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RESEARCH PAPER

Evaluation of Selected Polysaccharide Excipients in Buccoadhesive Tablets for Sustained Release of Nicotine

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ABSTRACT

Some naturally occurring biocompatible materials were evaluated as mucoadhesive controlled release excipients for buccal drug delivery. A range of tablets were prepared containing 0–50% w/w xanthan gum, karaya gum, guar gum, and glycol chitosan and were tested for swelling, drug release, and mucoadhesion. Guar gum was a poor mucoadhesive and lacked sufficient physical integrity for buccal delivery. Karaya gum demonstrated superior adhesion to guar gum and was able to provide zero-order drug release, but concentrations greater than 50% w/w may be required to provide suitable sustained release. Xanthan gum showed strong adhesion to the mucosal membrane and the 50% w/w formulation produced zero-order drug release over 4 hours, about the normal time interval between daily meals. Glycol chitosan produced the strongest adhesion, but concentrations greater than 50% w/w are required to produce a nonerodible matrix that can control drug release for over 4 hours. Swelling properties of the tablets were found to be a valuable indicator of the ability of the material to produce sustained release. Swelling studies also gave an indication of the adhesion values of the gum material where adhesion was solely dependent upon penetration of the polymer chains into the mucus layer.

Key Words: Buccal delivery; Mucoadhesion; Controlled release; Hydrophilic matrices.

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INTRODUCTION

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. The main advantages include the avoidance of first-pass metabolism 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.[1–4]

Mucoadhesive polymers may be used to produce controlled release dosage forms that are able to adhere to the buccal membrane for extended periods of time. Mucosal adhesive materials have been identified and investigated in previous work.[5] These materials are generally hydrophilic macromolecules containing numerous hydrogen bond forming groups, including hydroxyl and carboxyl groups that interact with functional groups in the mucus layer to produce secondary chemical bonds.

Some of the most widely studied mucosal adhesives are the poly(acrylic acids), which include Carbopol 934®, [structure, $(-CH_2CHCOOH)_n$] with a pKa value of between 5.35 and 7.2.[6] A number of studies have concluded that these polymers produce excellent adhesion to mucosal membranes.[2,5,7,8] Poly(acrylic acids) and cellulose derivatives have been used in combination to produce mucoadhesive, controlled-release formulations.[9–12] This type of matrix was employed in our previous work to provide controlled-release of nicotine to the buccal mucosa of human volunteers for 4 hours.[13] Although our previous work reported adequate mucoadhesion and nicotine release from buccal tablets containing Carbopol 934P® and hydroxypropylcellulose with no adverse effects, we decided to explore the use of biocompatible, naturally occurring polysaccharides to provide the dual purpose of sufficient mucoadhesion as well as sustained release of nicotine in vitro.

Xanthan gum is a polysaccharide produced as a secondary metabolite by a biotechnological fermentation process in aerobic conditions of the microorganism *Xanthomonas campestris*. Xanthan gum has been shown to produce moderate adhesion to biological membranes due to its strong swelling properties.[14,15] Other studies has shown xanthan gum to be a useful excipient in controlled-release, hydrophilic matrix tablets for oral drug delivery producing drug release approaching zero-order release.[16,17]

Karaya gum is a complex polysaccharide of high molecular weight, which comes from the dried exudate of the Indian tree *Sterculia urens*. Karaya gum is commonly used as a thickener in foods and cosmetics. Pharmaceutically, the swelling profile of karaya gum has been used to produce denture adhesive and a bulk laxative. Karaya gum has been evaluated as a controlled-release matrix former,[17] but little evidence is available with regard to the potential for karaya gum to be used as a mucoadhesive, controlled-release buccal excipient.

Guar gum is also a polysaccharide commonly used as a thickener in foods and cosmetics. It is obtained from the seeds of the *Cyanopsis teragonolobus*, a plant originating from India and Pakistan. Pharmaceutically, guar gum is used as a binder in solid dosage forms,[18] but little or no evidence is available to characterize the suitability of guar gum in a buccal formulation.

