International Journal of Pharma Sciences
Vol. 8, No. 6 (2018): 1975-1980
Research Article
Open Access

ISSN: 2320-6810

Formulation and Evaluation of Nicotine Buccal Patches

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Received: 10 November 2018 Accepted: 01 December 2018 Online: 04 December 2018

ABSTRACT

Nicotine is the primary component of tobacco, and it has a number of complex and sometimes unpredictable effects on the brain. It is recognized as one of the most frequently used addictive drugs, and it is very important for tobacco users to quit (1). Nicotine can cross biological membranes, and once absorbed, it is metabolized extensively in the liver into a number of major and minor metabolites. However, buccal drug delivery offers unique and compelling benefits because it overcomes the first pass effect of the liver (6–10). One of the major challenges associated with buccal drug delivery is retention of the formulation at the mucosa. The buccal route has been used for many years to deliver drugs, which undergo first-pass metabolism. The buccal route has a relatively robust mucosa, has the advantage of allowing excellent accessibility, and reasonable patient compliance. From the present research work that is development and evaluation of Nicotine patches for buccal drug delivery using polymers such as xanthan gum, Guar gum, and karaya gum. There was no drug-excipients interaction between the drug and excipients used in the formulation.The drug was distributed throughout the patch uniformly. More than 99 % of the drug was released from all the formulation F9 at the end of 12th hrs. From the result and conclusion of the research work we can summarize that Nicotine can be delivered via buccal route.

Keywords: Buccal Drug Delivery, Nicotine, xanthan gum, Guar gum, and karaya gum.

1. INTRODUCTION

Oral administration of pharmaceutical compositions has some drawbacks. For instance, it is difficult to keep the medicament at the desired location so that it can be absorbed, distributed and metabolized easily. Accordingly, there has been much interest in the use of the mucosal lining of body cavities. Regions in the oral cavity where effective drug delivery can be achieved are buccal, sublingual, palatal and gingival. Buccal and sublingual sectors are the most commonly used routes for drug delivery and they may be used for the treatment of local or systemic diseases. The permeability of the oral mucosa is probably related to the physical characteristics of the tissues[1]. The buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of controlled-release system which is well accepted by patients. The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. The buccal mucosa is relatively permeable, robust in comparison to the other mucosal tissues and is more tolerant to potential allergens which have a reduced tendency to irreversible irritation or damage. So, it has been largely investigate as a potential site for controlled drug delivery in various chronic systemic therapies. However, salivary production and composition may contribute to chemical modification of certain drugs. Moreover; involuntary swallowing can result in drug loss from the site of absorption. Furthermore, constant salivary scavenging within the oral cavity makes it very difficult for dosage forms to be retained for an extended period of time in order to facilitate absorption in this site. The relatively small absorption area and the barrier property of the buccal mucosa contribute to the inherent limitations of this delivery route[2]. Both the buccal and sublingual membranes offer advantages over other routes for administration. For example, drugs administered through the buccal and sublingual routes have a rapid onset of action and improved bioavailability of certain drugs. These routes can bypass the first-pass effect and exposure of the drugs to the gastrointestinal fluids. Additional advantages include easy access to the membrane sites so that

the delivery system can be applied, localized, and removed easily. Further, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity. The palatal mucosa is intermediate in thickness and keratinized thus lessening its permeability. All of these epithelia are coated with a layer of mucus[3]. Bioadhesive polymer can significantly improve the performance of many drugs, as they are having prolonged contact time with these tissues. These patient compliance controlled drug delivery products have improved drug bioavailability at suitable cost. Drug selection for oral transmucosal delivery is limited by the physicochemical properties of the drugs themselves. To be delivered transmucosally, drugs must have unique physicochemical properties, i.e. a proper balance between solubility and lipophilicity. Generally only a few milligrams of drug can cross the oral mucosa, even if the drug has a favourable profile for oral mucosal delivery[4].Since the early 1980s there has been renewed interest in the use of bioadhesive polymers to prolong contact time in the various mucosal routes of drug administration. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. Drug absorption through a mucosal surface is efficient because mucosal surfaces are usually rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation by gastrointestinal enzymes and first pass hepatic metabolism[5].

Drug Delivery Via Oral Cavity

The oral cavity can be used for local and systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism, or for the administration of proteins and peptides (Amir et al., 2001). The two main-routes for administration with oral cavity are:

- Sublingual route
- Buccal route.

Drug Delivery via Sublingual Route

Sublingual administration implies systemic administration of drugs via the membranes that line the floor of the mouth and ventral surface of the tongue. A rapidly dissolving tablet is generally given by the sublingual route (Amir et al., 2001). The sublingual region suffers with one major drawback. The two major salivary glands (submandibular and sublingual glands) open their ducts in sublingual area to release saliva. There is constant flushing of saliva in this region because of which it is difficult to retain drugs and delivery system and build or maintain high concentration of drug, in the sublingual region.

