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Dry mouth diagnosis and saliva substitutes – A review from a textural perspective

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Abstract

The aim of this review is to assess the objective and subjective diagnosis, as well as symptomatic topical treatment of dry mouth conditions with a clear focus on textural perspective. We critically examine both the current practices as well as outline emerging possibilities in dry mouth diagnosis and treatment, including a patent scan for saliva substitutes. For diagnosis, salivary flow rates and patient-completed questionnaires have proven to be useful tools in clinical practice. To date, objective measurements of changes in mechanical properties of saliva *via* rheological, adsorption and tribological measurements and biochemical properties of saliva such as assessing protein, mucins (MUC5B) are seldom incorporated into clinical diagnostics; these robust diagnostic tools have been largely restricted to application in non-clinical settings. As for symptomatic treatments of dry mouth, four key agents including lubricating, thickening, adhesive and moisturizing agents have been identified covering the overall landscape of commercial saliva substitutes. Although thickening agents such as modified celluloses, polysaccharide gum, polyethylene glycol (PEG) *etc.* are most commonly employed saliva substitutes, they offer short-lived relief from dry mouth and generally do not provide boundary lubrication properties of real human saliva. Innovative technologies such as self-assembly, emulsion, liposomes, microgels are emerging as novel saliva substitutes that hold promise for alternative approaches for efficient moistening and lubrication of the oral mucosa. Their adoption into clinical practice will be dependent on their efficacies, duration of relief, ease of application by the practitioners and patient compliance.

Keywords

Dry mouth, xerostomia, diagnosis; symptomatic treatment; rheology; tribology; adsorption; thickening agents; mucoadhesives; lubricants

1. Introduction

Xerostomia, clinically defined as the subjective complaint of "dry mouth" has an estimated prevalence of approximately 20% in the general population. The prevalence increases to 46% in older people aged >75 years, attributable in part to co-morbidity conditions and polymedication/ polypharmacy (Orellana *et al.*, 2006). Other causes, include, but not limited to, autoimmune exocrinopathy (*e.g.* primary Sjögren's syndrome (pSS), see Figure 1), radiotherapy, sarcoidosis, HIV, hepatitis C and poorly-controlled diabetes mellitus (Mortazavi *et al.*, 2014). Xerostomia has a detrimental impact on quality of life affecting the most essential activities such as speaking and eating, with dysphagia inhibiting easy entrance of nutrients and increases the risks of malnutrition (Vainshtein *et al.*, 2016). Furthermore, it increases the risk of dental complications such as, caries, periodontal disease, candidiasis, and oral ulceration (Hopcraft and Tan, 2010). Xerostomia patients may have both hyposalivation and also alteration in salivary composition (Jellema *et al.*, 2005; Mortazavi *et al*., 2014; Villa and Avati, 2011). It is also worth noting that xerostomia patients may or may not have hyposalivation, which is a sign of abnormally lower salivary flow rate. For example, besides hyposalivation, dehydration (in elderly or dialysis patients) could also result in xerostomia (Mortazavi *et al*., 2014). Xerostomia represents an enormous and growing health burden resulting from an increase in the global aging population and highlights the need for more effective topical dry mouth therapies (Ship *et al.*, 2002; Guggenheimer and Moore, 2003).

[Insert Figure 1 here]

Hyposalivation may lead to impairment in both the quantity and quality of saliva. Saliva, which is constituted mainly of water (99%), ions and proteinaceous compounds such as

mucins, amylases and others low molecular weight proteins (Sarkar *et al.*, 2019b), plays an important role in assuring the general and oral health as well as oral processing of food. It is generally the proteins that render saliva its rheological (viscosity, elasticity, stickiness), unique water-holding and lubrication properties (Alliende *et al.*, 2008; Tanasiewicz *et al.*, 2016; Sarkar *et al.*, 2017). Various functions of saliva can be classified into two aspects: 1) *protection of the oral tissues* including lubrication, dilution, antimicrobial activity, cleansing activity, buffering action, remineralisation and tissue repair, and 2) *facilitating speech and oral processing* including food disintegration and digestion, bolus formation and swallowing, medium for flavour and aroma compounds diffusion (Carpenter, 2013; Dodds *et al.*, 2015).

To address dry mouth conditions, various topical therapies are employed. Typical therapies for dry mouth can be classified into three main groups: 1) salivary stimulants, 2) symptomatic treatments and 3) emerging regenerative and gene therapies (Salum *et al.*, 2018).

Salivary stimulants are most commonly used but require some the salivary gland tissue to be functional. There are broadly three ways to stimulate the salivary secretion: acid, pharmaceutical and mechanical approaches. Citric and malic acids are the most commonly used as plant acids to stimulate the salivary secretion, the mechanism is that the topical acidification of the oral environment generates stimulation of salivary secretion to dilute the acid concentration (Han *et al.*, 2015; Salum *et al.*, 2018). Although improvement in dry mouth condition is shown by acid-based salivary stimulants, application of acid may increase the risk of dental erosion and hypersensitivity (da Mata *et al.*, 2009). Besides citric acid, umami taste substance like monosodium glutamate has been also found to stimulate

100 salivation (Sasano *et al.*, 2015).

101 Pilocarpine is the most commonly used pharmacological systemic medication given in a
102 tablet form typically for relieving the symptoms of radiotherapy-induced xerostomia; it
103 functions as muscarinic receptor agonists stimulating the secretion of saliva (Gil-Montoya
104 *et al.*, 2016). However, based on a recent meta-analsyis carried out using 39 studies that
105 randomised 3520 participants (Riley *et al.*, 2017), it can be inferred that insufficient
106 evidence exist to determine whether or not pilocarpine performed better or worse than a
107 placebo in terms of treatment of xerostomia, salivary flow rate, survival, and quality of life.
108 Thus, the pharmacological proposed benefits of pilocarpine can be questioned. In addition,
109 pilocarpine, as a parasympathomimetic drug can lead to adverse pulmonary and
110 cardiovascular side effects (Bernardi *et al.*, 2002) Mechanical salivary stimulation on the
111 other hand includes use of chewing gums, acupuncture, and electrostimulation, among
112 which sugar-free chewing gum is widely used because it is an easy way to mechanically
113 stimulate salivary secretion without side effects (Davies, 2000; Han *et al.*, 2015; Łysik *et*
114 *al.*, 2019).

115

116 **Symptomatic treatments** of dry mouth aim to moisten the oral mucosa (Narhi *et al.*, 1999).
117 The most frequently used symptomatic therapies include some form of water intake or
118 hydrating materials and commercial saliva substitutes (Salum *et al.*, 2018). Although fluid
119 intake can be useful for temporary relief of dry mouth symptoms (Łysik *et al.*, 2019), other
120 functions of saliva such as coating and lubrication cannot be achieved by this approach.
121 Existing commercial saliva substitutes in different forms like cleansers, sprays and gels are
122 commonly based on thickening agent and moisturizing agent such as cellulose-based
123 polymers (*e.g.* carboxymethyl cellulose (CMC)) and water-soluble polymers such as
124 xanthan gum, glycerine and carbomer (Nieuw Amerongen and Veerman, 2003; Oh *et al.*,

2008; Han *et al.*, 2015). It is thus important to understand how far these polymers are successful in mimicking the techno-functionalities of real human saliva.

Experimental regenerative and gene therapies to ameliorate dry mouth conditions are currently under development. Regenerative therapies aim to attenuate salivary gland dysfunction, whereas stem cell and gene therapies aim to repair or prevent the salivary glands damage by gene transfer (Lombaert *et al.*, 2008; Samuni and Baum, 2011).

