BUCCAL DRUG DELIVERY SYSTEMS: A SMART WAY TO DELIVER DRUGS

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Abstract

A considerable fraction of orally administered drug undergoes extensive first pass metabolism which poses a major challenge of bioavailability with certain drugs. The solution to this problem seems to exist with delivery of drug through buccal route. Owing to highly vascular area and relatively higher permeability, the buccal mucosa offers a smart option for local as well as systemic delivery of various drugs. In addition, it may prolong the contact time of drug with affected site. This review attempts to provide a brief idea about the buccal drug delivery including structural features of oral cavity, mechanism of buccal drug absorption, concept of bio adhesion, pharmaceutical considerations for dosage forms, methods of preparation and evaluation of buccal delivery systems along with some marketed products and patents granted thereon.

Keywords

Buccal drug delivery, Bio adhesion, Oral mucosa, First pass metabolism.

INTRODUCTION

Mucosal layers are often found to be potential sites of administration of drugs. They have many advantages for systemic drug delivery like pre-systemic elimination avoidance [1]. Although, oral administration is the most preferred route of administration but there are some drawbacks like pre-systemic clearance due to which drug bioavailability is low and enzymatic degradation within the gastrointestinal tract of protein/peptide-based drugs limit this route [2].

Moreover, many research works have been done on nasal cavity as a site for delivery of drug but due to the drawbacks like potential irritation to the mucous layer and damage (irreversible) to nasal cavity ciliary action, it is less commonly used route for the drug delivery [3]. Similarly, oral cavity is also an efficient drug delivery route and also has reached commercial status with various drugs, for example nitroglycerin sublingual tablets in case of angina and fentanyl in case of cancer pain as a trans mucosal device [4]. However, the patient compliance for the drug delivery through oral cavity is much more acceptable as compared to other trans mucosal routes such as mucosal linings of the nasal, ocular, vaginal, and rectal cavities [5].

The permeable nature of the mucosa helps in immediate exposure of drug in the systemic circulation as it is rich in blood supply and has a very little recovery time after stress or damage [6]. The oral/buccal cavity has been used for both local as well as systemic delivery of drug. Local drug therapy is used to treat various of the disease like oral lesions, candidiasis, gingivitis, dental caries & xerostomia type conditions while the systemic drug delivery is used in the treatment of diseased conditions like chronic asthma and angina [7].

Advantages of BDDS

1) One of the major advantages of buccal drug delivery system is that the drug, bypassing the first pass metabolism, enters the systemic circulation directly [8].
2) Some drugs are very sensitive to gastrointestinal fluids (GIT) and stability of such drugs cannot be achieved if they are exposed to GIT fluids. So, in this case buccal patches play an important role by avoiding the effect of instability of these drugs due to direct entry of drug into systemic circulation [9].

   Example: Steroids, peptides and insulin or other proteins.
3) Type of food or the gastric emptying rate does not affect the rate of drug absorption.
4) The area available for buccal patch adhesion is very large and convenient as there are two areas of buccal membranes in mouth and the patches can be alternatively placed on either side of the membrane [10].
5) Improved patient compliance as the pain and tissue damage associated with injections is completely eliminated in this route.
6) As the patch can be removed there is an ease of the termination of the therapy and can be discontinued if required.
7) Improvement of the drug performance as the patch has prolonged contact time with mucosa. And also increases the bioavailability of the drug.
8) Due to the localization of the drug at the disease site, dose related side effects reduced.
9) Self-administration of the drug is possible with this route.

Limitations

1) Some drugs that have irritable nature towards mucosal membrane cannot be used in BDDS.
2) Drugs having obnoxious odor, unpleasant or bitter taste cannot be taken into consideration for this route.
3) For the drugs that are unstable at buccal pH, this route is considered as undesirable.
4) Saliva is secreted continuously which is the main reason for following dilution of the drug. Due to involuntarily actions swallowing of saliva results in suspended or dissolved drug that has been released and may be removed from the site of action. Moreover, there is a risk of whole delivery system being swallowed unknowingly by the patient.
5) Large doses are very difficult to administer through this route [11].

