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A REVIEW ON BUCCAL DRUG DELIVERY SYSTEM

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ABSTRACT
The Buccal region is rich in blood supply, So the drugs administered in buccal region the patches are design and developed. The buccal mucosa is doing both systemic and local action. The buccal patches are preferred because they enter directly in systemic circulation and avoid hepatic first pass metabolism, due to this bioavailability of drugs are improved. The buccal patches of atenolol is design with hydrophilic polymers like Sodium alginate, Hydroxypropylmethylcellulose, Carbopol 931P, PVP, in their initial proportions and combinations were fabricated by solvent casting technique. The stability studies of patches were done in natural human saliva. Thusthe buccal patches are subject of great interest during recent years because it provides the possibility of avoiding the G.I.T. Contents. About 40% of drugs are lipophilic and failed to reach market due to their poor water solubility.

KEYWORDS: Atenolol, Buccalpatches, Hydrophilicpolymers, Solvent casting method.

INTRODUCTION

The main to design buccal patches to afford a therapeutic amount of drug to the proper site in the body to attain promptly and then maintain desired drug concentration. This route provides an attractive alternate to the oral route of drug administration, particularly in overcoming deficiencies associated with the later mode of dosing problems such as first pass metabolism and drug degradation in harsh gastrointestinal environment.[1]

Buccal route is an alternative route of oral administration. It has excellent portion of smooth muscles and immobile mucosa and thus it is suitable for administration of buccalpatches.The administration of drugs through buccal route provide a directly entrance of drug particles into systemic circulation, because by this route drug avoid the first-pass metabolism and degradation of drug in gastrointestinal tract .The buccalroute is safe and well accepted by patients.Buccal patches are easily administered and can be removed from its application site.[2]

Mucoadhesionis the important phenomenon generally acts in buccal patches. Mucoadhesion means interfacial force between two materials those are held together for prolong time period. It generally said that interaction between polymer and epithelial tissue.

TYPES OF BUCCAL DOSAGE FORM

1. Matrix Type

In this type of buccal dosage form designed in a matrix configuration which contains drug, adhesive and additives mixed together.

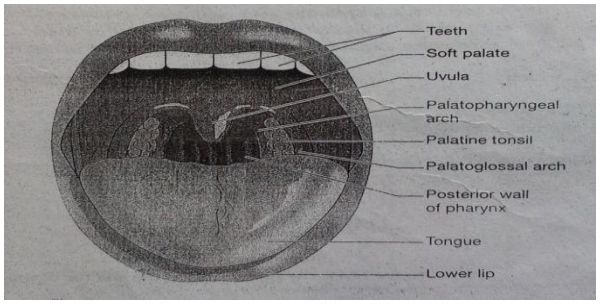
2. Reservoir Type

In this type of buccal dosage form designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive.

Anatomy of Oral Cavity[12]

The oral cavity is opens externally through upper and lowerlips.The oral cavity is bounded by muscles and bones.

Anteriorly-by the lips
Posteriorly-it is continuous with the oropharynx
Laterally- by the muscles of cheeks
Superiorly- by the bony hard palate and muscular soft palate
Inferiorly- by the muscular tongue and the soft tissue of the floor of the mouth.



The oral cavity is lined throughout with mucous membrane, consisting of stratified squamous epithelium containing small mucous-secreting glands. The part of the mouth between the gums and the cheeks is the vestibule and the remainder of the cavity is the oral cavity. The mucous membrane lining of the cheeks and the lips is reflected onto the gums or alveolar ridges and is continuous with the skin of the face.

The palate forms the roof of the mouth and is divided into the anterior hard palate and the posterior soft palate. The hard palate is formed by the maxilla and the palatine bones.

The soft palate is muscular, curves downwards from the posterior end of the hard palate and blends with the walls of the pharynx at the sides.