Chitosan, a poorly water-soluble cationic polysaccharide, has also been proposed as a novel mucoadhesive polymer.[19] As chitosan is cationic, electrostatic interaction with the negatively charged mucus is possible and is thought be the mechanism by which chitosan produces mucoadhesion.[20] Initial work found chitosan possessed minimal swelling properties in an aqueous environment, an important property for buccal adhesive dosage forms. Glycol chitosan, a derivative of chitosan, shows greater hydrophilicity and swelling due to the substitution of glycol groups onto the chitosan molecule. As a result, glycol chitosan was investigated in this study.

The purpose of this current work is to evaluate the above naturally occurring biocompatable materials, with respect to their ability to produce adhesion as well as controlled buccal nicotine release. Characterization of these materials for this purpose has not been fully explored in the literature, despite the obvious potential of the polysaccharides to hydrate and produce controlled drug release. Polymer swelling is an essential stage in the formation of a mucoadhesive bond between hydrophilic matrix formulations and the mucosa. In vitro swelling studies are therefore regarded as important investigations to help explain the performance of the dosage form. The study also aims to compare the performance of these novel buccal excipients with the widely studied and previously reported carbopol/hydroxypropylcellulose matrix.

MATERIALS AND METHODS

Materials

Nicotine hydrogen tartrate (NHT), glycol chitosan, guar gum, karaya gum, and mucin (type II crude) were obtained from Sigma (St. Louis, MO). Xanthan gum

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Table 1. Ingredient quantities used to prepare powder mixes for direct compression (adhesive material = xanthan gum, karaya gum, guar gum, glycol chitosan, or Carbopol 934).

	Ingredient quantity (mg/tablet)
Nicotine hydrogen tartrate	10
Adhesive material	10–50
Polyvinylpyrrolidone	6
Magnesium stearate	1
Spray-dried lactose	to 100

was obtained from Kelco International (London, UK). Carbopol 934 (C934) was purchased from B.F. Goodrich (Cleveland, OH). Spray-dried lactose was included as a diluent and was purchased from Thornton and Ross (Huddersfield, UK). Polyvinylpyrrolidone (PVP) was used as a binding agent and magnesium stearate as a lubricating agent. Both were obtained from B.D.H. (Poole, UK).

Tablet Preparation

The compositions of the adhesive, controlled release buccal tablets are shown in Table 1. All powdered excipients were mixed for 5 minutes using a mortar and pestle to form a homogenous, directly compressible powder mix. Uniformity of mixing was established by removing six approximately 100 mg samples from different depths and sides of the batches of mixed material. These samples were analyzed for NHT content by ultraviolet (UV) detection at 259 nm (model UV 300, Unicam Ltd., Cambridge, UK). The assayed amount of NHT in each sample did not deviate by >5% of mean content and hence the mixing process was deemed acceptable.

One hundred mg tablets containing 10 mg NHT were directly compressed using a single-punch tablet press (Manesty F3, Liverpool, UK) and 6-mm diameter flat punches. Tablet crushing strength was measured using a tablet hardness tester (model TBH 28, Erweka, Heusenstamm, Germany) to achieve a tablet crushing strength of 50–60 Newtons.

Swelling Studies

Five tablets from each batch were placed on a plastic mesh (1 cm^2) to allow handling of the tablet without directly touching it. The tablet/mesh assembly was weighed accurately to four decimal places and the weight noted (model AE240, Mettler Instruments Ltd, High Wycombe, UK). The axial and radial dimensions of the tablets were measured using sliding scale callipers. Each tablet assembly was placed in separate glass vials containing 4 mL of deionized water. At specific time intervals over 4 hours, the tablet assembly was removed from the vials and any surface moisture was carefully absorbed into filter paper. The assembly was reweighed and the axial and radial dimensions were again noted. The percentage increase in weight, axial, and radial dimensions was calculated.

In Vitro Determination of Bioadhesive Performance

Adhesive testing of the tablets was carried out using a texture analyzer with a 5-Kg load cell (TA-XT2i, Stable Micro Systems, Surrey, UK). Texture analysis is a useful tool and has been extensively used as a valid means for mechanical characterization of pharmaceutical mucoadhesive dosage forms.[21]

The method used is outlined in previous research using bovine buccal mucosa as the mucosal surface.[13] Briefly, bovine cheeks were used immediately after slaughter. A tablet was attached to the probe of the texture analyzer and the area of contact on the mucosa was moistened with 50 μL of mucin solution (type II crude). The tablet was lowered at 0.1 mms^{-1} and a contact force of 0.5 N maintained for 120 s, after which the probe was withdrawn at a rate of 5 mms^{-1}. Peak detachment force in Newtons (N) and the work of adhesion (area under the force/distance curve in millijoules (mJ) was recorded. Method precision was previously determined and judged to be suitable.[13]

