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# Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy

Calum R. Park *, Dale L. Munday

*School of Pharmacy, The Robert Gordon University, Schoolhill, Aberdeen AB10 1FR, UK*

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**Abstract**

Bilayer nicotine mucoadhesive tablets were prepared and evaluated to determine the suitability of the formulation as a nicotine replacement product to aid in smoking cessation. A range of formulations containing 0–50% w/w Carbopol 934® and 0–50% w/w hydroxypropylcellulose (HPC) were prepared and tested for adhesive properties and drug release. Mucoadhesion was assessed using bovine buccal mucosa. 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 (NHT) 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 (CRL) and a fast releasing layer provided an initial burst release of NHT followed by the controlled release for a period of up to 4 h. The same biphasic type of release was identified during an in vivo assessment using human volunteers This biphasic drug release could represent an improvement over current methods of nicotine replacement. © 2002 Published by Elsevier Science B.V.

*Keywords:* Nicotine; Nicotine replacement therapy; Buccal tablets; Bioadhesion; Controlled release

## 1. Introduction

Despite the well-publicised risks of tobacco use, cigarette smoking continues to be the leading preventable cause of death in Europe and the United States (Haxby, 1995; Ashvall, 1997). In the United Kingdom alone, smoking causes more than 120 000 deaths annually (Department of Health, 1998; Raw et al., 1999). The treatment of smoking related diseases costs the National Health Service in excess of £1.5 billion each year (Parrot et al., 1998). Today, between 28 and 32% of adults aged 16 or over continue to smoke cigarettes (Department of Health, 1998).

To assist smokers in abstinence from tobacco, nicotine replacement therapy (NRT) is available and can double smoking cessation rates at 6–12 months compared with placebo (Silagy et al., 1999). A range of formulations are available and may be classified by the rate at which nicotine is delivered. Type A products such as nicotine gum

* Corresponding author. Tel.: +44-1224-262-532; fax: 44-1224-262-555.

*E-mail address:* c.park@rgu.ac.uk (C.R. Park).

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deliver nicotine quickly in an attempt to satisfy initial cravings. Type B products such as patches deliver nicotine slowly to produce a constant level of nicotine in the bloodstream so as to suppress the need for tobacco smoke inhalation over a longer period. Recent research has suggested that a combination approach to NRT using a type A product (inhaler) and a type B product (patch) produces significantly greater cessation rates than the type A product alone (Bohadana et al., 2000).

When administered orally, nicotine is subject to extensive first pass metabolism by the liver resulting in a bioavailability of less than 20%. Therefore, NRT products are preferably formulated to deliver nicotine to the systemic circulation via routes that avoid hepatic first pass metabolism.

Drug delivery via the 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 (De Vries et al., 1991; Smart, 1993; Miyazaki et al., 1994; Parodi et al., 1996).

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 (Shojaei, 1998).

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 (Peppas and Buri, 1985; Mortazvi, 1995). 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' (Mortazvi, 1995). Mucosal adhesive materials have been identified and investigated in previous work (Smart et al., 1984). Some of the most widely studied mucosal adhesives are the poly(acrylic acids), which include Carbopol 934®, (structure; $(-CH_2CHCOOH)_n$) with a $pK_a$ value of between 5.35 and 7.2 (Mortazvi, 1995). A number of studies have concluded that these polymers produce excellent adhesion to mucosal membranes (Smart et al., 1984; Duchene et al., 1988; Smart, 1991, 1993).

The aim of the present study was to produce and evaluate a bilayer buccal adhesive nicotine tablet providing a drug release pattern combining the type A (fast release) and type B (prolonged release) approaches to NRT. A combination of these approaches may present an improvement over current NRT therapies and result in improved smoking cessation rates.

## 2. Materials and methods

### 2.1. Materials

Nicotine hydrogen tartrate (NHT), hydroxypropylcellulose (HPC) and mucin (type II crude) were obtained from Sigma (St. Louis, MO). The adhesive polymer Carbopol 934® (C934) was purchased from B.F. Goodrich (Cleveland, OH). Particle size analysis of NHT, HPC and C934 was performed using a Malvern Mastersizer S (Malvern Instruments, Worcs, UK). The mean particle sizes were; NHT 74.24 μm, HPC 419.59 μm and C934 4.01 μm. Pearlitol®, a directly compressible form of mannitol, was obtained from Roquette (Lestrem, France). Pearlitol® was used as a diluent and has the benefit of producing a pleasant cooling sensation in the mouth. Spray dried lactose was included as a diluent and was purchased from Thornton and Ross (Huddersfield, UK). Polyvinylpyrolidone (PVP) was used as a binding agent and magnesium stearate as a lubricating agent. Both were obtained from B.D.H. (Poole, U.K.).