The uvula is a curved fold of muscle covered with mucous membrane, hanging down from the middle of the free border of the soft palate. Originating from the upper end of the uvula are four folds of mucous membrane, two passing downwards at each side to form membrane arches. The posterior folds, one on each side, are the palatopharyngeal archesand the two anterior folds are the palatoglossal arches. On each side, between the arches, is collection of lymphoid tissue called the palatine tonsil.

Oral cavity is the main route for the administration of buccal dosage form. In oral cavity buccal dosage form administration systems are given below.

1. Sublingual delivery
It involves administration of drug via the sublingual mucosa to the systemic circulation.

2. Buccal delivery
In this route drug administration via buccal mucosa to systemic Circulation.

3. Localdelivery
It involves administration of bio adhesive system either to palate, the Gingiva or the cheek.[3][4]

ADVANTAGE[6][21]
1. Proper reduction in dose related side effects.
2. By this route drug enter direct into systemic circulation.
3. Through buccal route drug degradation in gastrointestinal environment can be circumvented.
4. In case of emergency drug absorption can be terminated.
5. By this route activation does not require because it offers passive system.
6. Due to local stress or damage rapid cellular recovery occur.
7. The patches have ability to withstand environment extremity like temperature and pH etc.
8. Drug can administered sustain drug delivery.
9. Peptide molecules unsuitable for the oral.

Limitations[6][22]
1. The dosage form should not be disturbed if drugs placed at absorption site.
2. When drug placed at buccal mucosa, eating and drinking restricted.
3. It is possibility that the patient may formulation.
4. Through the buccal route which are unstable at pH, irritate the mucosa or have a bitter
or unpleasant taste or an obnoxious odor cannot be administered.
5. Due to hydration it may cause slippery surfaces andthe structural integrity of formulation may get disrupted.
6. The buccal mucosa occur small surface area for adsorption.

Factor affecting buccal bioavailability[7][16]
1. Inherentpermeability of the epithelium
The oral mucosal epithelium is intermediate between skin epithelium that is highly specialized for barrier functions the gut, which is highly specialized for an adsorptive function. The oral cavity, the buccal mucosa is less permeable than the sublingual mucosa.

2. Blood supply
The oral mucosa is rich blood supply and lymphatic network, thus drug moieties which traverse the oral epithelium are readily absorbed into the systemic circulation. The blood flow in the buccal mucosa is 2.4ml cm/min.

3. Epithelium thickness
The thickness of oral epithelium plays important role in buccal administration. The buccal-mucosa occurs approximately 500-800 micrometer in thickness.

4. Metabolic activity
The drug adsorbed through oral epithelium are delivered directly into the blood, this avoid the first pass metabolism. This way oral mucosal delivery attractive for the delivery of enzymatically labile drugs such as therapeutics peptides and proteins.

5. Saliva and Mucous
The oral content are rich of saliva, the oral mucosal surface are constantly washed by a stream of saliva, approximately 0.5-2 L per day. Due to exposed to a lot of saliva which can enhanced drug dissolution and therefore increase bioavailability.

6. Species differences
Animal models are not suitable as buccal drug delivery because they contain highly keratinized epithelium.

7. Transport route mechanism
Across the epithelium barrier drug penetration occur via two main routes.

(a) Paracellular route – It occurs between adjacent epithelium cells.
(b) Trans cellular route–In this route various process occur like passive diffusion, carrier mediated transport via endocytic process. These process occurs across epithelial cells.

8. Ability to retain delivery system
The buccal mucosa contain high amount smooth and relatively immobile surfaces thus is ideally suited to the use of retentive delivery system.[16]

Character of ideal polymer[20][21]
1. The polymer should not be non-toxic and non-absorbable from the gastrointestinal tract.
2. Non-irritated to the mucous membrane.
3. Good polymer preferably form astrong non covalent bond with the mucin epithelial cell surface.
4. Adhere quickly to moist tissue and should possess some site specificity.
5. Allow easy incorporation of the drug and offer non hindrance to its release.
6. It should not be easily decomposed on storage or during the shelf-life of the dosage form.
7. The polymer should not be costly because due to this prepared dosage form remain competitive.

