WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 17, 613-629. Review Article ISSN 2277– 7105

AN OVERVIEW OF BUCCAL DRUG DELIVERY IN FORM OF BUCCAL POUCHES

Samrah Khan* and Ashutosh Badola

School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar Dehradun Uttarakhand, 248001, India.

Article Received on
03 November 2022,

Revised on 23 Nov. 2022,
Accepted on 13 Dec. 2022,

DOI: 10.20959/wjpr202217-26546

***Corresponding Author**
Samrah Khan
School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar Dehradun Uttarakhand, 248001, India.

ABSTRACT

The Buccal drug delivery strategy involves administering medications through the cheek lining and dominant buccal mucosa. A handy route of administration for both systemic and local pharmacological activities is the buccal drug delivery system. Buccal drug delivery has attracted a lot of interest and momentum since it provides outstanding benefits. Due to strong patient compliance, a longer localised medication action, and the avoidance of gastrointestinal drug metabolism and first-pass elimination, drug administration via buccal mucosa is a desirable drug delivery technique. In order to allow for drug release and absorption in the moist environment of the oral cavity, buccal drug delivery systems must maintain close contact with the mucosa lining for an extended period of time. The purpose of the current work is to design buccal pouches for the treatment of mouth ulcers by placing the pouch between the cheek and upper gingiva (gums). These pouches have the tendency to aid drugs in bypassing the hepatic first-pass metabolism and entering straight into the systemic circulation. This method of drug delivery is thought to be beneficial for increasing drug bioavailability.

1.0 INTRODUCTION

Drugs can be delivered in a variety of ways, but the oral route is the most practical for administration and dosage modifications. They are widely used because they are simple to prepare on an industrial scale and are convenient to apply.[1] When a drug or active ingredient is coupled with a polymer, controlled drug delivery happens because the release from the bulk material is pre-planned. Both controlled release and sustained release have a consistent and ambiguous history of usage. Both signify different delivery processes. Any dosage form

that releases drug gradually over time is considered sustained release, as is the system's ability to exert real therapeutic control, whether it be spatially, temporally, or both. Sustained release systems typically fail to achieve zero-order release and instead attempt to imitate zero-order release by slowly releasing drugs in the first order. The main goal of controlled drug delivery is to change the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by the use of innovative drug delivery systems or through the modification of physiological parameters and/or molecular structure.[2] Controlled drug delivery systems may result in fewer administrations, better usage of the drug in issue, maintenance of drug levels within a specific range, and higher patient compliance. While these benefits may be substantial, there are also potential drawbacks that should be taken into consideration, such as the higher cost of controlled-release systems compared to conventional pharmaceutical formulations, the potential toxicity or non-biocompatibility of the materials used, undesirable degradation products, any surgery needed to implant or remove the system, and the possibility of patient discomfort due to the delivery device. The ideal drug delivery system should be free of unintentional release, inert, biocompatible, mechanically robust, patient-friendly, capable of high drug loading, quick to insert and remove, and easy to manufacture and sterilise. A high blood level of the drug over an extended period of time was the aim of many of the earliest controlled-release systems' delivery profiles.[5] When a medicine is administered via a typical drug delivery method, the blood level of the drug rises after each dosage and then falls until the next. With conventional medication administration, it is important to keep the blood level of the agent between a maximum value—which may indicate a dangerous level—and a minimum value, beyond which the medicine loses its effectiveness.

Advantages of Controlled Drug Delivery[3-6]

- Maintaining medication levels within a predetermined range.
- Delivery of "difficult" medications: rapid release of medications with low solubility and gradual release of medications that are water soluble.
- Reduced dose and improved patient compliance
- Prevent overdosing and under dosing.
- Reducing adverse consequences.
- Cost-cutting in health care services.
- Increased treatment efficiency:
- Improvement in tolerance and reduction in undesirable side effects.

