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Formulation and Evaluation of Saliva Substitute

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Abstract

The development and evaluation of saliva substitutes play a vital role in managing xerostomia, a condition marked by insufficient saliva production that adversely affects oral health and overall well-being. This study investigates various formulations of saliva substitutes intended to replicate the functionality of natural saliva. The key goals are to assess their moisturizing effectiveness, physical and chemical properties, and in vitro performance. These formulations generally incorporate hydrators, lubricants, thickeners, and pH regulators to simulate the natural oral environment. Evaluation metrics include viscosity, texture, consistency, spreadability, adhesion, pH balance, and stability. Additionally, in vitro tests are conducted to measure the release and diffusion of active ingredients, mimicking their behavior in the oral cavity. Results reveal significant variability in the effectiveness of saliva substitutes, influenced by formulation and testing parameters. Effective substitutes must provide adequate hydration and lubrication, be compatible with oral tissues, and maintain stability while closely imitating natural saliva. The study underscores the need for continuous improvement and thorough evaluation of saliva substitutes to enhance their performance and user satisfaction. Future research should aim at refining formulations to better meet the needs of individuals with xerostomia and improve the clinical efficacy of these products.

Keywords: Saliva substitute, human saliva, xerostomia, salivary gland hypofunction (SGH), the clinical oral dryness score

INTRODUCTION

Saliva is a compound fluid excreted by major and minor salivary glands, with main glands being parotid, sublingual, and submandibular. It contains organic and inorganic chemicals, including glycoproteins, digestive catalysts, and lipid compounds. Saliva is crucial for good oral and overall health, providing physical cover to the oral mucosa and dental hard tissues through lubrication and formation of the salivary pellicle. It also buffers exogenous and endogenous acids and improves the reconstitution of enamel and dentine after acid attacks. Xerostomia, a chronic and subjective sensation of dry mouth, affects 30% of the general population and significantly impacts quality of life. Common complaints include generalized oral discomfort, difficulty speaking, dysphagia, and dysgeusia. Oral symptoms secondary to xerostomia may have high risks of dental caries, periodontal disease, non-carious tooth damage, and oral disease [1–4]. Management of xerostomia often involves pain-relieving treatments and external treatments, such as oral lubricants and saliva substitutes. The yam, a monocotyledonous family member, is a suitable source for saliva substitutes due to its viscoelastic and lubricating characteristics. However, limited research exists on the physical and biological characteristics of mucins and mucin-like entities from animal or plant origins. Saliva plays a critical role in maintaining oral health and is important for general health in humans. It is produced and

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excreted by major glands and minor glands, mainly consisting of water (99.5%) and a mix of inorganic salts, enzymes, and proteins (0.3%) [5]. The daily mean output is about 0.6 l per day. The salivary goes but also the ingredients can alter due to different reasons [3]. As a result, less amount of saliva is obtained (i.e., hyposalivation) or alterations in the composition may happen, in a loss of the previously described works, which influences the patient's standard of life. The term "xerostomia" is used clinically to describe the general sensation of dry mouth. Its occurrence in the general population ranges from 20% to 30%, with a higher prevalence among females compared to males. In elderly patients, the prevalence can reach up to 39% and increases to 50%–60% for older patients during hospital stays. Symptoms experienced by patients with xerostomia include difficulties in chewing and swallowing, altered taste sensations, speaking challenges, and overall oral discomfort [3–5]. The reduced quantity or altered composition of saliva can lead to damage to the mucosal pellicle and subsequent inflammation of the epithelium, resulting in pain, oral bleeding, infections, and dental damage.

Common causes of xerostomia include autoimmune diseases like Sjögren's syndrome, head and neck radiation therapy, and polypharmacy [3]. Other causes can be dehydration, infections, inflammatory diseases (such as rheumatoid arthritis), surgical trauma, salivary gland damage, or endocrine disorders [6–10].

Assessing the level of oral dryness and discomfort is challenging, and no gold standard for diagnosis exists. Current strategies consider the cause and severity of symptoms, which can range from mild discomfort to significant oral disease. Management guidelines recommend ensuring sufficient hydration, improving oral hygiene, increasing nighttime humidity, and avoiding hard or crunchy foods. Effective treatment and prevention options include topical agents and systemic sialagogues to stimulate salivary flow and saliva substitutes. Topical agents like sugar-free lozenges and chewing gums can increase salivary flow through physical and taste stimulation, and contain ingredients, such as xylitol or casein phosphor-peptide amorphous calcium phosphate for remineralization and caries reduction. Pharmacological agents like pilocarpine or cevimeline, which are muscarinic agonists, are used to promote salivation, though they often have intolerable side effects. For xerostomia induced by radiation therapy, cytoprotectives like Amifostine are used to preserve salivary glands, though its acceptance is limited due to severe side effects [11–17].