Method of preparation[5][13][14]
1. Solvent casting technique
It is also known as versatile tool for thin film production. It is the oldest technology in plastic film manufacturing. In the year 1950, film extrusion technique of thermoplastic polymers become the dominant production method for plastic films and the importance of solvent cast technology declined.

Nowadays, the solvent cast technology is becoming increasingly attractive for the production of films with extremely high quality requirements. This technology include uniform thickness distribution, maximum optical purity and extremely low haze. The most common solvent used in casting technique are methylene chloride, methanol. The optical orientation is virtually isotropic and the films have excellent flatness and dimensional stability. Mainly films made by different polymer/solvent combination. The key elements of cast films manufacturing are dope preparation, die design, casting support, film drying and solvent recovery are explained below.

1.1 Dope preparation
During this step, solid polymer dissolved in pure solvents or mixtures in various geometrical shapes such as flakes, granules chips or powder is dissolved in pure solvents or mixtures. In this process large difference in viscosity from pure solvents to highly viscous solutions the geometry of the stirrer or paddle elements has to be carefully selected. Horizontal and vertical mixing vessel can be used. Heating and cooling management by thermal jackets is generally required.

Raw materials
For raw materials of the dope making process there are some obvious prerequisites
(a) The polymer should be soluble in a volatile solvent or water.
(b) The stable solution with a reasonable minimum solid content and viscosity should be formed.
(c) Formulation of a homogeneous film and release from the casting support must be possible.

1.2. Casting process
The casting process is also called as casting support. In the casting process generally belt-machine is used. The typically structure measurement of belt machine is given below. The supporting belts are 1.0 to 20.0m wide and 10 to 100m long.

Stainless steel belts are between 1.0 and 2.00mm thick. The belt channel allows a stream of air to flow in machine direction or counter direction.

Two pulleys or drum is connected to a drive that requires extremely accurate speed control to avoid even slight speed variations.

1.3. Die design
In this the device such as selection of die done. The other key element for cast technology are caster spreader, hopper, is also important**.**

There are various types of die-systems are used some common dies are doctor bladedie and slot die is generally used in solvent casting technology.

1.4. Film drying process
There are various methods such as indirect heating, heating by radiation and air-stream drying are used in drying process. This techniques can be separated or combined in different zones to increase the accuracy of control over film formation and film drying at the support surface. The heated air with no solvent or a low solvent concentration is blown in the solvent loaded air is exhausted by fans and directed to the solvent recovery unit.

1.5. Solvent recovery and handling
The solvent casting cannot be mastered without detailed know-how and experience in handling organic solvents. The commonly used solvents are methylene chloride,

methanol and acetone. The use of these solvents is subjects to numerous restrictions.[13][14]

The common suitable recovery passes for solvents are given below

(a) Adsorption process
(b) Absorption process
(c) Cooling out
(d) Thermal oxidation

ADVANTAGES[16]

(a) This process occur homogeneous thickness distribution.
(b) It has highest optical purity, free of gels or specks.
(c) It occur excellent transparency low haze.
(d) By this isotropic orientation, low optical retardation, excellent flatness seen.

Evaluation parameters[22][23][24]

(1) Weight variation and thickness

Six films from each bath, were individually weighed and then averaged weights were calculated, the thickness of patches are assessed at six different points of the patch using thickness gauze.

(2) Folding endurance

The folding endurance was determined by randomly selected folding one patch at the same place till it broke. The number of times the patch could be folded at the same place without breaking the value of folding endurance.

(3) Drug content uniformity

The patch of 2.5cm diameter was cut and placed in a beaker at 100ml of phosphate buffer solution at pH 6.8.The contents then stirred by magnetic stirrer to dissolve patch, the solution then Transferred in volumetric flask (100ml). The absorbance of solution was measuredagainst the corresponding blank solution at 274nm. The drug content was measured from the calibration curve, which was built between 1 and 5microgram per milliliter concentration ranges.

