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EMERGING STRATEGIES IN BUCCAL DRUG DELIVERY: FROM CONCEPT TO CLINICAL APPLICATIONS

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Abstract

When a medication is administered through the buccal mucosa, it dissolves and is absorbed into your bloodstream through a systematic circulation. This is known as the buccal drug delivery system. There are medications, films, and sprays available for both buccal and sublingual use. The review gives information on the anatomy and physiology of the oral cavity, the components and structure of the buccal mucosa, the benefits and drawbacks of the mucus layer, and the buccal delivery system. Information on barriers, mucus, and saliva; the various polymers used in mucoadhesive drug delivery systems; theories of buccal drug delivery; adhesion and evaluation that occur in these drug delivery methods; and the various commercially available dosage forms on the market. In recent years, the Buccal Drug Delivery System (BDDS) has attracted a lot of interest as a successful systemic drug delivery technique. Buccal patches in particular have many benefits, including avoiding hepatic first-pass metabolism, increasing bioavailability, guaranteeing user-friendliness, and boosting patient compliance. These systems provide quick medication absorption and action onset because of the buccal mucosa's rich vascularization. Novel mucoadhesive polymers, nanoparticulate systems, enzyme inhibitors, and cutting-edge drug delivery technologies including 3D printing and thermos-sensitive patches are examples of BDDS advancements. The overall goal of this analysis is to offer insightful information about the state of buccal drug delivery today, as well as any new advancements and prospects in the field. There by aiding in the design and development of more effective.

Keywords: *Mucosal membrane, Mucoadhesive, Buccal absorption, Bio adhesive polymers, Buccal drug delivery system.*

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1. INTRODUCTION

One of the best methods for administering drugs for both systemic and local pharmacological effects is buccal administration. Bio-adhesion is the term used to describe tissues that stick to polymers, whether they are synthetic or natural [1]. Because of its ability to keep a delivery system in one location for a long period of time, the buccal has significant appeal for both local and systemic drug bioavailability. Because of the buccal mucosa's abundant blood supply, absorption is efficient in this area. Additionally, by avoiding hepatic processing first and avoiding gastrointestinal enzyme breakdown, the route swiftly gets medications into the systemic circulation [2]. Investigating alternate routes for the delivery of such medications was prompted by challenges related to parenteral administration and low oral availability. To increase the bioavailability of these medications, a number of tactics have been used, such as reversible chemical changes, absorption enhancers, innovative formulation techniques, and additional enzyme inhibitor dosing. The buccal region of the oral cavity is a desirable target for the delivery of the medication of choice because it has great accessibility, a smooth muscular expanse, and relatively immobile mucosa compared to other transmucosal routes [3]. One of the best transmucosal routes for administering controlled release dosage forms is the buccal mucosa because of its smooth muscular expanse, great accessibility, and generally immobile mucosa. In comparison to other non-oral transmucosal drug administration routes, buccal medication delivery also has a high patient acceptance rate. Due to its lower permeability compared to the sublingual location, buccal mucosa is a better option for long-term medication administration [4]. The buccal drug delivery system has drawn a lot of attention as a significant player in the pharmaceutical industry because of the advancements and progress it has made in the treatment of diseases and, consequently, in improving the quality of life. The Buccal

Drug Delivery System was developed in 1947 to deliver penicillin to the oral mucosa using a powdered dental adhesive combined with gum tragacanth [5, 6]. A The buccal mucosal membrane lining the oral cavity is used to administer the required medication in a buccal drug delivery system. Out of all the transmucosal routes for local and systemic medicines, buccal mucosa is the most effective. The buccal route becomes easily accessible for administration due to the existence of immobile mucosa and plain smooth muscle. The buccal mucosa is the ideal site for controlled release since it has a longer retention period for medication absorption [7,8]. An estimated 5- to 6-day turnover period for the buccal epithelium is probably representative of the oral mucosa as a whole. The buccal mucosa is 500–800 µm thick, while the hard and soft palates, floor of the mouth, ventral tongue, and gingiva are 100–200 µm thick [9]. Medication administrations like hepatic first-pass metabolism and GI enzymatic degradation hinder the oral delivery of some drug types. The absorptive mucosae are therefore thought to be possible sites for medication delivery. Techniques for delivering drugs through the mucosa, particularly the nasal and rectal mucosa [10], the employment of polymeric materials in medicine is rapidly growing [11].