Palliative oral care products include home remedies, such as water, olive oil, and milk, and saliva substitutes like mouthwashes, rinses, gels, and sprays. These products moisten the oral mucosa and alleviate discomfort without stimulating salivary flow. An ideal saliva substitute should mimic natural saliva in taste, consistency, and ease of use to enhance patient compliance [18–21]. Common ingredients include water-binding molecules, such as sodium carboxymethylcellulose (CMC), porcine mucin, polyethylene glycol, and xanthan gum [22, 23]. Studies have shown that mucin-based saliva substitutes more closely resemble natural saliva compared to those based on CMC, glycerol, or polyethylene oxide. However, some investigations have indicated no significant improvement compared to placebo.

Preventing enamel and dentin demineralization in saliva substitutes involves adding calcium, fluoride, or phosphate while considering buffer capacity and osmolality to maintain the hypotonic nature of saliva [17]. Currently, no saliva substitute fully replicates the complex properties of natural saliva, highlighting the need for further research [24, 25].

In the research study, there are three marketed products (Sialin-Sigma®, Glandomed®, and Xylitol CVS Health™ Dry Mouth Spray) commonly used in clinical practice. These were compared to unstimulated whole saliva from healthy volunteers [26–30]. Testing osmolality, pH, electrical conductivity, and buffer capacity through acid titration were done for saliva substitutes. Microscopic analysis was performed using Cryo-SEM (Cryogenic Scanning Electron Microscopy) and freeze-

fracture STEM (Freeze Fracture Scanning Transmission Electron Microscopy). and macrorheological properties were assessed via strain-controlled oscillation measurements. The surface tension of pure fluids was measured with the pendant drop method. Wettability studies were performed using human buccal epithelial cells to mimic physiological conditions.

Xerostomia, or dry mouth, is a condition causing oral dryness, difficulty with eating, swallowing, and speaking, nighttime discomfort, and increased risk of oral infections and dental caries. Treatment for severe xerostomia involves using gel-like saliva substitutes like oral balance and mucin-containing lozenges, while moderate xerostomia requires lower viscoelasticity substitutes like CMC or porcine gastric mucin. For mild xerostomia, residual salivary secretion should be stimulated through gustatory or pharmacologic methods. Mucin-containing saliva substitutes have shown potential in reducing oral flora pathogenic properties and reducing stomatitis and candidiasis.

MATERIALS

Materials formulated for saliva substitutes are designed to replicate the properties of natural saliva, offering lubrication, moisture, and protection to oral tissues.

These ingredients are combined to create products aimed at alleviating the symptoms of dry mouth (xerostomia) and providing relief to individuals with reduced salivary gland function (Tables 1 and 2).

Table 1. Formulations of saliva substitutes.

S.N.	Name of Ingredients	Role	Examples of Different Ingredients
1.	Water	Acts as the primary component for moisture.	*Purified water:* This is water that has been filtered or treated to remove impurities and contaminants, ensuring it is clean and safe for use in oral products. *Deionized water:* Water that has had its mineral ions (such as calcium, magnesium, sodium, and chloride) removed through ion exchange or other methods. It is often used to ensure consistency in formulations and to prevent mineral deposits. *Sterile water:* Water that has undergone a sterilization process to remove all microorganisms, ensuring it is free from bacteria, fungi, and viruses. This is crucial for products that need to be used in medical or sterile environments. *Distilled water:* Water that has been heated to create steam, which is then condensed back into liquid form, leaving behind impurities and contaminants. Distillation removes minerals and some chemicals, producing very pure water.
2.	Glycerin or sorbitol	Function as humectants to retain moisture and provide a slippery texture.	Glycerin: *Vegetable glycerin:* Derived from vegetable oils, such as palm, soy, or coconut oil. It is often preferred for its natural origin and is suitable for various oral care products. *Synthetic glycerin:* Produced through synthetic processes, ensuring consistent quality and purity. It is commonly used in pharmaceutical and personal care applications. *USP glycerin (United States Pharmacopeia):* Glycerin that meets the standards set by the USP for pharmaceutical use, ensuring high purity and quality suitable for medical applications. Sorbitol: *Sorbitol solution (70%):* A liquid form of sorbitol with a concentration of around 70%, often used for its humectant properties in oral care products. *Powdered sorbitol:* Sorbitol that has been crystallized and ground into a powder form. It is used in formulations where a dry ingredient is preferred or where solubility in water is required. *Liquid sorbitol:* Similar to sorbitol solution but with different concentrations, depending on the formulation requirements.

