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Research Paper

A novel tri-layered buccal mucoadhesive patch for drug delivery: assessment of nicotine delivery

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Abstract

Objectives The aim of this study was to assess the potential of a novel delivery device for administering drugs that suffer from a high degree of first-pass metabolism.

Methods A tri-layered buccal mucoadhesive patch, comprising a medicated dry tablet adhered to a mucoadhesive film, was prepared and characterized by its physicochemical properties and mucoadhesive strength. Nicotine was used as a model drug for the characterization of drug release and drug permeation. The influence of different adsorbents on the release of nicotine base from the patches was evaluated *in vitro*. Different molecular forms of nicotine (base and complex salt) were evaluated for their effect on release performance and permeation *in vitro*.

Key findings Results demonstrated acceptable physicochemical and mucoadhesive properties for the tri-layered patch. Rapid release of nicotine was observed when nicotine base was incorporated with calcium sulfate dihydrate as the adsorbent. Patches incorporating nicotine base showed distinct advantages over those containing nicotine polacrilex, in terms of drug release (complete drug release achieved at 30 *vs* 60 min) and transmucosal permeation (37.28 ± 4.25 *vs* $2.87 \pm 0.26\%$ of the dose permeating through mucosa within 120 min).

Conclusions The novel tri-layered patch can effectively adhere to, and deliver an active ingredient through the buccal mucosa, confirming its potential for buccal mucoadhesive drug delivery.

Keywords buccal mucoadhesive drug delivery; mucoadhesive patch; nicotine base; nicotine replacement therapy; nicotine polacrilex

Introduction

Buccal mucoadhesive drug delivery offers unique advantages for the systemic delivery of conventional drugs as well as biological entities such as peptides and proteins.[1] The buccal site offers some favourable properties as a site for drug delivery, such as a relatively large area for drug administration, reduced enzymatic activity, and direct access to the systemic circulation by avoiding the harsh gastrointestinal environment and the hepatic first-pass effect.[1–3] Devices for buccal mucoadhesive drug delivery have used various designs but usually require dispersion of the active ingredient into the mucoadhesive matrix.[4,5] Drug is dissolved in a polymer solution, cast and dried to form patches or mixed with polymers and compressed into tablets. The major limitation of this incorporation technique is delayed drug release, because polymers have to hydrate to allow drug to diffuse through the swollen polymer matrix to reach the mucosal surface.[4–7] Moreover, the applicability to a wide range of drugs may be complicated by the interaction between each drug molecule and the polymer matrix when a solvent casting technique is used in the preparation. Therefore, the development of an improved buccal mucoadhesive device to overcome the inherent problems of traditional devices would represent a significant contribution to the field of buccal drug delivery. The aim of this study was to evaluate a novel patch in which the drug itself is incorporated into a small dry tablet that is adhered to a mucoadhesive patch comprised of a mucoadhesive layer and a water-impermeable backing layer. The patch was required to have desirable physicochemical and mucoadhesive properties, and drug release and permeation kinetics. Nicotine was incorporated into the patch and was assessed as a potential alternative product for nicotine replacement therapy.

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Patches prepared by adsorbing nicotine base to different excipients were investigated for the influence of the adsorbent on the release behaviour. Patches prepared with ionized or non-ionized forms of nicotine were compared for their release and permeation properties. In-vitro swelling, mucoadhesion, drug release and transmucosal permeation assessments were performed to predict the in-vivo performance.

Materials and Methods

Materials

Nicotine base, hypromellose (HPMC 2910), calcium sulfate dihydrate ($CaSO_4 \cdot 2H_2O$), calcium phosphate ($Ca_3(PO_4)_2$), light magnesium oxide (MgO), β-cyclodextrin and dibutyl sebacate were purchased from Sigma-Aldrich Pty Ltd (Castle Hill, NSW, Australia). Nicotine polacrilex was purchased from Shaanxi Tianze Biological Technology Co. Ltd (Shaanxi, China). Carbopol 934P was a gift from Lubrizol (Wickliffe, OH, USA). Acetonitrile (high-performance liquid chromatography (HPLC) grade) was purchased from BioLab Ltd (Scoresby, Victoria, Australia). Krebs bicarbonate ringer (KBR) buffer (pH 7.4) was prepared with 115.5 mM NaCl, 4.2 mM KCl, 21.9 mM $NaHCO_3$, 12.2 mM glucose, 4.0 mM HEPES, 1.2 mM $MgSO_4 \cdot 7H_2O$, 2.5 mM $CaCl_2 \cdot 2H_2O$ and 1.6 mM $NaH_2PO_4 \cdot 2H_2O$. Milli-Q water was obtained from a Milli-Q purification system (Millipore Australia Pty Ltd, North Ryde, NSW, Australia). All other chemicals were of analytical grade and were used as received.