STRUCTURAL FEATURERS OF ORAL CAVITY

- Oral cavity is nothing but mouth consisting upper & lower lips, cheeks, hard/soft palate and also mouth floor [12].

Oral cavity is made up of 2 parts:

- Outer lies oral vestibule, it is covered by cheeks followed by lips, teeth and gingiva (gums) [9].

- Proper oral cavity is from teeth and gingiva to the fauces, which leads to the pharynx, with roof comprising of the hard and soft palate [13] as showing in fig 1. below
- Tongue is present at the floor of the cavity [14].

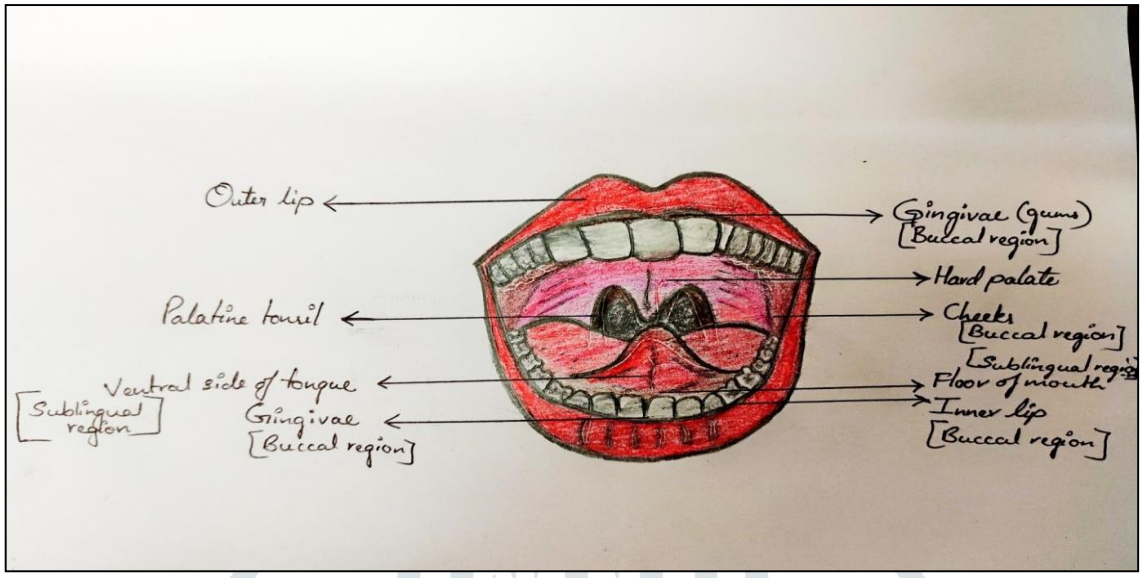

Fig. 1. Diagrammatic presentation of oral cavity.

Oral mucosa layers:

- Stratified Squamous Epithelium
- Basement Membrane
- Lamina propria
- Submucosa

Stratified squamous epithelium is the outermost layer, below it there lies a basement membrane, intermediate layer i.e., the lamina propria which is followed by the mucosa being the innermost layer.

The mean total surface area of the mouth is 214.7 +/- 12.9 cm^2. The estimated turnover time for buccal epithelium is five to six days.

The thickness of oral mucosa varies from site to site: the buccal mucosa measures at 500-800µm as shown in fig-2 given below, whereas thickness of mucosal layer of the hard and soft palates, the ventral tongue, the floor of mouth, and gingivae mostly measures about 100-200 µm.

The epithelium structure varies from site to site depending on the site of oral cavity. The areas of mucosa that are subjected to mechanical stress are keratinized that are very alike to epidermis. Sublingual and buccal region along with the mucosae of soft palate are non-keratinized [15].