Drug delivery via buccal route

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva[6].

Buccal Dosage Forms

Buccal Dosage forms are meant to be placed between gingiva and cheek.

Conventional Dosage Form

The conventional type of buccal dosage forms are buccal tablets, troches and lozenges, and mouth washers.

Advanced Buccal Dosage Forms

The novel type buccal dosage forms include buccal adhesive tablets, patches, films, tapes, semisolids (ointments and gels) and powders.

a. Mucoadhesive Tablets
b. Patches, Tapes & Films
c. Semisolid Preparations (Ointments and Gels)
d. Powders

Advantages of Bucco Mucoadhesive Systems[7]:

Drug administration via the oral mucosa offers several advantages:

- Ease of administration.
- Termination of therapy is easy.
- Permits localization of the drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients.
- Drugs, which show poor bioavailability via the oral route, can be administered conveniently.
- It offers a passive system for drug absorption and does not require any activation.

LIMITATIONS OF MUCOADHESIVE BUCCAL DELIVERY:

Drug administration via this route has certain limitations:

- Drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour, cannot be administered by this route.
- Drugs, which are unstable at buccal pH, cannot be administered by this route.
- Only drugs with small dose requirement can be administered.
- Drug contained in the swallowed saliva follows the peroral route and advantages of buccal route are lost.

2. MATERIALS AND METHODS

Materials

Nicotine procured by Cipla Pvt. Ltd., Mumbai. Xanthan gum, Guar gum, were purchased from Loba Chemical Pvt. Ltd., Mumbai., Karaya gum and Propylene glycol were purchased from Astra Zeneca Pvt. Ltd., Bangalore and other excipients were procured from Rankem-Mumbai, Otto Chemicals, Mumbai, Narmada chemicals, Hyderabad respectively.

Preparation of Backing Layer:
For preparing a formulation, a glass petri plate of 7.5 cm diameter was used as a casting surface. Initially, backing membrane of ethyl cellulose was fabricated by slowly pouring a solution containing 450 mg of ethyl cellulose and 4 drops Propylene glycol in 10 ml Dichloromethane and Methanol (1:1) to the glass petri plate and air dried for 9 hrs are given in Table-1.

Table 1: Formulation of backing layer

Ethyl cellulose(mg)	450
Propylene glycol	4 drops
Dichloromethane: Methanol(ml) 1:1	10

Table 2: Formulation of Nicotine Buccal Patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicotine	25	25	25	25	25	25	25	25	25
Guar gum (mg)	150	250	300	-	-	-	-	-	-
Xanthan gum(mg)	-	-	-	150	250	300	-	-	-
Karaya Gum (mg)	-	-	-	-	-	-	-	-	300
Propylene glycol	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
Aspartame(mg)	6	6	6	6	6	6	6	6	6
Benzalkonium chloride	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
DCM:Methanol(ml)	15	15	15	15	15	15	15	15	15

Preparation of Nicotine buccal patches (Incorporation of drug):
The calculated amount of Nicotine was incorporated in the polymeric solutions of different concentrations of (xanthan gum, guar gum, karaya gum) by using DCM:Methanol in 1:1 ratio after levigation with 30 % propylene glycol and then the permeation enhancer and sweetening agent were added. The solution was casted onto preformed ethylcellulose baking layer then kept in hot air oven at 40°C for 24 hrs (or at room temperature). The patches thus formed were cut into size of 10 mm diameter. Each patch contains 25 mg of Nicotine. The detailed compositions of the Nicotine patches are given in Table-2.

Evaluation of patches
The Nicotine buccal patches were evaluated for the following properties:

Physical properties
a) Physical appearance and surface texture of patch:

This parameter was checked simply with visual inspection of patches and evaluation of texture by feel or touch.

b) Weight uniformity of patches[8]:
Three patches of the size 10 mm diameter were weighed individually using digital balance and the average weights were calculated.

c) Thickness of patches[9]:
Thickness of the patches was measured using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at three different spots of the patches and average was taken.

d) Folding endurance of patches[10]:
The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding (10 mm) patches at the same place till it broke. The number of times patches could be folded at the same place, without breaking gives the value of folding endurance.

e) Swelling index of patches[11]:
The swelling index of the patches was determined by immersing preweighed patch of size 10 mm in 50 ml water. The patches were taken out carefully at 5, 10 upto 30 min. intervals, blotted with filter paper and weighed accurately.

f) Surface pH of patches[12]:
Surface pH was determined by the patches were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of patches and allowing equilibrate for 1 min.

