Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(10):122-127
(http://derpharmachemica.com/archive.html)

Mini-review and Comparative Study: Preparation and Evaluation of Nicotine-loaded Buccal Mucoadhesive Tablets/films designed for Smoking Cessation

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ABSTRACT

Smoking is a major cause of cardiovascular diseases, respiratory diseases and cancer. Despite the high prevalence of smokers worldwide, smokers are often neglected and not offered effective assistance with quitting their habits. In order to overcome this public health burden, effective treatment is needed to help smokers stop smoking. Nicotine replacement therapy is a way of getting nicotine into bloodstream without smoking. A number of smoking cessation dosage forms have led to increases in quitting and thus to significant benefits to public health. Nicotine buccal mucoadhesive dosage forms designed for smoking cessation have the advantage of not requiring chewing accompanied with high bioavailability. This review covered all the previous pharmaceutical preparation and evaluation of nicotine-loaded buccal mucoadhesive tablets/films since 2002 to 2016. The present concise review can be used as a guide for those who are interested in design and evaluation of a new buccal mucoadhesive nicotine formulation.

INTRODUCTION

Nicotine, (S) -3- [1-methylpyrrolidin-2-yl] pyridine (figure 1) is an alkaloid found in cigarettes. The aim of nicotine mucoadhesive formulations is to replace nicotine from cigarettes to reduce motivation to smoke and nicotine withdrawal symptoms, thus easing the transition from cigarette smoking to complete abstinence [1-3]. Different methods for preparation and evaluation of nicotine buccal mucoadhesive dosage forms are described in (table 1). Nicotine hydrogen tartrate, a crystalline powder, allows the formulation of tablets by simple dry blending and direct compression. It is extremely stable compared with nicotine base. At salivary pH there is good conversion of nicotine hydrogen tartrate to nicotine, which is readily absorbable by oral mucosal membranes. When administered orally, nicotine is subjected to extensive first pass metabolism by the liver resulting in a bioavailability of less than 20%. Therefore, nicotine replacement therapy products are preferably formulated to deliver nicotine to the systemic circulation via routes that avoid hepatic first pass metabolism.

Among the oral drug delivery routes, the mucus membrane of the mouth has been identified as a potential site for the absorption of drugs. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for drug delivery and has received considerable attention in the last decade [4]. Buccal route is an established route of drug delivery and has a number of advantages when compared with the oral route. These advantages include the avoidance of first pass metabolism, as mentioned above, and the ability to produce a systemic effect with a rapid

onset of action. Additionally, the route provides ready accessibility, reasonable patient acceptance and compliance and the dosage form can be removed at any time [5].

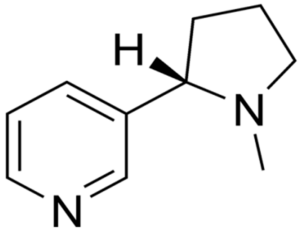

Figure 1: Chemical structure of nicotine

In contrast with the sublingual region, a formulation in situ in the buccal salcus, the area between gum and lip, is exposed to relatively low levels of salivary washout of drug. The buccal salcus is also relatively immobile and avoids contact with the tongue. As a result, the buccal route has been described as the most appropriate mucosa for sustained drug delivery using bioadhesive retentive systems such as buccal tablets [6]. The term 'bioadhesion' has been used to define the attachment of a synthetic or natural macromolecule to a biological tissue for an extended period of time [7]. When a substrate is a mucosal epithelium, a bioadhesive system adheres and interacts primarily with the mucus layer, this phenomenon being referred to as 'mucoadhesion' [7]. Mucosal adhesives are the poly (acrylic acids), which include Carbopol 934® with a p*K*a value of (5.35-7.2) and HPMC [7]. A number of studies have concluded that these polymers produce excellent adhesion to mucosal membranes [8].