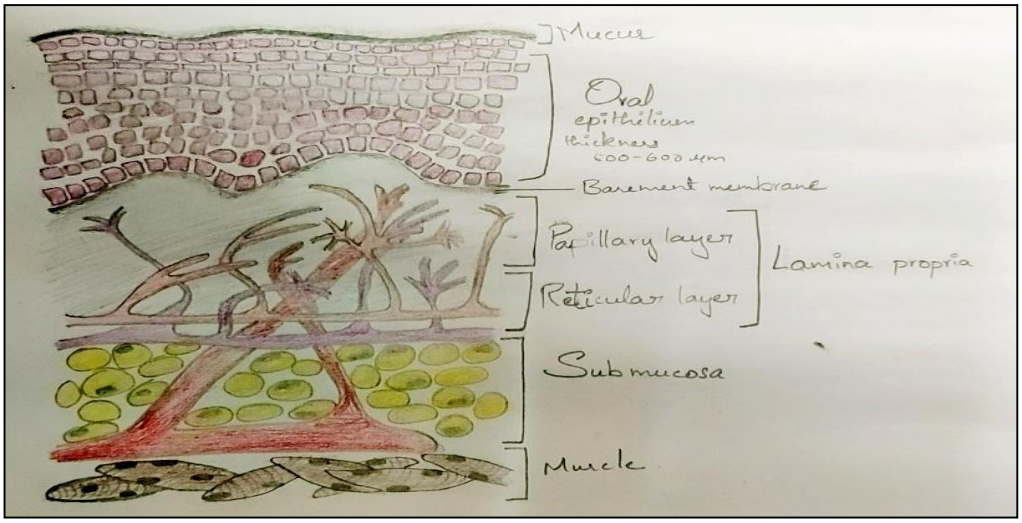

Fig. 2. Schematic presentation of oral mucosa

BUCCAL ABSORPTION

From buccal delivery system, there is drug release when placed in the outer vestibule region i.e. between gingiva and buccal mucosa.

Mechanism: Oral mucosal drug absorption takes place through non-ionic diffusion. The buccal mucosa behaves as lipid barrier to passage of drugs. The greater is the lipophilic nature of drug, more readily it gets absorbed. However, some molecules like a few vitamins & sugars are transported through carrier-mediated transport system which is capable of being saturated [15].

It has been considered that paracellular route is a predominant route for drug absorption as compared to transcellular route. Larger hydrophilic drugs are thought to be transported by this route.

Factors that affect buccal absorption are:

Membrane factor & environment factor

a) Saliva- is a protective fluid that protects whole oral cavity tissues. It is the protective fluid that protects all the soft tissues from chemicals and also abrasions that can be made by rough materials.

Saliva ranges from 5.5 to 7 in pH directly depends upon the flow rate of the saliva. An increase in sodium and bicarbonate concentrations at high flow rates leads to an increased saliva pH. On an average, daily salivary volume ranges from 0.5 - 2 liters. Only this fluid volume is available to maintain the hydration of the oral mucosal dosage forms.

b) Salivary Glands-Salivary glands are responsible for the secretion of the mucous in oral mucosa. The mucus network at physiological pH carries negative charge which plays a vital role in muco-adhesion.

c) Movement of oral tissue- Mucus is an intercellular ground substance and the cells of the oral epithelia are surrounded by it, and the major and principle components present in it are complexes which comprise several carbohydrates and proteins. These complexes have a role in adhesion of cell to cell and also act as a lubricant thus, allowing the cells to move [16].

Mechanism of bio adhesion

Three stages are involved in bio adhesion of patch.

1. Between bioadhesive and membrane an intimate contact occurs.

2. Then penetration of bioadhesive in the tissue occurs.

3. Inter-penetration of bioadhesive chains to mucus [1].

Due to the electrostatic & hydrophobic interactions, hydrogen bonding, dispersion forces, the bonding occurs between the mucus and biological substance, by physicochemical interactions which result from the enlargement of the bioadhesive material and chemical bonds as shown in fig 3. given below [4].