(4) Measurement of surface pH

The buccal patches placed on agar plate surface. This agar was prepared by dissolving agar 2%w/v in warmed phosphate buffer at pH 6.2 and then stirred and pour to petri dish to solidify at room temperature. And then allow to swell the patch for some time. The pH of surface is measured by glass electrode in content with surface of the patch and allow to equilibrate for 1min. Averages five reading recorded.

(5) Measurement of moisture content and moisture absorption

The patches were weight accurate and kept in desiccators which contains anhydrous calcium chloride. After 72hr, the patches were taken out and weighed. The moisture content was measured by using this formula-

Moisture content (%) = initial weight – final weight/ initial weight × 100

for absorption measurement the patch weight and place in desiccators contain 100ml of solution of aluminium chloride which maintain 76% and 86% relative humidity.

After 72hr the patches were taken out and weighed, the % of moisture absorption was calculated by using this formula-

Moisture absorption (%) = final weight – initial weight / initial weight × 100

(6) Swelling studies

with the help of digital electronic weighing balance the weight of the patch was determined without backing membrane. Then the patches were placed on the surface of agar plates and allowed to swell in incubator at 37°C. And the diameter is measured at time interval for 90min.

The swelling index is measured from this formula-

Swelling index = $(w_2\text{-}w_1/ w_1) \times 100$

where SI (%) is percent swelling, w2 is the swollen patch weight, w1 is the initial weight of the patch.

(7) Scanning electron microscopy

The dried film were coated with gold sputter and then observed under scanning electron microscope.

(8) Ex *vitro*mucoadhesion study

The mucoadhesive strength of fabricated buccal patchesmeasured on modified physical balance. A piece of porcine buccal mucosa tied to a open mouth of glass filled completely with isotonic phosphate buffer at pH 6.8. The glass tightly fitted in the center of beaker filled with isotonic phosphate buffer (pH 6.8, temperature 37±1ºC). The patches were stuck to the lower side of the rubber stopper with glue. The mass (in gram) required to detach the patches from the mucosal surface gave the measure of mucoadhesive strength. The parameters were calculated the mucoadhesive strength are given below.

Force of adhesion (N) = mucoadhesive strength/ 1000 × 9.81

Bond strength ($N/m^{2)}$= force of adhesion/ surface area.

(9) *In vitro* drug release study

The *in vitro* drug release study was carried out using a franz diffusion cell. The effective diffusion is was $1.8cm^2$. The receptor compartment (40ml) was filled with phosphate buffer (pH 6.8). Then the patches applied under on the dialysis membrane fitted between the donor and receptor compartments of the diffusion cell. The release of drug performed at 37± 0.5ºC, at a stirring speed of 50rpm using a magnetic stirrer. 5ml of sample from receptor immediately was withdrawn at regular intervals. And it replaced immediately with an equal volume of the phosphate buffer saline, pH 6.8. The amount of drug release into the receptor medium

examined by using UV spectrophotometer at 274nm against a blank.

(10) Stability studies

The selected patches were packed in an aluminium foil and stored in an amber colored glass bottles. These bottles were subjected to stability testing using stability chambers maintained at 37±0.5ºC and 75±5% RH for 6 months.

Stability of selected patches is also carried out in human saliva.

CONCLUSION

The buccal mucosa contains highly vascular mucosal site for the administration of drugs. The epithelial lining of the oral cavity differs both in type andthickness in different areas and the difference give rise to regional variations in permeability to drugs. The main advantage of buccal route of administration over the traditional per oral route are the drug degradation in the stomach is avoided and also first pass metabolism is avoided and therapeutic drug levelof drug can be achievedrapidly. Thus, in conclusion, the mucosal adhesive dosage forms are now on the startingline. The advantages are tremendous which make further study in this fixed extremely important.

The formulation of buccal drug delivery system depends on the developments ofsuitable polymers with excellent mucosal adhesive properties, stability biocompatibility.

Future potential

The future challenge in the development of mucoadhesive dosage forms is to modify the permeability barrier of the mucosa using safe and affective penetration enhancers.

The mucoadhesive formulation offers a great potential both for systemic and local use in the near future.

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