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Bucco-adhesive drug delivery systems

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ABSTRACT

All researchers in the field of pharmacy, and particularly pharmaceutics, always have patient compliance as their top research priority. Currently, there is a lot of researches being done to develop and manufacture a drug delivery system that is safer, more effective, and more patient-compliant. One of those delivery systems is the buccal film dosage form. Fast dissolving films bypass the hepatic system and deliver therapeutic effect/response, making them more palatable and accurate oral dosage forms. Oral films can take the place of over-the-counter (OTC) medications, due to consumer preference and inexpensive cost. When applied in the oral cavity, a fast-dissolving film quickly becomes hydrated, adheres to the application site, and then dissolves to release the drug. The current review gives a comprehensive overview of the polymers often used in drugs belonging to BCS Classes I through IV as well as factors influencing absorption. For the drugs belonging to BCS Class II and BCS Class III, solubility and permeability are the rate limiting step during the formulation of oral fast dissolving film. Furthermore, this review gives a brief account about the manufacturing methods of oral films.

Keywords:
Oral film, buccal film, patient compliance, polymer, absorption.

1. Introduction

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Drugs can be administered in the body through various routes including: oral, parenteral, transdermal, submucosal, etc. One of the most widely used route of administration is the oral route due to its relatively low cost and ease of administration. However, most paediatric and geriatric patients have problems in swallowing solid oral preparations as tablets and capsules leading to patient incompliance.

When a medicine is administered by the mouth either sublingually, through buccal mucosa or through the gum (gingival), it enters the bloodstream and travels throughout the body. The preferred region for buccal drug administration is the buccal mucosa due to the ease of accessibility and its relative permeability that allow the preparation of rapid release or sustained release dosage forms. One of the most attractive systems that is becoming highly interesting is Transmucosal drug delivery.

The term "bio adhesion" refers to the capacity of a natural or synthetic material to interact with biological surfaces and to be kept on them or to keep them together for an extended period of time. Mucoadhesive drug delivery systems take use of the bioadhesion ability of certain polymers that become adhesive when moistened to deliver drugs to a targeted location of the body for extended periods of time. The ability to maintain a delivery system at a particular place for a long length of time is desirable for both local and systemic medication bioavailability. The concept of mucoadhesion has gained popularity in recent years as a mean to avoid medication breakdown by stomach acids or first-pass hepatic inactivation [(1,2)].

2. Material and methods

2. Benefits of Oral Mucosal Administration

Advantages of buccal medication delivery over more traditional oral administration include:

1) Ease of administration to patients especially in cases of emergency, unconscious or trauma patient.
2) It can be used for drugs with unacceptable taste as it can overcome this problem.
3) Increasing the bioavailability of medications that are ineffective when given orally because they degrade in the stomach's acidic environment [3]
4) Maximized absorption rate as a result of the close contact with the absorbing membrane as the buccal mucosa is highly vascularized.
5) It doesn't require the use of water and can be designed to leave minimal or no residues after administration.
6) Buccal mucosa has a unique physiological character making it an ideal route for mucoadhesive drug delivery.
7) An increase in medication bioavailability is achieved by administering the drug directly into the bloodstream through the jugular vein, therefore avoiding first Pass metabolism and presystemic clearance. [4,5]
8) It can be used for both rapid drug delivery and Prolonged drug release.
9) Enhanced patient compliance.

3. Anatomical structure of the oral mucosa

These oral mucosal are sticky in nature and work as a lubricant, minimizing friction and facilitating the smooth movement of cells in close proximity to one another. The sublingual area, buccal cavity, gingival region, and palate are the routes of administration in this area. [6] Numerous locations in the oral mucosa exist, each with its own unique anatomy, drug permeability, and retention capacity. Stratified squamous epithelium (40-50 layers thick), basement membrane, lamina propria, and sub mucosa make up the outermost, middle, and innermost layers of the oral mucosa, respectively **(Figure 1).** Mucosa of the gingival and hard palate is keratinized and packed with neutral lipids such as ceramides, whereas mucosa of the soft palate, sublingual, and buccal regions are non-keratinized and have a different morphological structure [7,8] **Figure 2** illustrates this.