2. ANATOMY AND PHYSIOLOGY OF ORAL CAVITY [12, 13]

2.1mucuslayer

Mucus is the inner layer of mucoadhesive, and the fluid released by goblet cells covers the inner epithelial cell lining. When mucus is translucent, its sticky secretions create a thin, persistent gel blanket that sticks to the epithelial surface. Water and mucin make up its composition, which ranges in thickness from 40 to 30 µm. Other constituents include proteins, lipids, mucopolysaccharides, and electrolytes.

The mucus layers having several important roles and some of these are:

2.2 Protective Function: It is shielded against hydrophobicity and, in a similar vein, shields the mucosa from hydrochloric acid diffusion through the lumen.

2.3 Barrier Function: The mucus layer acts as a diffusion barrier for molecules, particularly to prevent the absorption of drugs. The average molecular weight between two junctions in the mucus networks, the cross-linking ratio, and the glycoprotein content all reveal the nature of the mucus inference at the level of diffusion phenomena.

3. STRUCTURE OF ORAL MUCOSA

A stratified layer of squamous epithelium lines the mouth cavity. The three types of oral mucosa-masticatory, lining, and specialized-can be distinguished from one another. The masticatory mucosa covers the gingiva and hard palate. The thickness of human epithelium varies by region; for instance, the floor of the mouth has 19µm and the hard palate has 310µm [14]. The oral mucosa is the outermost layer of stratified squamous epithelium. The sublingual epithelium has a slightly a smaller number of cell layers than the buccal mucosa's epithelium, which has between 40 and 50 [15]. Because it provides a direct route for drugs to enter the bloodstream, the buccal mucosa, the moist lining of the inner cheek, is a crucial part of the mucosal drug delivery system. The composition and shape of the buccal mucosa mucus layer have a major impact on drug adherence and absorption. The structure and makeup of the buccal mucosa's mucus layer [16]

3.1 PERMEABILITY

The permeability of the buccal mucosa is 4-4,000 times greater than that of the skin. The mouth cavity might pass through different places due to differences in the architecture and functions of the different oral mucosa. The oral mucosa's permeability is influenced by the degree and thickness of tissue keratinization. This implies that buccal permeability is more than palatal and sublingual permeability is greater than buccal [17].

4. THE MECHANISM OF BIOADHESION

When two materials, one of which may be an artificial substance like a polymer, attach to one another over an extended period of time due to interfacial forces, this phenomenon is known as bio adhesion. The mucin layer lining the mucosal tissue is the other substance [18].

Stage of Contact: During this phase, a strong bond is formed between the mucoadhesive substance and the mucosal membrane. It provides improved bioavailability, rapid onset of action, prolonged residence time, and better patient compliance, making it a suitable alternative to conventional oral drug delivery systems [19].

5. THEORIES OF ADHESION: [20, 21]

5.1- Wetting theory: The affinity for the surface to spread over it is described by this idea. For liquid systems, the wetting theory is applicable. For sufficient spread ability, the contact angle must be equal to or nearly equal to zero.

5.2- Diffusion theory: Diffusion theory explains how the mucus and polymer chains penetrate each other far enough to form a semi-permanent sticky bond. The degree of penetration of the polymer chains is thought to increase the adhesive force.

5.3-Electronic theory: This hypothesis states that electronic transmission causes a double electronic layer to form at the interface, these systems improve drug permeation, control release rate, and increase bioavailability [19].

5.4- Adsorption theory: According to this theory, a double electronic layer forms at the contact as a result of electronic transmission, and the attractive forces inside this electronic double layer dictate the mucoadhesive strength.

5.5- Fracture theory: The second most widely recognized theory for describing the force needed to separate two surfaces that have adhered to one another is fracture theory. This force is referred to as fracture strength or tensile stress.