With this overview in mind, the aim of this review is to examine the measurable symptoms of dry mouth and saliva properties as well as critically examine the saliva substitutes focussing on textural aspects, such as lubrication and adsorption properties. In particular, a key objective is to provide a concise overview on several challenges associated with dry mouth diagnosis and therapy and discuss how the food textural research community might contibute to overcome them. Firstly, we discuss the various approaches for diagnosis of dry mouth to identify the objective versus subjective assessment of dry mouth conditions clearly highlighting the type of dry mouth therapies needed for most patients. We also highlight what kind of diagnostic tools can be used in the future to estimate the objective changes in biochemical, rheological, adsorption and tribological quality of saliva in dry mouth patients. Then, we critically analyse the common formulation agents of salivary substitutes highlighting the importance of tribological (*i.e.* friction, wear and lubrication) and adhesive properties. We also evaluate the patents over the last two decades to clearly pinpoint the latest advancements in development and highlight the development needed for salivary substitutes. Specifically, our focus is on salivary substitutes for symptomatic treatments. Formulations with active stimulants or medicines are beyond the scope of this review. Complementary reviews that focus on therapeutic trials of salivary substitutes are

150 available (Brennan *et al.*, 2002; Furness *et al.*, 2011; Salum *et al.*, 2018; Assery, 2019; See
151 *et al.*, 2019). Abbreviations used throughout this review article are shown in Table 1.
152
153 [Insert Table 1 here]
154
155
156 ## 2. Diagnosis of dry mouth — objective and subjective assessment
157 Generally, diagnosis of xerostomia starts with a thorough evaluation of medical history,
158 focusing on the illness and past medical history of the patients in a clinical setting (Kho,
159 2014). The key diagnosis method that have been used are generally subjective in nature
160 such as questionnaires with rating scales for patients to fill and complementary objective
161 assessment such as salivary secretion tests (Fox *et al.*, 1987). Although other tests
162 deploying different imaging techniques (*e.g.* sialography and scintigraphy) were reported
163 for dry mouth diagnosis, their usage is limited by the invasive character or high cost. In
164 some medical settings, ultrasound is gaining interest as a useful diagnostic tool (Martire *et*
165 *al.*, 2018). Other measurements that have been primarily used in research settings to assess
166 salivary properties (*e.g.* salivary biochemical composition, adsorption, rheological and
167 tribological tests) might also be utilized for aiding the diagnosis of dry mouth in the future
168 and are discussed in the following sections.
169
170 ### *2.1 Questionnaires*
171 Questionnaires have played an important role in the evaluation of xerostomia. Since
172 xerostomia is a subjective complaint, questionnaires on dry mouth do not always reflect the
173 true hyposalivation. However, it is useful to identify certain questions that may predict true
174 salivary dysfunction. For instance, evaluation of the relationship between subjective

symptoms and objective salivary flow often helps in more efficient diagnosis of hyposalivation than using questionnaires alone (van der Putten *et al.*, 2011). Table 2 summaries the major xerostomia questionnaires developed from 1987 to 2007, where a relationship with objective salivary flow rates has been established, with three classical evaluation systems being included *i.e.* binary scale, categorical scoring scale and visual analogue scale (VAS).

[Insert Table 2 here]

Fox *et al.* (1987) employed useful questions in identifying salivary gland output dysfunction. They found that the responses to eating-dryness related questions (question 6-8) (Table 2) and saliva quantity question (question 9) were highly indicative of true salivary output deficiency reflected by stimulated and unstimulated flow, while questions concerning the presence or relief behaviour of mouth dryness (question 1-5) were not correlated significantly with the salivary hypofunction. The Xerostomia Inventory (XI) (Thomson *et al.*, 1999) was developed acting as a multi-item instrument estimating the severity of xerostomia symptoms with a continuous scale. Eleven items covering both experiential (experiences of awareness of dry mouth conditions *e.g.* "my mouth feels dry when eating a meal") and behavioural (consequent behaviours *e.g.* "I sip liquids to aid in swallowing food") aspects of patients' experiences of dry mouth, and the responses to these items were summated to give a single XI scale score. Although the resulting score had a very low correlation with resting saliva flow rate, it had a positive and much stronger correlation than the standard single dry-mouth question responses, and the XI itself showed concurrent validity (Thomson and Williams, 2000).

Pai, Ghezzi, & Ship (2001) developed an eight-item VAS questionnaire for hyposalivation diagnosis. Seven items (Table 2) showed significant reliability, while only one question ("rate how much saliva is in your mouth") regarding the quantity of saliva in mouth was not significantly correlated. Five items (1, 2, 3, 5 and 6) show significant validity with unstimulated submandibular saliva flow rates. Only item 1 and 6 were significantly correlated for stimulated submandibular flow rates, while only item 2 was significantly correlated for stimulated parotid flow rates.

Suh *et al.* (2007) developed a questionnaire with a combination of a binary scale, categorical scoring scale and VAS to evaluate the relationship between subjective dry mouth symptoms and salivary flow rate. They reported that the duration and frequency of oral dryness or usage of chewing gum are not significantly associated with salivary flow rate, while dry mouth-related symptoms and behaviours like awakening from sleep at night because of oral dryness were significantly associated with whole salivary flow rate. Comparing all these four questionnaires (Table 2) and their relationship with salivary flow rate indicates that the questions regarding the behaviour to relieve dry mouth like chewing gum and candy intake are less related to salivary flow rate, while dry mouth symptoms and eating behaviour related questions are more predictive for diagnosis of salivary dysfunction.

2.2 Salivary secretion test

Salivary secretion test is the most advocated clinical method for diagnosis of salivary dysfunction, which is typically defined by an unstimulated whole saliva flow rate *i.e.* less than 0.1 mL/min or a stimulated whole saliva flow rate *i.e.* less than 0.5-0.7 mL/min (Löfgren *et al.*, 2012). Accurate and standardized method for measurement of salivary secretion is essential since the quality and quantity of saliva are significantly affected by

the sources and methods used for saliva collection (Navazesh and Kumar, 2008). Different sources for saliva collection are from mixed or individual glands corresponding to whole saliva and individual gland saliva, respectively. While the unstimulated saliva is mainly secreted by submandibular glands, the stimulated saliva is mainly contributed by parotid glands (Navazesh and Kumar, 2008). Methods of whole saliva collection include draining method, spitting method, suction method and swab method (Navazesh, 1993). Among them, draining and spitting methods by dripping saliva off the lower lip or spitting the saliva from the floor of the mouth are reproducible and reliable for unstimulated whole saliva collection (Navazesh and Christensen, 1982). While the suction method and swab method by saliva ejector or pre-weighed saliva adsorption swab were found to be less reliable with some degree of variability, and thus were not recommended.

To stimulate whole saliva secretion, standard-sized gum base, paraffin wax, rubber bands and citric acid are commonly used, and spitting method is suitable for stimulated whole saliva collection (Navazesh and Kumar, 2008). As for individual gland saliva collection, custom-made collection devices are commonly required. For example, the parotid gland saliva is typically collected by the Lashley cup or Carlson–Crittenden collector, the submandibular and sublingual glands saliva is commonly collected through Wharton duct, and the minor salivary gland secretions can be collected by filter paper (Lashley, 1916; Eliasson and Carlén, 2010). By using the afore-mentioned collection methods, the salivary flow rate can be calculated as weight or volume of collected saliva divided by collection period time (Navazesh and Kumar, 2008). Saliva collection from individual gland is more reliable compared with whole saliva collection which, is a mixture of saliva, fluids, debris and oral mucosal cells. The flow rate of unstimulated parotid saliva was reported as 0.04 and 0.00 mL/min/gland for healthy controls and pSS patients, respectively (Pedersen *et al.*,

2005). Therefore, the techniques for individual glands are tedious and impractical with extremely limited salivary flow rate (Navazesh and Kumar, 2008)

2.3 Potential diagnostic tests for use in future

Salivary quantity and flow rate vary dramatically within and between individuals. In addition, accurate assessment of dry mouth according to the quantity of saliva is difficult. Therefore, biochemical and mechanical measurements offer promise to support diagnostic tests for dry mouth. Saliva quality in terms of its compositional feature and mechanical properties such as adsorption, rheological and tribological properties have been studied in research setting over the last decade. These tests can be employed to understand the changes in salivary quality in mechanical terms in dry mouth patients, which is discusesd in the following subsections.

