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Mucoadhesive polysaccharides modulate sodium retention, release and taste perception

Sarah L. Cook[a], Samuel Woods[b], Lisa Methven[b,*], Jane K. Parker[b], Vitaliy V. Khutoryanskiy[a,*]

[a] Department of Pharmacy, University of Reading, Whiteknights, Reading, Berks RG6 6AD, United Kingdom
[b] Department of Food and Nutrition Sciences, University of Reading, Whiteknights, Reading, Berks RG6 6AD, United Kingdom

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ABSTRACT

The mucoadhesion between polymeric substances and mucosal membranes, widely exploited in the pharmaceutics industry to prolong drug residence, has been investigated as a means of retaining taste or aroma molecules in the oral cavity. This study shows that the mucoadhesive properties of carboxymethyl cellulose, a commonly used polysaccharide in the food and pharmaceutics industry, can modify retention, release and perception of sodium over time. A three-part study was designed coupling *in vitro* retention using *ex vivo* porcine tongue, sensory perception with a trained panel and *in vivo* retention of sodium ions in human volunteers. The findings suggest that although salt perception is stunted in samples containing a random coil, ionic, mucoadhesive thickener, the retention of sodium ions in the mouth is prolonged due to the mucoadhesive nature of the polysaccharide. Not only has this study-investigated mucoadhesion of liquid formulations in the oral cavity but it is also the first to link the mucoadhesive nature of a commonly used polysaccharide to the organoleptic properties of a food.

1. Introduction

Mucoadhesion describes the adhesive forces between a polymeric substance (a mucoadhesive) and a mucosal membrane in the body. The mucoadhesive strength between a polymer and mucosal surface will depend on many factors including the polymer characteristics and the target environment. In pharmaceutics, mucoadhesives can be incorporated into various formulations such as tablets, patches, films, sprays and viscous liquids containing an active pharmaceutical ingredient (API). The mucoadhesive polymer excipient can be designed to control the residence time and rate of release of the API. The mechanisms leading to mucoadhesion and the various techniques to assess the mucoadhesion of formulations have been described in the literature (Davidovich-Pinhas & Bianco-Peled, 2010; Nair et al., 2013; Peppas & Huang, 2004; Smart, 2014). However, mucoadhesion has not been fully exploited by the food industry as a means of retaining small molecules, such as tastants, at the mucosal surfaces in the mouth.

Mucoadhesion in the oral cavity has been investigated with a regard to enhancing delivery of a diverse range of APIs by the prolonged contact on these surfaces (Perioli, Ambrogi, Angelici, et al., 2004; Perioli, Ambrogi, Rubini, et al., 2004; Salamat-Miller, Chittchang, & Johnston, 2005; Yehia, El-Gazayerly, & Basalious, 2009). Target areas for drug delivery in the mouth include buccal and gingival epithelia as these are typically thinner and non-keratinised. Various food grade polysaccharides are considered as mucoadhesives because they enhance retention and can control the release of APIs in the oral cavity. These include food grade polysaccharides such as carboxymethyl cellulose (Yehia et al., 2009), sodium alginate (Richardson, Dettmar, Hampson, & Melia, 2004) and pectin (Thirawong, Nunthanid, Puttipipatkhachorn, & Sriamornsak, 2007).

Polysaccharides are employed in the food industry for their use as thickeners, emulsifiers and stabilisers. They are commonly employed to mimic the functions that fat imparts to a food matrix in reduced fat, liquid or semi-solid products such as increased viscosity, lubricity and bulk. Gums such as xanthan, guar and carrageenan, starches, and modified cellulose derivatives such as carboxymethyl cellulose (CMC) and hydroxypropyl methylcellulose are frequently used for such products. Although polysaccharides increase viscosity of liquid and semi-solid foods their chemical and physical properties vary drastically. For example, CMC is a linear polysaccharide made of β 1 → 4 linked glucose units with some of the hydroxyl groups substituted with carboxymethyl groups to render it soluble in water. Starch, on the other hand, is a branched polysaccharide consisting of glucose units joined by α 1 → 4 glycosidic bonds in the form of amylose (helical) or amylopectin (linear). Unlike CMC, starch swells within granules, unless gelatinised, limiting the formation of interconnecting chains.

