IJBPR

Int. J. Biopharma Research
ISSN: 2287-6898
Review Article

Salbutamol Buccal Patches To Treat Blood Pressure

Swathi G, Rama Devi A, Somalingeswara Rao K, Prasad NLD and I Sudheer Babu
C.R.R. College of Pharmacy, Eluru-534007, West Godavari (DT), Andhra Pradesh, India

Received for publication: Dec 8th 2012; Revised: Jan 12h 2013; Accepted: Feb 30th 2013

Abstract: The aim of the present work is to investigate the formulation of salbutamol buccal patches for controlled release medication in order to treat blood pressure and cardiac diseases. The half life of salbutamol is 10 hrs and in order to treat the angina pectoris which required 24hr controlled drug release and to avoid degradation of drug in GIT, the buccal patches were prepared. The patches were prepared by solvent casting method using hydroxyl propyl methyl cellulose (HPMC K15) and carbopol 974. The patches were found to be smooth in appearance, uniform in thickness, weight uniformity, drug content, swelling index, folding endurance, surface pH and in vitro diffusion study using Keshery chien diffusion cell. The optimized patch of 1% HPMC K15 exhibit in vitro release of 80% through cellophane membrane and in vivo release 73.4% through egg membrane and the optimized patch of 1% Carbopol 974 exhibit in vitro release of 75.2% through cellophane membrane and in vivo release 71.1% through egg membrane in 8 hrs showing good muco adhesive strength and muco adhesive time.

Keywords: Salbutamol buccal patch, HPMC K15, Carbopol 974.

Introduction

These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption. Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection[1]. Over the decades muco-adhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. Buccal cavity). Well defined bio-adhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time[2]. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. The use of muco-adhesive polymers in buccal drug delivery has a greater application. Various muco-adhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability[3]. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation[4]. Versatility in designing as multi directional or uni directional release system for local or systemic action[5].

Advantages of Salbutamol buccal patches:

1. The salbutamol oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein.
2. Salbutamol buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect. Contact with the digestive fluids of gastrointestinal tract is Avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate.
3. The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, additionally; there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes[6].
4. Salbutamol buccal patch has been well known for its good accessibility to the membranes that line the oral cavity, which makes application painless and with comfort.
5. Patients can control the period of administration or terminate delivery in case of emergencies. The buccal drug delivery systems easily administered into the buccal cavity. The novel buccal dosage forms exhibits better patient compliance.

Limitations of Salbutamol Buccal Drug Delivery:

Depending on whether local or systemic action is required the challenges faced while delivering drug via Salbutamol as buccal drug delivery can be enumerated as follows[7].

***Corresponding Author:**
Dr. G. Swathi
C. R. Reddy College of Pharmacy
Eluru, West Godavari District, A.P, India

1. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
2. The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
3. For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue.

For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern[8].

Structure of Oral Mucosa:

The oral mucosa is comprised of squamous stratified (layered) epithelium, basement membrane, the lamina propria and sub mucosa9. It also contains many sensory receptors including the taste receptors of the tongue. Based on the environment of mucosa drug can be shown more effect. This mucosal environment can be shown as in fig: 1

Figure.1: Cross section of Oral Mucosa

Buccal Mucosa Environment:

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva10. Shown as in fig: 2

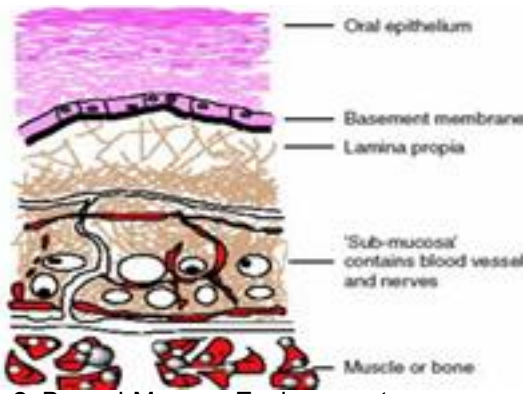

Figure.2: Buccal Mucosa Environment

Role of Saliva

•Protective fluid for all tissues of the oral cavity.

•Continuous mineralization/demineralization of the tooth enamel.

•To hydrate oral mucosal dosage forms.

Role of Mucus

•Made up of proteins and carbohydrates.

•Cell-cell adhesion

•Lubrication

•Bio-adhesion of muco-adhesive drug delivery systems

Structure and Design of Salbutamol Buccal Dosage Form:

Buccal Dosage form can be of:

1. Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.
2. Reservoir type: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive11. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Transmucosal drug delivery systems can be bi-directional or unidirectional. Bi-directional (Figure 1) patches release Salbutamol in both the mucosa and the mouth while, Unidirectional (Figure.2) patches release the drug only into the mucosa. Shown as in fig: 3&4

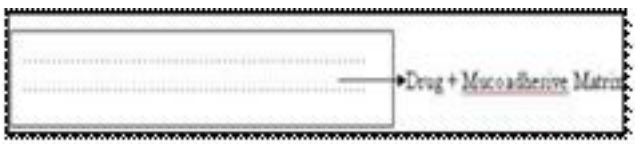

Figure.3: Buccal Patch designed for Unidirectional Salbutamol release

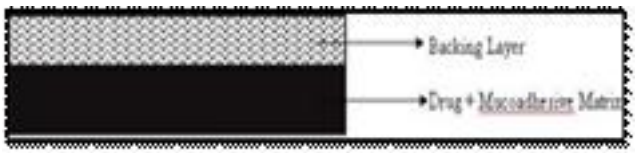

Figure.4: Buccal Patch designed for Bidirectional Salbutamol release

Permeability of Drugs through Buccal Mucosa:

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

i. Transcellular (intracellular, passing through the cell) and
ii. Paracellular (intercellular, passing around the cell).

Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules[12]. Although passive diffusion is the main mechanism of drug absorption, specialized transport mechanisms have been reported to exist in other oral mucosa (that of the tongue) for a few drugs and nutrients; glucose and cefadroxil were shown to be absorbed in this way. The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligonucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancers may be required to overcome this. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also reduce stability[13]. Disease states where the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such as lichen planus, pemphigus, viral infections and allergic reactions.

Mechanism of buccal drug absorption:

Salbutamol Buccal drug absorption occurs by passive diffusion of the no ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium[14]. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoid barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophilic the drug molecule, the more readily it is absorbed[15]. The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth16, shown as fig: 5 the linear relationship between salivary secretions follows

$$-dm/dt = kc/v\,ivt$$

M - Mass of drug in mouth at time t
Kc - proportional constant
VI - volume of saliva
VT - volume of saliva secretion

Factors effecting on absorption:

The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption[17].

Membrane factor:

This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug in blood.

Environmental factor:

A. Saliva: The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film affect the rate of buccal absorption.

B. Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

C. Movement of buccal tissues: Buccal region of oral cavity shows less active movements. The muco adhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.

Figure 5: Salbutamol patches

Method of preparation salbutamol buccal patches:

1. Solvent casting method

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry18.

2. Direct milling

In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no

differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

Materials and Methods

Preparation of salbutamol buccal patch:

The salbutamol buccal patches were prepared by solvent casting method. HPMC K15 and Carbopol 974 polymers in ratio of 0.5 to 1.5 % were incorporated in different buccal patches. The concentration of plasticizer was finalized differently for the two polymers from the plasticity of the film. It is varied from 10% to 20% for the patch. The composition of different formulation is shown in Table no.1. The component of each formulation were mixed and poured in the mould and dried in oven then removed from the mould and cut in to pieces of 1×1 cm and finally packed in aluminum foil19.

Folding Endurance:

Folding endurance was determined by repeatedly folding at the same place until it broke. The number of times the film folded at the same place without breaking was the folding endurance value.

Patch thickness:

Patch thickness measured at five different randomly selected spots using screw gauge.

Content uniformity:

The buccal Patch dissolved in phosphate buffer pH 6.8. The n solution is diluted and filtered through watchman filter paper, and analyzed at 271 nm using a UV Double beam spectrophotometer.

Surface pH study:

The Patch was allowed to swell by keeping it in contact with 2% agar gel plate for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 min.

Swelling study:

Buccal patches were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 1°C. At regular intervals (1, 2, 3, 4, 5& 6 hours) the patches were removed from Petri dishes and excess water removed carefully using filter paper. The swollen patch was then reweighed (W2) and the swelling index (SI) were calculated using the formula given in equation.

SI = [(W2-W1) ÷ W1] × 100 Where,

W1 = initial weight of the patch W2 = final weight of the patch.

Tensile strength:

F/a*b (1+L/l)

Where, F is force required to break; a, b, and L are width, thickness and length of patch respectively and l is elongation of patch at break point.

Elongation at break = lb- lo × 100 lo

Salbutamol Bio-adhesion properties:

The bio adhesive strength was measured using a modified version of the apparatus previously applied by Parody .The device was mainly composed of a two-arm balance. Both the ends are tied to glass plate for keeping weight. The right and left pans were balanced by adding extra weight on the left hand. The piece of goat buccal mucosa was tied to the two glass slide separately. Buccal patch was placed between these two slides containing goat buccal mucosa, and extra weight from the left pan was removed to sandwich the two pieces of glass and some pressure was applied to remove the presence of air. The balance was kept in this position for 5 min. Weight was added slowly to the left hand pan until the two glass slides got detached from each other the weight require to detach the patch from buccal mucosa of goat gave the measure of bio-adhesive strength. Force of adhesion (N) = Bio-adhesive strength/1000*9.81 Bond strength (Nm-2) = Force of adhesion/Surface area.

Conclusion

Buccal patches of Salbutamol using polymers like HPMC K15 and CP 974 in various proportions and combinations showed satisfactory Physico-mechanical and muco adhesive characteristics[20]. The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release from these formulated Salbutamol buccal patches. From the present investigation, it can be concluded that such buccal patches of Bisoprolol Fumarate may provide sustained buccal delivery for prolonged periods in the management of hypertension, which can be a good way to bypass the extensive hepatic First-pass metabolism.

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Source of support: Nil
Conflict of interest: None Declared