Design and preparation of nicotine tri-layered buccal mucoadhesive patch

The tri-layered patch consists of a medicated tablet bound to a bi-layered mucoadhesive patch (Figure 1). The two components were prepared separately and the final formulation incorporating nicotine base (TPNB) or nicotine polacrilex (TPNP) was prepared by direct manual attachment of the medicated tablet to the mucoadhesive layer with the aid of ethanol as a moistening agent.

Preparation of the bi-layered mucoadhesive patch

The mucoadhesive layer of the bi-layered patch was prepared by dissolving polymers in appropriate solvents and drying the polymer solution on glass plates in an oven. The solution was obtained by dissolving 4.6% (w/v) polymers (Carbopol 934P / HPMC 2910 10 : 1.5) and 1.6% (v/v) plasticizer (PEG 300) in 60% ethanol solution under overhead stirring at 600 rev/min for 30 min. For the ethylcellulose layer, 5% (w/w) ethylcellulose ethanol solution with different ratios of plasticizer (dibutyl sebacate, 0.2, 0.33, 0.4, 0.6, 0.8 and 1.0% w/v) was sprayed via a nozzle onto one side of the mucoadhesive layer (approx. 2 µl/cm^2) and allowed to dry. The patch was then cut with a circular punch (diameter 20 mm) and stored in airtight containers until required.

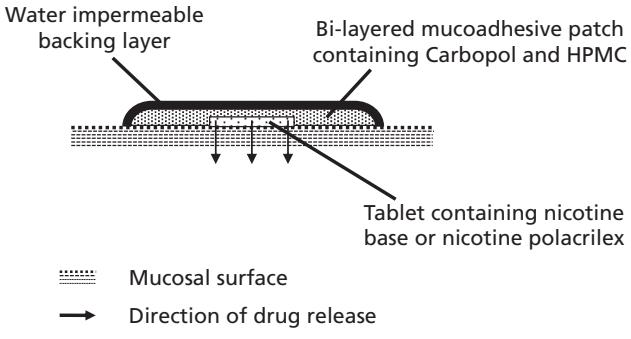

Figure 1 Tri-layered nicotine buccal mucoadhesive patch adhered to the mucosal surface. Diagram is not drawn to scale.

Preparation of the medicated tablet

For the medicated tablet, drug and excipients were mixed homogenously and then compressed in a 7-mm diameter die, using a Korsch XP-1 tablet press (Korsch AG, Berlin Germany). Prior to the preparation of tablets containing 2 mg of nicotine base per tablet, nicotine was adsorbed to a solid adsorbent ($CaSO_4 \cdot 2H_2O$, $Ca_3(PO_4)_2$, MgO, or β-cyclodextrin) by mixing the nicotine base with the solid adsorbent. The formulation of the tablet was optimized in a preliminary study showing that adsorbent and nicotine base at a ratio of 1 : 4 (w/w) was sufficient to produce tablets with uniform drug content, and suitable strength and disintegration properties. For the nicotine polacrilex tablet, each tablet contained 8 mg nicotine polacrilex, which is equivalent to 2.4 mg nicotine base.

Determination of the optimum ratio of plasticizer for the ethylcellulose layer

The bi-layered mucoadhesive patch containing different amounts of dibutyl sebacate as described above was swelled on the surface of milli-Q water in a plastic weighing boat. The integrity of the patch including any separation of the mucoadhesive and ethylcellulose layers was noted. A minimum of 2 h before loss of patch integrity or separation of the two layers was required for satisfactory performance.

Animal tissue preparation

Porcine buccal mucosa was prepared for the measurement of mucoadhesive strength and drug permeability. Pig cheek tissue was obtained from a local abattoir within 1 h after slaughter and transported to the laboratory in ice-cold KBR buffer. The mucosal epithelium was carefully separated from the underlying tissues using forceps and surgical scissors, wrapped in aluminium foil and stored at −20°C for up to 1 month until required.[8]