### 2.2. Rationale for using nicotine hydrogen tartrate (NHT)

NHT, a crystalline powder, was used in the study to allow the formulation of tablets by sim-

ple dry blending and direct compression. This approach is not easily possible using pure basic nicotine, a liquid alkaloid. NHT is also beneficial as it is extremely stable compared with nicotine base, which is known to be highly unstable and difficult to contain in coventional packaging materials (Place et al., 1992). At salivary pH there is good conversion of NHT to unprotonated nicotine, which is readily absorbable by oral mucosal membranes (Place et al., 1992).

Table 1
Composition of nicotine buccal adhesive CRL for adhesion testing, expressed as mg per tablet

| Ingredient | Formulation | | | | | |
|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI |
| NHT | 10 | 10 | 10 | 10 | 10 | 10 |
| PVP (44 000) | 6 | 6 | 6 | 6 | 6 | 6 |
| C934 | – | 10 | 20 | 30 | 40 | 50 |
| HPC | 20 | 20 | 20 | 20 | 20 | 20 |
| SDL | 63 | 53 | 43 | 33 | 23 | 13 |
| MGS | 1 | 1 | 1 | 1 | 1 | 1 |

NHT, nicotine hydrogen tartrate; PVP, polyvinylpyrolidone; C934, Carbopol 934®; HPC, hydroxypropylcellulose; SDL, spray dried lactose; MGS, magnesium stearate.

Table 2
Composition of nicotine buccal adhesive CRL for dissolution testing, expressed as mg per tablet

| Ingredient | Formulation | | | | | |
|---|---|---|---|---|---|---|
| | A | B | C | D | E | F |
| NHT | 10 | 10 | 10 | 10 | 10 | 10 |
| PVP (44 000) | 6 | 6 | 6 | 6 | 6 | 6 |
| C934 | 20 | 20 | 20 | 20 | 20 | 20 |
| HPC | – | 10 | 20 | 30 | 40 | 50 |
| SDL | 63 | 53 | 43 | 33 | 23 | 13 |
| MGS | 1 | 1 | 1 | 1 | 1 | 1 |

NHT, nicotine hydrogen tartrate, PVP, polyvinylpyrolidone, C934, Carbopol 934®, HPC, hydroxypropylcellulose, SDL, spray dried lactose, MGS, magnesium stearate.

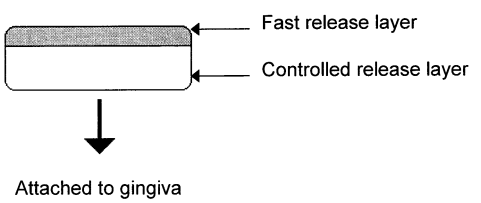


Fig. 1. Diagrammatic representation of a bilayer nicotine buccal adhesive tablet.

### 2.3. Tablet preparation

The compositions of the controlled release layers (CRL's) for adhesion testing and for dissolution testing are shown in Tables 1 and 2, respectively. All powdered excipients were mixed for 5 min using a mortar and pestle to form an homogenous directly compressible powder mix.

Bilayer tablets were prepared in two stages. Initially, 100 mg CRL containing 10 mg NHT was lightly compressed using a single-punch tablet press (Manesty F3, Liverpool, UK) and 6 mm diameter flat punches. Following light compression of the CRL, the bottom punch was lowered and 50 mg of the fast release layer (FRL) powder mixture was added, covering the CRL, and a second compression cycle using a greater compression force was carried out. The FRL contained either 2 or 5 mg of NHT, 4 mg of PVP (molecular weight 10 000) and Pearlitol® to 50 mg. Tablet crushing strength was measured using a tablet hardness tester (model TBH 28, Erweka, Heusenstamm, Germany) and found to range from 156 to 184 N, the average value was 158 N $\pm$ 11.8% relative standard deviation (R.S.D.).

A diagram of a bilayer tablet (6 mm in diameter and 4.5 mm in height) is shown in Fig. 1.

### 2.4. In vitro determination of bioadhesive performance

Adhesive testing of the CRL was carried out using a texture analyser with a 5 kg load cell (TA-XT2i, Stable Micro Systems, Surrey, UK). The method used was based on the method described by Tobyn et al., 1997. Texture analysis is a useful tool and has been extensively used as a valid means for mechanical characterisation of pharmaceutical mucoadhesive dosage forms (Eouani et al., 2001).

