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Oil-based compositions as saliva substitutes: A pilot study to investigate in-mouth retention

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ABSTRACT

Objectives: This pilot study aimed to compare the in-mouth retention of an oil-based saliva substitute (emulsion, consisting of rice bran oil, soy lecithin and water) with water and a 1% w/v methylcellulose suspension (polymer) in healthy volunteers.
Methods: Each formulation was tagged with 1 mmol/L lithium and participants (n = 30) rinsed their mouth with one randomly assigned formulation (emulsion, polymer or water) for 30 s, before expectorating into a cup. Concentration of lithium expectorated was measured and amount of each formulation remaining in the mouth was estimated. Patient acceptability was investigated using questionnaires, and Fourier-Transform Infrared spectroscopy (FTIR) was used to determine the presence of oil in expectorated samples.
Results: Immediately after rinsing, taste was rated lower in the emulsion group compared to the polymer or water groups ($p > 0.05$), although variability was high. Mean retention was highest in the emulsion group, with a difference of $8.34 \pm 2.71\%$ ($p = 0.003$) and $4.57 \pm 2.71\%$ ($p = 0.06$) compared with the water and polymer groups, respectively. FTIR confirmed the presence of oil in all expectorated emulsion samples.
Conclusion: The emulsion was not inferior to the polymer in terms of retention immediately after rinsing. The next step is to conduct larger clinical studies over longer time periods in participants with salivary hypofunction.

1. Introduction

Xerostomia, defined as the subjective feeling of dry mouth, is often associated with a severe reduction in the quality or quantity of saliva produced, leading to a number of complications that severely impact the quality of life of sufferers (Thomson, 2007). There are numerous rinses, lozenges, toothpastes, sprays, gels and chewing gums available to alleviate dry mouth symptoms, but their efficacy is limited by their short duration of action and many individuals report a preference for sipping water frequently throughout the day and night (Epstein and Stevenson-Moore, 1992; Ferguson and Barker, 1994; Olsson and Axell, 1991; Sweeney et al., 1997). In a Cochrane review of topical saliva substitutes published in 2011, it was concluded that there was no strong evidence that any specific topical intervention was effective for symptomatic relief of dry mouth (Furness et al., 2011). The fundamental issue is that in the absence of continual secretion, a saliva substitute must be retentive in the oral cavity. Although many commercial saliva substitutes are available, only one extemporaneously compounded product (1% w/v methylcellulose in water) (Wilson et al., 2012) is Government-funded in New Zealand. Water is often the preferred treatment option for xerostomia (Epstein and Stevenson-Moore, 1992; Ferguson, 2002), but offers only temporary relief and fails to lubricate oral surfaces (Ferguson, 2002; Frost, 2008).

Saliva is shear thinning and has a unique viscoelasticity, for which glycoproteins such as mucin are thought to be responsible (Yakubov et al., 2009). While researchers have identified the importance of rheological properties in the efficacy of potential saliva substitutes (Salom et al., 2015; Vissink et al., 1984), much of this work has focused on the use of mucin-based substitutes, as these have comparable rheological properties to natural saliva (Park et al., 2007; Yakubov et al., 2009). However, saliva is intrinsically regulated and continually secreted in response to a range of both internal and external factors (Catalan et al., 2009; Edgar et al., 2004; Melvin et al., 2005; Sreebny et al., 1992). Hence, a

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saliva substitute needs to remain in the oral cavity for extended periods of time. While rheological properties are thought to be important in developing effective saliva substitutes, retention in the absence of continual secretion is a key consideration and therefore, the rheological profile of an effective substitute can be expected to differ from natural saliva. This might explain why many comparative studies fail to find any significant difference in the efficacy of mucin-based substitutes compared to placebo (Sweeney et al., 1997). Emulsions are hypothesised to offer advantages over current substitutes by combining the moisturising and lubricating properties of oil with the palatability of water. Emulsions consist of both an oil and aqueous phase. Therefore, they are potential delivery systems for both lipid-soluble and water-soluble excipients. Previous research has examined the physicochemical properties of emulsions composed of rice bran oil (RBO), lecithin and water (Hanning et al., 2013a). Compositions with frequency-dependent rheological behavior are thought to offer sustained relief of xerostomia, with viscous properties at low frequencies improving lubrication at rest and elastic behaviour at higher frequencies improving retention during high-shear tasks such as swallowing and speaking.

Sensory perception is important when considering patient acceptability (Momm et al., 2005). Studies of the sensory perception of foods in the oral cavity often use quantitative 100-mm continuous scales (Ali et al., 2011; Kilcast and Clegg, 2002; van Aken et al., 2011) with anchor points appropriate to the property being tested, such as 'like extremely' and 'dislike extremely' in order to determine overall taste acceptability. Emulsion droplets have been shown to influence textural sensory perception of liquid emulsions by incorporating into the coating in the oral mucosa, increasing the viscosity and spreading of oil at surfaces in the oral cavity (van Aken et al., 2011). The feeling of textural thickness has been demonstrated to be directly proportional to the viscous force between the tongue and the roof of the mouth (Kokini et al., 1977).