In Vitro Nicotine Release

The rate of NHT release from the tablets was investigated using United States Pharmacopoeia (USP) (XXI) apparatus IV (Erweka, Heusenstamm, Germany). Five 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 mLh^{-1} by a peristaltic pump (model 202u, Watson–Marlow, Falmouth, UK) and at 37°C±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.[22] The effluent from the cells was collected over a 4-hour period and assayed for nicotine at certain time intervals using UV detection at 259 nm. Using calibration curves, NHT release could be easily calculated.

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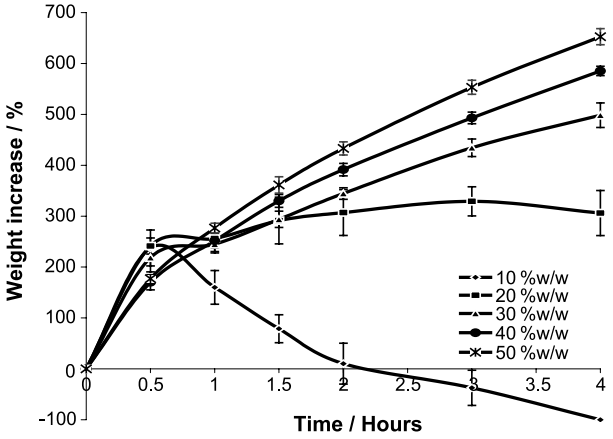

Figure 1. Weight increase (%) vs. time (hours) for buccal adhesive layers containing xanthan gum ± SD (n = 5). (*View this art in color at www.dekker.com.*)

Eq. 1, a well-known exponential expression, was used to establish the mechanism of drug release from the in vitro release data.[23]

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t/M_∞ = the fraction of drug released (0.1–0.6), k = the kinetic constant, and n = the release exponent describing the mechanism of release. A plot of log (M_t/M_∞) vs. log t gives a straight line of gradient n and intercept log k.

Statistical Analysis

All tests were carried out in replicates of five. Statistical analysis of all relevant data was performed using Student's *t*-tests.

RESULTS AND DISCUSSION

Swelling Studies

The swelling profiles of formulations varying in the adhesive material content (10–50% w/w) are shown in Figs. 1–3. These profiles indicate the uptake of water into the tablet matrix, producing an increase in weight.

Xanthan gum formulations (Fig. 1) take up water over the first 30 minutes, the rate depending on the concentration of gum present (lower concentrations swell more rapidly). Higher xanthan gum concentrations showed slower initial water uptake, but take longer to become fully hydrated. After 30 minutes the 10% w/w formulation displays loss of weight due to tablet disintegration. The 20% w/w formulation swelling profile levels off after approximately 1.5 hours, suggesting complete hydration of the xanthan gum. The remaining formulations continue to swell over the 4-hour test with the degree of swelling being dependent on the xanthan gum concentration, higher concentrations display a greater hydration capacity. These results suggest that 30% w/w xanthan gum is the suitable concentration in the hydrophilic swellable matrix in order to achieve controlled drug release.

The 10% w/w karaya gum formulation disintegrated completely in under 30 minutes and hence is omitted from Fig. 2. The other karaya gum formulations (Fig. 2) showed initial swelling (the degree and duration of swelling dependant on the karaya gum concentration), followed by loss of weight from the tablet due to erosion. The 50% w/w formulation was able to maintain a positive weight gain until 3.5 hours, after which erosion of the tablet and weight loss began to dominate. This study suggests that at these concentrations, a combination type matrix may be formed, affecting drug release by a combination of swelling and polymer erosion.