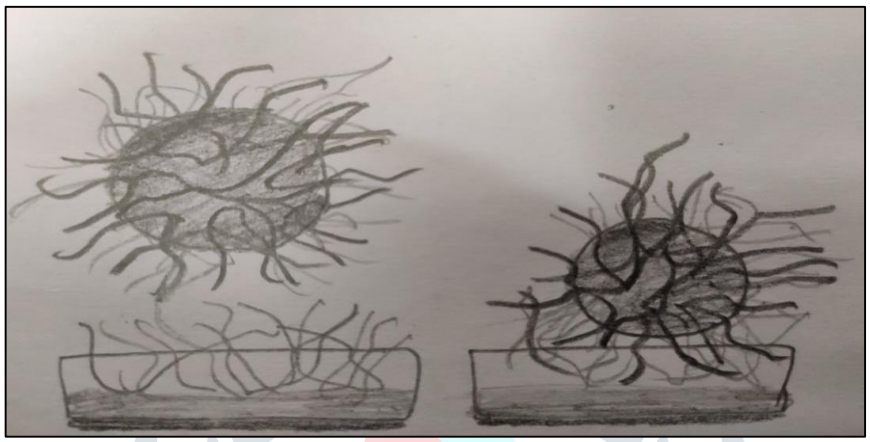

Fig. 3. Bio adhesion mechanism

The theories of bio adhesion:

1) Wetting theory: Predominantly it is applicable to liquid bio adhesive systems which analyze adhesive with contact behavior in terms of spread of liquid or paste over biological system. Terms like surface tension and interfacial tension (γ) are used to express the work of adhesion [17].

2) Diffusion Theory: It states, the "Polymer chains and the mucus mixed with each to form semi-permanent adhesive bond". Diffusion coefficient is responsible for exact depth by which polymer chains penetrate mucus and also time of contact. This diffusion coefficient, in turn, depends on the "value of molecular weight between cross links and decreases significantly as the cross-linking density decreases".

3) Electronic theory: This theory says, "Electronic transfer occurs upon contact of adhesive polymer and the mucus glycoprotein network because of differences in their electronic structure. This result in the formulation of an electronic double layer at the interface adhesion occurs due to attractive forces across the double layer".

4) Fracture theory: It states, "Separation of two surfaces after adhesion "and the fracture strength is said to be equivalent to adhesive strength and is and given as [18]–

$$G = \left(\frac{E\varepsilon}{L}\right) ½$$

Where, E= Young's module of elasticity

ε = fracture energy

L = Critical crack length when two surfaces are separated

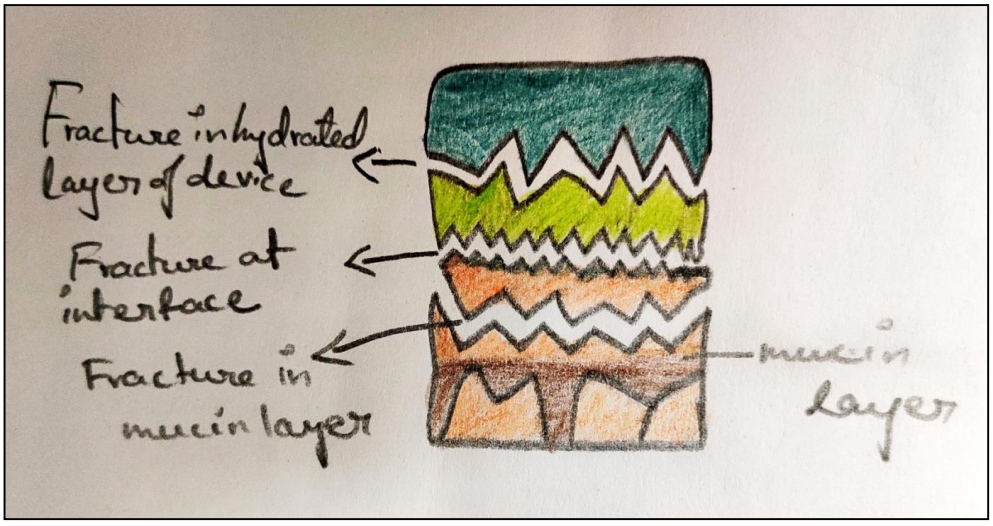

Fig. 4. Fracture at interface

5) Adsorption theory: - "After an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces". Two types of chemical bonds like primary covalent (permanent) and a secondary chemical bond (electrostatic forces; vander-Waals forces; hydrogen and hydrophobic bonds) are involved in the process of adsorption [19].