2.3.1 Biochemical composition measurements

One obvious change in the saliva of dry mouth patients is the alteration in biochemical composition, while detailed changes in saliva depends on the particular cause of hyposalivation. For example, increased Na^+, K^+, Cl^-, Ca^{2+}, immunoglobulin A (IgA) and amylase were found in patients with oral sensorial complaints who were not having any psychiatric disorders or any major diseases such as cancer or sepsis (Granot and Nagler, 2005). Increased calcium, parathyroid hormone (PTH) and cortisol concentrations, in contrast to decreased oestrogen and progesterone concentrations were found in menopausal women with xerostomia (Agha-Hosseini and Moosavi, 2013). Reduced sulfation of mucin was found in pSS patients with xerostomia (Alliende *et al.*, 2008).

Mucin plays an important role in the rheological, tribological and surface adsorption properties of saliva, mainly because of their highly hydrated oligosaccharide side-chains,

275 "bottlebrush" configuration *i.e.* oligosaccharide chains like "brushes" are attached to
276 protein backbone of mucin and negatively charged sialic acid residues (Coles *et al.*, 2010;
277 Xu *et al.*, 2019). MUC5B (~1 to 20 MDa) and MUC7 (~150 kDa) are two major physically
278 distinct salivary mucins that are rich in *O*-glycosylation with an extended linear structure
279 and a high degree of sialylation (Thomsson *et al.*, 2002; Morzel *et al.*, 2014). Structural
280 changes of these two mucins have been found in dry mouth patients (Alliende *et al.*, 2008;
281 Dijkema *et al.*, 2012; Chaudhury *et al.*, 2015; Chaudhury *et al.*, 2016). For example, relative
282 levels of sulfo-MUC5B were found to be substantially decreased in gland extracts from
283 patients with Sjögren syndrome and dry mouth (n=10) as compared with the healthy control
284 group (n=9), indicating a notable reduction of MUC5B sulfation level in the former group
285 (Figure 2a) (Alliende *et al.*, 2008). Reduced MUC5B and MUC7 glycosylation were also
286 found in patients with Sjögren syndrome associated oral dryness, although the mucin
287 concentrations were found to be similar between the patients and the control group
288 (Chaudhury *et al.*, 2016). These findings indicate that changes in mucin quality are
289 indicative of dry mouth symptoms and could be a potential objective diagnostic tool for
290 xerostomia patients with pSS.
291
292 *2.3.2 Rheological measurements*
293 Researchers have demonstrated that rheological properties of saliva alter in dry mouth
294 patients (Chaudhury *et al.*, 2015) or with growing age (Pushpass *et al.*, 2019a). Figure 2b
295 shows that patients complaining of xerostomia (n=34) exhibited significantly lower saliva
296 spinnbarkeit (*i.e.* extensional viscosity) in comparison to healthy control subjects (n=30)
297 (Chaudhury *et al.*, 2015). Such statistically significantly reduction ($p < 0.05$) in saliva
298 spinnbarkeit is also shown in another study with Sjögren's patients (n=21) as compared to
299 healthy controls (n=30) (Chaudhury *et al.*, 2016).

300

301 [Insert Figure 2 here]

302

303 Viscosity is another important rheological property which is usually used as an essential
304 objective assessment of mechanical properties of both saliva and salivary substitutes.
305 Viscosity changes of unstimulated human saliva in different age and gender groups have
306 been reported (Gittings *et al.*, 2015). As shown in Figure 2c, the viscosity of unstimulated
307 saliva for the age group 28-35 (n=8) was significantly higher than that of 20-27 (n=22) at
308 low shear rate region. The viscosities of unstimulated saliva in males (n=13) were reported
309 to be higher than those in females (n=17). In another study, a slightly higher viscosity was
310 found for unstimulated whole saliva of younger groups (1.73± 0.2 mPa·s, 18-30 years old,
311 n=30) compared with older groups (1.55 ± 0.2 mPa·s, 60+ years old, n=24) (Pushpass *et*
312 *al.*, 2019b). To the best of authors' knowledge, no study exist comparing the salivary shear
313 viscosity of dry mouth patients versus healthy controls. Nevertheless, these aforementioned
314 salivary viscosity measurements suggest potential use of flow curve as a reproducible tool
315 to indicate age-dependent alteration of salivary viscosity in dry mouth patients in the future
316 (Schein *et al.*, 1999).

317

318 *2.3.3 Adsorption measurements.*

319 Both MUC5B and MUC7 are major constituents of the mucosal pellicle which coats and
320 protects the oral surface (Thomsson *et al.*, 2002; Morzel *et al.*, 2014). Therefore, changes
321 of these two mucins can lead to an alteration of pellicle properties. One quantitative
322 approach to measure the adsorption properties of salivary pellicles is quartz crystal
323 microbalance with dissipation monitoring (QCM-D), which is a real-time, surface sensitive
324 technique for analysis of layer properties, surface phenomena, and to derive quantitative

information on thin film formation on a substrate (Veeregowda *et al.*, 2012; Ash *et al.*, 2014). For example, the real-time dissipation and frequency profiles of whole mouth saliva (n=10) pellicle and parotid saliva (n=10) pellicle adsorbed onto hydroxyapatite (main component of enamel) surfaces are shown in Figure 2d (Ash *et al.*, 2014). A rapid decrease in frequency of both whole mouth saliva and parotid saliva pellicle is observed. In comparison to a plateau reached after 20 minutes of whole mouth saliva addition, the frequency of parotid saliva keeps a decreasing trend in the overall 120 minutes time period, indicating a continuous saliva pellicle adsorption. A slower increase in dissipation of parotid saliva pellicle compared to whole saliva was observed, indicating a more rigid layer being formed by parotid saliva. Flow rate changes of whole saliva and parotid saliva with age were also found to be different, with a significant lower whole salivary flow in 80+ individuals in compared with no age-related decline for parotid saliva (Percival *et al.*, 1994). In this way, differences in rate and degree of adsorption between whole and parotid saliva can be used as a suitable analytical tool to evaluate the changes in the saliva pellicle properties of dry mouth patients, which has received limited attention so far in dry mouth diagnosis.

2.3.4 Tribological measurements

Poor lubrication performance is a key complaint in dry mouth conditions and therefore tribological analysis *i.e.* measuring the frictional properties could be an important diagnostic tool. The comparison of dry mouth patient (n=4) and healthy individuals (n=4) salivary lubrication has been once implemented in a tongue-enamel friction system (an *ex vivo* laboratory-based friction tester) with the tooth enamel sliding against the porcine tongue for 10 cycles mimicking dry mouth (Figure 2e) (Wan *et al.*, 2020). Then, a drop of

stimulated whole saliva from healthy controls or Sjögren syndrome patients was placed and spread for 4 cycles, followed by another drop of buffer for 4 cycles and finally another drop of healthy or patient saliva. A sharp decrease in friction coefficient from around 2.5 in dry mouth condition to 0.5 was observed after the addition of healthy or patient saliva, representing the relief feeling after rinsing the mouth with a particular lubricant in dry mouth patients. The upcoming duration period with remaining low friction coefficient under continuous sliding was called 'relief period'. As shown in Figure 2e, healthy saliva resulted in a longer 'relief period' compared to that of patient saliva, indicating the relatively weak lubrication performance of dry mouth patients' saliva.