Literature review

Table 1: Different preparation methods, and its evaluation, of nicotine buccal mucoadhesive tablets/films

Formulation and its preparation	Evaluation/ observations or results	Remarks/ conclusion
Buccal mucoadhesive chitosan-magnesium aluminum silicate nanocomposite films were prepared using casting/solvent evaporation technique.	**Investigations:** The effects of chitosan-magnesium aluminum silicate ratio on the physicochemical properties, release and permeation, as well as on the mucoadhesive properties, were investigated. Molecular interactions between the components of the film were also investigated. **Results**: The greater the magnesium aluminum silicate ratio in films, the higher the nicotine content that was observed because intercalated nano-composites could be formed by electrostatic interactions. Release and permeation of nicotine were related to the square root of time indicating a diffusion-controlled mechanism.	The developed films have a potential adhesion to the mucosal membrane [9].
Buccal mucoadhesive nicotine hydrogen tartrate films were prepared using 2%, 3%, or 4% hydroxypropylmethylcellulose (HPMC E3 LV or HPMC E5 LV) in the presence of poly ethylene glycol and propylene glycol as plasticizers in different concentrations using solvent casting method.	**Investigations:** The in-vitro dissolution, in-vitro disintegration, tensile strength, folding endurance, and morphology of films were evaluated. **Results:** All formulations prepared using PG as the plasticizer had good appearance, almost 30% of the films prepared using PEG 400 as the plasticizer did not possess good appearance and/or were somewhat sticky to touch. All formulations exhibited essentially similar release patterns, i.e., rapid release during the initial few minutes, followed by a relatively slow release, finally approaching a plateau level in about 10 min. The type and concentration of plasticizer had negligible effect on release from the films. The in-vitro disintegration time of all formulations was greater at high polymer concentration. The tensile strength was found to be directly proportional to polymer concentration and inversely proportional to plasticizer concentration. Films prepared using HPMC E5 LV resulted in higher folding endurance while higher plasticizer concentration exhibited.	Fast dissolving films is a promising therapy to provide relief for nicotine craving [10].
Buccal mucoadhesive tablets were prepared using different conventional bioadhesive polymers such as HPMC50cps, NaCMC, and carbapol934 in singular or mixture form; magnesium hydroxide as the pH increasing agent; magnesium stearate as the lubricant; and lactose as the diluents & filler of different products of nicotine hydrogen tartrate, which is more stable than the nicotine using direct compression method.	**Investigations:** Degree of adhesion and rate of drug release were evaluated. **Results**: Increasing of HPMC50cps in the formulations decrease release rate of nicotine. The carbapol in formulations beget slow releasing of nicotine. With increasing the percent of lactose, the rate of release in formulations was increased. Formulations which have HPMC 50cps has best adhesiveness. Formulations contain carbapol had not suitable adhesiveness. Formulations contains NaCMC showed very fast release and had not suitable adhesiveness.	The formulation contains mixture of HPMC50cps and Cp934 showed suitable adhesive-ness and minimum fluctuation in release [11].

