International Journal of Trend in Scientific Research and Development (IJTSRD)
International Open Access Journal
ISSN No: 2456 - 6470 | www.ijtsrd.com | Volume - 2 | Issue – 4

A Review on Aspects of Dental Drug Delivery

Sashi Bhusan, Pranshu Tangri, Preeti Kothiyal, Ganesh Kumar
Division of Pharmaceutical Sciences, SGRRITS, Shri Gururam Rai University,
Dehradun, Uttarakhand, India

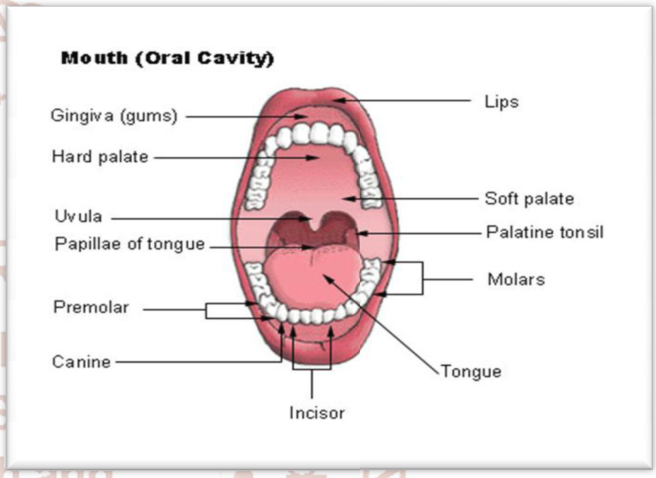
ABSTRACT

Buccal mucosa can be used for local drug delivery as in for periodontitis, dental caries or for oral mucosal drug delivery as for analgesia or transmucosal systemic effect or delivery of biotechnological products like proteins and peptides. This review article is an overview of buccal drug delivery systems encompassing a review of oral mucosa, formulation considerations, theories and mechanism of mucoadhesion, different mucoadhesive formulations for buccal drug delivery and active ingredients delivered via the buccal route. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity.

Keywords: *dental, drug delivery, mucoadhesion*

INTRODUCTION

The advances and progress made by pharmaceutical industry have greatly contributed in terms of treatment of disease, thereby enhancing the quality of life 1. Over the time, scientists and researchers in the drug development industries are focusing on alternate routes of administration to add to the potential of approved drug products, or to overcome the drawbacks of the oral route. Although oral route is preferred for administration of drugs, it is associated with some restrictions for example: hepatic first pass metabolism, local GI toxicity and enzymatic degradation within the GI tract. One strategy that has been reasonably successful to circumvent such problems is to deliver drugs systemically via an alternate route of administration such as intranasal (IN), buccal/sublingual, pulmonary.



Oral ingestion is the preferred route for administration of therapeutic agents, providing a convenient method of effectively achieving both local and systemic effects. Routes ofdrug administration that can be utilized in order to achieve systemic delivery of a drug include: parenteral, oral, buccal, transdermal, nasal and pulmonary. No single route matches all the physiological requirements of an "ideal" absorption site. But, considering surface area, low metabolic activity, contact time, blood supply, accessibility, lack of variability and permeability, relatively oral route is having more suitable characteristics for absorption of drugs. Among the pharmaceutical dosage forms, oral dosage forms are having maximum attribute of ideal dosage forms. Patients are usually accustomed to orally delivered drugs and find the method noninvasive. Today it is estimated that around 80% of all medications used utilize the oral route, in which tablets, capsules and granules continue to remain the dosage form of first choice. It is therefore important that oral drug delivery technology continues to advance and improve the safety and efficacy of treatment.

Oral dosage forms represent the vast majority of the drug-delivery market because of the safety, efficacy, economic, and consumer compliance advantages they possess over alternative routes of delivery. Transdermal, injectable, and inhalation routes possess significant regulatory, technical and compliance barriers to their economical application towards a wide a range of compounds. In conventional oral drug delivery systems, there is very little control over release of drug. Effective concentration at target site can be achieved by intermittent administration of grossly excessive doses, which, in most situations, often results in constantly changing, unpredictable, and often sub- or supra therapeutic plasma concentrations leading to marked side effects. Once-a-day formulations are a holy grail of sorts for scientists working with oral dosage forms. An ideal drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release systems provide a uniform concentration of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.