To further promote the usage of these emerging mechanical, chemical and adsorption tests, there are still some aspects that need improved. For instance, reduction in the volume of saliva samples needed for measurements, decreasing the time of testing and the cost of measurements will be the obvious way forward to make these tests suitable in a clinical setting.

3. Salivary substitutes

Salivary substitutes are frequently used as symptomatic treatments for patients with decreased salivary flow rate or poor salivary quality. Commercial salivary substitutes can be categorized into eight platform technologies according to their functions (Figure 3). Four key functions of saliva substitutes *i.e.* lubricating, thickening, adhesive and moisturizing are discussed in this review. These functions are related directly to the wear and dryness of oral surfaces. Buffering functions are needed to neutralize product pH and protect dental health, while optional agent such as sweetener, surfactant, colorant and preservative are usually added to further improve patient's acceptance and adherence (Scott *et al.*, 2010).

375 Although saliva stimulant agent is also included in some artificial saliva to stimulate the
376 salivary flow (Furness *et al.*, 2011), such stimulants do not mimic any salivary functions
377 and thus not discussed in this review.
378
379 [Insert Figure 3 here]
380
381 *3.1 Thickening and lubricating agents*
382 Hydrocolloids with a large number of hydroxyl (-OH) groups such as xanthan, guar gum,
383 starch, alginate, pectin, gellan, agar, carrageenan and cellulose derivatives are commonly
384 used as thickening agents not only in food but also in saliva substitutes (Van der Reijden
385 *et al.*, 1994; Saha and Bhattacharya, 2010). Thickening agent is usually added to increase
386 the viscosity of commercial salivary substitute products, such as high-viscosity saliva
387 substitutes or gels with an objective to extend the duration of dry mouth relief (Partenhauser
388 and Bernkop-Schnürch, 2016). For instance, hydroxyethyl cellulose- (HEC) based Biotène
389 Oral balance dry mouth system (OB) and BioXtra (BX) gel have similar composition, while
390 BX is more viscous than OB (23.0 vs 16.8 Pa s) (Shahdad *et al.*, 2005). A small double-
391 blind, crossover study (n=20 xerostomia patients) found that the moisturizing effect of OB
392 gel lasted no more than 2 hours. However, nine patients reported the effect of BX gel lasting
393 for more than 2 hours. This supports the beneficial effects of thickening agents in enhancing
394 the relief period.
395
396 One of the most important function of saliva is lubrication, which minimize the wear of
397 mucosal surfaces and therefore supports food oral processing (Carpenter, 2013). Therefore,
398 it is crucial for salivary substitutes to exhibit similar or even better lubrication properties
399 as compared to healthy human saliva. Typical manifestation of lubrication properties is
400 Stribeck curve with friction coefficient plotted as a function of film thickness *i.e.*

entrainment speed (speed at which the lubricant is entrained into the contact) multiplied by the lubricant viscosity and divided by the normal force (Sarkar *et al.*, 2019a). According to the adsorbed film thickness between two moving surfaces, the Stribeck curve can be divided into three regimes: boundary, mixed and hydrodynamic lubrication regime. Boundary lubrication regime occurs at low entrainment speeds where the moving surfaces are almost in full contact. In this regime, the surface characteristics account for the friction coefficient. So, a tightly adhered lubricant of thickness of few molecules to the moving surfaces can facilitate boundary lubrication (Coles *et al.*, 2010). As the entrainment speed increases, the hydrodynamic forces of fluid rise causing a reduction in friction coefficient. Then, in hydrodynamic lubrication regime, the surfaces are fully separated by fluid where viscosity plays an important role (Sarkar *et al.*, 2019a). Whole unstimulated saliva shows excellent lubricating behaviour in all the three regimes, which is probably due to the presence of salivary proteins that contribute to hydration lubrication (Xu *et al.*, 2020). Highly glycosylated mucins (MUC5B) and other low molecular weight proteins such as lactoferrin in synergy contributes to both boundary and fluid film lubrication of salivary pellicle (Xu *et al.*, 2020). Especially the aforementioned MUC5B, which is dysregulated in dry mouth patients, is a major gel-forming mucin in human saliva (Wickström *et al.*, 1998). Therefore, mucin-based salivary substitutes have been also developed. Saliva Orthana® is the only saliva substitute containing an animal-derived mucin currently on the market, probably due to the risk of transmissible spongiform encephalopathy (Kelly *et al.*, 2004; Partenhauser and Bernkop-Schnürch, 2016).

In addition to mucin, other commonly used lubricating agents that act in the hydrodynamic regime include glycerine, polyethylene glycol (PEG), cellulose-based polymer such as HEC and carboxymethyl cellulose (CMC), and water-soluble polymers such as carrageenan

and xanthan gum (van der Reijden *et al.*, 1996; Vinke *et al.*, 2020). However, unlike saliva, the afore-mentioned substitutes do not offer any boundary lubrication *i.e.* lubrication in the low speeds, which is more relevant in oral conditions. Glycerine and water-soluble polymers also work as thickening agents with high shear viscosity at low concentrations (de Vicente *et al.*, 2005). Glycerine-based salivary substitutes were found to be less effective in boundary lubrication in comparison to mucin-based ones, despite an approximately 300 times greater viscosity than other fluid samples (Aguirre *et al.*, 1989).

Hydrodynamic lubrication behaviour of mucin and CMC-based salivary substitutes have been widely studied (Vissink *et al.*, 1983; Hatton *et al.*, 1987; Christersson *et al.*, 2000), saliva substitutes based on mucin has been proven to provide better lubrication than CMC in biocompatible hard interface (tooth-glass interface) with relative lubrication values (77 ± 6% of the positive control) comparable to those of whole human saliva (63 ± 7% of the positive control) (Hatton *et al.*, 1987). Clinical studies (n=137 dry mouth patients) (Vissink *et al.*, 1983) have also found higher patient preference for mucin-containing saliva substitute over the CMC ones. Such performance may result from more similarity of mucin-containing artificial saliva and real human saliva as compared to CMC counterparts. On the other hand, a recent oral lubrication study of various commercially available saliva substitutes containing active ingredients such as mucin, HEC, PEG-hydrogenated castor oil, xanthan gum, CMC, plant polysaccharide and oxidized glycerol triesters found that all those saliva substitutes lack optimum lubricating properties (Vinke *et al.*, 2020). Therefore, more effective combination of thickening and lubricating agents and standardised subjective and objective clinical test to understand the effect of the salivary substitutes are needed for development of effective saliva substitutes that mimic real salivary lubrication.