It was not possible to measure the swelling of any guar gum formulations (0–50% w/w) at 30 minutes. The tablets appeared to form a soft gel that, when disturbed for measurement, resulted in complete disintegration. The guar gum formulations did not maintain the physical tablet integrity that was evident in all other adhesive polymer formulations. The maintenance of physical integrity is important for a sustained-release buccal dosage form, as the formulation must be able to withstand both the shearing forces present in the buccal cavity and drug washout by the

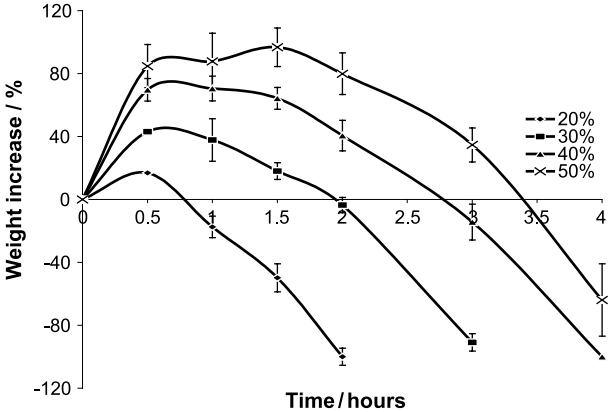

Figure 2. Weight increase (%) vs. time (hours) for buccal adhesive layers containing karaya gum ± SD (n = 5).

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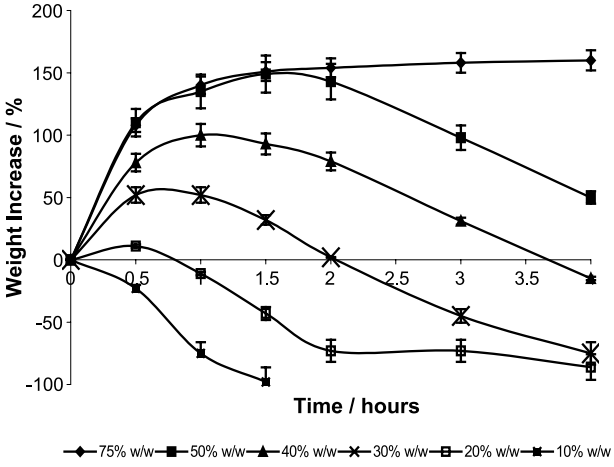

Figure 3. Weight increase (%) vs. time (hours) for buccal adhesive layers containing glycol chitosan ± SD (n = 5).

saliva. The swelling study for guar gum suggests that a soft hydrated gel matrix is formed that may be unable to sustain the release of NHT for the required minimum of 4 hours.

Glycol chitosan (Fig. 3) displays initial swelling followed by erosion during the study comparable to the trend noted with karaya gum. The degree of swelling increases with glycol chitosan concentration and higher concentrations delay the onset of tablet erosion. This swelling study again indicates the probable combination of drug diffusion and erosion mechanisms being responsible for drug release over the concentration range tested. The formulation containing 75% w/w glycol chitosan showed rapid initial swelling, followed by further swelling over the remaining 3 hours but at a lower rate. No erosion of the matrix was evident over this time period and confirms the suggestion of previous workers[24] that higher concentrations (>50% w/w) are required to produce a nonerodible matrix.

In Vitro NHT Release Studies

Our previous work found that a matrix containing a combination of 20% w/w Carbopol 934P and 20% w/w hydroxypropylcellulose produced in vitro NHT release approaching zero-order.[13] Using similar methods, the natural adhesive materials were tested and the release mechanism determined. The release profiles of the formulations are shown in Figs. 4–7.

In Fig. 4 it is evident that the formulations containing 10% and 20% w/w xanthan gum released 100% NHT within 1 and 2 hours, respectively. Formulations containing 30% w/w and above were able to sustain NHT release for at least the 4 hours required. This release behavior was predictable from the swelling study. Table 2 shows values resulting from the analysis of the dissolution data using Eq. 1. It is evident that the formulations containing 30–40% w/w xanthan gum produced n values characteristic of anomalous transport but are approaching zero-order release (n→0.89). Anomalous transport is a type of drug release controlled by a combination of polymer swelling, drug diffusion, and erosion of the hydrated matrix as is typical in many buccal adhesive dosage forms. The 50% w/w formulation had a mean n value of 0.896, which is characteristic of Case II transport (zero-order NHT release).

