulose and polyacrylic derivatives in order to obtain new formulation containing MTZ for periodontal disease treatment. All tablets were characterized by swelling studies, ex vivo and in vivo mucoadhesive time, ex vivo mucoadhesion force, in vitro and in vivo release. The best mucoadhesive performance and the best in vitro drug release profile were achieved by using HEC and Carbomer 940 in 2:2 ratio. The optimized tablet, containing 20 mg of MTZ, released the drug over 12 hr period with buccal concentration always higher than its MIC.[19]

Doshi *et al* prepared pharmaceutical dental gel preparation comprised of MTZ, CHX gluconate and local anesthetic as the active ingredient, glycol as the solvent medium, carboxyvinyl polymer, cross linked polymer of acrylic acid copolymerized with polyalkylsucrose as a gelling agent. [20]

Okamoto H. *et al* examined the penetration rate of Lidocaine (LC) through excised oral mucosa from hamster cheek pouch and the in vitro release rate of LC from film dosage forms with hydroxypropylcellulose (HPC) as a film base. Addition of glycyrrhizic acid (GL) to the HPC films increased the LC release rate almost GL-content-dependently, while an optimum GL content was observed for the LC penetration rate. No LC penetration was observed from an acidic aqueous solution (pH 3.4) of LC, suggesting only unionized LC can substantially penetrate through the mucosa. [21]

Senela S. *et al* prepared gels (at 1 or 2% concentration) or film forms of chitosan containing 0.1 or 0.2% Chlorhexidine and their in vitro release properties were studied. The antifungal activity of chitosan itself as well as

the various formulations containing Chlorhexidine was also examined. Release of Chlorhexidine from gels was maintained for 3 h. A prolonged release was observed with film formulations. No lag-time was observed in release of Chlorhexidine from either gels or films. The highest antifungal activity was obtained with 2% chitosan gel containing 0.1% Chlorhexidine. [22]

Kumar M. *et al* formulated Choline salicylate as a lozenge tablet to provide prolonged relief from pain associated with mouth ulcers. The lozenges were prepared using mannitol as base and gelatin dispersion as binder. Lozenge tablet formulation can provide an attractive alternative formulation in the alleviation of pain in recurrent aphthous mucosal ulcers. [23]

The buccal mucosa is promising delivery route for drugs that need to avoid the gastrointestinal tract due to degradation by the gastric pH, intestinal enzymes, or due to substantial hepatic first pass effect. Currently solids, liquids and gels applied to oral cavity are commercially successful. The future direction of buccoadhesive drug delivery lies in vaccine formulation and delivery of small protein/peptides. Micro particulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet resolved before the safe and effective delivery through buccal mucosa.

CONCLUSION

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