2. Mechanical properties
a) Tensile strength of patches[13]:
Tensile strength of the patch was determined with digital tensile strength tester (Tinius-Olsen). The sensitivity range of the machine is 1-10 Newton's. It consists of two load cell grips. The lower one was fixed and upper one was movable. The test patch of size (1x4 cm2) was fixed between these cell grips and force was

applied till it breaks. The tensile strength of the patch was directly taken from the dial reading in Newton's, which was converted into kilogram.

3. Evaluation of Nicotine buccal patches

a) Drug content uniformity study of patches[14]:

The patches were tested for drug content uniformity by UV-Spectrophotometric method. Patches of 10 mm diameter were cut from three different places from the casted patches. Each patch was placed in 100 ml volumetric flask and dissolved in pH 6.8 phosphate buffer and 0.2 ml is taken and diluted with pH 6.8 phosphate buffer upto 10 ml. The absorbance of the solution was measured at 259 nm using UV/visible spectrophotometer (PG Instruments T60). The percentage drug content was determined using the standard graph and the same procedure was repeated for three patches.

b) *In-vitro* drug release of patches[15]:

In-vitro release studies were carried out by attaching sigma dialysis membrane to one end of the open cylinder which acted as donor compartment prepared buccal patches containing drug was placed inside donor compartment which is agitated continuously using magnetic stirrer and then temperature was maintained at 37 ± 1ºC. Receptor compartment consist of 100 ml of pH 6.8 phosphate buffer, sample of 2 ml were withdrawn at periodic intervals from receptor compartment and replaced with fresh pH 6.8 phosphate buffer immediately, and drug release was analyzed spectrophotometrically at 259 nm. Release rate was studied for all prepared formulations.

3. RESULTS AND DISCUSSION

Determination of Nicotine λ-max:

Determination of Nicotine λ-max was done in 6.8 ph buffer for accurate quantitative assessment of drug dissolution rate. The Nicotine peak value is 259. The linearity was found to be in the range of 2-12 µg/ml in 6.8 pH buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

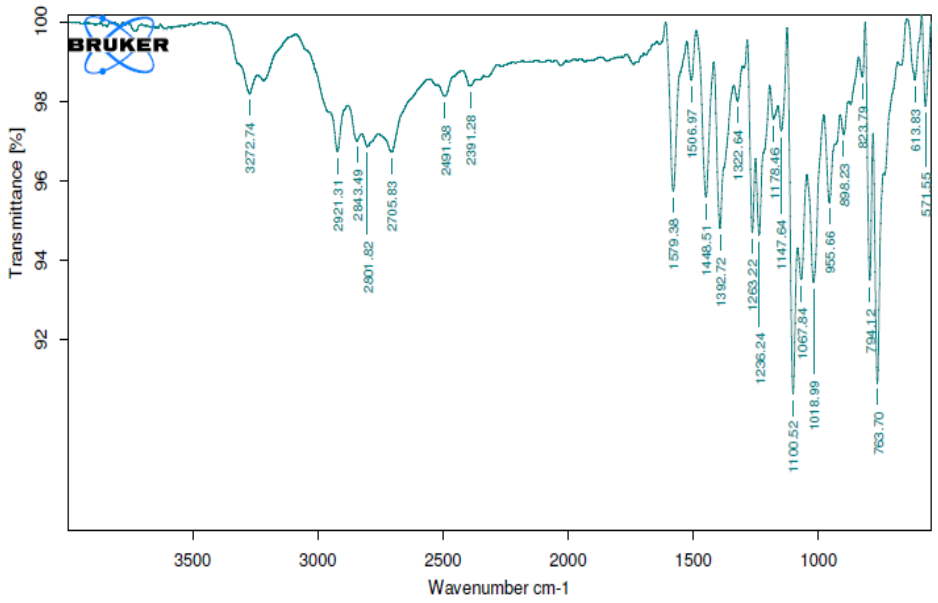
Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