Figure 5 demonstrates NHT release from formulations containing karaya gum. The rate of NHT release is dependent on the concentration of the karaya gum in the matrix. The 10% w/w formulation released 100% NHT within 30 minutes, which was predictable from the swelling study, and the profile is hence is omitted from Fig. 5. The 20% and 30% w/w formulations release 100% NHT in about 2 and 3 hours, respectively, while the 40% and 50% w/w formulations continued to release NHT for up to 4 hours. Analysis of the dissolution data (Table 2) produced Super Case II transport (n > 1) in the 40% w/w (n = 1.186 ± 6.06% R.S.D.) and 50% w/w formulations (n = 1.201 ± 3.14% R.S.D.). Super Case II transport is characteristic of formulations where drug release is increased by disintegration of the tablet, as seen in the results of the swelling study for karaya gum.

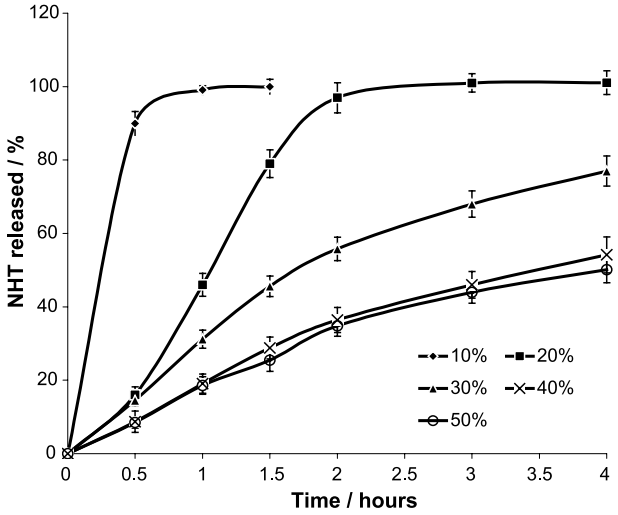

Figure 4. Nicotine hydrogen tartrate released (%) vs. time (hours) for buccal adhesive layers containing xanthan gum ± SD (n = 5).

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Table 2. Mean diffusional exponents (n) and kinetic constants (k) for NHT dissolution from buccal adhesive nicotine tablets containing a polysaccharide matrix (n=6).

Adhesive material and content	Diffusional exponent (n) (RSD/%)	Kinetic constant/hr^{-1} (k) (RSD/%)	r^2 (RSD/%)	Release mechanism
Xanthan gum 30% w/w	0.835 (8.54)	1.227 (7.20)	0.971 (0.99)	Anomalous transport
Xanthan gum 40% w/w	0.840 (11.59)	1.210 (8.68)	0.984 (0.61)	Anomalous transport
Xanthan gum 50% w/w	0.896 (6.81)	1.228 (4.72)	0.977 (1.00)	Case II transport
Karaya gum 40% w/w	1.186 (6.06)	1.343 (2.58)	0.995 (0.15)	Super Case II transport
Karaya gum 50% w/w	1.201 (3.14)	1.381 (3.82)	0.984 (2.43)	Super Case II transport
Guar gum 30% w/w	0.771 (11.28)	1.512 (8.58)	0.983 (0.70)	Anomalous transport
Guar gum 40% w/w	0.823 (17.89)	1.454 (8.58)	0.983 (0.70)	Anomalous transport
Guar gum 50% w/w	0.953 (18.69)	1.335 (9.32)	0.983 (1.17)	Case II transport
Glycol chitosan 75% w/w	0.829 (3.42)	1.457 (1.30)	0.999 (0.04)	Anomalous transport

Figure 6 shows that sustained release of NHT over the 4-hour test was achieved in guar gum formulations containing 30% w/w or higher. During the swelling test it was evident that a gel-like system was formed and this was again evident in the dissolution study where a swollen expanded gel formed within 10 minutes and gravitated to the bottom of the dissolution cell. The gel expanded to the diameter of the dissolution cell (2.5 cm) and, as there was no stirring or agitation of the medium in the flow through dissolution apparatus, the gel remained intact. Analysis of the dissolution data (Table 2) found the 30% and 40% w/w formulations displayed NHT release by the anomalous transport mechanism discussed above (n=0.791±11.28% R.S.D. and n=0.823±17.89% R.S.D., respectively). The 50% w/w guar gum formulation displayed Case II transport with an n value of 0.953±18.69% R.S.D.). Although guar gum formulations produced sustained NHT release in vitro, it is unlikely that such formulations would produce similar release under in vivo conditions due to the lack of physical integrity of the gel layer, which would allow easy washout of the formulation by the saliva.