* Corresponding authors.
E-mail addresses: L.methven@reading.ac.uk (L. Methven), V.Khutoryanskiy@reading.ac.uk (V.V. Khutoryanskiy).

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Many studies have investigated the impact on the sensory perception and *in vivo* aroma release when increasing liquid and semi-solid foods viscosity with polysaccharide thickeners (Boland, 2004; Cook, Linforth, & Taylor, 2003; Han et al., 2014; Keršiene, Adams, Dubra, Kimpe, & Leskauskaite, 2008; Koliandris, Lee, Ferry, Hill, & Mitchell, 2008; Secouard, Malhiac, Grisel, & Decroix, 2003). It is well known that an increase in viscosity results in a stunted perception of most tastants and some aromas. This is very apparent at the critical point where random coils of polymers in solution begin to overlap and pass one another, referred to as the coil overlap concentration (c^*) (Hollowood, Linforth, & Taylor, 2002). However, the temporal release and perception of these compounds, particularly the non-volatile components, is seldom investigated. Of these that have used temporal experiments, the adhesive nature of polysaccharides has never been investigated separately to perception and only seldom alluded to as a potential mechanism (Mälkki, Heiniö, & Autio, 1993).

Flavour balance is a challenge presented in low fat food formulations as the reduction of the hydrophobic matrix of a food results in the increased release of hydrophobic aroma compounds from food matrices. This results in an aroma release that peaks and rapidly falls compared to higher fat counterparts where the release is more uniform over time (Malone & Appelqvist, 2003). Furthermore, the relative increase in the hydrophilic component of the food can reduce the perception of hydrophilic tastants such as sodium (Boisard et al., 2014). Flavour perception is a combination of the senses of taste and smell, with tastants and aroma molecules having a complex relationship that results in signals transmitted to the brain interpreting the flavour of a food. It has been shown in numerous studies that perception of taste influences aroma perception, even when the in-nose aroma concentration stays the same (Cook et al., 2003; Koliandris et al., 2008). Therefore, if mucoadhesives can deliver tastants at a lower rate over time, then aroma perception may be adjusted accordingly, resulting in a product with a flavour profile like that of a high fat product.

Lian, Malone, Homan, and Norton (2004) and Malone and Appelqvist (2003) attempted to prolong aroma delivery using gelled emulsion particles of calcium alginate. The results suggest that aroma release can be controlled by particle size. Emulsions and encapsulation of aromas have been widely researched, however, utilising mucoadhesion to prolong flavour delivery is a relatively novel concept. For the past few decades mucoadhesion has been researched in relation to pharmaceutical applications, however, more recently the potential for their use in food products to prolong flavour delivery has been considered (Le Révérend, Norton, Cox, & Spyropoulos, 2010; Malone, Appelqvist, & Norton, 2003; Modh & Bakalis, 2011). This current study investigates the temporal retention, release and subsequent perception of a tastant, sodium chloride, in a model liquid food prepared containing two different polysaccharide thickeners and water. Firstly, the retention of matrices was tested on *ex vivo* porcine tongue to determine differences in residence time between each matrix. Mucoadhesion on the dorsal mucosa of the tongue has been reported in only one study to date which investigated the binding of different milk proteins to distinct areas of the tongue in an attempt to explain negative sensory attributes such as drying (Withers, Cook, Methven, Godney, & Khutoryanskiy, 2013). Therefore, this current study is the first to develop a method for assessing the adhesion of viscous polysaccharide solutions to *ex vivo* porcine tongue tissue.