6. FACTORS AFFECTING BIO-ADHESION / MUCOADHESION: [22,23]

6.1 POLYMER RELATED FACTORS:

i)Molecular weight:

✓ At least 1,00,000 molecular weights are required for successful mucoadhesion.

✓Buccal adhesiveness rises as molecular weight does.

ii) Polymer concentration:

• A more concentrated buccal-adhesive dispersion was kept on the mucous membrane for a longer duration.

iii) Flexibility of polymer chains:

✓ The mobility of individual polymer chains declines as water-soluble polymers cross-link.

7. BASIC CONCEPT OF BUCCAL DRUG DELIVERY SYSTEM

7.1 Drug Substance

Before developing Bucco adhesive drug delivery systems, it is important to ascertain whether rapid or prolonged release and a local or systemic action are the intended results. The selection of a suitable drug for the creation of Bucco adhesive drug delivery should be guided by pharmacokinetic properties [24]. The medication should be passively absorbed when taken orally [25]

7.2 Bio-adhesive Polymer

The first step in developing Bucco adhesive dosage forms is selecting and characterizing the appropriate bioadhesive polymers for the formulation [26]. The diffusion of bioadhesive polymers across biological surfaces is explained by this concept. The angle of contact between the two surfaces is measured in this instance. The best adhesion to epithelial surfaces is exhibited by wettable polymers [27]. Bioadhesive polymers are crucial in Bucco adhesive drug delivery systems. Furthermore, polymers are used in matrix devices, which embed the drug in the polymer matrix to regulate the duration of drug release. Oral drug delivery is significantly improved by bioadhesive polymers that adhere to the mucin/epithelial surface [28].

7.3 Selection criteria for polymers [29]

It needs to work well with biological cells.

7.4 Backing Membrane The backing membrane is essential for connecting bioadhesive devices to the mucosal membrane. Backing membranes should be made of inert materials that are impermeable to the drug and penetration enhancer [30].

7.5 Penetration Enhancers

Penetration enhancers are also required when a drug must enter the systemic circulation to function. These are believed to be non-irritating and reversible; the epithelium should resume its barrier properties after the drug has been absorbed. The most common categories of buccal penetration enhancers include alcohols, fatty acids, surfactants, bile salts, and a zone [31].

7.6 Bio-adhesives

Bioadhesive are substances that can interact with biological material and stay on it or hold it together for an extended period of time Examples of commonly used bioadhesive include gelatine, sodium alginate, carbomers, polycarbophil, HPMC, HPC, and others [32].

8. IDEAL CHARACTERISTICS OF BUCCAL DRUG DELIVERY [33]

• It is important to use the optimal molecular weights.
• It is necessary to specify the acceptable shelf-life.
• Space confirmation is necessary.
• Excellent bonding skills are required.

9. ADVANTAGES

- The medication is simple to administer and can help with therapeutic withdrawal in an emergency.
- Patients who are traumatized or unconscious can nevertheless receive medication.
- A comparatively large surface area of the buccal mucosa facilitates extensive and quick medication absorption.

10. DISADVANTAGES

- It is not possible to deliver medications that are unstable in buccal ph. It is not possible to deliver an unpleasant or bitter flavour.
- Food and beverages are limited.
- Local ulcerous effects brought on by extended drug contact.

11. APPROACHES OF BUCCAL DRUG DELIVERY SYSTEM: [34, 35]

11.1 Non-attached drug delivery systems

These comprise chewing gum, microporous hollow fibers, and quickly dissolving tablet dosage forms. The physiological environment in the area has a big impact.

11.2 Drug delivery systems that are bioadhesive

a) Doses of solid buccal adhesive
c) Adhesive semi-solid dose forms
c) Doses of liquid buccal adhesive.

12. METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE [36, 37]

12.1 PERMATION ENHANCERS: The buccal mucosal epithelium is one of the main barriers in the BDDS. High molecular weight substances, such proteins and peptides, typically have poor buccal absorption rates. Absorption enhancers are substances added to the medicine that allow buccal penetration in order to overcome the barrier. The majority of absorption enhancers were created to reduce drug toxicity, boost efficacy, and improve drug absorption. The most widely used substances to improve absorption are fatty acids, bile salts, and surfactants like sodium dodecyl sulphate.