3.2 Adhesive and moisturizing agent

Adhesive agent is often added to saliva substitutes facilitating the formation of a coating, which provides sufficient barrier for oral tissues from external irritation. Mucoadhesive materials are ideal adhesive agents, which demonstrate attractive interactions with mucosal surface (Partenhauser and Bernkop-Schnürch, 2016). Such mucoadhesive materials usually possess good wettability properties with numerous hydrogen bond forming groups (Ben-Zion and Nussinovitch, 1997), therefore can also act as moisturizing agent in saliva substitutes. Effective mucoadhesive materials can spread over and diffuse into substrate increasing the surface area of contact, through dominant attractive forces such as covalent force, hydrogen bond or electrostatic interaction (Lee *et al.*, 2000). According to the origin, mucoadhesive materials can be classified into four types (Partenhauser and Bernkop-Schnürch, 2016): 1) natural mucoadhesive materials, such as guar gum, xanthan gum, starch, pectin and gellan gum, chitosan, natural glycosaminoglycans such as hyaluronic acid (HA), and natural polypeptides such as gelatine; 2) semi-synthetic mucoadhesive materials, such as cellulose ethers *e.g.* hydroxypropyl cellulose (HPC) and methyl cellulose (MC), HEC and CMC; 3) synthetic mucoadhesive materials, such as PEG and polyacrylic acid (PAA, also known as carbomer) and 4) innovative mucoadhesive materials, such as thiolated polymers *e.g.* thiolated chitosan, thiolated PAA and thiolated xanthan gum. Among these materials, some are anionic polymers such as CMC, HA, PAA, pectin and gellan gum are rich in carboxylic moiety (-COOH) and function by virtue of hydrogen bonding with mucosal surfaces (Park and Robinson, 1987). Some materials are cationic polymers such as chitosan and cationic HEC which are hypothesized to undergo electrostatic interactions with residual anionic mucin in the mucus layer of the dry mouth patients, where hydrogen bonding and hydrophobic effects also happen, resulting in the enhanced mucoadhesive property (He *et al.*, 1998; Sogias *et al.*, 2008). Non-ionic polymers

such as PEG and MC can also be used as adhesive agents. Although PEG lacks the functional groups *e.g.* carboxylic, hydroxyl or amine groups (Smart, 2005), it can interpenetrate into the mucus layer by diffusion and facilitate mucoadhesion (Serra *et al.*, 2006). As for thiolated polymers, they can form covalent disulfide bridges with the mucus layer *via* thiol–disulfide exchange reactions with mucus, thereby achieving strong mucoadhesion.

The bio-adhesion effectiveness of salivary substitutes containing proper adhesive and moisturizing agent has been proven. For example, bio-adhesive properties of three saliva substitutes including Biotène® (HEC based), Oasis® (PEG and xanthan gum based) and Saliva Orthana® (mucin based) have been proven to be close to those of real human saliva tested by *ex vivo* indentation tests with pig tongues indicating adhesion force (Pailler-Mattei *et al.*, 2015). In the meantime, CMC, HEC or PEG-hydrogenated castor-based saliva substitutes are widely investigated. For example, in a study with 17 commonly applied saliva substitutes, only 3 items did not contain the aforementioned three mucoadhesive materials (Vinke *et al.*, 2020). Four of these tested 17 saliva substitutes including BioXtra gel (HEC based), Biotène gel (HEC based), Gum Hydral gel (xanthan gum, carrageenan and PEG-hydrogenated castor oil based) and Glandosane spray (CMC based) showed capability to increase the adsorption of saliva to these substitutes-coated surface of quartz crystals in QCM-D. The bio-adhesive properties of three saliva substitutes including Biotène® (HEC based), Oasis (PEG 60 hydrogenated based) and Saliva Orthana® (mucin based) were also reported to be similar to those of human saliva on pig tongues *ex-vivo*, except for the Aequasyal® (oxidised glycerol triesters based) (Pailler-Mattei *et al.*, 2015). However, in another study comparing the film-forming properties of CMC-based MAS 84 or porcine mucin-based Saliva Orthana®, CMC-based saliva substitute showed negligible

adsorption on hydrophilic or hydrophobic silica surfaces tested by ellipsometry, while mucin-based Saliva Orthana® was adsorbed onto hydrophobic surfaces (1.4 $mg\,m^{-2}$) although not as effective as whole saliva (2.8 $mg\,m^{-2}$) (Christersson *et al.*, 2000).

As for moisturizing properties, contact angle measurements have been frequently used. For example, the contact angle of CMC-based and mucin-based saliva substitutes on human mucosa were comparable or even lower than that of human whole saliva on human mucosa layer, indicating good wetting properties of these saliva substitutes (Vissink *et al.*, 1986). Contact angle of saliva substitutes on buccal epithelial cell surface was also studied, proving a very high wettability of xylitol based mouth spray ($38.78 \pm 1.78°$) compared with $71.64 \pm 2.20°$ of unstimulated whole saliva (Spirk *et al.*, 2019). While contact angle of CMC based (Sialin-Sigma®) and macrogol based (Glandomed®) were $86.97 \pm 5.91°$ and $89.83 \pm 1.49°$ respectively, indicating poor wettability. These studies indicate the importance of standardised evaluation method for adsorption properties of saliva substitutes, such as standard surface, equipment and adsorption protocol.

Many clinical tests have also evaluated the effectiveness of aforementioned salivary substitutes. Furness *et al.* (2011) assessed the risk of bias of 36 randomised controlled trials on topical interventions such as CMC, mucin, glycerol, xanthum gum, HEC citric acid and carbopol based salivary substitute gel or spray, in terms of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias. However, no strong evidence was found for the effectiveness of any salivary substitutes due to the high risk of bias in most of the clinical trials. Therefore, further studies are needed for the design of promising salivary substitutes and controlled trials to guide clinical care.

526

527 *3.3 Innovative technologies for salivary substitutes*

528 In addition to these active agents added for different aspects of properties, some innovative
529 technologies were also investigated for potential usage in salivary substitutes. For example,
530 a self-assembly of mucin and lactoferrin has been shown by Xu *et al.* (2020), demonstrating
531 promising wettability of hydrophobic surfaces, which was restored over 72 hours with
532 similar adsorption compared to that of real human saliva. The study demonstrated that a
533 synergistic lubrication by salivary components *i.e.* mucin and low molecular weight protein
534 such as lactoferrin was key to mimic the lubricity (*i.e.* similar friction coefficients) of real
535 human saliva (Xu *et al.*, 2020). The important role of low molecular weight proteins in
536 saliva lubrication were also mentioned in other papers (Singh *et al.*, 2014; Yakubov *et al.*,
537 2015). This indicates future potential of such proteinaceous self-assembly as a novel
538 technique to create salivary substitutes with better adsorption, lubrication and wettability
539 properties. For instance, recently, in our laboratory, we fabricated microgel-reinforced
540 hydrogel as a new, patented aqueous lubricant formulation (Hu *et al.*, 2020) that performs
541 better than saliva in terms of lubrication performance. The synergistic effect between the
542 components i.e. lactoferrin microgel and κ-carrageenan hydrogel was demonstrated to offer
543 both boundary and viscous lubrication, respectivelu, resulting in significantly lower friction
544 coefficient values in comparison to the sole components as well as real human saliva. The
545 lubricant offers prospects in terms of acting as a salivary substitute in the future.

546

547 Table 3 summarises patents on salivary substitutes that have surfaced in the last 20 years
548 focusing on textural property improvements.

549

550 [Insert Table 3 here]

For instance, polymers with gelling abilities might be converted into microgels thereby potentially improving the hydration properties. Gellan gum-based microgel spray has been evaluated for prevention of oral dryness by *in vitro* study and clinical test (Table 3). Results showed that microgels were particularly effective for relieving dry mouth symptoms for patients with cancer (Ota *et al.,* 2012). In another instance, liposomes prepared by surrounding water with lipid bilayers have also demonstrated promise to act as effective salivary substitutes due to slower water release and prolonged moisture protection. For example, phosphatidylcholine-based (soya-PC) liposomes have shown to obtain higher water binding capacity than pectin (Adamczak *et al*., 2016). Polymer-coated liposomes showed even better properties with improved water binding capacity as compared to non-coated ones. High mucoadhesion and mucosal biocompatibility of polymer-coated liposomes were also demonstrated (Table 3). These findings indicate the great potential of liposomes and its derivatives in hydrating oral mucosa and relieving dry mouth symptoms.