HPLC analysis of nicotine

Analysis of nicotine in diffusion medium was performed after chromatographic separation on a reversed phase Phenomenex Luna 5 µm C18(2) column (150 × 4.6 mm; Phenomenex, Torrance, CA, USA). The HPLC system comprised a chromatography pump and a UV variable wavelength UV-vis detector set to 254 nm. The mobile phase was acetonitrile/water (30 : 70% v/v) and triethylamine (1% v/v), apparent pH 6.8, the flow rate was 1.0 ml/min and the injection volume was 10 µl. Precision of the method was assessed by regression

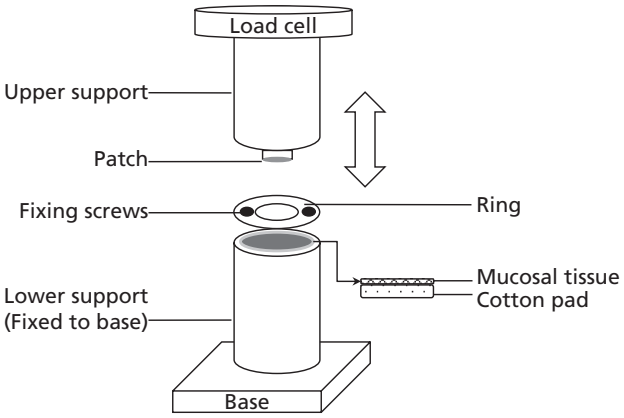

Figure 2 Tensile test jig.

from 6-point calibration lines, within 1 day and on 5 consecutive days. The results varied by 1% RSD (within day) and by 2.5% RSD (day to day).

Ex-vivo measurement of mucoadhesive strength

The tri-layered patch or the bi-layered patch was measured for mucoadhesive strength using a specially designed 2-part jig (Figure 2) connected to a tensile tester.

The jig consisted of a lower support for the mucosal tissue and an upper support to which the patch was attached using double-sided tape. A cotton pad was fixed to the lower support to provide a cushioning effect for the tissue and a ring was used to secure the tissue in position with two screws. The ring had a circular hole of 20 mm diameter allowing exposure of the tissue for contact with the patch. The upper and lower supports, fixed to the upper probe and the base of the tensile tester, respectively, were aligned to ensure that the patch would come into direct contact with the exposed buccal membrane when the upper support was lowered.

During measurement, the upper support was lowered at a speed of 0.5 mm/s to contact with the tissue at a contact force of 100 N and a contact time of 60 s. It was then withdrawn at a speed of 1.0 mm/s, and the peak detachment force was recorded as the mucoadhesive strength. The measurements were conducted at 20 ± 0.5°C, and all tests were carried out in triplicate.

In-vivo performance of mucoadhesive patches

Human ethics approval for the in-vivo mucoadhesive evaluation of buccal mucoadhesive patches (prepared without nicotine or nicotine base) was obtained from the Human Research Ethics Committee of the University of South Australia. Ten healthy volunteers were recruited and asked to evaluate one bi-layered patch (without tablet attached) and one tri-layered patch (with tablet attached), with at least a 4-h wash-out period between formulations. Subjects were asked to adhere the mucoadhesive patch to their buccal mucosa without moistening by applying a light force with a finger tip for 30 s. After applying the patch correctly, subjects were asked to note the time for complete erosion or detachment of the patch if it happened before 2 h, which was recorded as the retention time and used as the parameter to measure the mucoadhesive properties. Subjects were asked to comment on whether they considered the mucoadhesive patch to be a suitable drug administration device in terms of the extent of irritation and unpleasant feeling.

In-vitro drug release evaluation

Drug release was evaluated using Franz diffusion cells (diffusion area 1.77 cm^2). The patch was clamped between donor and receptor compartments with the medicated tablet facing the receptor compartment with the support of a filter membrane (diameter 22 mm). The receptor compartment (volume 15 ml) was filled with dissolution medium (KBR buffer) and maintained at 37°C with constant stirring by a magnetic stirrer. The cumulative amount of drug reaching the receptor compartment at each time point was determined by removing aliquots (0.1 ml) through the sampling arm and immediately replacing the same volume of dissolution medium. Samples were filtered through Acrodisc syringe filters (0.45-μm Supor membrane; Paul Co. Ltd, Ann Arbor, MI, USA) and analysed by HPLC as described above. TPNB prepared with each adsorbent described previously and TPNP were evaluated, all experiments were conducted with six replicates, and results were expressed as mean ± SD. Drug release from the backing layer side was also investigated, and the patch was placed in position with the ethylcellulose layer facing the receptor compartment.

Ex-vivo drug permeation evaluation

Porcine buccal mucosa was mounted between the donor and receptor cells filled with KBR solution, maintained at 37°C and allowed to equilibrate for 1 h before the permeation study.