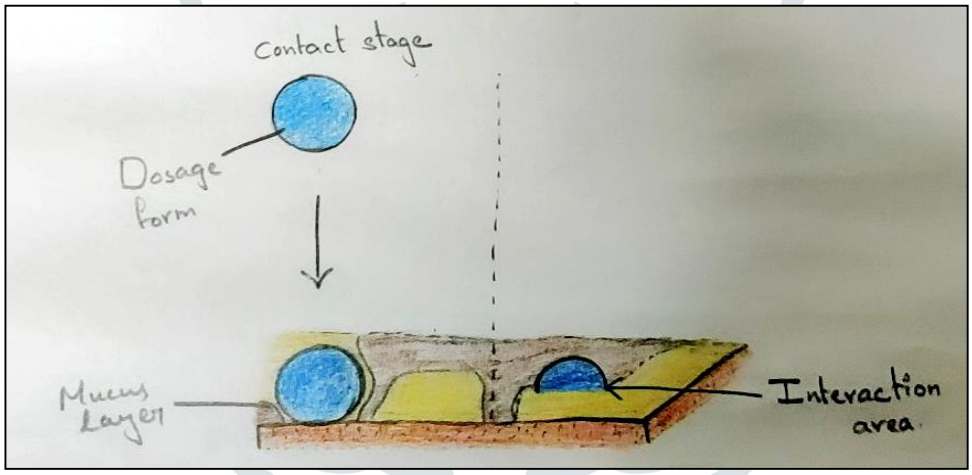

Fig. 5. Adsorption theory

WHAT ARE BUCCAL PATCHES?

Buccal patches are modified matrix dosage form and are made up of 1 or more layers of polymer films or layer which contains drug along with other excipients. The patch is adhered to the oral mucosal surface, gingiva or teeth for a controlled release of drug by mucoadhesive polymer layer. The release of drug maybe unidirectional release or bidirectional release i.e., into oral mucosa or oral cavity or both. After its use the patch maybe removed from mouth and disposed i.e., disposed after specific time [20].

Types of buccal patches:

Patches basically are classified into following types:

1. Matrix type
2. Reservoir type

Matrix type: It is a bi-directional buccal patch and contains drug, adhesive, additives and these are blended together. While designing these kinds of the patches the main consideration which has to be taken in mind is that the drug must release in mouth as well as in the mucosa.

Reservoir type: It is a unidirectional buccal patch in which the drug and additives are present in the cavity which is separated from the adhesive. To this buccal patch an impermeable backing laminate is employed to control the rate & direction of drug that is to be delivered. Backing laminate is also used to minimise the drug loss and leaking of drug when it is adhered to the mouth.

Pharmaceutical considerations

To develop a safe and effective buccal patch great care must be taken. Various factors are to be taken in consideration while designing these kinds of the formulation those factors are basically additives and their effect on the release of the drug, organoleptic factors, drug release and penetration through buccal mucosa, irritation factor which can be observed at the site of the application [21].

Penetration enhancers:

These are chemical substances or compounds that are used to enhance the permeability of the oral epithelium. They mainly help achieve higher drug concentration. They basically modified the barrier function of oral epithelium chemically and hence lead to increased permeability.

Pressure sensitive adhesive:

These are the substances that are used in maintaining the close contact between buccal patch and the surface of mucosa. It must possess given properties such as:

- Feasible to remove from the site of application without leaving any residue at the surface.
- Physiochemical and biological compatibility.
- Should be strongly and permanent tacky.
- Should exert strong holding endurance between patch and oral surface.
- Last and most important property is it should not alter drug release at any cost.