Oil-based emulsions have also been investigated as potential saliva substitutes. The viscoelastic properties of lecithin-based emulsions were observed, with viscous behaviour at low frequency and increased elasticity at higher frequencies (Table 3). Clinical tests of lecithin-based emulsion showed superior retention compared with water and similar retention to that of methylcellulose solution. However, another clinical study of lecithin-based emulsion showed that no significant benefit of oily emulsion for relief of xerostomia (Table 3). These studies indicate larger well-designed clinical studies for product property assessment are needed to understand the future applications of these innovative technologies.

A variety of measurements were used to evaluate the properties of these patented formulations such as clinical trials, rheological tests, adsorption tests, wettability tests and tribological tests (Table 3). Among them, the most widely used evaluation is rheological tests. One major trend in these patents is the use of food-sourced components such as yam, okra and plant oil, since they are natural material easily accepted by human (Table 3). For example, similar viscoelastic properties were found between yam solutions and human saliva (Kho and Park 2011). In summary, the saliva substitute development is a highly topical area of research and more efficient substitutes emulating the boundary lubrication properties of saliva appear to be a gap in the literature.

4. Conclusions

This review provides a comprehensive summary of various diagnostic tools for assessment of dry mouth conditions and examined the salivary substitutes providing textural properties emulating those of real human saliva for treatment of dry mouth condition. In terms of diagnosis, salivary flow rate test and questionnaire are commonly used in clinical setting with subjective questionnaires being the most common approach. However, to date, there has been little attention on assessing the alternation in biochemical composition and mechanical properties of saliva in dry mouth patients. Biochemical composition, rheological, adsorption and tribological properties are important feature of saliva contributing to its unique functions, which are widely studied by researchers. It is thus crucial to employ these mechanical measurements on saliva from dry mouth patients in order to rationally tailor the kind of saliva substitute needed for their relief. For instance, if the dry mouth patient has residual saliva which contains high levels of lubricating

salivary proteins but lacking in the hydrodynamic properties, then a thickening agent might be an ideal solution. However, if the salivary quality of the dry mouth patient suffers from lack of adsorption and boundary lubrication properties that are measured using QCM-D and tribological analyses, respectively, more effective saliva substitute that can act as boundary lubricants should be approached. Such group-personalized design of saliva substitutes would likely provide optimum treatment outcome of xerostomia. Another important challenge is to find a correlation between objectively measured salivary properties (*e.g.* lubrication, adsorption, mucin content) and subjective assessment of dry mouth. The lack of correlations hinder clinical adoption of these techniques for routine evaluation of dry mouth conditions by dental practitioners.

For treatment, eight composition agents have been identified within the commercial saliva substitute products, while four of them were directly related to relief of oral dryness including lubricating, thickening, adhesive and moisturizing agents. Materials such as polysaccharides, mucin and cellulose-based derivatives were commonly discussed materials in literature. In addition to these commonly used component agents, innovative development of saliva substitutes were summarised at the end of this review, indicating a trend of employing food-related materials such as yam, okra and colloidal technologies, such as self-assembly, emulsion, liposomes and microgels. In summary, further pre-clinical characterization of innovative technologies are needed and clear benefits of these technologies in terms of mucoadhesion, lubrication ad relief period over existing saliva substitutes need to be established before such materials can be used for clinical trials.

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Ethical Statements

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Tables

Table 1. A list of abbreviation used in this review article.

Abbreviation	Meaning
BX	BioXtra
COOH	carboxylic moiety
CMC	carboxymethyl cellulose
HEC	hydroxyethyl cellulose
HA	hyaluronic acid
HPC	hydroxypropyl cellulose
MC	methyl cellulose
MTM	mini traction machine
OB	Biotène Oral balance dry mouth system
PTH	parathyroid hormone
PAA	polyacrylic acid
PEG	polyethylene glycol
pSS	primary Sjögren's syndrome
QCM-D	quartz crystal microbalance with dissipation
VAS	visual analogue scale
XI	Xerostomia Inventory

942 **Table 2.** Questionnaires for subjective diagnosis of dry mouth and their relationship with salivary flow
943 rates.
944

Questions/statements	Rating scales/ Scores	Correlation with salivary flow rate	Reference
Fox et al Questionnaire			
1. Does your mouth feel dry at night or on awakening? 2. Does your mouth feel dry at other times of the day? 3. Do you keep a glass of water by your bed? 4. Do you chew gum daily to relieve oral dryness? 5. Do you use hard candies or mints daily to relieve oral dryness? 6. Do you sip liquids to aid in swallowing dry foods? 7. Does your mouth feel dry when eating a meal? 8. Do you have difficulties swallowing any foods? 9. Does the amount of saliva in your mouth seem to be too little, too much, or you don't notice it?	Binary scale (Positive or negative answer)	Question 1-5 were not indicative of a decreased salivary output (stimulated and unstimulated salivary flow), while the responses to questions 6-9 were highly indicative of diminished salivary output.	(Fox *et al.*, 1987)
The Xerostomia Inventory			
1. I sip liquids to help swallow food 2. My mouth feels dry when eating a meal 3. I get up at night to drink 4. My mouth feels dry 5. I have difficulty in eating dry food 6. I suck sweets or cough lollies to relieve dry mouth 7. I have difficulties swallowing certain foods 8. The skin of my face feels dry 9. My eyes feel dry 10. My lips feel dry 11. The inside of my nose feels dry	Categorical scoring scale Never, hardly, occasionally, fairly often and very often (scoring 1-5, respectively)	The single Xerostomia Inventory (XI) scale score has a very low correlation with resting salivary flow rate but a much stronger correlation with the standard dry mouth question responses.	(Thomson *et al.*, 1999)
Visual Analogue Scale questionnaire for subjective assessment of salivary dysfunction			
1. Rate the difficulty you experience in speaking due to dryness 2. Rate the difficulty you experience in swallowing due to dryness 3. Rate how much saliva is in your mouth 4. Rate the dryness of your mouth 5. Rate the dryness of your throat 6. Rate the dryness of your lips 7. Rate the dryness of your tongue 8. Rate the level of your thirst	Visual Analog Scale (100-mm horizontal scale)	Significant reliability for 7 VAS items (excluding item 3). Five items (1, 2, 3, 5 and 6) show significant validity with unstimulated submandibular saliva flow rates. Two items (1 and 6) show significant validity with stimulated submandibular flow rates. Only item 2 was significantly correlated for	(Pai *et al.*, 2001)

		stimulated parotid flow rates.	
Combination questionnaire			
1. Duration of oral dryness 2. Frequency of oral dryness 3a. Oral dryness at night or on awakening 3b. Oral dryness at other times of the day 3c. Oral dryness during eating 3d. Difficulty in swallowing foods 3e. Amount of saliva in usual, everyday life 3f. Effect of oral dryness on daily life 4. Awakening from sleep at night because of oral dryness 5. Taking a water to bed 6. Sipping liquids to aid in swallowing dry foods 7. Using candy or chewing gum because of oral dryness 8.Dry mouth-associated complaints (sensation of burning mouth, taste disturbances and oral malodour)	Combination of binary scale, categorical and VAS: 1. Recently, Several months, Several years 2. Occasionally, Frequently, Always 3. Visual Analog Scale (0-10, 10 means worst possible) 4 and 5. Never, 1-2 per week, 3-4 per week, 5-6 per week, Everyday 6 and 7. Never, Occasionally, Frequently, Always 8. Yes/No	Dry mouth-related symptoms and behaviours (question 3a-3f) are significantly associated with whole salivary flow rate. While question 1, 2 and 7 are not significantly associated with salivary flow rate.	(Suh *et al.*, 2007)

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947 **Table 3.** Patents on inventions of salivary substitute formulations for dry mouth therapy filed in the last 20
948 years (Source of database: Espacenet).