Controlled release (CR) dosage forms are defined as a technique or approach by which active pharmaceutical ingredients are made available to a specified target.

Advantages[3],-:

1. It is richly vascularised and additional reachable for administration and removal of formulations.
2. Patient accessibility is high.
3. Retentive dosage forms are suitable for administration.
4. Improves bioavailability by eliminating first pass metabolism.
5. Surface of buccal mucosa achieves a fast cellular recovery.
6. Low enzyme activity.
7. Non-invasive method of drug administration.
8. Ability to incorporate permeation enhancer in the formulation.

DISADVANTAGES [4]-:

1. Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents non-keratinized tissues, including buccal membrane.
2. Barrier properties of the mucosa.
3. The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
4. The hazard of choking by involuntarily swallowing the delivery system is a concern.
5. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

The oral mucosa is composed of an outermost layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer. The epithelium of the buccal mucosa is about 40–50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The permeability of buccal mucosa is 4-4000 times greater than that of skin. In general, the permeability of the oral mucosa decreases in the order of, sublingual greater than buccal, and buccal greater than palatal. This is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized .

Functions of Mucus Layer[5,6] -:

1. Protective: resulting particularly from its hydrophobicity.

2. Barrier: The role of the mucus layer as a barrier in tissue absorption of the drugs and influence the bioavailability.

3. Adhesion: Mucus has strong cohesion properties.

4. Lubrication: mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

Theories of mucoadhesion -: Although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon. Mucoadhesion is a complex process and numerous theories have been presented to explain the mechanism involved. The theories include electronic

theory, adsorption theory, wetting theory, diffusion theory, and fracture theory.

There are five classical theories adapted from studies on the performance of several materials the phenomenon. These theories include mechanical-interlocking, electrostatic, diffusin-interpentration, adsorption and fracture processes.

1. Electronic theory-: It is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength (Mathiowitz, Chickering, Lehr, 1999).

2. Adsorption theory-: According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions.

3. Wetting theory -: It applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (Figure 3). The contact angle should be equal or close to zero to provide adequate spreadability (Mathiowitz, Chickering, Lehr, 1999).

4. Fracture theory -: This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion (Mathiowitz Chickering, Lehr, 1999). It analyses the force required to separate two surfaces after adhesion is established (Hä- gerström, 2003; Smart, 2005). This force, sm, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, Fm, and the total surface area, A0 , involved in the adhesive interaction .

5. Mechanical Theory-: The mechanisms governing mucoadhesion are also determined by the intrinsic properties of the formulation and by the environment in which it is applied (Lee, Park, Robinson, 2000). Intrinsic factors of the polymer are related to its molecular weight, concentration and chain flexibility. For linear polymers, mucoadhesion increases with molecular weight, but the same relationship does not hold for nonlinear polymers. It has been shown that more concentrated mucoadhesive dispersions are retained on the mucous membrane for longer periods, as in the case of systems formed by in situ gelification. After application, such systems spread easily, since they present rheological properties of a liquid, but gelify as they come into contact the absorption site, thus preventing their rapid removal. Chain flexibility is critical to consolidate the interpenetration between formulation and mucus (Lee, Park, Robinson, 2000)

Mechanism of Mucoadhesion -: The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and hence increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction . In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over the membrane. In other cases, the deposition is promoted by the aerodynamics of the organ to which the system is administered, such as for the nasal route. On the other hand, in the gastrointestinal tract direct formulation attachment over the mucous membrane is not feasible. Peristaltic motions can contribute to this contact, but there is little evidence in the literature showing appropriate adhesion. Additionally, an undesirable adhesion in the esophagus can occur. In these cases, mucoadhesion can be explained by peristalsis, the motion of organic fluids in the organ cavity, or by Brownian motion. If the particle approaches the mucous surface, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (van der Waals forces and electrostatic attraction). Therefore, the particle must overcome this repulsive barrier .

Factors Affecting Mucoadhesion[7,8,9-:]

1. Molecular weight

The mucoadhesive strength of a polymer increases with molecular weights above 100,000. Direct correlation between the mucoadhesive strength of polyoxyethylene polymers and their molecular weights lies in the range of 200,000–7,000,000.