12.2 PRODRUGS: The bitter drugs nalbuphine and naloxone, which are given to dogs through the mucosa, generate excessive salivation and have reduced absorption when swallowed. Naloxone and nalbuphine are used to get around this because they have relatively high bioavailability and don't have any negative side effects.

13. EVALUATION OF BUCCAL DELIVERY SYSTEM

1) Weight Variation- Ten tablets with different polymer concentrations are collected from each formulation. Determine the single weight of each tablet from the chosen formulas, then compare it to the average weight to determine the average weight.

2) Thickness- Take three pills at random from each formulation batch, then use a vernier calliper to measure their thickness. Determine the average thickness.

3) Friability-Six precisely weighed pills (W1) were taken from each batch, put in the Roche Friabilator, and rotated for four minutes at 25 rpm. Weigh the tablets once again when the rotations are finished, which is (W2). Calculate the percentage.

4) Hardness- Each batch's average hardness is determined by measuring the hardness of five tablets. For, hardness measurement Using a Monsanto hardness tester

5) In-vitro swelling studies: A 2%w/v agar gel plate is used to measure the amount of swelling of bioadhesive tablets. Three pills are weighed for each formulation, and the average weight (w1) is determined. After placing the tablets on the Petridis' gel surface, incubate them at 37 +/- 0.10 °C. The tablets are then taken out at intervals of 0.5, 1, 2, 3, 5, and 6 hours. The extra liquid on the surface is then wiped off using filter paper, and the enlarged tablet is weighed. After determining the average weight (w2), use the formula % Swelling index= [(W2-W1)/W1] X 100 to determine the swelling index.

14. RECENT ADVANCEMENTS IN BUCCAL DRUG DELIVERY:

Many researchers have recently started working on classic drug design methods. Today, however, things are significantly different because research is being done on new and better medication delivery methods to reduce adverse drug reactions and improve patient adherence. Enhancing the bioavailability and safety of pharmaceuticals is now possible thanks to advanced drug delivery technology. Notably, improvements in the buccal drug delivery mechanism have been noted recently [38, 39]. Nowadays, a lot of vaccines are administered parenterally through several routes. Vaccines administered by buccal drug delivery systems may be essential in the future for preventing infectious diseases. [40, 41]

15. LIMITATIONS OF BUCCO-ADHESIVE DRUG DELIVERY SYSTEM [42].

1. Drugs that irritate the oral mucosa, smell bad, or taste harsh are not allowed to be administered.
2. Drugs that are unstable at buccal PH cannot be administered.
3. The appropriate dosage of medication can be given in small doses.
4. Excessive salivation can lead to drug ingestion.
5. Drugs that are absorbed by passive diffusion can be administered.

16. CURRENT STATUS AND THE FUTURE OF BUCCAL DRUG DELIVERY SYSTEMS

The skin and the rapid rate of digestion. Because cells divide quickly, a mucoadhesive device can be worn for several hours or even days without losing its adherence Therefore, unlike changing the circumstances in a large fluid compartment, changing the physicochemical conditions in a tiny volume of biological fluid can be done with few adverse effects. The low permeability and lesser absorptive surface area compared to the small intestine's absorptive surface area are the primary drawbacks of this drug delivery method, though [43].

17. CONCLUSION

The structure, permeability, and environment of oral delivery of buccal dosage forms are presented in this paper. Depending on the mucoadhesive and bioadhesive dose forms, the buccal medications have varied characteristics This benefit makes the method a desirable choice for medications that have trouble being administered orally. Additional investigation and advancement of buccal administration devices could enhance patient compliance.

18. AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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None

20. DECLARATION COMPETING INTEREST

The authors have no conflicts of interest to declare.

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22. INFORMED CONSENT

Not applicable

23. ETHICAL STATEMENT

Not Applicable.

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