Patent number	Filing date	Assignee	Key technology in the invention	Property evaluation of the formulation (invention)	Reference
JP2005104966A	2004-06-30	Lion Corp	Microgel particle	(A) Average particle size measurement (B) Viscosity measurement (C) Evaluation of appearance, usage, dispersion stability and spray ability (D) Clinical test (n= 20 healthy persons) for the evaluation of residual feeling in the oral cavity and cleaning feeling between teeth and gums	(Nakamoto and Ryoji, 2004)
US2005226822A1	2003-04-25	Gaba International Ag	Mannoprotein and ovomucin	(A) Rheological behaviour measurement	(Garbers *et al.*, 2003)
US8540970B2	2008-02-22	Biocosmetic SL	Olive oil, trimethylglycine and xylitol	(A) Clinical test (n=20 xerostomia patients) of unstimulate salivary flow rate at the beginning and after one week of application of composition (B) Clinical test by xerostomia VAS questionnaire	(Rodriguez-Vilaboa, 2008)
KR101291413B1	2011-08-22	Seoul National University Industry-Academic Cooperation Foundation	Yam mucilage extraction	(A) Viscosity measurement (B) Lysozyme or peroxidase activity in solution	(Kho and Park 2011)
WO2012095774A1	2012-01-06	Indian Institute of Technology, Bombay, India	Gellan gum linked with dipalmitoylphosphatidylcholine and palmitoyloleoylphosphatidylethanolamine	(A) Fourier-transform infrared spectroscopy of composition (B) Surface pressure (C) Amphiphilic nature (D) Viscosity measurement (E) Viscoelasity measurement (F) Atomic force microscopy of the formed films (G) Height and roughness analysis (H) Particle size analysis	(Banerjee and GuhaSarkar, 2012)
US2014093582A1	2013-09-24	Golden Pearl Investment LLC	Serum composition	(A) Evaluation of the effect of serum extract on cell growth. (B) Clinical test (n= 32 healthy female volunteers)	(Qian, 2013)

				to evaluate the effect of formulation (invention) on skin, focusing on satisfactory of maintenance, absorbance, moisturizing and so on. (C) Animal test (n= 4 mice) to evaluate the effect of the formulation (invention) on burn injury.	
US9334312B2	2013-10-04	Rijksunvie rsiteit Groningen, Academisc h Ziekenhuis Groningen	Recombinant cationic polypeptides	(A) Adsorption test on salivary conditioning films. (B) Friction forces, repulsive force and glycosylation testa.	(Sharma *et al.*, 2013)
WO2018212771A1	2016-06-24	Colgate-Palmolive Company	Combination of hemp seed oil and caprylyl glycol	(A) Friction measurement. (B) *In vitro test* of moisture retention.	(Prencipe *et al.*, 2016)
WO2019102354A1	2018-11-20	3M Innovative Properties Company	Emulsion (oil in water): combination of plant based oils, an aqueous phase, surfactants and viscosity modifier.	(A) Viscosity measurement. (B) Friction measurement. (C) Stability (no phase separation) measurement. (D) High temperature stability test. (E) Freeze/ Thaw/ Centrifugation stability measurement. (F) Spray-ability measurement. (G) *In vitro* hydration retention measurement (Thermal gravimetric Analysis). (H) Long term wash-off measurement (with artificial saliva) (I) Biofilm disruption test (J) Bovine tooth hardness measurement	(Wlaschin *et al.*, 2018)
CN109662981A	2019-01-28	UNIV Zhejiang Gongshang	Okra extraction	(A) Shear rheological property test (B) Friction coefficient test (C) Oral tensile rhdological properties test (D) Taste test (n=30 healthy paticipants)	*(Chen et al.*, 2019)

Figures

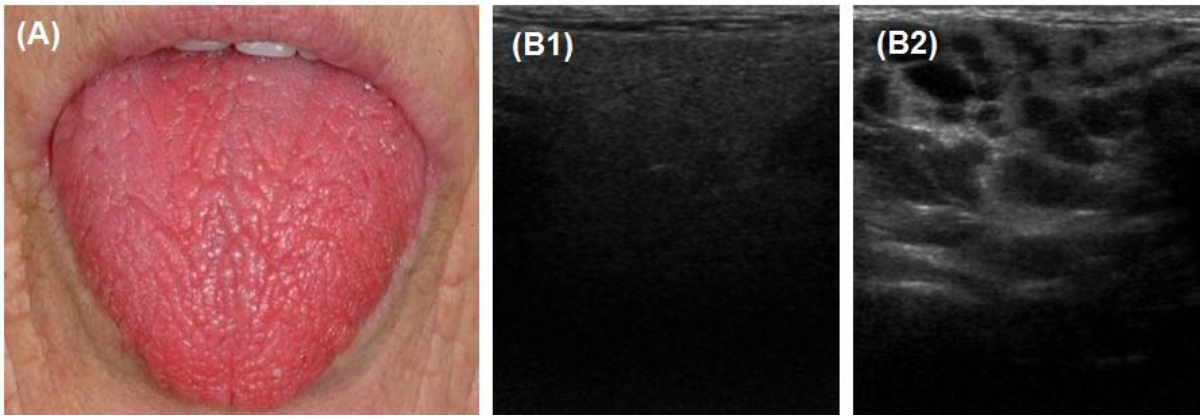

Figure 1. Diagnosis of dry mouth conditions by visual imaging of (A) an extreme dry mouth condition due to primary Sjögren's syndrome (pSS) and ultrasound images of the partotid gland in a healthy people (B1) and in a pSS patient (B2) where multi-hypoechoic areas reflect salivary gland damage. Images have been captured by co-author Dr. Alan Mighell in Leeds Teaching Hospitals NHS Trust, UK.