2. Flexibility

Mucoadhesion starts with the diffusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the

desired entanglement with the mucus. The increased chain interpenetration was attributed to the increased structural flexibility of the polymer upon incorporation of polyethylene glycol. In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, as higher flexibility of a polymer causes greater diffusion into the mucus network.

3. CROSS-LINKING DENSITY

The average pore size, the number and average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and inter-related structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin.

4. HYDROGEN BONDING CAPACITY

Hydrogen bonding is another important factor in mucoadhesion of a polymer. Desired polymers must have functional groups that are able to form hydrogen bonds, and flexibility of the polymer is important to improve this hydrogen bonding potential. Polymers such as poly(vinyl alcohol), hydroxylated methacrylate, and poly(methacrylic acid), as well as all their copolymers, have good hydrogen bonding capacity.

Buccal Dosage Forms[10,11-]:

Over the past few years, different dosage forms intended for buccal drug delivery have been developed. Lists the active ingredients delivered via the buccal route . Buccal mucoadhesive dosage forms can be categorized into several parts-:

1.Buccal Mucoadhesive Dosage-: Buccal dosage forms can also be classified as either a “reservoir” or “matrix” type. In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug’s release rate. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network.

2. **Buccal Tablets:** Tablets have been the most commonly investigated dosage form for buccal drug delivery. Buccal tablets are small, flat, and oral shaped dosage form and unlike conventional tablets allow for drinking. If necessary, the drug may be formulated in certain physical states, such as microspheres, prior to direct compression in order to achieve some desirable properties, e.g. enhanced activity and prolonged drug release.

3. **Buccal patches:** Buccal patches are described as laminates which comprise of an impermeable backing layer, a drug-containing reservoir layer which releases the drug in a controlled manner, and a bioadhesive surface for mucosal attachment. Two methods, namely, solvent casting method and direct milling are used to prepare adhesive patches. 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.

4. **Buccal films:** In recent times, a number of mucoadhesive dosage forms for buccal drug delivery have been developed such as tablet, films, patches, discs, ointments and gels 74-75 and 90-97. However, buccal films are preferable over mucoadhesive discs and tablets in terms of patient comfort and flexibility and they ensure more accurate drug dosing and longer residence time compared to gels and ointments. Buccal films also reduce pain by protecting the wound surface and hence increase the treatment effectiveness.

5. **Buccal gels and ointments:** These are semisolid dosage forms having the advantage of easy dispersion throughout the oral mucosa. The problem of poor retention of gels at the application site has been overcome by using bioadhesive formulations. Certain bioadhesive polymers for example, sodium carboxymethylcellulose82 undergo a phase change from a liquid to a semisolid. This change enhances or improves the viscosity, resulting in sustained or controlled release of drugs.

Limitations[13]-:

1. There is a chance of swallowing and the effect of salivary scavenging.
2. Protective characteristics of buccal mucosa.
3. Relatively small absorption area.
4. Should have good patient compliance
5. Should not hinder normal functions such as talking, eating and drinking.
6. Should accomplish unidirectional release of drug towards the mucosa.

7. Should not aid in development of secondary infections such as dental caries.
8. Possess a wide margin of safety both locally and systemically.
9. Should have good resistance to the flushing action of saliva.

Novel approaches for treatment of orodental diseases[14,15] -:

A) Vesicular systems

Liposomes -:

The localized drug delivery to the intra-periodontal pocket is beneficial as it lowers the incidence of the undesirable side effects, results in improved therapeutic efficacy and increased patient compliance. Liposomes have been found to be the most promising in this approach as they mimic the bio-membrane in structure and behavior. The potential of liposomes as a drug delivery system for use in the oral cavity has been investigated specifically targeting for the teeth, the in vitro adsorption of charged liposomal formulations to hydroxyapatite (HA), a common model substance for the dental enamel, has been conducted by Sanko Nguyen et al.Various liposomal formulations have been used as carriers to deliver bactericides to inhibit the growth of biofilms [43], and *in vitro* experiments have proven that liposomes adsorb to hydroxyapatite (HA), a commonly accepted model substance for tooth enamel[44]. Liposomes can thus be designed to be bioadhesive, e.g. being retained on enamel surfaces to increase the contact time, thereby prolonging the residence time in the oral cavity. In addition to its encapsulating ability of active pharmaceutical ingredients, e.g. antibacterial or anti-plaque agents affecting the attachment of cariogenic microorganisms onto the enamel, liposomes may protect the enamel against deterioration by physically covering the enamel surfaces.