4. Mechanism of buccal absorption:

The penetration of drugs through the oral epithelium occurs by two main ways as shown in **Figure 3**:

- Transcellular (pass through the cells)
- Paracellular (pass around the cell through the intercellular spaces)

According to the compounds' physicochemical properties, the penetration route will be determined. The intercellular spaces are hydrophilic in nature, therefore act as a barrier for the lipophilic drugs whereas the cell membranes are lipophilic acting as a barrier for hydrophilic drugs [9]. Non-ionic medicines are absorbed via the buccal mucosa by passive diffusion, with the concentration gradient acting as the driving force for the drug molecules as they travel through the intercellular gaps of the buccal epithelial cells [10,11].
The process of medication absorption via the buccal mucosa is thought to be first order in rate.

5. Factors affecting buccal absorption:

The oral cavity serves as a composite location for drug delivery because a variety of dependent and independent factors can influence how much of a drug is absorbed at the site of absorption. [12]

5.1. Membrane Factors:

This includes the epithelium's intercellular lipids, the basement membrane, the lamina, the mucus layer of the salivary film, and the keratinization level of the membrane. Also, the absorptive membrane's thickness, blood supply, lymph outflow, cell renewal, and enzyme content may all affect the total quantity of a medicine that enters into the systemic circulation.

5.2. Environmental Factors:

a. Saliva:

The thin layer of saliva is called the salivary film and it protects the buccal mucosa from the outside environment. Thickness of the salivary film, the content of the saliva, and its movement all have a role in buccal absorption.

b. Salivary glands:

In the buccal mucosa, minor salivary glands secrete mucus continuously. These glands may be found in either the epithelium or the deep epithelium. As much as mucus helps
mucoadhesive dosage forms stick around, it's also regarded to be an obstacle for drug penetration.

6. Methods to increase drug delivery via buccal route

6.1. Absorption enhancers:

Since peptides often exhibit a poor rate of buccal absorption, absorption enhancers have been utilized successfully for the administration of high molecular weight molecules like these. They demonstrate their efficacy using a variety of techniques, such as:

- enhancing the fluidity of the cell membrane.
- extraction of intra- and intercellular lipids.
- Modification of surface mucins or cellular proteins.

The most widely used absorption enhancers are fatty acids, azones, surfactants as sodium dodecyl sulfate and bile salts. The transport of fluorescent-labeled dextran's and mannitol across a buccal epithelium tissue culture model are promoted by Solutions/gels of chitosan whereas Glyceryl mono oleates were found to enhance the absorption of peptide by a co- transport mechanism [13].

6.2. Prodrugs

Nalbuphine and naloxone are bitter drugs that caused excessive salivation and swallowing in dogs when administered through the buccal mucosa resulting in low bioavailability of those drugs. Compared to oral administration, which normally results in a bioavailability of 5% or less, prodrug delivery of nalbuphine and naloxone resulted in no adverse effects and enhanced bioavailability by 35% to 50%. This was documented by a group of researchers [14].

6.3. PH adjustment

At pH levels ranging from 3.3 to 8.8, as well as with the absorption enhancer sodium glycocholate, the permeability of acyclovir was examined. It was discovered that acyclovir's invitro permeability is a pH-dependent process, with enhanced coefficients at both pH extremes (pH 3.3 and 8.8) as opposed to the middle values (pH 4.1, 5.8, and 7.0) [15].

6.4. Patch Design

Numerous in vitro investigations revealed a correlation between the backing material type, quantity, and medication release profile. Where the medication release pattern differs between patches with one layer and those with multiple layers [13].