The aim of this study was to estimate the oral retention of a selected emulsion containing 20% w/w RBO, 40% w/w surfactant mix and 40% w/w water after rinsing, compared with water and a polymer solution. Retention was investigated using lithium ions as a marker (Hanning et al., 2013b) Sensory perception, which is an important consideration for patient acceptability, was also tested.

2. Materials and methods

2.1. Materials

Lithium carbonate was purchased from Merck KGaA (Darmstadt, Germany). A 100 mmol/L, pH 7.4 sodium phosphate buffer was prepared using sodium dihydrogen phosphate and disodium hydrogen phosphate (Sigma Aldrich, St. Louis, MO, USA). Propylene glycol was also from Sigma Aldrich (St. Louis, MO, USA). Methylcellulose was purchased from ABM Pharma Ltd. (North Shore City, New Zealand), RBO was from Bespoke Foods (UK) and Lipoid S-100 soy lecithin was purchased from Lipoid GmBH (Ludwigshafen, Germany). Distilled water was used where required and all materials were used as received without any further purification.

2.2. Preparation of formulations

The aqueous rinse ('water') was prepared by spiking the sodium phosphate solution (100 mmol/L, pH 7.4) with 1.0 mmol/L lithium as described previously. (Hanning et al., 2013b) The standard saliva substitute ('polymer') was prepared by suspending 1% w/v methylcellulose in distilled water spiked with 1.0 mmol/L lithium. The emulsion ('emulsion') was prepared in the same way as described previously, (Hanning et al., 2013a) using a composition of 20% w/w RBO, 40% w/w soy lecithin and propylene glycol at a weight ratio of 1:1 (surfactant mix; SM) and 40% w/w water. The aqueous phase was spiked with 1.0 mmol/L lithium. Formulations were used within 48 h of preparation and refrigerated before being brought to room temperature one hour prior to use.

2.3. Test procedure for determining the retention of formulations

This parallel study was independently reviewed and approved by the University of Otago Ethics Committee (Dunedin, New Zealand, reference code 12/252) and took place in a single clinic at the University of Otago, New Zealand. Thirty participants aged between 19 and 36 (median age 27) gave informed consent to participate. All were dentate individuals who considered themselves to be in good general health. Participants taking antipsychotic/anxiolytic (including lithium), antimicrobial, antineoplastic, antiepileptic or cardiovascular medication within one month of recruitment were excluded from the study. Subjects were asked to refrain from eating or drinking for 60 min prior to participation. Each participant was randomly assigned to the water, polymer or emulsion group using a three-digit random integer generator (Haahr and Haahr, 2012) so that there were ten participants in each group. The study was single-blinded in that participants were unaware of their group allocation. Each participant rinsed their mouth with 200 mL tap water, swallowed any residual saliva, then basal salivary flow rate was measured using the expectorating technique (Hanning et al., 2013b; Stokes and Davies, 2007). The mass expectorated over five minutes was determined immediately to establish a basal salivary flow rate (mL/min) for each participant, where the density of saliva was assumed to be 1 g/mL (Kerr, 1961; Lentner, 1981).

Each participant gently swilled 10 mL of their assigned formulation for 30 s before expectorating into a cup in a single discharge. Expectorated mass was determined immediately and participants ranked the taste, intensity and thickness of their formulation using a 100-mm continuous analogue scale labelled with anchors 'like extremely' and 'dislike extremely' for taste acceptability; 'extremely intense' and 'not intense at all' for intensity in the mouth; and 'the thickness of water' and 'the thickness of yoghurt' for perceived thickness. Participants remained seated for a further five minutes, during which time they were able to speak and swallow as normal, before swilling 10 mL water around their mouth for 30 s. This was expectorated into a pre-weighed collection cup, mass was determined and a further assessment form completed. This process was repeated again after another five minutes.

Expectorated samples were centrifuged using a centrifugal device with 0.45 μm filter (Pall Corporation, Ann Arbor, MI, USA) for ten minutes (3220*g*, 4 °C) to remove contaminants from the aqueous phase and in the case of the emulsion group, separate the aqueous phase from the emulsion. The concentration of lithium in the aqueous filtrate was analysed in a clinical laboratory (Southern Community Laboratories, Dunedin, New Zealand) using Cobas C® lithium reagent (Roche Diagnostics, Mannheim, Germany), to determine the concentration of lithium expectorated (C_{exp}). The amount of liquid retained in the mouth was then estimated using Eq. 1, where initial volume (V_i) was 10 mL, initial concentration (C_i) was measured lithium concentration in each initial formulation and V_{exp} was volume expectorated.

$$\text{Liquid retained}(\%) = \left(\frac{(C_i V_i) - (C_{exp} V_{exp})}{(C_i V_i)}\right) \times 100 \quad (1)$$

FTIR measurements were performed using a Varian 3100 Excalibur Series FTIR spectrometer (Varian Incorporated, California,