Disadvantages of Controlled Drug Delivery[3-6]

- Delayed onset of medication effects
- In the event of a poor formulation strategy, the possibility of dose dumping exists.
- Enhanced first-pass metabolism potential
- a greater reliance on the dose form's GI residence duration
- Possible less precise dosage adjustment in particular circumstances
- Compared to typical doses, the price per unit of medication is higher.
- Not all medications can be prepared into ER dosage forms.

2.0 Factors affecting the controlled drug delivery system's performance and design[5,20]

1. Biopharmaceutic characteristics of the drug

- The molecular weight of the drug
- The aqueous solubility of the drug
- Apparent partition coefficient
- Drug pKa and ionization physiological pH
- Drug stability
- Mechanism and site of absorption
- Route of administration.

2. Pharmacokinetic characteristics of the drug

- Absorption rate
- Elimination half-life
- Rate of metabolism
- Dosage form index

3. Pharmacodynamic characteristic of the drug

- Therapeutic range
- Therapeutic index
- Plasma–concentration-response relationship

2.1 Characteristic futures of drug to design CDDS.[10-13]

The pharmacokinetics and pharmacodynamics of the medicine must be thoroughly understood in order to build controlled release systems that work optimally. A variety of factors need to be considered while designing the controlled-release product.

Drug properties

The physiochemical properties of the drug including stability, solubility, partitioning characteristics, charge, and protein binding properties, have a significant impact on the design and performance of controlled release systems.

Route of drug delivery

Other routes of administration may be considered as well, because the drug delivery system in some routes of administration can have a negative impact on drug efficacy, particularly when used chronically.

The physiological restrictions imposed by the specific route, such as first-pass metabolism, GI motility, blood flow, and sequestration of small foreign particles by the liver and spleen, may also affect the CR system's performance.

Target sites

It is preferable to administer drugs locally or via carriers, which can partially accomplish this, to optimise the fraction of the administered dose that reaches the target organ or tissue and reduce undesirable side effects.

Acute or chronic therapy

Acute or chronic therapy: When designing controlled release systems, it's crucial to consider whether the goal is to cure or control the diseased condition, as well as the anticipated length of drug therapy. Rate-controlled drug delivery systems typically have a different long-term toxicity than conventional dosage forms.

The disease

The design of an effective medication delivery system can be significantly influenced by pathological changes that occur during the course of a disease. When developing an ocular controlled release product for an external inflammation, for example, the time course of changes in the protein content of ocular fluids and the integrity of the ocular barriers must be considered.

The patient

The patient, whether mobile or bedridden, young or old, chubby or emaciated, can have an impact on the design of a controlled-release product. The design of delivery systems for controlled and targeted releases must take each of these factors into account. It is worthwhile emphasising how the medication behaves in its delivery system in order to provide a framework for discussions of how drug characteristics and the method of administration affect the design of sustained or controlled release products.

3.0 Buccal Drug Delivery System

One of the novel medicine delivery technologies is buccal drug delivery. Additionally, it is a safer method of drug delivery. The internal jugular vein provides direct access to the systemic circulation through the buccal mucosa, bypassing the drug's hepatic first-pass metabolism. Direct drug molecule entrance into the systemic circulation is made possible by the buccal mode of delivery.[3] The resistance time of the dose form at the site of absorption is increased by mucoadhesive drug delivery systems' interactions with mucin molecules and the mucus layer covering the mucosal epithelial surface. Because buccal patches are so flexible, patients can tolerate them considerably better than they can with tablets.[4] For most medications, mucoadhesive drug delivery is a faster, non-invasive method of systemic administration through the buccal, sublingual, rectal, and nasal mucosa. Mucoadhesive administration results in faster medication distribution and increased bioavailability.[7]

3.1 Buccal Drug Delivery System Advantages[9,14-19]

Multiple benefits are provided by drug administration through the buccal mucosa:

- Compared to traditional medication delivery systems, the buccal drug administration system has the following benefits.
- Maintains the dosage form's residence time at the absorption site, increasing bioavailability.
- Excellent availability and potential for quick action.
- The buccal mucosa is relatively permeable, has a rich blood supply, and is robust in comparison to the other mucosal tissues, resulting in fast absorption due to the high blood supply and good perfusion rates.
- Bypass the first-pass effect and non-exposure of the drugs to the gastrointestinal fluids.
- Simple access to the membrane locations, allowing for simple application, localization, and removal of the delivery system.