7. Structure of the buccal medication delivery system

The primary parts of a buccal medication delivery system are:

1. Active pharmaceutical ingredient
2. Film forming polymer
3. Plasticizer
4. Sweetening agent
5. Saliva stimulating agent
6. Flavoring agent
7. Coloring agent

7.1. Active pharmaceutical ingredient

Prior to developing mucoadhesive drug delivery systems, it is necessary to determine if the desired impact is a fast release, sustained release, or local/systemic one. A medication's pharmacokinetic characteristics should be considered during the formulation phase of buccoadhesive drug delivery systems. The ideal medication should have the following qualities: [16]

- Small conventional single dose
- Drugs have a biological half-life of two hours to eight hours
- are good candidates for controlled drug administration.
- The drug's Tmax displays wider-fluctuations, or higher values, when taken orally.
- When administered orally, a medication may undergo passive absorption as well as first pass effect or presystemic drug elimination.

A typical film composition has 1-25% weight/weight of the medication.

7.2. Film forming polymer:

Bioadhesive polymers are defined by Shojaei et al.,1998 as polymers that can adhere to the biological surface. These polymers should show the following characteristics:

- Non-irritant.
- Non-toxic
- Small and flexible
- Have good wetting and spreading capacities
- As the films should generally disintegrate in the saliva of the mouth, it must be water soluble.
- It should be able to adhere to the surface of wet tissues and be site specific [17].

7.2.1. Classification of mucoadhesive polymers:

Ramineni et al.,2014 showed that there are many ways to classify the mucoadhesive polymers based on their solubility, source and charge. Examples of these polymers are shown in **table 1.2** [10]

Synthetic polymers are prepared through the modification of some of the properties of the natural polymers. These modifications may include: adding new functional group, increasing the molecular weight and introducing a charge to the polymer. The most common example of these polymers is the Cellulose derivatives

as HPMC (hydroxypropyl methyl cellulose), CMC (carboxy methyl cellulose), MC (methyl cellulose) and HEC (hydroxy ethyl cellulose).

7.3. Plasticizer:

The produced film may benefit from an improvement in flexibility and a decrease in brittleness if plasticizers are added. The compatibility of the plasticizer with the polymer and the solvent used to prepare the film are key factors in selecting the suitable one. The most often used plasticizers are propylene glycol, polyethylene glycol, and glycerol.

8. Methods for the preparation of the films:

Oral films may be prepared in a number of different ways, as:

- **Casting and drying methods:** (a) Solvent casting (b) Semisolid casting
- **Extrusion methods:** (a) Hot melt extrusion (b) Solid dispersion extrusion
- **Rolling method.**

8.1. Solvent casting

One of the most widely employed method of the preparation is the solvent casting due to the low cost and easy preparation [(18)]. The solvent casting operation involves six steps **Figure 4** including:

- making the casting solution, deaerating it, and putting it into the mould,
- the solution is kept overnight in oven for drying at 50-60℃
- finally cutting the films containing the desired dose of the drug.

The de-aeration step is the removal of any air bubbles entrapped in the solution. It is considered important to ensure the homogeneity and uniformity of the produced films.

8.2 Hot Melt Extrusion

For the first step of the hot melt extrusion method, the medication and carriers are mixed in solid form. The mixture is then melted in an extruder with heating.

Finally, the dies form the melt into films. The advantages of hot melt extrusion are numerous including:

o better content uniformity,

o Anhydrous process,

o Fewer operating units

8.3 Rolling method

To use the rolling technique, a medication solution or suspension is rolled onto a carrier. The most common solvents are water and a mixture of water and alcohol. After the film has dried on the rollers, it is then cut to the specified dimensions.

Disclosure statement

No potential conflict of interest was reported by the authors.