Backing layer:

Backing layer is used in the buccal patch so as to provide good adherence to the drug reservoir along with it also prevent the leaking of the drug through top of the patch, it should exhibit high flexibility or lowest module.

Release liner:

Release liner can be defined as a part of primary packaging material. Basically, it is used to cover the patch so as to provide protection. At the time of application release liner is removed from the patch and discarded. As the liner is in direct contact with the drug delivery system, it should be chemically inert.

Solvents: Some of the solvents like water, methanol, acetone, isopropanol, chloroform, and CH_3Cl_2 used to for preparation of drug reservoir.

Plasticizers: Propylene glycol, dibutyl phthalate, polyethylene glycol, triethyl citrate are some of the plasticizers that are used to provide plasticity to buccal patches.

Bio adhesive polymers: These are the polymers that are very long chained molecules composed of structural units and repeating units that's connected by covalent bonds. Bio adhesive polymers have to possess some physicochemical features such as hydrophilicity, flexibility of penetration through mucus & epithelial tissue, various hydrogen bond-forming groups, and viscoelastic properties [22].

METHODS OF PREPARATION:

There are two methods of preparation of buccal patches:

Solvent casting:

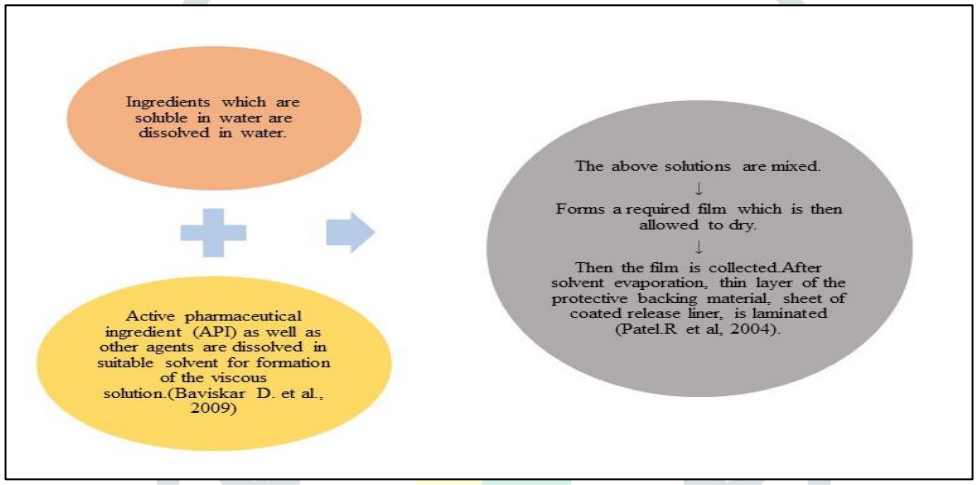

Fig. 6. Method of solvent casting

Direct milling:

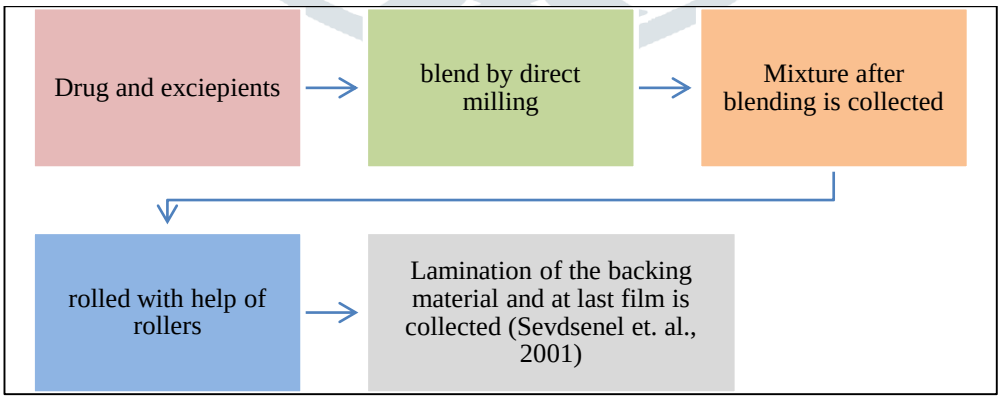

Fig.7. Direct milling process flow chart

EVALUATION OF BUCCAL PATCHES OR FILMS

Evaluation of buccal films is practiced by the following parameters:

Weight & thickness of film

In this, individual weights of three patches are taken and average weight is to be calculated in the same way individual thickness of three films are to be measured with the help of screw gauge from three different sites and then average mean is calculated [23].

Swelling index

Swelling test is done after when we determine the original film diameter and its weight, then on surface of the agar plate sample is allowed to swell and then the sample is incubated in incubator at temperature 37 $\pm$ 0.2°C. After doing this procedure weight of the films (n=3) is determined at various time intervals [24]. With the help of the following equation we can find the swelling index.

$$\text{Percent swelling } [\%\ S] = [(Xt - Xo)/Xo \times 100]$$

Xt= weight of the swollen film after time t,

Xo= initial weight of the film at t=0

Folding endurance

This test is determined by folding a single piece of film from the same site repeatedly until it breaks. This breaking of the film gives the value of folding endurance [25].

Moisture content

For moisture content, the films are weighed individually and kept in desiccator which contains $CaCl_2$ for 24 hrs at room temperature. Then the films are to be weighed again after specific interval and weighing is continued in the same way until they show a constant weight [26]. The moisture content (%) is calculated using the given formula-

$$\%\ \text{Moisture content} = \frac{[\text{Initial weight} - \text{Final weight}]}{\text{Final weight}} \times 100$$

Moisture uptake

This test is performed in the apparatus called as the desiccators. A pre weighed films of particular size is placed in desiccators having a solution of calcium or potassium chloride for 24 hours. After 24 hours films are taken out from the desiccators and again weighed.

Moisture uptake can be calculated by using the given formula [27].

$$\%\ \text{Moisture uptake} = \frac{[Final\ weight - Initial\ weight]}{Initial\ weight} \times 100$$

Drug content uniformity

3-4 film units each one having the minimum diameter of 20nm is to be taken in different volumetric flasks of volume 100 ml. The given solvent then added in the flasks alongside proper stirring is to be provided up to 24 hours. After 24 hours the sample is filtered, diluted with the solvent and then analyzed in spectrophotometer at a specific nm at the end average of the films has to be taken as the final reading [28].

***In vitro* dissolution studies**

Dissolution studies can be done by using several of the USP dissolution apparatus having stated volume of 900 ml at a temperature 37± 0.5, with constant rotation of 50-90 rpm as required by the particular. In each testing procedure a separate film is used, a limited amount of the sample is withdrawn from the dissolution medium at a particular time. The amount which is been taken from the dissolution medium is replaced by same amount of the fresh dissolution medium. After collecting the various of the samples, they are then analyzed in spectrophotometers at a particular nm according to the drug specified [29].

Content uniformity

A piece of the patch having drug is dissolved in 100 ml beaker having phosphate buffer of pH 6.8 with continuo's stirring serial dilution is prepared and then the amount of the drug is measured by using spectrophotometer at λ max of 226 nm (n = 3) [30].

Bio adhesion force

A measure of the bio adhesion performance is taken as "the tensile strength required detaching the bio adhesion patch from the mucosal surface. The apparatus is mainly composed of two arm balance. A small platinum lamina vertically suspended through a wire is placed instead of the left arm of the balance. At the same side, a movable platform is maintained in the bottom in order to fix the mucosal membrane. For determination of bio adhesion force, the mucoadhesive patch is fixed to the platinum lamina using cyanoacylate adhesive. A piece of rabbit intestinal mucosa was also glued to the platform. The patch surface is moistened with 10 µL of phosphate buffer and left for 20 s for initial hydration. On the right pan, a constant weight of 5 g is added at 2 min interval, until the hydrated patch is brought into contact with the mucosal surface". The total weight required for the complete detachment of patch is recorded and the bio adhesion force is calculated per unit area of the patch by using following formula [31].

$$F = \frac{(Ww \times g)}{A}$$

where,

F is force of bio adhesion (kg $m^{-1} S^{-2}$),

Ww is the mass applied (g), g is the acceleration due to gravity (cm s^{-2}),

A is the surface of the patch (cm^2).