- Many medications will perform better because they have more time to interact with the mucosa.
- Compared to alternative non-oral medication delivery methods, high patient acceptance.
- Tolerance to possible sensitizers (in contrast to the skin and nasal mucosa).
- Longer residence times combined with regulated API release may result in lower administration frequency.
- The localization of API at the illness site may also result in significant cost savings and a decrease in dose-related side effects.
- The formulation remains at the delivery site for a longer period of time due to adhesion and close contact, which increases API bioavailability while allowing for lower API concentrations throughout disease therapy.
- Buccal drug delivery avoids the harsh environmental conditions that can affect oral drug delivery.
- It provides a passive drug absorption method that does not require any activation.
- In contrast to rectal or transdermal routes, the presence of saliva assures a relatively significant volume of water for drug dissolution.
- Allows for the administration of hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents, and other medications via a different route.
- It permits localised changes to tissue permeability, protease activity inhibition, and an immunogenic response decrease. As a result, it is simple to distribute therapeutic substances such as peptides, proteins, and ionised species.

Buccal Drug Delivery System Drawbacks[15,17]

The main challenges of buccal administration are

- Limited absorption area: The buccal membrane and other non-keratinized tissues make up around 50 cm2 of the total 170 cm2 of oral cavity membranes that can be used for drug absorption.
- The rate and extent of medication absorption via the mucosa are slowed down by barriers like saliva, mucus, membrane coating granules, basement membranes, etc.
- Additionally, the drug is diluted as a result of the continual flow of saliva (0.5-2 l/day).
- The loss of a medicine that has been dissolved or suspended in saliva could also result in the dosage form being removed unintentionally.
- There is a risk of choking if the delivery system is unintentionally swallowed.

Ideal characteristics[10,11]

- The polymer should have good spreading, wetting, swelling, solubility, and biodegradability qualities.
- The polymer and its breakdown products should be non-toxic, non-irritating, and free of leachable contaminants.
- The pH should have good viscoelastic qualities and be biocompatible.
- Must have sufficient mechanical strength and adhere quickly to the buccal mucosa.
- It must have shear, peel, and tensile strengths that are within the bio adhesive range.
- Polymers need to be readily available and affordable.
- It should have bio adhesive qualities both in the liquid and dry states.
- It should have the ability to inhibit local enzymes and increase penetration;
- It should have the ability to inhibit local enzymes and increase penetration.
- A long shelf life is expected.
- The molecular weight ought to be ideal.
- It must have groups that are adhesively active.
- It ought to have called for spatial conformation. It should be sufficiently cross-linked, but not to the point where bond-forming groups are completely suppressed.
- It must not encourage the growth of secondary infections such as dental caries.

3.2 Buccal Mucosa Overview[27,30]

Oral mucosa is divided into two parts

A. Epithelium

- The non-keratinized surface of the soft palate mucosa, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks serve as the epithelium's protective barrier for the tissues.
- Keratinized epithelium, which is present in the non-flexible areas of the oral cavity and the hard palate. connective tissue and the basement membrane: Between the connective tissue and the basal layer of the epithelium, there is a membrane called the basement membrane. It is made up of extracellular components. The majority of connective tissue makes up the organisation that controls the mechanical stability, resistance to deformation, and extensibility of tissue. Mucus, an intercellular ground substance, surrounds the oral epithelial cells. The saliva secreted by the salivary glands identifies the oral cavity. The main and minor glands both release mucus along with saliva.