Bovine buccal mucosa was used as the buccal mucosal surface. Bovine cheeks were collected immediately after slaughter of the animals and were rapidly frozen ( − 20 °C). Before testing, a bovine cheek complete with buccal mucosal membrane was defrosted at room temperature. The cheek was then placed on the base of the texture analyser with the buccal membrane facing upward. Tests showed there was no significant difference ($P > 0.05$, Student's $t$-test) in adhesion results from defrosted buccal mucosa and fresh mucosa used within an hour of animal slaughter ($n = 5$). A CRL was attached to the base of an aluminium probe (using double-sided adhesive tape) fixed to the mobile arm of the texture analyser. The area of contact on the mucosa was moistened with 50 μl of a mucin solution (type II crude). The CRL was lowered at a rate of 0.1 mm $s^{-1}$ until contact with the buccal mucosa was made. A contact force of 0.5 N was maintained for 120 s, after which the probe was withdrawn from the buccal membrane at a rate of 5 mm $s^{-1}$. The peak detachment force (N) and the work of adhesion (area under the force/distance curve in mJ) was recorded. Day to day precision was determined by repeat measurement ($n = 5$, formulation III) of peak detachment force and work of adhesion on 5 consecutive days. There was no significant difference in the adhesion results on any of the days ($P > 0.05$, Student's $t$-test). Peak detachment force (N ± S.D.) results on each of the days were: $0.20 \pm 0.04$, $0.17 \pm 0.03$, $0.15 \pm 0.03$, $0.18 \pm 0.04$ and $0.192 \pm 0.03$. Work of adhesion (mJ ± S.D.) results were: $0.96 \pm 0.14$, $0.97 \pm 0.19$, $0.97 \pm 0.11$, $1.09 \pm 0.21$ and $1.12 \pm 0.35$.

### 2.5. In vitro nicotine release

Dissolution testing was initially carried out to investigate the effect of HPC on NHT release. The rate of NHT release from the CRL's and bilayer tablets was investigated using USP (XXI) apparatus IV. Three tablets from each batch were weighed and the theoretical nicotine content calculated. The tablets were placed separately in a 20 ml cell in the flow through dissolution tester. The dissolution medium was distilled water supplied at a flow rate of 100 ml $h^{-1}$ by a peristaltic pump (model 202u, Watson–Marlow, Falmouth, UK) and at 37 ± 0.5 °C from an electric water heater (model W14, Grant Instruments, Cambridge, UK). Upon exposure to aqueous fluid, NHT dissociates to form tartrate ions and nicotine (Place et al. 1992). The effluent from the cells was collected over a 4 h period and assayed for nicotine at certain time intervals using U.V. detection at 259 nm (model UV 300, Unicam LTD, Cambridge, UK). Using callabration curves NHT release could be easily calculated.

### 2.6. In vivo nicotine release

The Grampian Research Ethics Committee, Grampian Health Board, Aberdeen, granted ethical approval for the study. Five volunteers were recruited for the study. All volunteers were habitual cigarette smokers ( > 20 per day), at least 18 years of age, with no history of drug or alcohol abuse and none were receiving treatment with any other medication.

Bilayer tablets were manufactured as described above and consisted of CRL formulation C (Table 2) combined with a FRL containing 5 mg NHT. Each bilayer tablet contained a total of 15 mg of NHT. A bilayer tablet was weighed and the theoretical NHT 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. While the tablet was in-situ 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 analysed using an HPLC analytical method described below. A seven-point calibration was

carried out on the morning of each day of the study. Following the determination of the residual NHT content, nicotine release from the formulation was calculated using the theoretical NHT content based on tablet weight.

### 2.7. HPLC analytical method

Chromatographic separation was achieved on a reversed phase $C_{18}$ column. The HPLC system comprised a Jasco (Tokyo, Japan) PU-980 isocratic chromatography pump and a UV-875 variable wavelength UV–vis detector. Quantification of detector response was performed at 260 nm using a Hewlett Packard (Avondale, PA, USA) HP 3395 integrator. A Rheondyne 7125 injection valve (Crotati, CA, USA) fitted with a 20 μl fixed volume loop was used for sample introduction by direct injection. The analytical column used was a $100 \times 4.6$ mm I.D. packed with 3 μm octadecylsilyl-modified silica (ODS-Hypersil, Cheshire, UK). The mobile phase was methanol–citrate phosphate buffer (7.5:92.5% v/v) and triethylamine (0.1% v/v), apparent pH 2.4 and the flow rate was 0.7 ml $min^{-1}$. Precision of the method was assessed by calculating the regression statistics from three point calibration lines, within 1 day ($n = 5$) and on 5 consecutive days. The results varied by 1% R.S.D. (within day) and by 2.5% R.S.D. (day-to-day) proving the precision of the method.

### 2.8. Statistical analysis

Statistical analysis of all relevant data was performed using Student's *t*-tests.

## 3. Results and discussion

### 3.1. In vitro determination of bioadhesive performance

It has been proposed that mucoadhesion occurs in three stages (Duchene et al., 1988). The first stage involves the formation of an intimate contact between the mucoadhesive and the mucus. Secondly, the mucoadhesive macromolecules swell and interpenetrate with the mucus macromolecules, becoming physically entangled. Thirdly, these molecules interact with each other via secondary, non-covalent bonds such as hydrogen bonds.

