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Development of a buccal bioadhesive nicotine tablet formulation for smoking cessation

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Abstract

Bioadhesive buccal tablet formulations for delivery of nicotine into the oral cavity were developed. Carbomer (Carbopol®974P NF) (CP) and alginic acid sodium salt (NaAlg) were used as bioadhesive polymers in combination with hydroxypropyl methylcellulose (HPMC) at different ratios. Magnesium carbonate was incorporated into the formulations as a pH increasing agent. In vitro release and bioadhesion studies were performed on the developed tablets. In the formulations containing CP:HPMC, the NHT released increased with the increasing HPMC concentration whereas a decrease was observed with increasing HPMC concentration in formulations containing NaAlg:HPMC. The bioadhesive properties of the tablets containing NaAlg:HPMC was not affected by the concentration of the NaAlg ($P > 0.05$) but increased significantly with the increasing CP concentration ($P < 0.05$). A decrease in pH of the dissolution medium to acidic values was avoided by incorporation of magnesium hydroxide into the formulations. The developed formulations released NHT for 8 h period, and remained intact except for the formulation containing CP:HPMC at 20:80 ratio.

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1. Introduction

Estimates of tobacco related world-wide deaths are anticipated to rise from 4 million during 1998 to almost 10 million by the year 2030 (Hays, 2000). Several treatments are available to aid smoking cessation, the most widely used of which is nicotine replacement therapy (NRT). As the oral bioavailability of nicotine is less than 30% due to its wide hepatic first pass metabolism (Svensson, 1987), NRT products are designed to deliver nicotine via the routes that min-

imise this effect. The current range of commercially available products include chewing gums, transdermal patches, inhalators, sublingual tablets and intranasal sprays although some formulations are sub-optimal in terms of mimicking the desired PK profile associated with pulmonary absorption.

Buccal administration of drugs which exhibit a low oral bioavailability is a useful method to achieve higher bioavailability. Sublingual tablet and chewing gum are widely used systems but upon their administration a large proportion of the administered dose can be swallowed before being absorbed (Benowitz et al., 1987). It is proposed that a sustained release bioadhesive tablet can help to avoid this undesirable effect and also exhibit a longer duration of action.

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Bioadhesive buccal tablets appear to be suitable for the delivery of nicotine, since modulation of the release rate can be achieved by changing the formulation excipients. Carbomer (CP) and alginic acid sodium salts (NaAlg) have had wide application as bioadhesive polymers for buccal tablet formulations (Save and Venkitachalan, 1994; Miyazaki et al., 1994; Yazıksız-İşcan et al., 1998; İkinci et al., 2000; Emek-Çiftçi et al., 2001).

Nicotine, which is a diacidic base ($pK_a = 3.4$ and 8.2), is ionised at low pH values (Oakley and Swarbrick, 1987). The permeation of nicotine is reported to be higher for the unionised species than for the ionized species through various regions of skin and mucosae (Nair et al., 1997). In a previously reported study, we have shown that magnesium hydroxide increases the pH and enhances the permeation of nicotine hydrogen tartrate (NHT) through bovine buccal mucosa (İkinci et al., 2002).

The aim of this study was to prepare a tablet formulation for nicotine delivery via the buccal route. NHT which is more stable than nicotine base (Place et al., 1992; Cheng et al., 2002), was used in the formulations. Magnesium hydroxide was also added into the formulations as a pH increasing agent would be expected to increase the absorption of NHT through the buccal mucosa.

2. Materials and methods

2.1. Materials

NHT and NaAlg (medium viscosity) (Sigma, St. Louis, USA), hydroxypropyl methylcellulose (HPMC) (Methocel K4M, Colorcon, England), carbomer (CP) (Carbopol® 974P NF, BF Goodrich, Cleveland, USA), magnesium stearate (MgSt) (E. Merck, Germany) were used as received.

2.2. Preparation of tablets

Tablets were prepared by direct compression of the mixture of HPMC either with CP or NaAlg at different ratios. 1% MgSt was used as the lubricant. Tablets were compressed on a single punch-tablet machine Korsch EK/O using flat non-bevelled punch of 12 mm diameter with a thickness of 1.0–1.2 mm. Composition of the formulations is given in Table 1.