B. Mucus: Proteins and carbohydrates make up the mucus. Mucus is essential for the absorption of buccal dosage forms. There is cellular adhesion. The buccal mucosa's permeability is thought to be 4–4000 times greater than the skin.

Saliva: Saliva is regarded as a fluid that protects all oral cavity tissues. In addition to proteins, glycoproteins, and electrolytes, saliva contains 99.5% water. Enamel on teeth continues to mineralize over time. to hydrate oral mucosa dose formulations.

Mechanism of Buccal Absorption

Drug absorption in the buccal cavity happens as a result of passive diffusion of non-ionized species. Passive diffusion occurs within the epithelium's intercellular gaps and is primarily controlled by a concentration gradient. The lipoidal barrier to drug passage is thought to be the buccal mucosa.

Factors influencing buccal absorption: The oral cavity is a challenging environment for drug delivery since there are numerous independent and interdependent variables that lower the absorbable concentration at the site of absorption. The following list of elements are:

1. **Membrane-related factors:** These mostly include the level of keratinization, the amount of surface area that can be absorbed, the mucus layer of the salivary pellicle, the intercellular lipids of the epithelium, the basement membrane, and the lamina propria.[13]
2. **Environment-related factors**

- **Saliva:** Salivary film refers to the thin layer of saliva that covers the buccal mucosa throughout. The salivary film is 0.07 to 0.10 mm thick. The pace of buccal absorption has an impact on the film's thickness, composition, and mobility.
- **Salivary glands:** The small salivary glands are located in the buccal mucosa's epithelium or deep epithelial region. On the buccal mucosa's surface, they continuously release mucus.
- **Buccal tissue movement:** less vigorous movements are seen in the buccal portion of the oral cavity. It is necessary to contain mucoadhesive polymers to maintain the dose form in the buccal region for extended periods of time in order to withstand tissue movements during talking and, if possible, during eating or swallowing.

3.3 The Oral Mucosa: A General Overview[29-30]

A. Structure

The outermost stratified layer of epithelium makes up the oral mucosa. A basement membrane, a lamina propria, and the submucosa—the deepest layer—are found underneath. The epithelium resembles the stratified squamous epithelia that can be found throughout the body. It differs from other epitheliums in that it starts with a basal cell layer that is actively mitotic and progresses through a number of developing intermediate layers to the superficial layers, where cells are lost from the epithelium's surface. The sublingual epithelium includes slightly less cells than the buccal mucosa's epithelium, which has roughly 40–50 cell layers. Moving from the basal layers to the surface layers causes the epithelial cells. The oral mucosa as a whole probably has a turnover time of between five and six days, which has been estimated for the buccal epithelium. The buccal mucosa measures at 500–800 μm, whereas the mucosal thickness of the hard and soft palates, the mouth floor, the ventral tongue, and the gingiva measures at roughly 100–200 μm.

B. Function of Saliva

1. Fluid that protects all oral cavity tissues.
2. The enamel of the teeth continues to mineralize.
3. To moisten dosage formulations for oral mucosa.

C. Mucus Function

1. Contains both carbohydrates and proteins.
2. Cell-cell adhesion.
3. Lubrication
4. Mucoadhesive drug delivery method: bioadhesion.

D. Permeability The intestinal mucosa, epidermis, and mouth mucosa are all relatively leaky epithelia. The buccal mucosa's permeability is thought to be 4–4000 times greater than the skin. Oral mucosa permeabilities typically decrease in the following order: buccal greater than sublingual, and buccal greater than palatal. The buccal mucosa is thicker and nonkeratinized, the sublingual mucosa is relatively thin and keratinized, and the palatal mucosa is intermediate in thickness but keratinized. This ranking is predicted on the relative thickness and degree of keratinization of tissues.