The formulations used for adhesion tests (I, II, III, IV, V and VI) are shown in Table 1. From Fig. 2 it is evident that the peak detachment force of formulations containing increasing amounts of C934 reaches a maximum at approximately 20% w/w C934. Higher concentrations of C934 do not significantly alter the peak detachment force ($P > 0.05$). Fig. 2 also shows that work of adhesion values increase linearly ($r^2 = 0.98$) with C934 concentration up to 50% w/w. No measurements were carried out at higher concentrations. Peak detachment force is considered to be dependent on the formation of hydrogen bonds between the functional groups of the bioadhesive and the mucus. It is proposed that at 20% w/w C934, the potential for hydrogen bonding reaches a maximum due to saturation of the functional groups at the tablet/mucus interface. Therefore, peak detachment force cannot be increased by addition of more adhesive polymer. The maximum peak detachment force measured at 20% w/w C934 confirms previous work with poly(acrylic acid) containing systems in the literature (Ishida et al., 1983).

Work of adhesion values continue to increase with C934 concentration, which suggests that there are mechanisms other than chemical bonding alone that account for this phenomenon. Ponchel et al., 1987, suggest that the work of adhesion is also dependent on the interpenetration of C934 chains into the mucus. Interpenetration depth is greater at higher concentrations of C934 due to the increased swelling of the polymer. This results in increased physical entanglement, producing a broader force/distance curve and thus increases the work of adhesion values recorded by the texture analyser.

Further tablets similar in composition to formulation III were produced, but excluding the NHT. This NHT-free CRL was similarly tested and the adhesion results compared with those obtained with the NHT-containing formulation

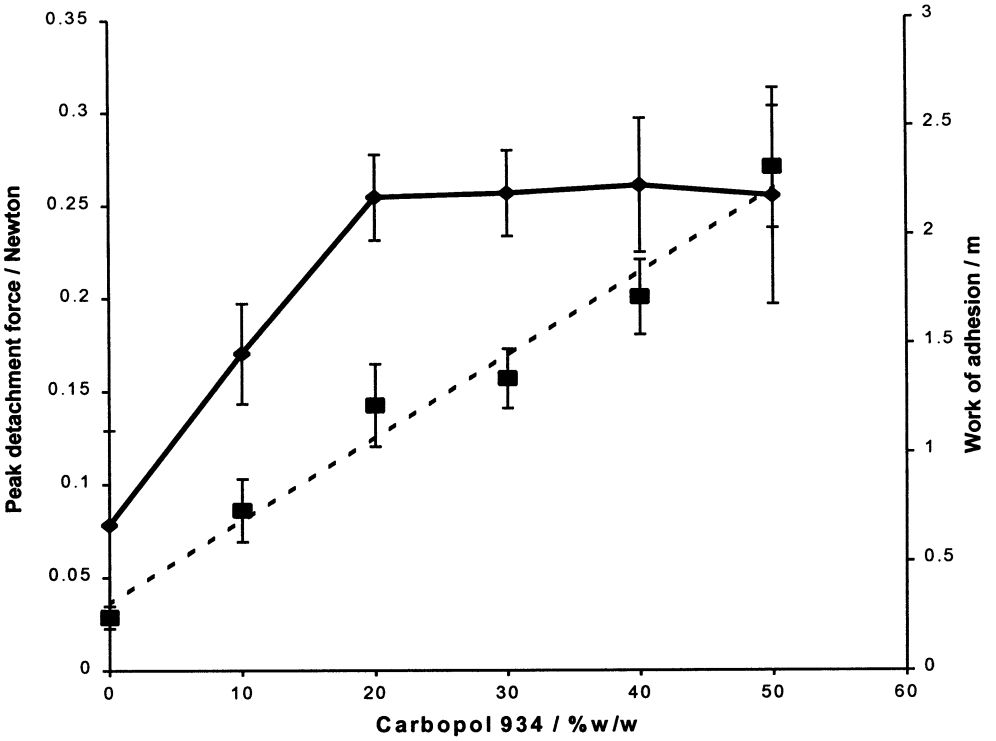


Fig. 2. Peak detachment force (N) and work of adhesion (mJ) versus Carbopol 934 concentration (%w/w) for adhesive CRLs adhering to bovine buccal mucosa ± S.D., $n = 5$. Key: (■) Work of adhesion; (◆) peak detachment force.

III. Statistical analysis found no significant difference in adhesive values between the drug free and the drug containing layers ($P > 0.05$). These results suggest there is no significant interaction between the drug and the polymers responsible for mucoadhesion.

A C934 concentration of 20% w/w was, therefore, used in all further formulations. This selected concentration was based on the peak detachment force results and the fact that this concentration is substantially lower than the 50%w/w proven to cause mucosal irritation in vivo (Bottenberg et al., 1991).

In vitro results are useful to characterise and compare adhesive performance of dosage forms, however, do not necessarily prove the adhesive quality of the formulation in vivo. A bioadhesive study with a formulation containing 20% w/w C934 was carried out in 5 human volunteers and the formulation was found to maintain firm adhesion to the gingiva in all the subjects over the 4 h period.