In-vitro permeation evaluation of nicotine from aqueous solutions was conducted in Franz diffusion cells (diffusion area 0.64 cm^2). The receptor cells were filled with KBR buffer (5 ml) and maintained at 37°C by continuous magnetic stirring. After tissue equilibration, 0.1 ml of donor cell KBR buffer was removed and replaced with 0.1 ml nicotine solution (2.5, 12.5, 25 mg/ml). Samples (0.07 ml) were removed from the sampling arm at fixed intervals over 4 h and replaced with fresh KBR buffer (0.07 ml). The cumulative amount of drug reaching the receptor compartment was determined, from which the steady-state flux (J_s) was calculated using Equation 1:

$$J_s = dQ / Adt \quad (1)$$

Where dQ is the amount of drug permeated through the mucosa during time dt and A is the diffusional area.

All experiments were conducted with six replicates. The transmucosal flux was plotted against the donor nicotine concentration.

Nicotine permeability of TPNB and TPNP was evaluated in the same manner as the drug release evaluation except the mucosa was used in substitution for the filter membrane. Experiments were conducted with six replicates and the

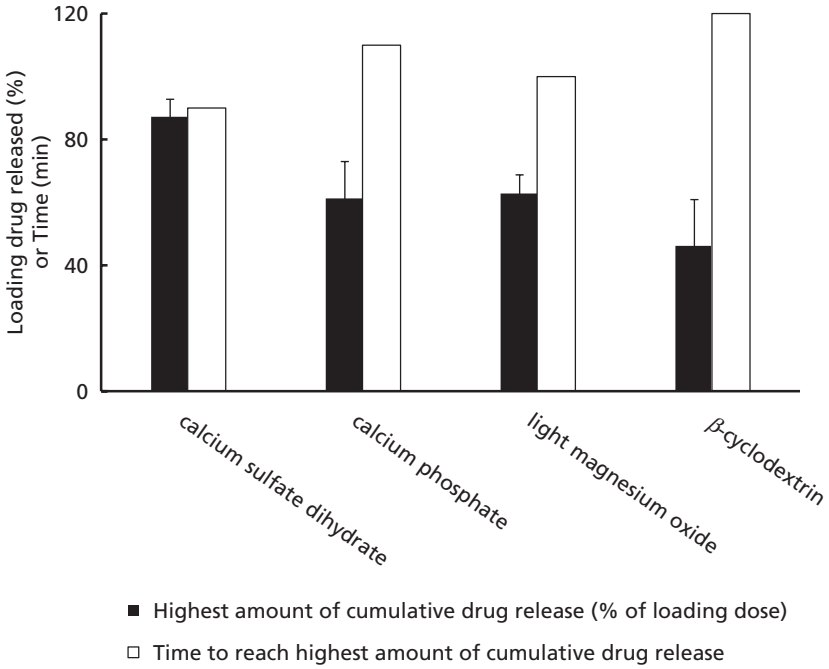

Figure 3 Effect of adsorbents on drug release from tri-layered patch containing nicotine base (TPNB).

fraction of the initial dose moving through the mucosa was plotted against time.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 17 for Windows (SPSS Inc, Chicago, IL, USA). Data were transformed and *t*-tests were performed to determine the *P* value. A *P* value of ≤0.05 was considered to be statistically significant.

Results

Preparation of nicotine tri-layered buccal mucoadhesive patch

Patch integrity during the 120-min swelling evaluation was achieved when 0.4% dibutyl sebacate was added for the preparation of the ethylcellulose layer, while separation of the ethylcellulose layer from the mucoadhesive layer occurred when less than 0.4% of dibutyl sebacate was included. Patch dimensions were specified with consistent diameter and thickness. Drug content uniformity was achieved and each patch (using $CaSO_4 \cdot 2H_2O$ as the adsorbent) contained 2.03 ± 0.07 mg nicotine base. No significant difference was observed for ex-vivo mucoadhesive strength between the bi-layered and the tri-layered patches ($P > 0.05$), which was 89.92 ± 3.12 N and 84.61 ± 0.74 N, respectively. Furthermore, the ten subjects evaluated in the in-vivo performance of the patches commented that the patches could remain in the human buccal cavity for at least 2 h without any fragmentation, the patches could be easily removed after 2 h and the administration did not cause any irritation or unpleasant feeling.