Table 1

Composition of the tablet formulations (mg)

	NHT	Ratio	Mg(OH) ₂	MgSt
CP:HPMC				
A1	20	20:80	30	1.5
A2	20	40:60	30	1.5
A3	20	60:40	30	1.5
A4	20	80:20	30	1.5
NaAlg:HPMC				
B1	20	20:80	30	1.5
B2	20	40:60	30	1.5
B3	20	60:40	30	1.5
B4	20	80:20	30	1.5

NHT: Nicotine hydrogen tartrate; CP: Carbopol®974P NF; NaAlg:Alginic acid sodium salt; HPMC: Hydroxypropyl methylcellulose; MgSt: Magnesium stearate; Mg(OH)₂: Magnesium hydroxide.

2.3. In vitro NHT release studies

The release of NHT from tablets was studied using modified Franz diffusion cells. The dissolution medium was 22 ml phosphate buffer saline (PBS) (pH 7.4) at 37 °C. Uniform mixing of the medium was provided by magnetic stirring at 300 rpm. To provide unidirectional release, each bioadhesive tablet was embedded into paraffin wax in a die with a 12 mm central hole, which was placed on top of the tissue (Fig. 1). Samples of 1 ml were taken from the medium at certain time intervals and replaced with the same amount of PBS. The samples were filtered and assayed for NHT at 259 nm using a UV 160A Shimadzu spectrophotometer (Japan). pH of the samples were also measured during the release studies.

2.4. Bioadhesion studies

Bioadhesion studies were carried out ex vivo using freshly obtained bovine buccal mucosa without any further treatment. The peak force of detachment ($N\text{ cm}^{-2}$) and the work of adhesion (J) were measured on a tensile strength apparatus (Zwick Z010, Germany). Cyanoacrylate adhesive was used to fix the tablet on the upper metallic support. Freshly excised bovine buccal tissue ($\sim 5\text{ cm} \times 5\text{ cm}$) was fixed on polystyrene and placed on the base of the tensile test apparatus with the mucosal membrane facing upward. 1 kN load cell was used. The tablet was brought in contact with a force of 0.5 N and kept in this condition

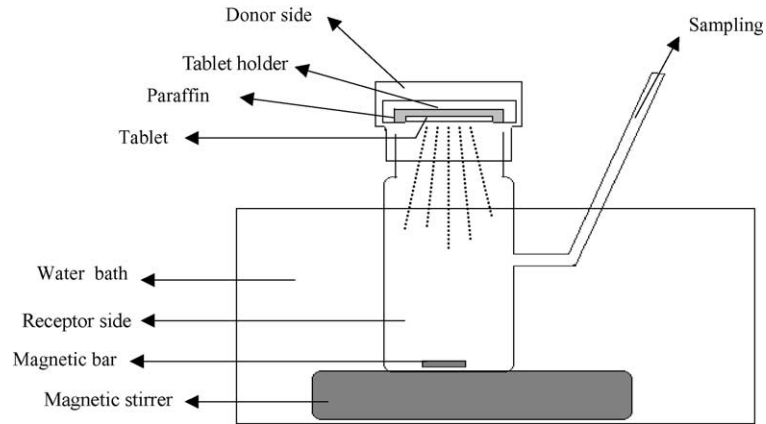


Fig. 1. Schematic representation of the system used in the in vitro release studies.

for 5 min. The tensile test was performed at a constant rate of 0.5 mm min^{-1} .

3. Results and discussion

3.1. In vitro release of NHT

The amount of NHT released from formulations containing CP:HPMC mixture rose with increasing HPMC concentration (Fig. 2.) The percentages of NHT released from the formulations A1 and A4 were

54 ± 3 and 45 ± 2 at 4 h, and 77 ± 3 and 88 ± 5 at 8 h, respectively. All formulations remained intact during the 8 h period, except for formulation A4 in which the HPMC concentration was the lowest. The mechanism of release was investigated using the following equation (Eq. (1)):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t/M_∞ is the fraction of drug released up to time t (h), k is the release rate ($\% \text{ h}^{-1}$) and n is the release exponent describing the mechanism of drug