### 3.2. In vitro nicotine release

Dissolution was first carried out on the CRLs only. Eq. (1), a well known exponential expression, was used to establish the mechanism of drug release from the tablets in vitro (Peppas and Sahlin, 1989).

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where $M_t/M_\infty$ is the fraction of drug released (0.1–0.6), $k$ is the kinetic constant and n is the release exponent describing the mechanism of release. A plot of log $(M_t/M_\infty)$ versus log $t$ gives a straight line of gradient $n$ and intercept log $k$. The data from these plots are presented in Table 3.

All formulations display n values indicative of an anomalous non-Fickian release mechanism ($n = 0.45–0.89$) (Peppas and Sahlin, 1989). This type of drug release is controlled by a combination of polymer swelling, erosion and diffusion through the hydrated matrix. Formulation C ($n = 0.851$) and D ($n = 0.834$) containing 20 and 30% HPC, respectively, show $n$ values approaching Case II transport ($n = 0.89$) i.e. approaching zero order NHT release.

For formulations E and F, containing 40 and 50% HPC, respectively, the $n$ values recede to a certain extent. This suggests the most appropriate matrix for NHT release contains around 20–30% HPC and 20% C934, the combination of which provides release approaching zero or-

Table 3
Mean release exponents ($n$ values) and kinetic constants ($k$) for NHT dissolution from buccal adhesive CRL layers ± S.D., $n = 3$

| Formulation | HPC content /% w/w | Diffusion exponent ($n$) ± S.D. | Kinetic constant per hour ($k$) ± S.D. | Correlation coefficient ± S.D. |
|---|---|---|---|---|
| A | 0 | 0.686 ± 0.080 | 0.252 ± 0.035 | 0.974 ± 0.003 |
| B | 10 | 0.720 ± 0.049 | 0.217 ± 0.016 | 0.987 ± 0.006 |
| C | 20 | 0.851 ± 0.024 | 0.194 ± 0.008 | 0.982 ± 0.008 |
| D | 30 | 0.834 ± 0.044 | 0.185 ± 0.001 | 0.994 ± 0.007 |
| E | 40 | 0.778 ± 0.072 | 0.190 ± 0.007 | 0.976 ± 0.014 |
| F | 50 | 0.777 ± 0.076 | 0.191 ± 0.017 | 0.983 ± 0.004 |

HPC, hydroxypropylcellulose.

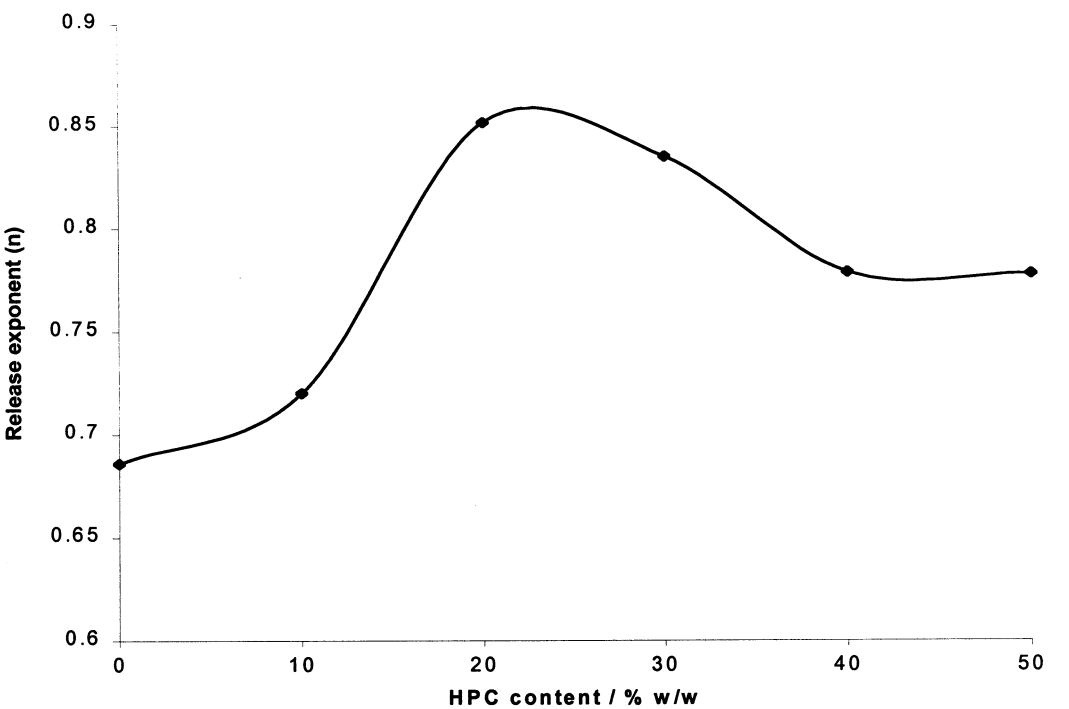


Fig. 3. Effect of HPC concentration (% w/w) on release exponent ($n$) values for adhesive CRLs.