Buccal mucoadhesive tablets containing sodium alginate and nicotine-magnesium aluminum silicate complexes were prepared using direct compression method.	**Investigations:** The effects of the preparation pH levels and the complex/ sodium alginate ratios on release, permeation across mucosa, and mucoadhesive properties of the tablets were investigated. **Results:** Measurement of unidirectional release and permeation across porcine esophageal mucosa using a modified USP dissolution apparatus 2 showed that nicotine delivery was controlled by the swollen gel matrix of the tablets. Tablets prepared at pH 9 showed remarkably higher permeation rates than those containing the complexes prepared at acidic and neutral pH levels. Larger amounts of sodium alginate in the tablets decreased release and permeation rates. Additionally, the presence of sodium alginate could enhance the mucoadhesive properties of the tablets.	Sodium alginate plays important role not only in controlling release but also in enhancing the mucoadhesive properties of the complex [12].
Buccal mucoadhesive films were prepared using sodium alginate - magnesium aluminum silicate dispersions at different pHs using homogenizer-dispersion method.	**Investigations:** The physicochemical properties, nicotine content, in vitro bioadhesive property, release and permeation of the developed films were investigated. **Results**: Incorporation of nicotine into Sodium alginate - magnesium aluminum silicate dispersions changed particle size and flow behavior. Surface morphology of the NCT-loaded SA films prepared at pH 10 showed a smooth surface. While a rough surface was observed on the NCT-loaded SA-MAS films. The NCT-loaded SA films showed an amorphous with a broad peak MAS powder showed a distinct diffraction peak which represented basal spacing of MAS of 1.4 nm. The SA-MAS films showed similar basal spacing peak with MAS whereas this peak was shifted in NCT loaded SA-MAS films prepared at various pHs. Incorporation of NCT into the SA films prepared at pH 10 shifted the characteristic exothermic peak of SA to a lower temperature. Broad endothermic peak of NCT was not observed in thermo-gram of the NCT-loaded SA films. Release and permeation could be described using a matrix diffusion controlled mechanism.	The films prepared at pH 5 yielded the highest nicotine content due to non-significant loss during drying. Moreover, pH of the preparation also affected the crystallinity and thermal properties of the films [13].
Buccal mucoadhesive nicotine hydrogen tartrate tablets were developed using chitosan and carbomer at different ratios. Magnesium hydroxide was incorporated into the formulations as pH increasing agent by direct compression.	**Investigations:** In vitro release and bioadhesion properties were investigated. **Results:** Release of nicotine hydrogen tartrate from the tablets was increased with increasing amount of chitosan in formulations whilst the bioadhesion of tablet was decreased. In vivo studies were carried out in non-smoker volunteers in comparison to a commercially available transdermal patch.	No significant difference was found between the maximum plasma nicotine concentrations obtained with the mucoadhesive tablet and the reported transdermal patch [14].
Three types of buccal mucoadhesive tablets were developed each containing two mucoadhesive components (HPMC, K4M and sodium alginate), (HPMC, K4M and carbopol) (Chitosan and sodium alginate). For each of these types, batches were produced changing the quantity of polymers resulting in nine different formulations by direct compression method.	**Investigations:** The tablets were evaluated for release pattern, and mucoadhesive performance. Pharmacokinetic studies were conducted in smokers. **Results:** polymers having high molecular weight and high viscosity exhibited higher adhesion with low effect of increasing contact time. The release rate of nicotine decreased with increasing concentration of HPMC and with decreasing concentration of alginate while the presence of carbopol resulting in increasing nicotine release.in case of chitosan/sodium alginate; tablets having higher alginate content showed faster release than those with low alginate content. A peak plasma concentration of 16.78 ± 2.27 ng was obtained in two hours, which suggests potential clinical utility of the developed tablets	These formulas were able to provide good bioavailability. The impermeable backing layer facilitates unidirectional and controlled release of nicotine. Finally pharmacokinetic results indicate that all formulas are able to continuously deliver nicotine within the mouth to buccal membrane [15].
Buccal mucoadhesive hydrogel tablets with modified release based on polyethylene oxide (molecular weights from 1 × 106 to 8 × 106 D) were prepared by the direct compression method with Cytisin.	**Investigations:** 0.4-cm^2 films containing anabasine (1.5 mg), cytisine (1.5 mg), or their mixture (0.75 mg + 0.75 mg). The effect of these 3 types of films was studied in 281 smokers across 4 different samples. First, a clinical sample of 41 smokers and Second, a sample of 21 healthy smokers received these films for 15 days, Third 18 healthy smokers were treated for 6 to 14 months, Fourth, a sample of 201 smokers, including some psychiatric patients, were treated with these films and followed up after 6 months. **Results:** The carried out technological and biopharmaceutical studies with the model tablets containing Cytisine showed that the including of polyethylene oxide with different molecular weight in different proportion leads to significant decrease in the rate and degree of release of the included drug and thus gives good possibilities for achievement of desired pharmacokinetic release profile.	The polyethylene oxide and its derivatives are suitable carriers in formulation of hydrogel drug releasing systems because of their unique properties, multi-funcionality, lack of toxicity and immunogenesis. Films have positive effect in 75.8% of patients with nicotinism, 46.8% of the patients giving up smoking completely. Films containing cytisine or mixture of cytisine and anabasine are most efficacious [16].
Buccal mucoadhesive tablets were prepared. Carbomer (Carbopol®974P NF) (CP) and alginic acid sodium salt (NaAlg) were used as bioadhesive polymers in combination with hydroxypropyl methylcellulose (HPMC) at different	**Investigations:** in vitro release and bioadhesion studies were performed on the developed tablets. **Results:** in the formulations containing CP: HPMC, the nicotine hydrogen tartrate release increased with the increasing HPMC concentration whereas a decrease was observed with increasing HPMC concentration in formulations containing NaAlg:HPMC.	The developed formulations released nicotine hydrogen tartrate for 8 hours period and remained intact [17].