Dissolution profiles for glycol chitosan in Fig. 7 demonstrate the rapid release of NHT from the 10% w/w formulation as a result of tablet erosion and disintegration. Tablets containing 20–50% w/w demonstrate slower NHT release due to a combination of swelling and erosion in the matrix. All of the formulations in the 20–50% w/w concentration range release 100±5% NHT within 4 hours. The 75% w/w formulation was able to produce gradual NHT release over 4 hours through the nonerodible matrix identified in the swelling study. Analysis of the dissolution data using the 75% w/w formulation was carried out and the diffusional exponent value (n) was found to be 0.829±3.42% R.S.D. This value is approaching Case II transport i.e., zero-order release

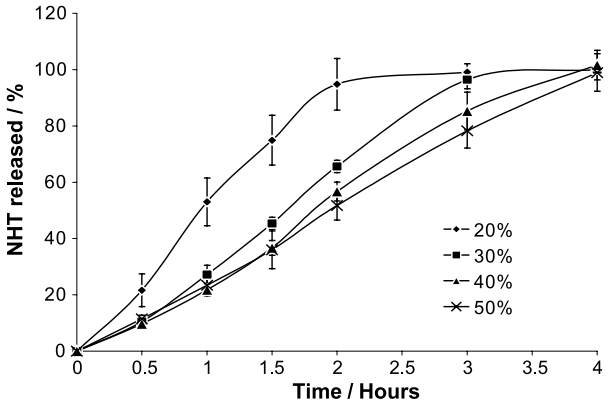

Figure 5. Nicotine hydrogen tartrate released (%) vs. time (hours) for buccal adhesive layers containing karaya gum±SD (n=5).

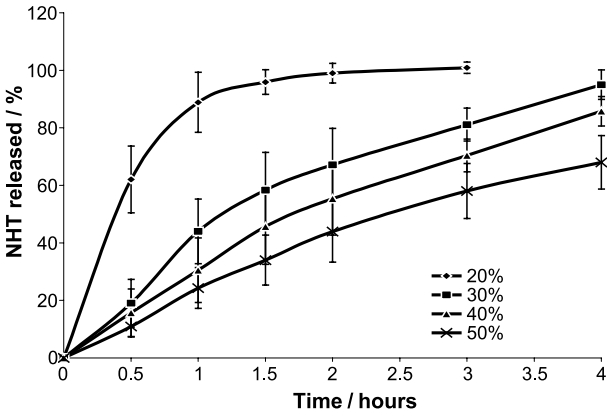

Figure 6. Nicotine hydrogen tartrate released (%) vs. time (hours) for buccal adhesive layers containing guar gum±SD (n=5).

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($n \approx 0.89$) and suggests, therefore, that to achieve zero-order release of NHT, higher glycol chitosan concentrations are required.

Higher concentrations of xanthan gum, karaya gum, and guar gum were not tested, as these materials were able to satisfactorily sustain NHT release over the 4-hour period at lower concentration levels.

Adhesion Studies

Work of adhesion has been said to be the most accurate predictor of mucoadhesive performance.[25] Figure 8 demonstrates the work of adhesion profiles for the natural adhesive polymers. The almost linear trend for work of adhesion of Carbopol is evident in all of the adhesive gums tested, suggesting that the adhesion of these materials may also be dependent on the physical entanglement of polymer chains with the mucus chains. As the polymer content of the formulation is increased, the degree of swelling increases, which in turn allows formation of a greater number of interpenetrating chains between the polymer and the mucus. This physical interaction results in the linear increase of adhesion with polymer concentration. However, it has been previously reported that there is an optimum concentration of polymer that corresponds to the best mucoadhesion[26] and in higher concentrations, the adhesive strength drops significantly.

In our previous study,[13] we found the Carbopol/hydroxypropyl cellulose system produced an almost linear increase in work of adhesion with increasing Carbopol concentration. Carbopol formulations were included in this study as a proven mucoadhesive material and allowed comparison with the natural adhesive materials in the study. The three gum materials showed lower work of adhesion values. The rank order of adhesion in the gums followed the ability of the material to hydrate and swell, i.e., xanthan gum > karaya gum > guar gum. As mentioned above, swelling is an important step in mucoadhesion, as the adhesive polymers must be hydrated to facilitate penetration into the mucus. This does present a rather complex interaction, as the hydration of the polymers by water extraction from the mucus gel will tend to change the mucus rheology.