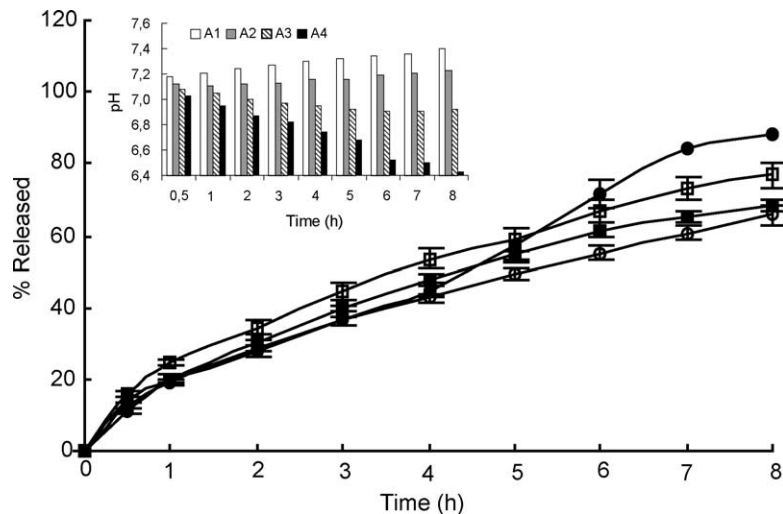


Fig. 2. The release of NHT from formulations containing CP:HPMC. (A1 (□); A2 (■); A3 (○); A4 (●)). The change in pH of the dissolution medium over time is shown as insert.

Table 2

Kinetic constants (k), release exponents (n) and determination coefficients (r^2) following linear regression of dissolution data of buccal adhesive NHT tablets

	k (% h ⁻¹)	r^2	n
A1	29.09	0.998	0.57
A2	26.93	0.996	0.59
A3	25.00	0.997	0.59
A4	23.66	0.998	0.66
B1	27.76	0.984	0.56
B2	28.09	0.996	0.52
B3	32.24	0.991	0.60
B4	36.32	0.983	0.58

release. The calculated parameters from this equation are given in Table 2. The release of NHT from formulation A4 showed a biphasic profile ($n = 0.66$), which can be attributed to the rapid hydration and erosion of the tablet. Most of the n values were found to be around 0.5, which indicates a drug release following the Fickian diffusion mechanism.

It has been shown that the swelling of CP was slightly increased in the acidic conditions up to pH 4 and a great increase was observed between pH 6 and 7 whereas there was a decrease at alkaline pH values (Anlar et al., 1993). In our study, incorporation of an alkaline compound (magnesium hydroxide) into the formulations increased the pH of the microenvi-

ronment on the tablet surface to alkaline pH thus resulted a decrease in the swelling of CP. As HPMC is a non-ionic polymer, pH had no effect on its swelling behaviour.

Release profiles of NHT from NaAlg containing formulations are shown in Fig. 3. The released percent of NHT at 4 h for the formulations B1, B2, B3 and B4 were 57 ± 2 , 55 ± 1 , 59 ± 3 , and 73 ± 2 , respectively. No significant difference in release profiles was obtained between the formulations containing NaAlg:HPMC at the ratios of 20:80, 40:60 and 60:40 ($P > 0.05$); however formulation B4 (NaAlg:HPMC ratio 80:20) showed a higher release ($P < 0.05$). Increasing the amount of NaAlg, which is a water-soluble polymer, in the formulations probably results in formation of porous channels causing a faster release of NHT whereas in the presence of HPMC which is a water-swellaible polymer, at higher concentrations a decrease in the release rate is obtained most likely due to its higher swelling property (Table 2).

The pH of the medium was increased over the release period with formulations containing NaAlg whilst a decrease in the pH was observed with CP containing tablets (Figs. 2 and 3). This can be explained by the anionic character of CP which contains between 56 and 68% carboxylic groups on the dry basis, and cationic character of NaAlg. Similarly, in a study where clotrimazole muco-adhesive tablet