Microparticles -:

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy or other protective materials, that is biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes[46]. It consists of encapsulation of drug into a polymer, which dissolves gradually releasing the drug at the target site. It is highly stable system for delivering a optimum concentration in the pocket. Nakahara et al demonstated regeneration of periodontal tissues in 4 weeks by using a sandwich membrane composed of a collagen sponge scaffold and gelatin microspheres containing basic fibroblast growth factor (bFGF) *in situ.* [47] Renvert *et al.* treated perimplantits patients with arestin (minocycline microspheres) with sustainance of improved results for 12 months[48]. Biodegradable poly alpha hydroxy acids such as poly lactide (PLA) or poly (lactide – co-glycolide) PLGA containing drug dosages can be used to treat periodontal disease.

Films -:

Films are implantable devices with encapsulation of drug, in a manner that it is distributed throughout the polymer with control release occurring through diffusion, dissolution or erosion. The release action depends on type of polymer used to manufacture the chip. Ease of insertion with minimal pain, control on dosage, dimension and shape of the films makes it an ideal device to be used in periodontal pocket. Thickness of film should not exceed 400 µm as well as have sufficient adhesiveness An ideal film should be flexible, elastic, and soft, yet adequately strong to withstand breakage due to stress from mouth movements. It must also possess good mucoadhesive 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. a film composed of cross-linked hydrolysed gelatin and glycerine for local delivery of chlorhexidine digluconate has been developed and commercialised under the tradename Periochip.

Strips and Compacts -:

Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of antimicrobial agents. Strips were fabricated either by solvent casting or pressure melt method. Strips containing tetracycline, Metronidazole or chlorhexidine demonstrated a decrease in number of motile rods, notably spirochetes. In a later development, the evaluation of amoxycillin-clavulainic acid loaded acrylic strips is reported. Highest level of antibacterial agent was released during the first 24 hours period followed by release of therapeutic level of drugs for a subsequent 9 days period. Effect persisted even after 3 week of removal of acrylic strips. Tissue adhesive implants were made using n-butyl-2-cyanoacrylate as a drug trapping material and slowly release drug when used in the structure of a biodegradable local drug delivery device .

According to career center information posted on the Minnesota Dental Association's website:

"A dental therapist is a licensed oral health professional who practices as part of the dental team to provide educational, clinical and therapeutic patient services. There are two types of dental therapists in Minnesota, one is a traditional licensed Dental Therapist and the other is a licensed Dental Therapist that has met certain criteria and achieved certification for Advanced Dental Therapist distinction. Dental Therapists and Advanced Dental Therapists have a specific scope of practice and are required to have a collaborative management agreement with dentists."

DENTAL PRODUCT[16]-:

Somayaji et al. used an ethylcellulose strip as delivery medium for tetracycline and metronidazole to reduce sub-gingival microorganisms in periodontal pockets. Patients were given supragingival scaling and then divided into five groups, depending on the length of time the medication was in place. Sites were marked for tetracycline, metronidazole, and placebo. Sites were wiped and isolated, and baseline microbiology samples were taken for gram staining and culture methods. After treatment, subgingival microbiological samples were taken again. The ethylcellulose strips were removed and analyzed for any remaining drug. Results showed that tetracycline and metronidazole could both be applied locally to periodontal sites using ethyl cellulose strips and markedly supress the subgingival bacteria over a period of several days. The tetracycline showed a faster release; however, the metronidazole required a lesser concentration to achieve complete reduction of the subgingival flora. A saliva activated bio-adhesive drug delivery system was developed for lidocaine hydrochloride and compared its effect with topical gel preparation in dentistry. It was found that DDS adhered to gingival within a minute and produced peak effect in 15 minutes and produced greater depth of anesthesia than the marketed topical gel

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