E. Buccal dosage form, structure, and design

1. Matrix type: A matrix-configured buccal patch contains a mixture of a drug, an adhesive, and additives.

2. Reservoir-style buccal patch: The reservoir-style buccal patch has a cavity for the drug and any additives separate from the adhesive. The use of an impermeable backing helps to regulate the direction of drug distribution, decrease patch deformation and disintegration while in the mouth, and guard against drug loss.

F. Drug Permeability via Buccal Mucosa

The squamous stratified epithelium of the oral mucosa can absorb drugs in one of two ways:

- Transcellular (intracellular, passing through the cell).
- Paracellular (intercellular, passing around the cell).

According to reports, intercellular lipids produced by membrane-coating granules are primarily what allow substances to pass through the buccal mucosa via the paracellular route.

Bioadhesion Theories

It is simple to expand the theoretical framework for polymer-polymer adhesion to describe how polymeric materials adhere to biological surfaces. The electronic, adsorption, wetting, diffusion, and fracture theories are pertinent theories.

A. Electronic theory: The bio adhesive polymer and the glycoprotein network, which have distinct electronic structures, are likely to transfer electrons upon contact. This will result in the formation of a double layer of electrical charge at the bio adhesive interface.

B. Theorem of Adsorption The adsorption theory states that Vander walls, hydrogen bonding, and other associated phenomena are what cause bio adhesive solutions to stick to tissue.

C. Wetting Theory: The establishment of a strong adhesive bond requires close molecular contact, necessitating analysis of the wetting equilibrium and dynamic behaviour of the bio adhesive candidate material with the mucus.

I. A zero or almost zero contact angle is one significant property of liquid bio adhesive materials.

II. A low viscosity

III. Close contact that prevents air entrapment. The interfacial tension is smaller than the specific work of adhesion between the bio adhesive controlled release system and the tissue, which is equal to the sum of the two surface tensions.

D. Theory of Diffusion A layer of chains that is sufficiently thick may form as a result of the interpenetration of the mucus and polymer chains. The intimate interaction between two polymers or two fragments of the same polymer is the diffusion mechanism. The dangling chains of the glycoproteinic network and the molecules of the polymer come into close contact during chain interpenetration. The bio adhesive polymer chains penetrate at rates determined by the diffusion coefficient of a macromolecule through a cross-linked network and the chemical potential gradient as a result of the concentration gradient. In order to accomplish bio adhesion, the bio adhesive medium must also be well soluble in the mucus. Therefore, the difference in solubility characteristics between the glycoprotein and the bio adhesive medium should be as close to zero as possible. Therefore, the bio adhesive medium must have a chemical structure that is similar to that of glycoproteins.

E. Fracture Theory According to the "fracture theory" of bio adhesion, the strength of the adhesive bond is correlated with how difficult it is to separate two surfaces following adhesion.

3.4 Buccal Absorption Mechanism[15-19]

Drugs are absorbed through the buccal mucosa via passive diffusion of nonionized species across the epithelium's intercellular gaps, which is primarily controlled by a concentration gradient. The main transport mechanism is the passive movement of non-ionic species through the lipid membrane of the buccal cavity. Like many other mucosal membranes, the buccal mucosa has been described as a lipoidal barrier to the passage of drugs; the more lipophilic the drug molecule, the more easily it is absorbed. The kinetics of drug absorption in the buccal cavity could be well characterised by a first-order rate process. It has been determined that a number of obstacles could prevent buccal medication absorption. According to Dearden and Tomlinson (1971), salivary secretion influences the kinetics of buccal absorption of drug solution by varying the concentration of the drug in the mouth. The following table shows the linear relationship between salivary secretion and time:

$-dm/dt = KC/ViVt$

Where,

M - Drug quantity in the mouth at time t

K - Proportionality constant

C - Drug concentration at that moment in the mouth

Vi - The volume of solution put into mouth cavity

Vt - Salivary secretion rate.