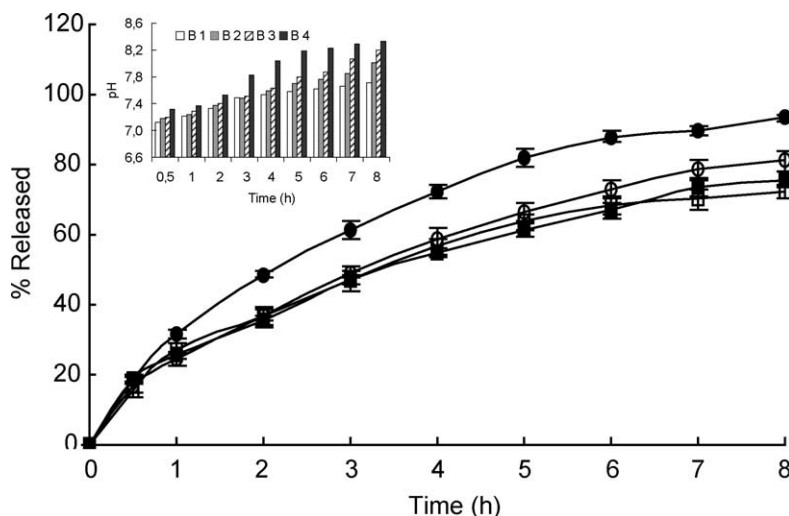


Fig. 3. The release of NHT from formulations containing NaAlg:HPMC (B1 (□); B2 (■); B3 (○); B4 (●)). The change in pH of the dissolution medium over time is shown as insert.

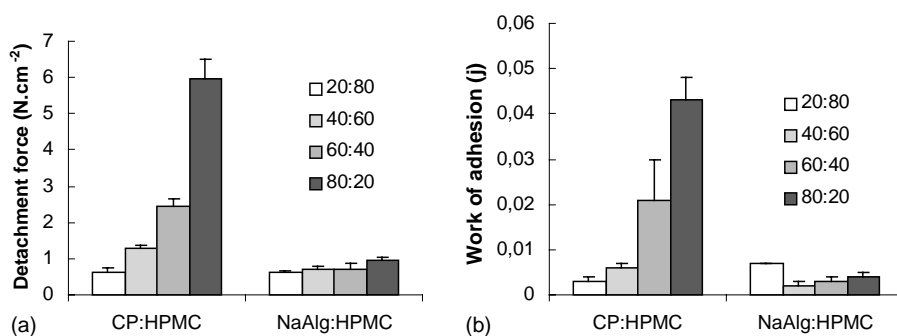


Fig. 4. Bioadhesion test results for buccal adhesive tablets in contact with bovine buccal mucosa: (a) detachment force; (b) work of adhesion.

formulation was prepared with HPMC and Carbopol 974P, a decrease in the pH of the tablet surface was reported from 6.31 to 5.63 with increasing CP ratio from 2.5% to 7.5% (Khanna et al., 1997). Our preliminary studies showed that in the absence of magnesium hydroxide the pH of the dissolution medium decreased significantly in parallel to the NHT dissolving amount. The fall in pH to acidic values was avoided by incorporation of magnesium hydroxide into the formulations. Similarly Alur et al. (1999) incorporated sodium bicarbonate into chlorpheniramine maleate buccal tablet formulations to increase the pH of the microenvironment around the tablet/mucosa interface. A slight increase in the pH was obtained in the presence of sodium bicarbonate whereas there was a significant decrease in the pH with formulation in the absence of the excipient.

3.2. Bioadhesion studies

Bioadhesion test results showed that there was a correlation between the detachment force and work of adhesion (Figs. 4a and b). With tablets containing NaAlg, the concentration of the polymer had no effect on bioadhesive properties whereas with the CP containing formulations, the bioadhesion was increased significantly with the increasing CP concentration in the tablets ($P < 0.05$). As the swelling behaviour of CP is dependent on pH with the increasing pH values, the number of carboxyl groups of the polymer which interact with the mucin would decrease thus a decrease in bioadhesion would be expected. At lower CP concentrations (formulations A1 and A2), upon exposure to the moist surface, the pH of the microenvironment

became alkaline which caused a decrease in bioadhesion (Fig. 4a).

4. Conclusion

It was shown that with the developed formulations, the NHT release and bioadhesion properties of buccal tablets can be controlled by changing the polymer type and concentration. The use of NHT instead of nicotine base allowed to prepare the tablets by a simple direct compression. Incorporation of magnesium hydroxide into the buccal tablet formulations avoided the fall in the pH following the release of NHT, which would be expected to increase the absorption of NHT from the buccal mucosa on simple pH-partition considerations. Bioadhesion of the developed formulations will provide a longer period of residence time reducing loss of drug by swallowing, which should result in higher bioavailability.

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