Assessment of in-vitro drug release

With the TPNB formulations, the adsorbents appeared to affect the drug release with faster and more complete drug release achieved when $CaSO_4 \cdot 2H_2O$ was used ($P \leq 0.05$, Figure 3).

A significant difference between TPNB and TPNP was observed in the early stages of drug release (Figure 4). For TPNB, more than 30% of the loading dose was released at 5 min, 78.84 ± 4.55% at 20 min, and 83.82 ± 4.00% at 30 min. While the drug release for TPNP was 54.84 ± 9.96% at 20 min and 68.76 ± 7.74% at 30 min. Drug release from TPNB was complete within 40 min, which was 20 min earlier than that from TPNP (Figure 4).

Assessment of ex-vivo drug permeation

By calculating the transmucosal flux of nicotine aqueous solutions, a linear relationship was observed between the flux and the donor nicotine concentration ($R^2 = 0.998$, Figure 5).

Figure 6 shows a significant difference in the transmucosal permeability between TPNB and TPNP. For patches loaded with nicotine base (TPNB), nearly 40% permeated through the mucosa after 2 h, compared with less than 3% with the nicotine polacrilex patches (Figure 6). The permeation of nicotine from TPNB demonstrated a fast-to-slow behaviour, with the transmucosal flux of nicotine decreased from approximately 0.010 mg/cm^2·min for the first 30 min to 0.002 mg/cm^2·min over the latter 90 min.

Discussion

The drug release profile required of a buccal mucoadhesive drug delivery system depends on the intended application of the device. Traditional buccal mucoadhesive patches are

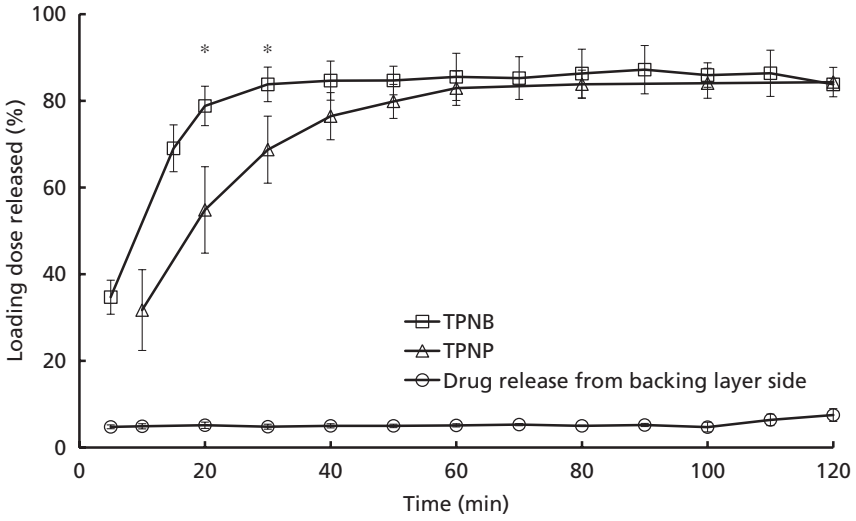

Figure 4 Release of nicotine from tri-layered patch containing nicotine base (TPNB) or nicotine polacrilex (TPNP) and release of nicotine from the backing layer side of TPNB. $*P \leq 0.05$, significantly different compared with TPNP.

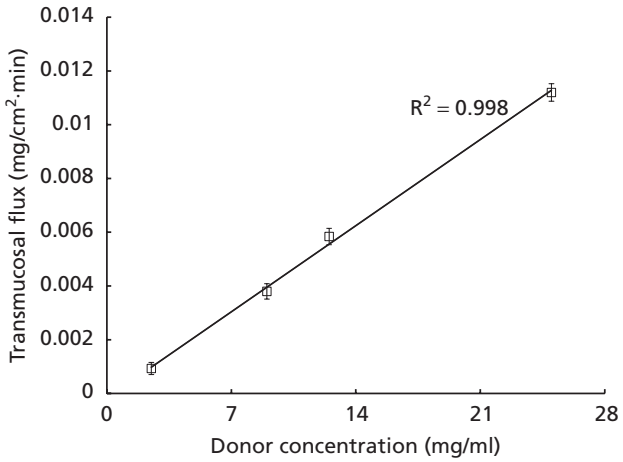

Figure 5 Relationship between the nicotine transmucosal flux and the initial concentration of nicotine aqueous solution in the donor compartment.