Factors Affecting Bdds[16-20]

1. In general, a polymer's bio adhesive strength rises as its molecular weight rises above 100,000.
2. Flexibility: The diffusion of polymer chains in the interfacial area is what causes bioadhesion to begin. For optimum entanglement with the mucus, it is crucial that the polymer chains have a significant amount of flexibility. Viscosities and diffusion coefficients can be used to connect the mobility and flexibility of polymers, with more flexibility of a polymer leading to greater diffusion into the mucus network.
3. Hydrogen bonding capacity: Another crucial aspect of a polymer's mucoadhesion is hydrogen bonding. Desired polymers must contain functional groups capable of forming hydrogen bonds in order for mucoadhesion to take place. The polymer's flexibility is crucial to increasing this hydrogen bonding potential.
4. Cross-linking density: The amount of cross-linking. Three significant and interconnected structural factors of a polymer network are the average pore size, the number of average molecular weights of the cross-linked polymers, and the density of cross-linking. Therefore, it makes sense that as cross-linking density increases, water transport into the polymer network happens at a lower rate, resulting in insufficient polymer swelling and a slower rate of interpenetration between the polymer and mucin.
5. Charge: Numerous researchers have noted that non-ionic polymers seem to experience less adhesion than anionic polymers. A cationic high-molecular-weight polymer known as chitosan has demonstrated to have effective adhesive properties.
6. Concentration: A low concentration of the polymer results in fewer penetrating polymer chains per unit volume of mucus and an unstable connection between the polymer and mucus. In general, a more concentrated polymer would have a longer penetrating chain length and higher adherence.

4.0 Buccal Pouches[27-29]

This article provides a pouch product designed to release a releasable component from it. The pouched product can consist of a water-permeable fabric pouch with a cavity in it, a composition inside the cavity, one or more releasable components that can move through the water-permeable fabric pouch and are released from the composition when it is consumed, and a release modifying agent designed to react with at least one of the one or more releasable components.

5.0 Polymeric Fibres and Treatments[27-29]

The complete range of extrudable polymers, such as polypropylene, polyethylene, PVC, viscose, rayon, polyester, and PLA, can be used to make the fibres for the fabric described here. The fibres may occasionally be mouth-stable fibres. The FDA has granted food contact approval to the mouth-stable fibres, which may also have low extractables or be produced by GMP-certified sources. Materials that are simple to prepare and reasonably simple to approve for oral use are highly desirable (e.g., quality, low extractables, FDA food contact approval, GMP-approved suppliers). Mouth-stable structural fibres can occasionally be elastomers.

Hydroxypropyl cellulose (HPC), methyl hydroxypropyl cellulose (HPMC), polyvinyl alcohol (PVOH), PVP, polyethylene oxide (PEO), starch, and other materials can be used to create mouth-dissolvable fibres. These fibres might have flavours, sweeteners, drug ground into them, and other useful components. Both solvent techniques and extrusion could be used to create the fibres. In some circumstances, mouth-stable and mouth-dissolvable fibres can be mixed to create the 360' or 360" pouching fabric. Both melt-blown and centrifugally force-spun fibres can be treated, as was said above, with a treatment fluid 142 or 442 using a spray nozzle 140 or 440 as the fibres come out of the melt-blowing device 120 or the centrifugally force-spinning spinneret 420. The fibres may occasionally be used downstream as a component of a fabric 360' or 360."Any acceptable material from which it is desired to extract flavour, nutrients, or any other chemical, such as for oral delivery, may be enclosed in pouches formed from the nonwoven fabric of the invention.The ability of a fabric to withstand deterioration brought on by repeated mechanical deformation in the presence of saliva or water is referred to as "chewability" in this context. The degradation resistance should last for at least as long as a pouched product is typically consumed, which is at least 10 minutes.

The duration of the diffusion

The medicine is frequently released over a longer period of time, up to an hour, in large pouches. The effectiveness of smaller medication pouches ranges from twenty to forty-five minutes.