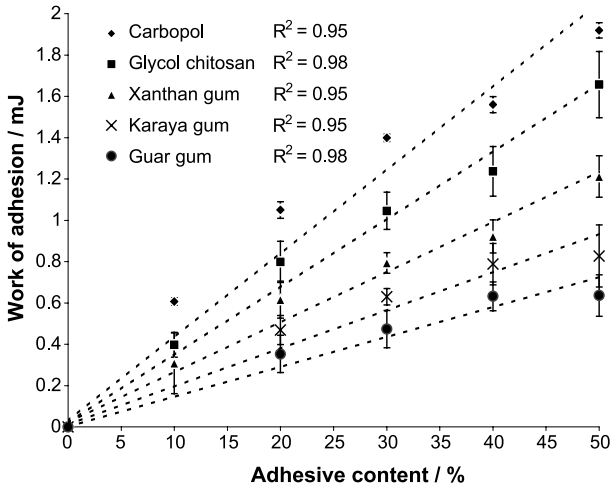

Figure 8. Work of adhesion (mJ) vs. adhesive content (%w/w) for buccal adhesive layers containing nicotine hydrogen tartrate ± S.D. (n = 5). (*View this art in color at www.dekker.com.*)

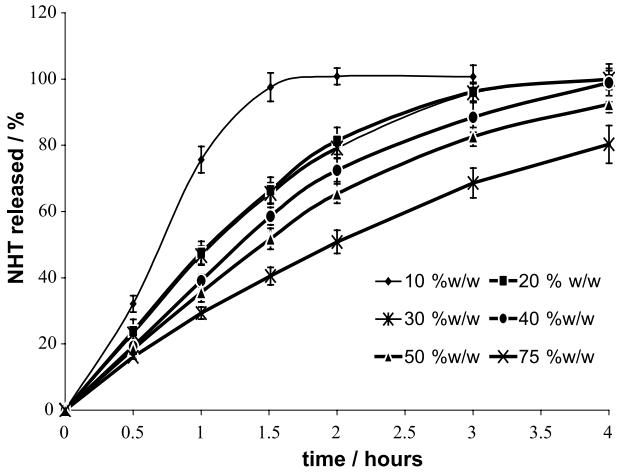

Figure 7. Nicotine hydrogen tartrate released (%) vs. time (hours) for buccal adhesive layers containing glycol chitosan ± SD (n = 5).

Glycol chitosan produces good adhesion to the mucosal surface and is second only to Carbopol values. This maybe due to the cationic nature of the polymer, which allows electrostatic interaction with the negatively charged mucus. This interaction, in addition to the physical entanglement of the polymer chains with the mucus, results in the higher values observed.

CONCLUSIONS

The tests performed in this study have allowed the characterization of some naturally occurring materials for potential use in buccal adhesive dosage forms. Guar gum was found to have weak adhesion and form a gel, which, despite the ability to sustain release of NHT in vitro, did not possess sufficient physical integrity for in vivo drug release.

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Karaya gum showed increased levels of adhesion as a result of an improved swelling profile compared with guar gum. Karaya gum also showed the ability to produce zero-order nicotine release until 4 hours but may require higher concentrations to provide longer sustained release.

Xanthan gum demonstrated a further improvement in adhesion again related to improved swelling of the formulations. Concentrations of 30–40% w/w xanthan gum were able to produce controlled NHT release over 4 hours at levels approaching zero-order while the 50% w/w formulation achieved zero-order release. This study provides evidence for the potential use of xanthan gum in buccal adhesive formulations.

Glycol chitosan produced strong adhesion to the buccal mucosa, probably due to electrostatic interactions with the negatively charged mucus layer. Formulations containing up to 50% w/w glycol chitosan released 100% NHT within 4 hours via a combined drug diffusion, matrix erosion mechanism. A 75% w/w formulation was able to produce an almost non-erodible matrix that was able to sustain NHT release at a level that was approaching zero-order nicotine release. These data suggest that glycol chitosan is a good mucoadhesive at lower concentrations, but the addition of a controlled-release excipient to help sustain NHT release may be required for a buccal adhesive dosage form.

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