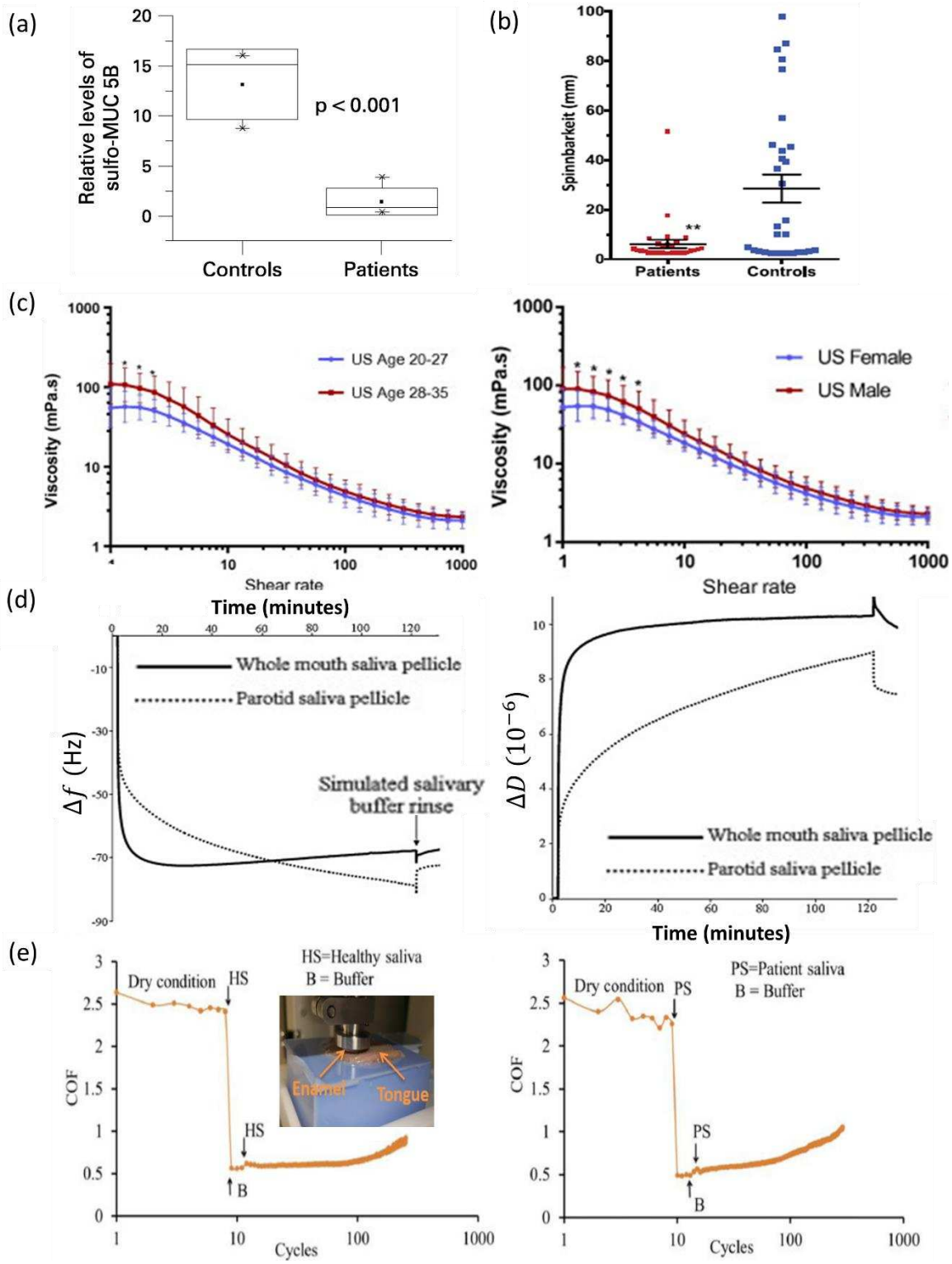

Figure 2. Potential dry mouth diagnostic tests of saliva. (a) relative levels of sulfo-MUC5B in labial salivary glands from Sjögren syndrome patients and control group (Alliende *et al.*, 2008) (Reproduced with permission from BMJ Publishing Group Ltd. & European League

964 Against Rheumatism), (b) Spinnbarkeit measurement of saliva in the groups of patients
965 with dry mouth patients and healthy controls (Chaudhury *et al.*, 2015) (Reproduced with
966 permission from SAGE Publications), (c) viscosity of unstimulated saliva (US) in different
967 age (age 20-27 versus 28-35) and gender (female versus male) group as a function of shear
968 rates (Gittings *et al.*, 2015) (Reproduced with permission from Elsevier), (d) adsorption
969 profile of whole mouth saliva and parotid saliva measured at 3rd overtone by quartz crystal
970 microbalance with dissipation monitoring (QCM-D) on hydroxyapatite-coated sensors
971 (Ash *et al.*, 2014) (Reproduced with permission from Elsevier), and (e) friction coefficient
972 of healthy saliva and Sjögren syndrome patients' saliva at different sliding cycles in an *ex-*
973 *vivo* tongue-enamel tribological system (Wan *et al.*, 2020) (Reproduced with permission
974 from SAGE Publications).
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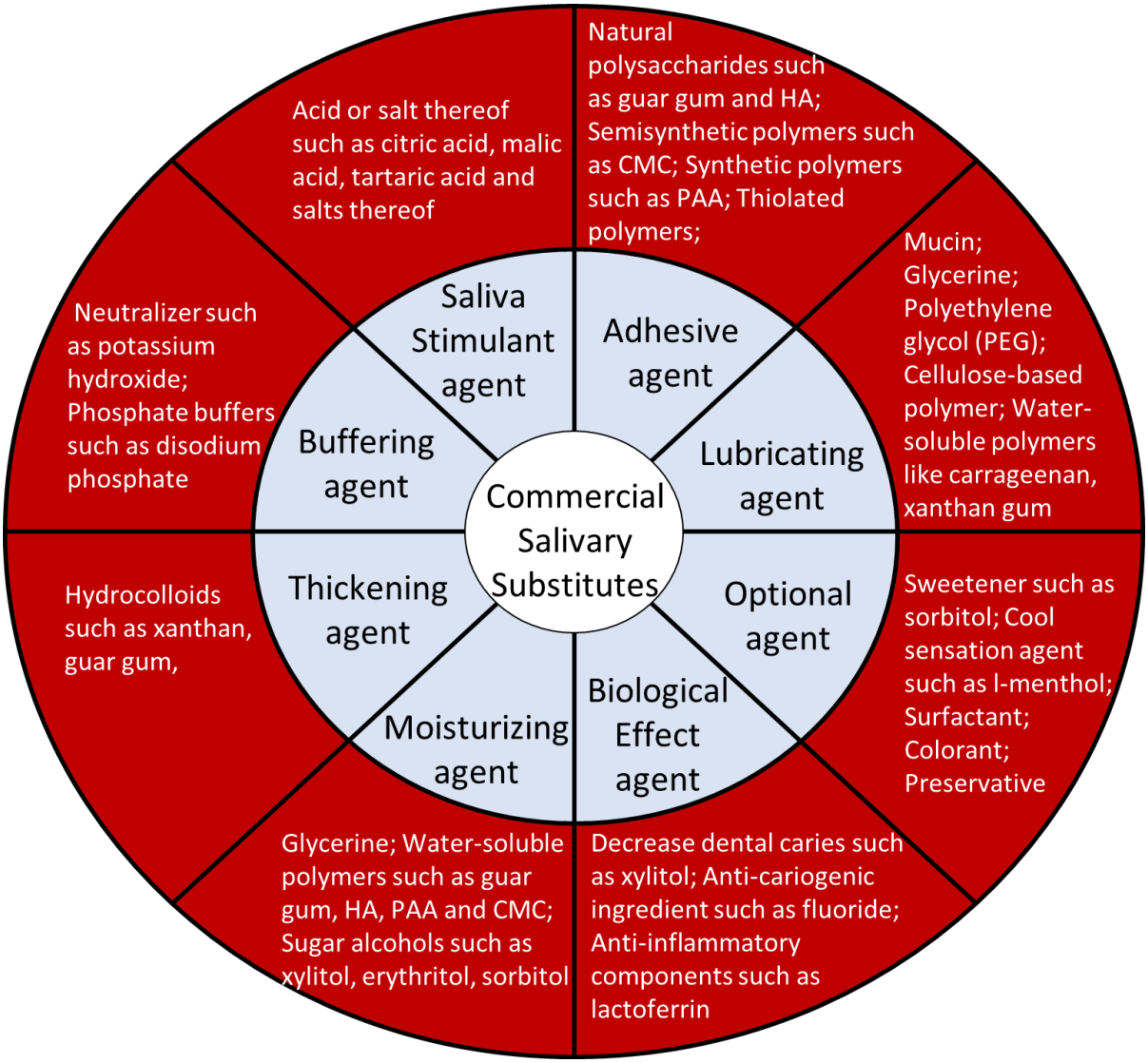

Figure 3. Common ingredients used in commercial salivary substitutes and the rationale behind their use.