Tables and graphs

Table 1.2. Mucoadhesive polymers commonly used in buccal drug delivery preparation (10,19)

Criteria	Categories	Examples
Source	Natural/semi-synthetic	Gelatin, chitosan, and agarose Inorganic hyaluronic acid Many different types of gum (hakea, guar, xanthan, gellan, carragean, pectin and sodium alginate)
	Synthetic	**Derivatives of cellulose** (Carboxymethyl cellulose, thiolated carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose hydroxypropyl cellulose) **Polyacrylic acid-based polymers** [copolymer of acrylic acid and polyethylene glycol [PEG]], poly (methylvinylether-co-methacrylic acid), poly (2-hydroxyethyl methacrylate), poly (acrylic acidco-ethylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly (isobutylcyanoacrylate) Polyoxyethylene, polyvinyl alcohol, polyvinyl pyrrolidone, and thiolated polymers are among **others.**
Water solubility	Water-soluble	Sodium CMC, Sodium Alginate, CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA
	Water-insoluble	EC, PC, and chitosan (soluble in weak aqueous acids)
Charge	Cationic	Amino dextran, chitosan, (DEAE)-dextran, and TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly (ethylene oxide), PVA, PVP, scleroglucan
Potential Bio adhesive Forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly (methacrylic acid)], CP, PC, PVA
	Electrostatic Interaction	Chitosan

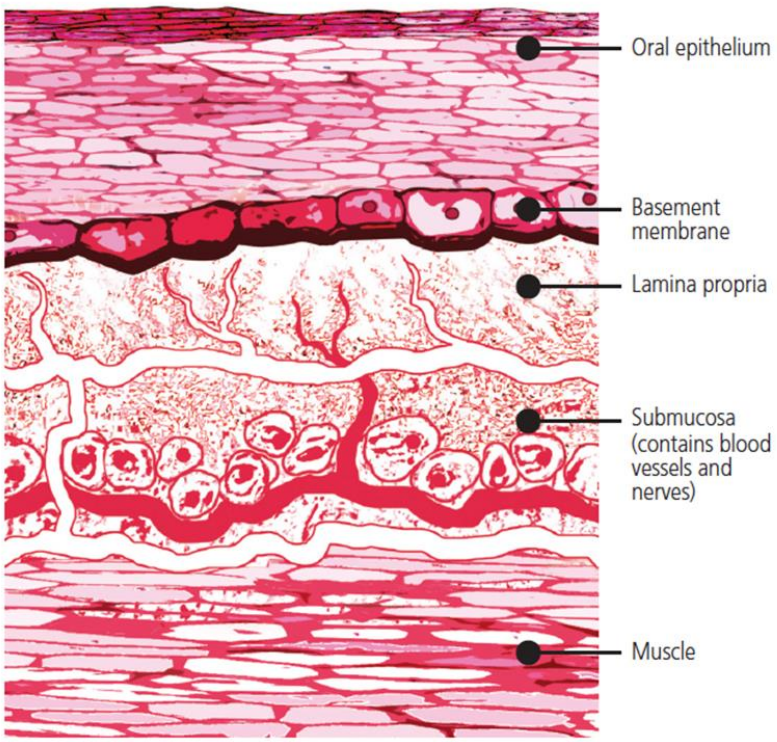
Oral epithelium
Basement membrane
Lamina propria
Submucosa (contains blood vessels and nerves)
Muscle