Discretion

It makes reasonable that a smaller pouch would be less obvious under the lip. It is up to you to decide whether you like a smaller, discrete packet that has to be changed more frequently or a larger packet that you may store for a longer period of time.

Large

These medication pouches are the largest. Their ability to weigh up to 1 gram on a scale gives them their name. Although not particularly discrete, these buccal pouches do have the advantage of having a long service life—you may wear them under your lip for up to an hour.

Slim

The most prevalent format is this one. They are slimmer even though they are as long as the Large pouches. Slim buccal pouches that are comfortable and discrete under the lip spread the medication and flavours for twenty to forty-five minutes.

Super Slim

The Super Slim pouches are even slimmer than the Slim pouches. They promise excellent user comfort and secrecy in every situation. The Super Slim pouches are the perfect travelling companion. They optimally release both drugs and scents.

Mini

The smallest format is this one. Completely undetectable under the lip. For discrete enjoyment, the Mini pouches disperse drugs and aromas for roughly thirty minutes.

6.0 CONCLUSION

This review article provides an overview of buccal drug delivery methods, including information on the oral mucosa, formulation issues, theories and mechanisms underlying buccal drug administration, as well as active substances that are administered via the buccal route. A handy route of administration for both systemic and local pharmacological activities is the buccal drug delivery system. By boosting medication absorption through the oral mucosa, which increases drug bioavailability by lowering the hepatic first-pass effect, a buccal pouch can enhance the therapeutic efficacy of drugs. The buccal medication administration method offers a number of benefits for the drug delivery process. The buccal mucosa has a robust circulatory and lymphatic system that allows medicines to enter the systemic circulation directly, avoiding first-pass liver metabolism and pre-systemic gastrointestinal evacuation. Additionally, a buccal medicine can be stopped if it becomes harmful, making it a safe and simple way to administer medication. However, the usage of this delivery method in the future for the treatment of various buccal disorders may expand given the recent advancements of new formulation types, such as buccal pouch preparations.

REFERENCE

1. Mamatha Y, Selvi A, Prasanth VV, Sipai MA, Yadav V. Buccal drug delivery: a technical approach. Journal of Drug Delivery and Therapeutics, 2012 Mar 13; 2(2).
2. Redddy C, Chatanya KS, Madhusudan RY. A review on bioadhesive drug delivery system: current status of formulaton and evaluation method. DARU J. Phama. Sci., 2011; 19(6): 385-403.
3. Shojaei AH, Chang RK, Guo X, Burnside BA, Couch RA. Systemic drug delivery via the buccal mucosal route. Pharmaceutical technology, 2001 Jun; 25(6): 70-81.
4. Singh J, Deep P. A review article on mucoadhesive buccal drug delivery system. International journal of pharmaceutical sciences and research, 2013 Mar 1; 4(3): 916.
5. Mujoriya R, Dhamande K, Wankhede U, Angure S. A review on study of buccal drug delivery system. Inn Syst Design Eng, 2011; 2(3): 1-3.
6. Bhanja S, Ellaiah P, Martha SK, Sahu PK, Tiwari SP, Panigrahi BB, Das D. Formulation and in vitro evaluation of mucoadhesive buccal tablets of Timolol maleate. Int J Pharm Biomed Res., 2010; 1(4): 129-34.
7. Wani MS, Parakh SR, Dehghan MH, Polshettiwar SA, Chopade VV, Pande VV. Current status in buccal drug delivery system. Pharmainfo. net., 2007; 5(2).
8. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. Journal of controlled release, 2011 Jul 30; 153(2): 106-16.
9. Tangri P, Madhav NS. Recent advances in oral mucoadhesive drug delivery systems: a review. International Journal of Pharmaceutical Research and Development, 2011; 3(2): 151-61.
10. Gandhi SD, Pandya PR, Umbarkar R, Tambawala T, Shah MA. Mucoadhesive drug delivery systems-An unusual maneuver for site specific drug delivery system. Int J Pharm Sci., 2011 Jul; 2(3): 132-52.
11. Rajput GC, Majmudar FD, Patel JK, Patel KN, Thakor RS, Patel BP, Rajgor NB. Stomach specific mucoadhesive tablets as controlled drug delivery system–A review work. Int J Pharm Biol Res., 2010; 1: 30-41.
12. Khurana SH, Madhav NS, Tangri PR. Mucoadhesive drug delivery: mechanism and methods of evaluation. Int J Pharm Biosci, 2011; 2(1): 458-67.
13. Singh J, Deep P. A review article on mucoadhesive buccal drug delivery system. International journal of pharmaceutical sciences and research, 2013 Mar 1; 4(3): 916.