We are the first to show that food grade mucoadhesives are retained on the tongue *in vitro*, alter the temporal perception of saltiness over time compared to non-mucoadhesives, and prolong sodium retention in the mouth despite a reduction in perception. Perception data was collected after consuming samples by a progressive profiling method to understand changes in perception over time. Furthermore, an *in vivo* retention experiment was developed to ascertain the differences in sodium levels retained by the mucoadhesive sample compared to non-mucoadhesive samples. Our hypothesis is that mucoadhesives may retain tastant and aroma molecules, extending the residence time in the oral cavity, delaying release and prolonging flavour perception.

2. Methods

2.1. Materials

The 3 matrices were prepared for all parts of this experiment; they were all aqueous solutions made with deionised water, or deionised water plus sodium carboxymethyl cellulose (CMC) as the mucoadhesive polysaccharide, or an amylase resistant starch (Nutrilis brand, Boots UK Ltd). The CMC used was kindly provided by Akucell upon request (sample code: AF0305, molecular weight of 140 kDa and a substitution degree of 0.8). The starch was purchased from a local Boots store to be used for thickening liquids for patients with dysphagia. It is a modified maize starch resistant to amylase due to its composition with more amylose units than amylopectin. Other minor ingredients in the amylase resistant starch are maltodextrin, xanthan gum, tara gum and guar gum.

The aqueous samples were freshly prepared on the day that they were used for analysis. Both CMC and starch were dispersed in deionised water to obtain a final concentration of 2.6% (w/w). CMC samples were prepared on the morning before experiments and left in the fridge for at least 3 h to remove air bubbles. Starch and water samples were prepared no longer than 30 min before commencing experiments to prevent the starch from thinning. All samples contained the same concentration of sodium (final concentration 0.18% Na^+ or 786 μM) either from NaCl salt added or Na^+ inherently present in the polysaccharide. The CMC contains a high amount of Na^+ to make it soluble in water. Flame photometry (Economical Flame Photometer; 230 VAC, 50/60 Hz) was used to determine the amount of Na^+ in CMC (51.5 mg/g) and therefore, the amount of NaCl added to these samples was adjusted to account for this inherent sodium concentration. This ensured that the dosage of sodium in each matrix was the same, but the amount of accompanying chloride was different.

The viscosities of the CMC and the starch sample were determined using a TA AR2000 rheometer with 40 mm parallel plate geometry (TA Instruments, Herts, UK). After the initial amplitude sweep to determine the linear viscoelastic regions of the samples, the amplitude was set to 1% strain and frequency sweeps were then carried out to determine the complex viscosity over increasing frequency (Fig. S1a & b). Various concentrations of CMC were measured to match the 2.6% (w/w) starch viscosity (55 mPa.s) at a shear rate of 50 rad/s (Fig. S3) as this is typically quoted as the shear rate in the mouth (Richardson, Morris, Ross-Murphy, Taylor, & Dea, 1989; Wood, 1968).

2.2. Ex vivo retention experiments

A dynamic retention method previously developed by Khutoryanskiy and coworkers (Cave, Cook, Connon, & Khutoryanskiy, 2012; Cook, Smith, & Khutoryanskiy, 2015; Irmukhametova, Mun, & Khutoryanskiy, 2011; Withers et al., 2013) was adapted for this experiment. The retention experiment allows indirect quantification of the amount of sample retained on a mucosal surface after being repeatedly washed with an artificial eluent. To visualise retention of the sample sodium fluorescein (0.01%) was added to the solutions prior to placement on the tissue. For this experiment, *ex vivo* porcine tongue was used as the mucosal surface and an artificial saliva (AS) formulation was used as adapted from Madsen, Sander, Baldursdottir, Pedersen, and Jacobsen (2013), as the eluent. This AS recipe was found to best simulate the retention profile achieved with real human saliva (Madsen et al., 2013). The AS was comprised of $CaCl_2$ (4 mM), KCl (10 mM), $NaHCO_3$ (2 mM), NaCl (7 mM), KH_2PO_4 (6.7 mM) and pig gastric mucin (2.5 % w/v) (Sigma Aldrich Poole, UK).

2.2.1. Tissue preparation

Pig tongues were collected up to 24 h post slaughter from P & D