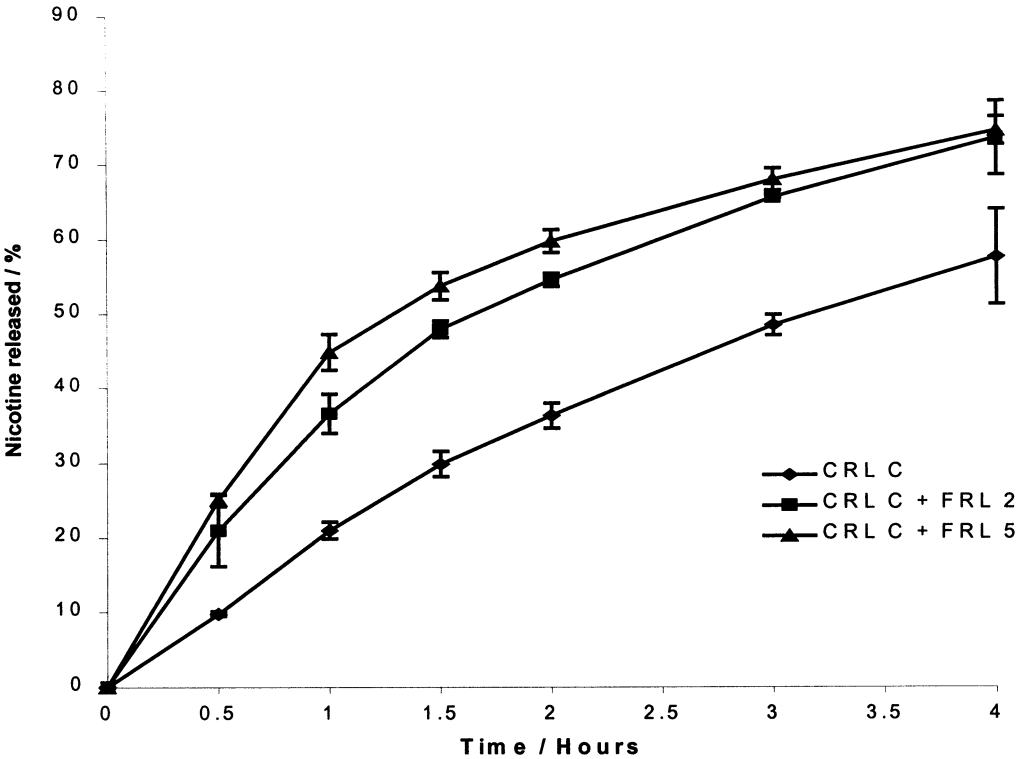


Fig. 4. Percentage of nicotine hydrogen tartate released from mucoadhesive tablets against time (hours) using CRL C with and without a FRL containing either 2 or 5 mg of NHT ± S.D., $n = 3$.

Table 4
Mean release exponents ($n$ values) and kinetic constants ($k$) for CRL C with and without a FRL containing either 2 or 5 mg NHT ± S.D., $n = 3$

| CRL | FRL | Diffusion exponent ($n$) ± S.D. | Kinetic constant per hour ($k$) ± S.D. | Correlation coefficient ± S.D. |
|---|---|---|---|---|
| C | – | 0.851 ± 0.024 | 0.194 ± 0.008 | 0.982 ± 0.008 |
| C | 2 | 0.602 ± 0.084 | 0.344 ± 0.029 | 0.970 ± 0.020 |
| C | 5 | 0.485 ± 0.033 | 0.415 ± 0.026 | 0.932 ± 0.019 |

der. The variation of the release exponent ($n$) with HPC content is portrayed graphically in Fig. 3.

NHT release from bilayer tablets (laminated tablets consisting of a FRL and a CRL) was also investigated. Release profiles for formulation C without a FRL or with a FRL containing either 2 or 5 mg NHT are shown in Fig. 4. The corresponding release exponents ($n$ values) and kinetic constants ($k$ values) are presented in Table 4. These trends noted with formulation C are characteristic for all the formulations listed in Table 2.

As expected, the addition of a FRL provides rapid initial release of NHT. For every tablet batch, the kinetic rate constants ($k$ values) were greatest for the bilayer tablets with FRL's containing 5 mg NHT, decreasing in tablets with FRL's containing 2 mg NHT and decreasing further for the CRL layers alone.

The release exponent ($n$ value) for formulation C approached zero order drug release ($n = 0.89$)

as mentioned above. From Fig. 4 it is evident that the addition of a FRL containing 2 mg NHT results in a dissolution profile with two distinct phases. Initially the slope is steep when rapid NHT release occurs, followed by a more constant NHT release, which is controlled by the CRL. This type of drug release results in lower $n$ values compared with that for the CRL alone. The use of a FRL containing 5 mg NHT provides an even greater degree of initial NHT release as shown by the greater slope of the initial portion of the dissolution profile. The mean n value for the bilayer tablets with the FRL containing 5 mg NHT decreased further. This trend was evident for formulations A–F with and without the FRL.