14. Giradkar KP, Channawar MA, Kajale AD, Sridhar E, Kamble RS, Bakde BV, Chandewar AV. Design development and in vitro evaluation of bioadhesive dosage form for buccal route. International journal of pharma research & development, 2010; 2: 21-3.
15. Khana R, Agarwal SP, Ahuja A. Preparation and evaluation of muco-adhesive buccal films of clotrimazole for oral Candida infections. Indian Journal of pharmaceutical sciences, 1997; 59(6): 299.
16. Ebert CD, Heiber SJ, Dave SC, Kim SW, Mix D. Mucosal delivery of macromolecules. InAdvances in Drug Delivery Systems, 1994 Jan 1; 37-44.
17. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. Indian journal of pharmaceutical sciences, 2008 Jan; 70(1): 43.
18. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci., 1998 Jan 1; 1(1): 15-30.
19. Hoogstraate JA, Wertz PW. Drug delivery via the buccal mucosa. Pharmaceutical Science & Technology Today, 1998 Oct 1; 1(7): 309-16.
20. Khairnar GA, Sayyad FJ. Development of buccal drug delivery system based on mucoadhesive polymers. Int J PharmTech Res., 2010; 2(1): 719-35.
21. Frey SE. Indoor air quality investigations on particulate matter, carbonyls, and tobacco specific nitrosamines. Arizona State University, 2014.
22. Caraway JW, Chen PX. Assessment of mouth-level exposure to tobacco constituents in US snus consumers. nicotine & tobacco research, 2013 Mar 1; 15(3): 670-7.
23. Lee PN. Summary of the epidemiological evidence relating snus to health. Regulatory Toxicology and Pharmacology, 2011 Mar 1; 59(2): 197-214.
24. Lee J, Kellaway IW. Peptide washout and permeability from glyceryl monooleate buccal delivery systems. Drug development and industrial pharmacy, 2002 Jan 1; 28(9): 1155-62.
25. Velmurugan S, Deepika B, Nagaraju K, Vinushitha S. Formulation and in-vitro Evaluation of Buccal Tablets of Piroxicam. International journal of pharmTech research, 2010 Jul; 2(3): 1958-68.
26. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs. Journal of controlled release, 2006 Aug 10; 114(1): 15-40.
27. Manivannan R, Balasubramaniam A, Anand DC, Sandeep G, Rajkumar N. Formulation and in vitro evaluation of mucoadhesive buccal tablets of diltiazem hydrochloride. Res J Pharm Tech, 2008 Oct; 1(4): 478-80.

28. Kumar V, Aggarwal G, Zakir F, Choudhary A. Buccal bioadhesive drug delivery—a novel technique. International Journal of Pharmacy and Biological Sciences, 2011 Jul; 1(3): 89-102.
29. Peh KK, Wong CF. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties. J Pharm Pharm Sci., 1999 Aug; 2(2): 53-61.
30. Gupta SK. Buccal Adhesive Drug Delivery System: A Review Asian Journal of Biochemical and Pharmaceutical Research.