ratios. Magnesium carbonate was incorporated into the formulations as a pH increasing agent by direct compression method.	The bioadhesive properties of the tablets containing NaAlg:HPMC was not affected by the concentration of NaAlg (P>0.05) but increased significantly with the increasing CP concentration (P<0.05).	
Buccal mucoadhesive tablets containing 0-50% w/w Carbopol 934® and 0-50% w/w hydroxypropylcellulose (HPC) were prepared using PVP binding agent and magnesium stearate as a lubricating agent, Pearlitol® was used as a diluent producing a pleasant cooling sensation in the mouth. The tablets were prepared in two stages, initial light compression followed by second compression cycle using a greater compression force by direct compression.	**Investigations:** Mucoadhesion was assessed using bovine buccal mucosa. **Results:** Peak detachment force of the tablets was found to reach a maximum at 20% w/w Carbopol 934®, whilst work of adhesion continued to increase with Carbopol 934® concentration. HPC concentrations of 20-30% w/w were found to provide nicotine hydrogen tartrate release approaching zero order kinetics over a 4 h test period. A combination of 20% w/w Carbopol 934® and 20% w/w HPC was thus found to provide suitable adhesion and controlled drug release.	The formulation of a bilayer tablet containing the adhesive controlled release layer and a fast releasing layer provided an initial burst release followed by controlled release for a period of up to 4 hours [18].

Table 2: Compositions of various mucoadhesive tablets/films

Ingredient	Function
Chitosan	Ionic polymer
HPMC	Non-ionic bioadhesive polymers as film former for buccal delivery systems
NaCMC	Ionic bioadhesive polymers
Carbapol934/Carbopol®974P	Non-ionic bioadhesive polymers
Sodium alginate	Charged anionic bioadhesive polymers
Magnesium aluminum silicate	Mixture of natural montmorillonite and saponite clays, reduce NCT volatilization during film preparation resulting in slower drug release
Lactose	Diluents & filler
Magnesium stearate	Lubricant
Magnesium carbonate	pH increasing agent
Magnesium hydroxide	pH increasing agent
PVP	Binding agent
Pearlitol®	Diluent/cooling sensation agent
Polyethylene oxide	Bio-soluble bio-absorbable polymer

***In vivo* Nicotine release using buccal tablets**

Nicotine release from some formulations was calculated using HPLC analytical method. Bilayer tablets were consisted of (controlled release) CRL formulation C (that contains lowest amount of sprayed lactose) combined with a (fast release) FRL containing 5 mg nicotine hydrogen tartrate. Each bilayer tablet contained a total of 15 mg of nicotine hydrogen tartrate. A bilayer tablet was weighed and the theoretical nicotine hydrogen tartrate content of the tablet was calculated. The bilayer tablet was then inserted in the buccal salcus of the volunteer with the CRL in contact with the upper gum in the region of the canine tooth. The FRL was, therefore, in contact with the buccal membrane (lining of the cheek). The length of time that the tablet remained in-situ was varied each day ranging from 0.5 to 4 h. A fresh tablet was inserted each day and a minimum period of 24 h was allowed between insertions [18].

Volunteers were asked to refrain from eating and to drink only water. At the stated time, the buccal tablet was removed and placed in a vial containing a citrate/phosphate HPLC buffer solution, detailed below. The residual nicotine content of the tablets was analyzed using an HPLC analytical method in which precision was assessed by calculating the regression statistics from three point calibration lines, within 1 day and on 5 consecutive days. The results varied by 1% (relative standard deviation) R.S.D. (within day) and by 2.5% R.S.D. (day to- day) proving the precision of the method. The *in vivo* study showed that the 5 mg of nicotine hydrogen tartrate from the FRL was released in approximately 30 min. This was thought to be due to the slight abrasion of the FRL surface by the buccal mucosa. There after nicotine hydrogen tartrate release occurred from the CRL and between 1 and 4 h was almost linear ($r2=0.98$) (nicotine hydrogen tartrate release about 6.2% h−1 or 0.32 mg h−1 of nicotine base) [18].

***In vivo* Nicotine release using buccal film**

Many *in vivo* release studies of buccal films were carried out in human healthy volunteers by applying the film in the lower side of the buccal cavity. The saliva was collected periodically and analyzed for the amount of drug released [19, 20 and 21]. Nafee et al. have assessed the in vivo release of miconazole from the buccal patches in five healthy human volunteers by placing the patches on the buccal mucosa between the cheek and gingiva in the region of the upper canine with slight pressure for 30 s. The amount of drug release was determined by collecting the saliva at regular intervals [22].