Figure 1

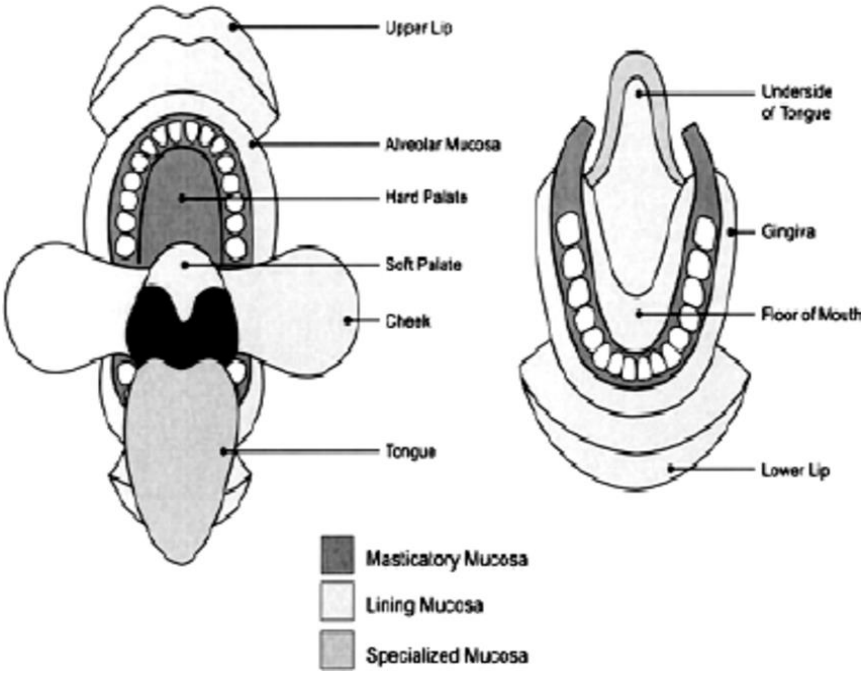
Upper Lip
Alveolar Mucosa
Hard Palate
Soft Palate
Cheek
Tongue
Underside of Tongue
Gingiva
Floor of Mouth
Lower Lip
Masticatory Mucosa
Lining Mucosa
Specialized Mucosa

Figure 2

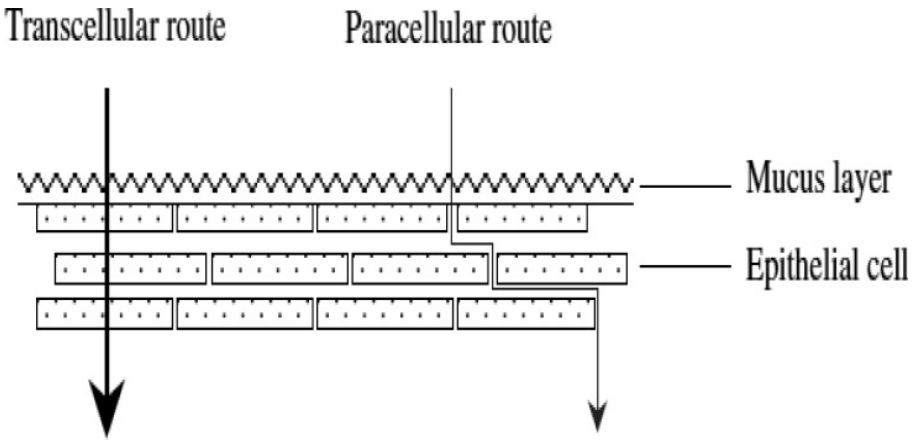

Figure 3

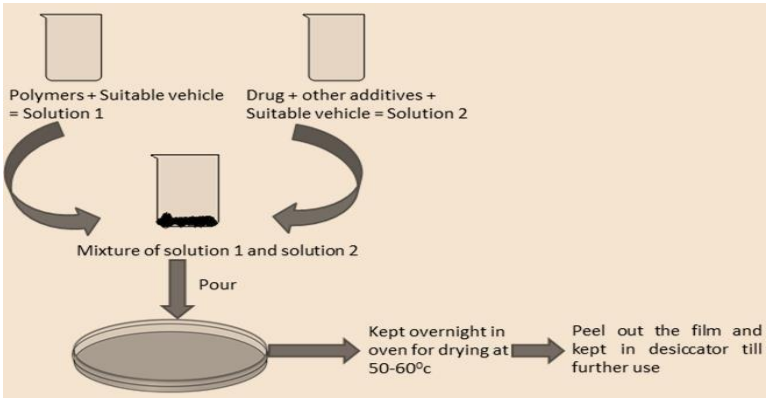

Figure 4

Figure legend

Figure 1: Anatomical structure of the human oral mucosa.
Figure 2: the anatomical location, size, and type of specialized mucosa in the oral cavity.
Figure 3: Paracellular and transcellular pathways in buccal drug delivery.
Figure 4: Solvent casting preparation method diagram.

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