Rapid release from the FRL's was confirmed by further dissolution studies with more frequent sampling over 1 h. The dissolution over the first hour from bilayer tablets remained constant as the FRL dissolved. The 2 mg FRL dissolved in approximately 30 min (28 min, 8.4% R.S.D.) and the 5 mg FRL in approximately 40 min (43 min, 8.8% R.S.D.). A typical dissolution profile over the first hour for bilayer tablets is shown in Fig. 5.

### 3.3. In vivo nicotine release

The biphasic type NHT release identified during in vitro dissolution testing was also present in the in vivo study and is shown in Fig. 6. The 5 mg of NHT from the FRL was released in approximately 30 min and was faster than during in vitro testing. This was thought to be due to the slight abrasion of the FRL surface by the buccal mucosa. Thereafter NHT release occurred from the CRL and between 1 and 4 h was almost linear ($r^2 = 0.98$) (NHT release about 6.2% $h^{-1}$ or 0.32 mg $h^{-1}$ of nicotine base). The release rate of NHT over this period was slower than during in vitro dissolution test-

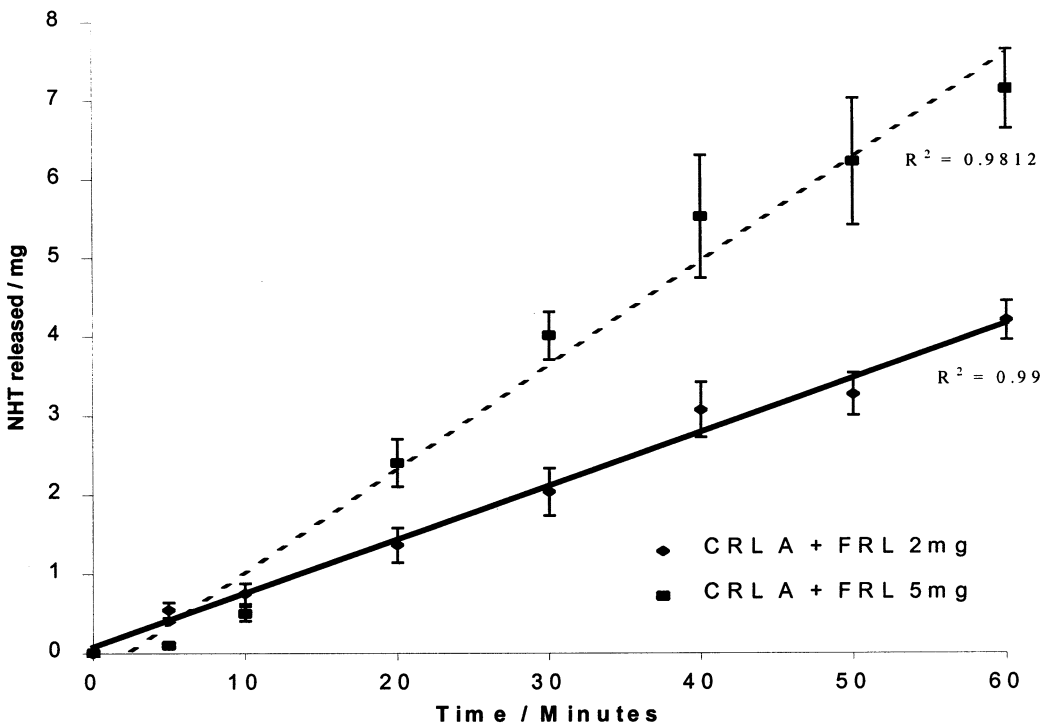


Fig. 5. Nicotine hydrogen tartate released (%) from mucoadhesive tablets against time (minutes), for 1 h, using CRL A with FRL containing either 2 or 5 mg of NHT ± S.D., $n = 3$.