Drug absorption studies of buccal dosage forms

Bioavailability of many formulated buccal dosage forms was carried out in both animal models and human. Both direct and indirect methods were reported in the literature in assessing the drug absorption. In one attempt, the

absorption of metoprolol from the buccal patches was carried out in rabbits by placing the patch to the buccal section of the oral cavity and applying gentle pressure with a finger for 1 min. The blood samples were collected from the ear vein and the various pharmacokinetic parameters were determined [23]. Similarly, the absorption of carvedilol and testosterone following buccal administration of the prepared films was assessed in rabbit model [24-25]. Alternatively, Lala et al. have assessed the drug absorption from the ketorolac buccal films in Sprague–Dawley rats [26]. Formulated film (0.5 cm × 0.5 cm) was applied to the buccal cavity bilaterally under light ether anesthesia and the blood samples were collected at regular intervals. On the other hand, an indirect method has also been designed and used to assess the absorption of drug from solution using dog as model. Briefly, a small perfusion chamber is attached to the upper lip of anesthetized dogs and the drug solution is circulated through the device.

The absorption of nicotine was found to be faster from the oral mucosa when compared to the absorption from skin even though the ratio of the amount of nicotine in the tablet and the transdermal patch was 1: 5.5. The C_{max} values obtained with both delivery systems were found to be similar. This is a very important result as faster absorption of nicotine is a desirable situation in replacement therapy for acute relief of craving. Several studies have been reported on the development of buccal bioadhesive tablet formulation for nicotine delivery [27-28]. When compared to the sublingual tablet, a higher AUC value was with one tablet which contained nicotine. The higher AUC values obtained with the buccal tablet indicates that rapid dilution with saliva and swallowing of nicotine before absorption from the oral cavity was avoided [14].

Evaluation of nicotine formulation (*in vivo*) by sensitive determination of nicotine in plasma

Many HPLC/UPLC-UV methods [29-39] were reported for determination of nicotine in human plasma and they are suitable for further pharmacological studies while design of new nicotine formulations. Furthermore, the reported methods may be used to investigate the pharmacokinetic parameters *in vivo* in comparative studies using another dosage forms or cigarettes. The authors are going through future work include preparation and *in vivo* evaluation of new nicotine dosage form and they will use this review as a guide for their work. C_{18} was the most common column in the literature and it was selected by the authors for their future investigation as cyano column failed to give satisfactory validation parameters for analysis of nicotine and its internal standard in the preliminary investigations in spite of its successful use by the same authors with sharp peaks for the analysis of many pharmaceutical formulations [40-43]. UPLC methods are preferable than HPLC, with many associated advantages such as that UPLC operates at much higher pressure. This ultra-pressure ensures the advantages of improved resolution and fewer consumables. One of the key advantages is the resolution, as demonstrated by the peak shape. HPLC typically produces broad peaks that skilled operators can characterize very well, including peak heights and peak widths. Another important advantage is a faster run time. The significant reduction in solvent use is another important advantage of UPLC [44]. Some methods for nicotine analysis in the literature included spiking technique in which nicotine was spiked onto the sample so that the total nicotine content after spiking was twice the amount prior to spiking [45] similar to the common well established spiking technique that commonly used in spiking pharmaceutical formulations [46]. The use of spiking sample enrichment technique may be applicable to nicotine analysis in plasma to increase the sample concentration up to the level which can be measured using the ultraviolet detector instead of the high cost mass detector.

CONCLUSION

The evaluation of formulation in general plays a key role during the formulation development; however, the method which has been employed is more critical. Hence the availability of a proper evaluation method can assist in developing a successful formulation. Several in vitro, ex vivo and in vivo methods have been employed for the evaluation of the buccal films & tablets. The most crucial characterization of the buccal films & tablets is their mucoadhesive property, which is evaluated by the residence time or the mucoadhesive studies. In vivo studies have also been successfully employed to assess the mucoadhesive potential of this dosage form. Further, routine tests such as the in vitro drug release and ex vivo permeation are carried out during the formulation development stage which provides an indication of the efficiency of the proposed buccal films & tablets. The in vivo studies are carried out in animal models or human. These bilayer buccal adhesive formulas demonstrate possible advantages over the use of other nicotine preparations such as gums and patches. These findings suggest that the nicotine-loaded films & tablets show strong potential for use as a buccal drug delivery system.

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