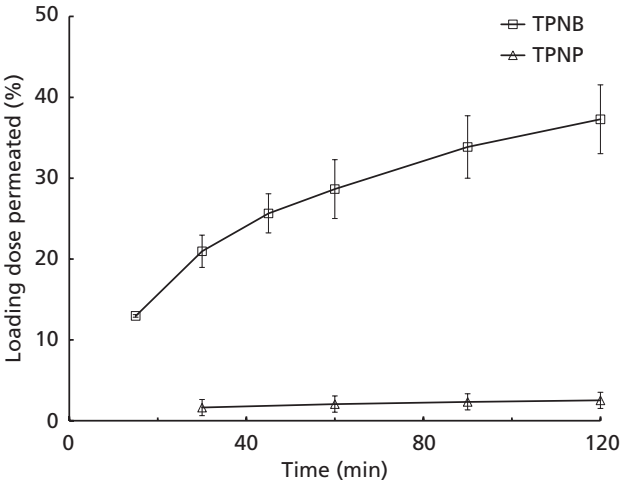

Figure 6 Nicotine permeated through the buccal mucosa from TPNB and TPNP (as a percentage of loading dose).

commonly reported to exhibit delayed drug release,[4,5] which limits their application when a rapid onset of therapeutic effect is required, such as in nicotine replacement therapy. The tri-layered patch provided rapid release of nicotine onto the mucosal surface. The rapid drug release is advantageous as it generates a high permeation gradient across the membrane and resulted in high initial drug permeation followed by a more sustained period of slow permeation. This permeation pattern can be considered desirable for nicotine replacement therapy, whereby rapid permeation is required to provide the initial relief of nicotine craving and the sustained permeation is necessary for prolonged relief from craving.[9–11]

Mucoadhesion is an important strategy to improve drug efficacy by retaining the drug in the buccal cavity for longer. The interaction that occurs between mucus and the mucoadhesive polymers is a result of entanglement of polymer chains with the mucus network.[1,12] The length and flexibility of the polymer chains are dominant factors for mucoadhesive strength,[13] but incorporating a drug within the mucoadhesive matrix is known to influence the structure of the polymer chains and affect the mucoadhesive properties.[14] Perez-Marcos *et al*.[15] reported that the release of propranolol hydrochloride from matrix tablets containing HPMC and Carbopol was largely dominated by the polymer composition. In the case of the tri-layered patch, the inclusion of a small medicated tablet in direct contact with the mucosa was found to not compromise mucoadhesive strength, and it is theoretically possible to modify the composition of the tablet without the need to redevelop the patch for each drug molecule.

Results of the studies on mucoadhesive strength and in-vivo performance showed that the tri-layered patch can provide prolonged retention at the buccal site without any direct irritation. Moreover, the drug release data showed unidirectional drug release, which suggests that applying the

patches to the buccal mucosa will not produce an undesirable nicotine taste.[5,6] As such, the new tri-layered patch, consisting of a medicated dry tablet bound to a mucoadhesive film, could be considered as a platform technology for the systemic delivery of a wide range of drugs via buccal mucoadhesive drug delivery.

Both non-ionized and ionized nicotine forms have been used as active compounds in the development of nicotine replacement therapy products, but there is little commentary on the rationale for the selection of the different molecular forms. An ionized form of nicotine, such as nicotine polacrilex, is usually preferred because of its solid state and higher stability under normal storage conditions, whereas nicotine base is normally considered to be undesirable for manufacturing due to the highly volatile liquid nature.[16] However, results in terms of drug release and drug permeation obtained by the in-vitro evaluations performed in this study, suggest that there are distinct advantages of using nicotine base rather than nicotine polacrilex in achieving more rapid release and higher transmucosal permeability. The problems normally associated with the high volatility of nicotine base were resolved by adsorbing it to calcium sulfate dihydrate prior to incorporation into the dry tablet.

Conclusions

This study describes a novel tri-layered buccal mucoadhesive patch, consisting of a thin dry tablet and a bi-layered mucoadhesive film. The drug incorporation technique, where the active ingredient is incorporated in the tablet, could avoid many of the inherent problems associated with traditional buccal mucoadhesive devices. The tri-layered patch prepared in this study could provide a platform technology for the systemic delivery of a wide range of drugs due to the physicochemical and mucoadhesive properties. Applying the tri-layered patch to nicotine delivery could provide products with rapid initial drug release and fast-to-slow permeation. Nicotine base was found to be more advantageous than nicotine polacrilex as the active agent for nicotine replacement therapy, with more rapid drug release and higher permeation, while the volatility issue was resolved by the use of calcium sulfate dihydrate as an adsorbent.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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