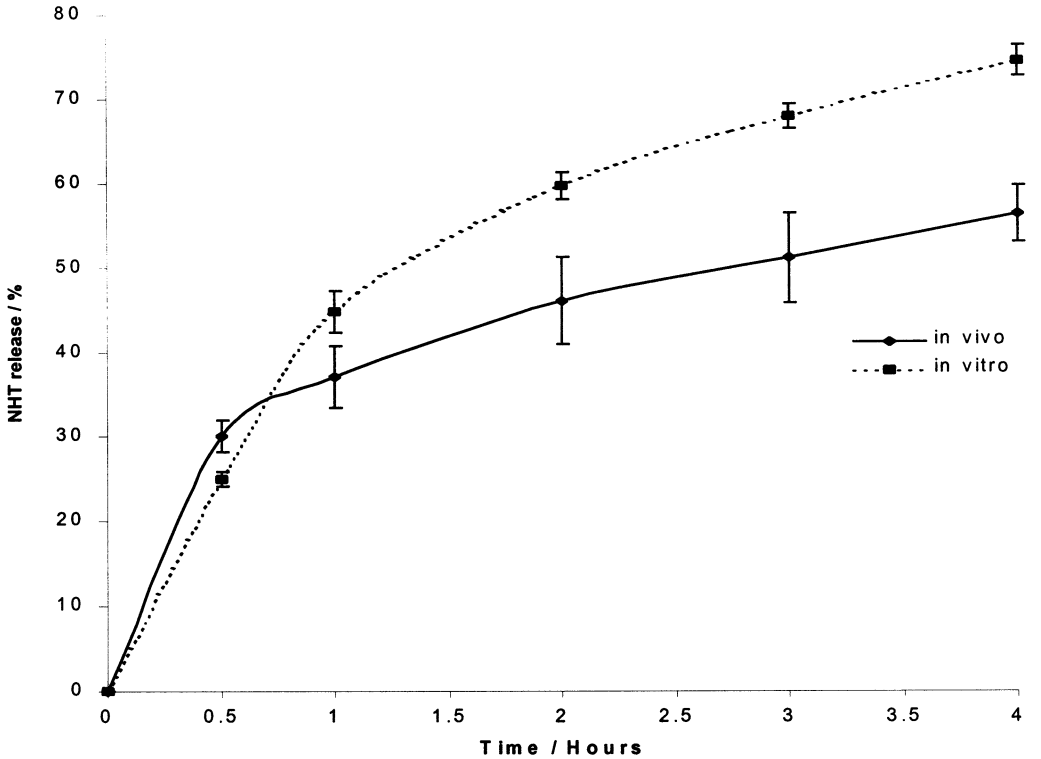


Fig. 6. NHT released (%) with time (hours) from nicotine bilayer tablets consisting CRL C and a FRL containing 5 mg NHT in human volunteers (in vivo) $\pm$ S.D., $n = 5$, and in in vitro dissolution tests $\pm$ S.D., $n = 3$.

ing. This trend was expected due to the comparatively smaller volume of the salivary fluid and the difficulty in producing an in vitro drug release method representative of buccal absorption. Despite these differences, the same biphasic drug release pattern was evident using both methods.

As discussed above, NHT was selected for the formulation due to its excellent stability and ease of formulation. However, when determining the content of NHT, conversion to active nicotine base must be considered. 5 mg of NHT contained in the FRL equate to 1.75 mg of active nicotine base. A study has been carried out using the 2 and 4 mg nicotine gum formulations in human volunteers (Benowitz et al., 1987). In that study, smokers were asked to chew nicotine gum for 20 min, after which the residual nicotine base in the gum was determined. The nicotine absorbed by the chewer was then calculated by subtracting the residual nicotine from the original nicotine content of the gum. Over the 20 min period, $0.85 \pm 0.33$ mg was released from the 2 mg nicotine gum and $1.22 \pm 0.46$ mg from the 4 mg gum ($n = 7$). Using the new bilayer buccal adhesive tablets, $1.58 \pm 0.22$ mg nicotine base was released in 30 min from the FRL. At 20 min this corresponds to 1.05 mg comparing favourably with the nicotine base release from the 2 and 4 mg nicotine gum over the same time period using the same residual assay method. It is assumed that nicotine release will not necessarily equate to the amount of nicotine absorbed due to salivary washout of the drug and to swallowing. This effect should be reduced using the buccal tablet compared with the gum as chewing gum stimulates saliva secretion and the gum is not in contact with the buccal mucosa for the whole 20 min test period. On the other hand, the bilayer buccal tablet re-

mains stationary in the buccal salcus, an area of relatively low salivary washout and is in constant contact with the absorbing buccal membrane.

## 4. Conclusions

Mucoadhesive biphasic buccal tablets containing 20% w/w C934 achieved a maximum peak detachment force in vitro, whereas the work of adhesion continued to increase with increasing polymer concentration. These tablets maintained satisfactory gingival adhesion in human volunteers over a 4 h period.

In vitro dissolution studies demonstrated an initial burst release of NHT from the FRL followed by a slower rate of release from the CRL. Although the release exponents ($n$ values) of all formulations containing the CRL only indicated non-Fickian release, the formulation containing 20% w/w of HPC had a release exponent approaching Case II transport. In vitro release from the bilayer tablets was biphasic, a steeper initial slope being obtained when 5 mg of the NHT was incorporated in the FRL. Biphasic dissolution profiles of this nature will produce lower release exponent values approaching Fickian transport.

The biphasic nature of release from the bilayer tablets was even more pronounced when release of NHT was measured in human volunteers, slightly faster during the initial 30 min and then at a slower nearly constant rate thereafter.

These bilayer buccal adhesive tablets demonstrate possible advantages over the use of nicotine gums and patches in NRT.

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