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Nicotine stabilization in composite sodium alginate based wafers and films for nicotine replacement therapy

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ABSTRACT

Composite wafers and films comprising HPMC and sodium alginate (SA) were formulated for nicotine (NIC) replacement therapy via the buccal route. Magnesium aluminium silicate (MAS) was added in different concentration ratios (0.25, 0.5, 0.75) to stabilize NIC and its effect on mechanical properties, internal and surface morphology, physical form, thermal properties, swelling, mucoadhesion, drug content and release behaviour of the formulations was investigated. MAS changed the physico-mechanical properties of the composite formulations causing a decrease in mechanical hardness, collapsed wafer pores, increased roughness of film surface, increase in crystallinity and decreased mucoadhesion of the wafers. However, MAS increased swelling in both films and wafers as well as interaction between NIC and SA, which increased drug-loading capacity. Further, MAS resulted in rapid and slow release of NIC from wafers and films respectively. The results suggest that the ideal formulation for the stabilization of NIC in the composite formulations was MAS 0.25.

1. Introduction

Nicotine has been utilised as an active ingredient in the development of NIC replacement therapy (NRT) via the oral mucosa (chewing gum, sublingual tablets, lozenges), nasal mucosa (nasal spray and inhalers) and the skin (transdermal patch). NIC liquid is volatile, alkaline and colourless with two well-separated pK_a values of 3.04 and 7.84, which can form diprotonated, mono-protonated and neutral NIC species in an acidic, neutral or basic solvent respectively (Pongjanyakul & Suksri, 2009). These species can permeate membranes such as nasal, buccal and sublingual mucosae with unionized species showing higher permeation than ionized forms (Nair, Chetty, Ho, & Chien, 1997).

The oral mucosa of delivery has gained increased interest because of its ability to avoid gastric acid, enzymes in the small intestine and first pass metabolism in the liver, common with the conventional oral route (Sattar, Sayed, & Lane, 2014). The buccal mucosa is highly vascular, less vulnerable to irritation and has a lower amount of enzyme activities compared to intestinal, rectal, vaginal and nasal mucosae (Boateng & Okeke, 2014). Though the use of the buccal mucosa for NIC delivery has been demonstrated in NIC chewing gum, Nicorette®, a large percentage of the drug is swallowed before achieving complete absorption (Adrian, Olin, Dalhoff & Jacobsen, 2006; Benowitz, Jacob, & Savanapridi, 1987; Nair et al., 1997).

Alternative buccal delivery systems, which can be utilised in NRT using mucoadhesive polymers have been under investigation including films (Aguzzi, Cerezo, Viseras, & Caramella, 2007) and wafers (Aguzzi et al., 2007; Boateng & Areago, 2014) and demonstrated improved functional properties when different

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polymers were combined. Hydroxypropylmethylcellulose (HPMC) and sodium alginate (SA) have been widely used as mucoadhesive polymers in the development of buccal-adhesive drug delivery systems (Adhikari, Nayak, Nayak, & Mohanty, 2010; Boateng & Areago, 2014; Khan, Boateng, Mitchell, & Trivedi, 2015; Manivannan, Balasubramaniam, Anand, Sandeep, & Rajkumar, 2008; Pandey, Hingawe, Das, & Patil, 2014). HPMC is a hydrophilic non-ionic semi-synthetic polymer widely used in the pharmaceutical and food industries while SA is a poly-anionic polysaccharide polymer made up of alginic acid (a polyuronic acid composed of mannuronic and guluronic acid residues), extracted from brown seaweed. HPMC-SA composites were reported for the formulation of buccal NIC tablets for smoking cessation (İkinci, Şenel, Wilson, & Şumnu, 2004).

The challenges posed by NIC are its volatility and oxidative degradation of the free base. To address these challenges, there has been research into the adsorption of NIC onto several materials such as cellulose powder (Mihranyan, Andersson, & Ek, 2004), cation exchange resins (Rakić et al., 2010) and inorganic clays such as magnesium aluminium silicate (MAS) (Pongjanyakul & Suksri, 2009). In particular, polymer-clay composites having improved mechanical properties, thermal behaviour and modified drug release have attracted interest in the field of drug delivery (Aguzzi et al., 2007; Gilman, 1999; Pavlidou & Papaspyrides, 2008).

MAS results from the combination of natural smectites (montmorillonite and saponite clays) that forms a layered structure (Pongjanyakul & Suksri, 2009; Rowe, Sheskey, & Owen, 2006), comprising three-lattice layers of octahedral alumina or magnesia and two tetrahedral silica. Upon hydration, the MAS layered structure separates, exposing the weakly positively charged edges and negatively charged faces. This can readily interact with amine drugs such as NIC, as well as demonstrate electrostatic interaction, which contributes to slow drug release in formulations (Pongjanyakul & Suksri, 2009; Rowe et al., 2006). MAS incorporated into NIC loaded single polymer (SA) based films demonstrated interaction of MAS with anionic SA polymer as well as increase in NIC retention within the films (Pongjanyakul & Suksri, 2010).