The bio adhesion force data reported represent the mean of three determinations".

***In vitro* drug release study**

The patches are evaluated for drug release *in vitro* study by using Franz diffusion cells. For *in vitro* release study, "goat buccal mucosa membrane is used as a barrier membrane with Phosphate buffer (pH 7.4) as a medium. Buccal mucosa membrane is mounted between the donor and receptors compartments. Over the mucosal membrane, patches are placed. The diffusion cell is placed in simulated saliva maintained at

37±2°C.The receptor compartment is filled with 50 mL phosphate buffer (pH 7.4) and hydrodynamics is maintained by stirring with a magnetic bead at 300 rpm. Five mL sample are withdrawn and replaced with 5 mL fresh medium to maintain the sink condition. The samples are analyzed in U.V. spectrophotometer at 226 nm" [31].

MARKETED PRODUCTS

Tab. 1: List of a few marketed products

Brand name	Dosage form	Active drugs	Manufacturer	Uses
Onsolis	Buccal soluble film	Fentanyl citrate	Meda pharmaceuticals, Inc.	Opioid analgesic
BEMA	Buccal soluble film	Buprenorphine	Biodelivery Sciences International, Inc.	Opioid analgesic
Nicoderm CQ	Oral patch	Nicotine	Pfizer	Smoking cessation agent
Anadrol-50	Oral patch	Androgen	Thomson Healthcare Products	Hormonal agent

Table 2. Patent available on BDDS

Inventor	Title	Patent number	Year of patent
Abeer M. Al-ghananeem	Compositions and methods for transmucosal delivery of lofexidine	US12410114	2009
Hao Zhang	Oral transmucosal drug dosage using solid solution	US6264981	1999
Michael S. Balkin	Oral transmucosal delivery tablet and method of making it	US5656284	1995
Brian Hague	Sugar-free oral transmucosal solid dosage forms and uses thereof	US10771046	2004
Hao Zhang	Dissolvable backing layer for use with a transmucosal delivery device	US7276246	2007
Kazuyoshi Furusawa	Fentanyl compound-containing edible patch to be applied to oral mucosa	US10668284	2003
Janet Anne Halliday	Oral transmucosal delivery	US6488953	2001
Christopher N. Jobdevairakkam et al.	Composition of fentanyl citrate oral solid transmucosal dosage form	US11271767	2005
Roy L. Mcquinn et al.	Transmucosal drug delivery device	US5780045	1996
James E. Biegajski et al.	Water soluble pressure sensitive mucoadhesive and devices provided therewith	US5700478	1995
Jhon M. Pinney et al.	Two-stage transmucosal medicine delivery system for symptom relief	US6358060	2002
Katsumi Ihara et al.	Phentanyl-containing adhesive patch for application to oral cavity mucosa	US10524024	2006

CONCLUSION

Due to degeneration and degradation of the drug by several of the factors such as gastric pH, intestinal enzymes, or due to the hepatic first pass effect the buccal mucosa is a preferred delivery route for drugs came into existence. The buccal cavity consists of a highly vascular mucosal membrane which provides large site of administration of drugs. Different thickness and types of epithelial lining (keratinized or non-keratinized) are

present in the oral cavity which gives rise to the regional variations in permeability of drugs. The major drawback of this route is only small dose of the drug is administered. The only way to develop an efficient buccal patch is to formulate the patch in such a way that it can overcomes the above drawback. The advantages at present are clinically relevant only for a certain number of drugs. Moreover, with the developments of new formulations which overcome the above drawbacks gives an efficient buccal patch in the future.

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