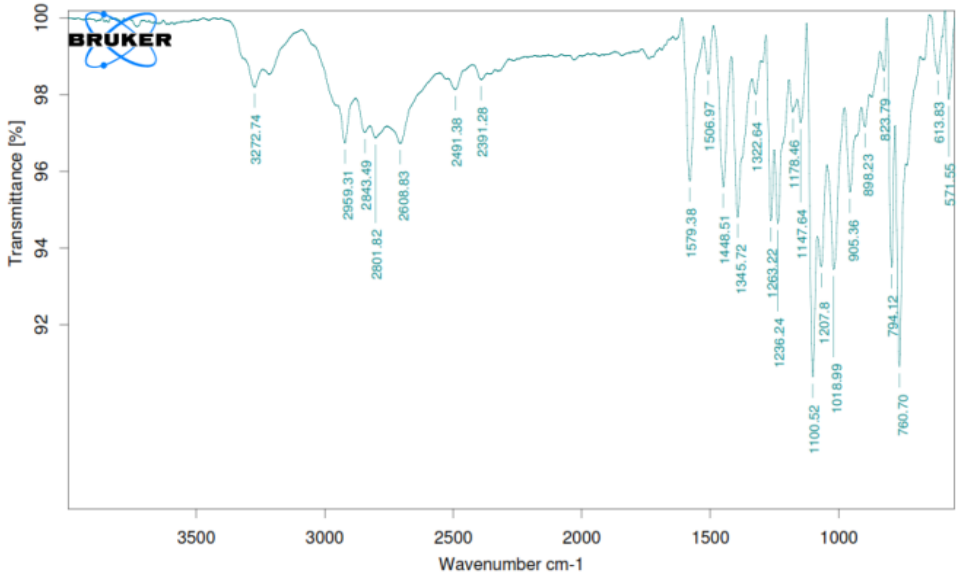
Evaluation of Physical Parameters of compressed tablets of Nitrendipine:

From the result of various evaluation parameters, we can summarize:

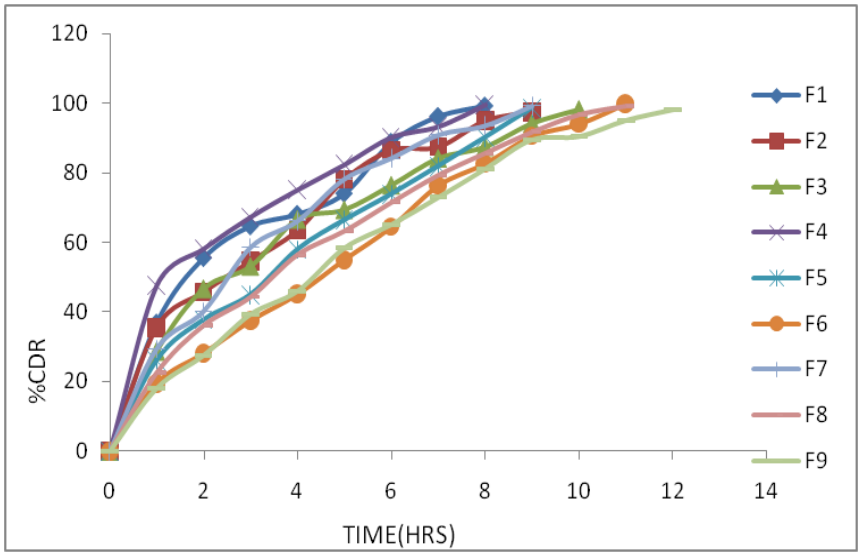
1. The patches prepared were checked visually for its appearance and surface texture. All the prepared patches were of smooth surface and elegant texture.
2. All the prepared patches using different concentration of various polymers are weighing in between 150 to 300 mg.
3. The patches show thickness values in between 0.38 to 0.52 mm.
4. The patches show folding endurance values in between 190 to 258
5. The patches show swelling index values in between 29.93 to 48.16 %
6. Similarly surface pH of all the patches prepared is ranging in between 6.2 to 6.8 pH.
7. The tensile strength of all the patches prepared is ranging in between 4.52 to 6.35 Kg/cm2 respectively.
8. The FTIR studies indicate that Nicotine showed complete entrapment within the polymer carrier bonding is suggested and there were no chemical interaction.
9. Similarly, the patches are also subjected to drug content uniformity study and it lies in between 855.20to 95.42 %, which suggest that uniform dispersion throughout the buccal patches.
10. The detailed *in-vitro* drug release data were plotted between percent drug released from the formulation and time. The present study indicates a good potential of erodible mucoadhesive buccal patches containing Nicotine for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The result of the present study shows that therapeutic levels of Nicotine can be delivered buccally. It may be concluded that the formulations F9 shows promising controlled drug release. Finally the *in-vitro* drug release study was carried out for all the patches and release profile were subjected to various kinetic equations like Higuchi diffusion equation and Peppas exponential equation. The regression coefficient values of this kinetic equation are very nearer to one (1) suggesting that plots are fairly linear and slope values of the Peppas equation is (>1) suggest that drug was released by diffusion mechanism following super case II transport.



FTIR Spectra of Nicotine (pure drug)



FTIR Spectra of optimized formulation



Percentage Drug Release of F1-F9

4. CONCLUSION

From the evaluation studies it can be concluded that Nicotine can be delivered in the form of buccal patches. Release pattern of drug from these patches can be altered by using different formulation variables.

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