In this study, composite SA based films and wafers containing different concentrations of MAS, loaded with NIC were characterised and compared for the first time. The hypothesis is that the presence of SA and MAS within a composite formulation will stabilize NIC and result in high drug loading suitable for NRT via the buccal mucosa.

2. Materials and methods

2.1. Materials

Hydroxypropylmethylcellulose – HPMC (Methocel K100 premium LV) and Magnesium aluminium silicate (MAS) were gifts from Colorcon Limited (Dartford, UK) and R.T. Vanderbilt Company Inc (Norwalk, CT, USA) respectively. Sodium hydroxide, potassium dihydrogen phosphate, gelatine were purchased from Fluka Analytical (Buchs, Switzerland). Nicotine (liquid form), sodium alginate–SA (molecular weight 120,000–190,000 g/mol, mannuronate/guluronate ratio 1.56), and mucin from porcine stomach were all obtained from Sigma Aldrich (Dorset, UK); sodium acetate, trimethylamine and glycerol were purchased from Fisher Scientific (Loughborough, UK).

2.2. Preparation of composite films

NIC loaded MAS films were prepared in different ratios with a total polymer (HPMC-SA) concentration of 2% w/v. The concentrations of polymers, MAS, plasticizer and drug used in each polymer solution have been summarised in Table 1a. The polymeric solutions for film formulation were prepared by dissolving glycerol (GLY) in 80 ml of distilled water while stirring at of 25 °C before gradually adding HPMC and SA powder one after the other and stirred between 500 and 700 rpm for 2 h. MAS on the other hand was dissolved in 20 ml of hot distilled water (50 °C) for 30 min, and mixed with the dispersed polymeric solution. The resulting final solutions were left overnight (16–20 h) to eliminate air bubbles, NIC added to the MAS composite mixture and stirred at low rpm (100–200 rpm) for 30 min. 30 g of the NIC loaded MAS solutions was poured into a Petri dish (90 mm diameter) and dried in an oven at 30 °C for 18–20 h.

Table 1
(a) Composition of selected polymers, plasticizer, MAS and NIC used in composite solutions for film formulation and (b) Composition of selected polymers, MAS and NIC used in composite solutions for formulating wafers.

(a) Films

Sample name	HPMC (% w/v)	SA (% w/v)	GLY (% w/v)	MAS (% w/v)	NIC (g)
MAS 0.00	1.25	0.75	2.00	0.00	0.20
MAS 0.25	1.25	0.75	2.00	0.25	0.20
MAS 0.50	1.25	0.75	2.00	0.50	0.20
MAS 0.75	1.25	0.75	2.00	0.75	0.20

(b) Wafers

Sample name	HPMC (% w/v)	SA (% w/v)	MAS (% w/v)	NIC (g)
MAS 0.00	1.25	0.75	0.00	0.20
MAS 0.25	1.25	0.75	0.25	0.20
MAS 0.50	1.25	0.75	0.50	0.20
MAS 0.75	1.25	0.75	0.75	0.20

2.3. Preparation of composite wafers

NIC loaded HPMC-SA-MAS solutions were prepared in a similar manner to films but without using GLY. The solutions (1 g) were poured into each well of a 24 well plate (diameter 15.5 mm). The concentrations of polymers, MAS and drug present in each solution are summarised in Table 1b. The freeze-dried wafers were prepared using an automated lyophilisation cycle, Virtis Advantage XL 70 freeze-dryer (Biopharma process systems, Winchester, UK). The well plates containing the solutions were loaded onto the shelves of the freeze-dryer and programmed for freezing, primary drying and secondary drying steps. The freezing step involved cooling the sample from room temperature to 5 °C (40 min), 5 °C to −10 °C (40 min), and then from −10 °C to −55 °C (120 min). An annealing step was incorporated into the freezing cycle by increasing the temperature from −55 °C to −35 °C (2 h) and then cooling back down to −55 °C (3 h). Additional freezing was performed at −55 °C (1 h) with a condenser temperature of −55 °C under pressure (200 mTorr). The primary drying occurred under high pressure of 50 mTorr. The temperature was raised from −55 °C to −20 °C (8 h) and further increased from −20 °C to −15 °C ° (10 h). Secondary drying occurred at 50 mTorr, from −15 °C to 25 °C (12.5 h).

2.4. Polymer solution properties

The polymeric solutions were analysed for surface stickiness, stringiness and ‘gel’ strength using a texture analyser (HD plus, Stable Micro System, Surrey, UK) equipped with a 5 kg load cell. A 25 mm probe was lowered onto the solution at a speed of 1 mm/s, held for 2 s, and then withdrawn at a speed of 8 mm/s. The maximum force at withdrawal of probe from sample was recorded as surface stickiness while the distance from the onset and offset of force while moving the probe away from the sample was recorded as stringiness. The viscous ‘gel’ strength was recorded as the max-