3.	CMC or Hydroxyethylcellulose (HEC)	Serve as thickening agents to increase viscosity and simulate the lubricating properties of natural saliva.	CMC: *High viscosity CMC:* CMC with a higher molecular weight and degree of substitution, providing greater thickening and viscosity enhancement. It is suitable for formulations requiring a gel-like consistency. *Low viscosity CMC:* CMC with a lower molecular weight and degree of substitution, offering moderate thickening and flow properties. It is often used in formulations where a thinner consistency is desired. *Purified CMC:* CMC has undergone additional purification processes to remove impurities, ensuring high quality and stability in formulations. HEC: *Standard grade HEC:* HEC with a medium molecular weight and degree of substitution, providing balanced thickening and rheological properties suitable for various applications. *High purity HEC:* HEC that has been refined to a high degree of purity, ensuring minimal impurities and consistent performance in formulations. *Fast hydrating HEC:* HEC is designed to hydrate quickly in aqueous solutions, making it easier to incorporate into formulations and achieve desired viscosity rapidly.
4.	Mucopolysaccharides	Natural or synthetic polymers that mimic mucin in saliva, providing lubrication and forming a protective film.	Mucopolysaccharides are natural or synthetic polymers that mimic the mucin in saliva, providing lubrication and forming a protective film in saliva substitutes. Here are some examples of mucopolysaccharides used in oral care products, including saliva substitutes: *Hyaluronic acid:* A natural mucopolysaccharide found in the connective tissues of the body, including the saliva. It has exceptional moisturizing and lubricating properties, helping to retain water and maintain hydration in the mouth. *Chondroitin sulfate:* Another natural mucopolysaccharide found in connective tissues, cartilage, and bones. It can help maintain tissue structure and hydration, contributing to the protective film in saliva substitutes. *Gellan gum:* A microbial polysaccharide produced by the bacterium Sphingomonas elodea. It is used as a thickening agent and stabilizer in saliva substitutes, contributing to the gel-like consistency and lubricating properties. *Xanthan gum:* Though not strictly a mucopolysaccharide, xanthan gum is a polysaccharide derived from the bacteria *Xanthomonas campestris*. It is often used in oral care products, including saliva substitutes, for its thickening and stabilizing properties. These mucopolysaccharides and polysaccharides are chosen for their ability to mimic the lubricating and protective functions of natural saliva, helping to alleviate dry mouth symptoms and maintain oral health.
5.	Xylitol	A sugar alcohol that can stimulate saliva production and help reduce dental cavities.	Xylitol is a sugar alcohol commonly used in saliva substitutes and oral care products due to its ability to stimulate saliva production, prevent dental cavities, and provide a pleasant taste without contributing to tooth decay. While there are different sources and forms of xylitol, the variations in xylitol used in saliva substitutes typically relate to their purity and formulation compatibility. Here are some common types or forms of xylitol used in oral care products: *Natural xylitol:* Derived from natural sources, such as birch trees or other hardwoods. It is often preferred for its natural origin and may be labeled as “birch-derived xylitol.”

			Corn-derived xylitol: Produced from corn cobs or other parts of the corn plant. It is widely used in commercial production due to its cost-effectiveness and availability. *Non-GMO xylitol:* Xylitol is certified as a non-genetically modified organism (non-GMO), appealing to consumers seeking products with minimal genetic modification. *Purified xylitol:* Xylitol has undergone additional purification processes to remove impurities and ensure high quality and consistency in formulations. *Granular xylitol:* Xylitol in crystalline or granular form, suitable for direct use in products like gums, candies, or powder formulations. *Liquid xylitol:* Xylitol in liquid form, is often used in formulations where solubility and ease of incorporation are desired, such as mouth rinses or sprays. These variations in xylitol types allow formulators to select the most suitable form based on the specific application needs, formulation requirements, and consumer preferences for saliva substitutes and other oral care products.
6.	Electrolytes	Such as potassium, calcium, and phosphate, to replicate the ionic composition of natural saliva.	Electrolytes used in saliva substitutes are essential for replicating the ionic composition of natural saliva, which helps maintain oral pH balance and support various physiological functions. Here are some common types of electrolytes used in saliva substitutes: *Potassium:* An essential electrolyte involved in maintaining cell function and regulating fluid balance in the body. In saliva substitutes, potassium ions help maintain osmotic balance and support normal cell function in oral tissues. *Sodium:* Another crucial electrolyte that regulates water balance in cells and helps maintain blood pressure. Sodium ions in saliva substitutes contribute to osmotic pressure and aid in maintaining hydration in oral tissues. *Calcium:* Important for maintaining bone health and muscle function, calcium ions in saliva substitutes can help support tooth enamel remineralization and maintain oral pH balance. *Phosphate:* Plays a role in energy metabolism and bone mineralization. Phosphate ions in saliva substitutes help buffer acidity and maintain pH balance in the mouth. *Chloride:* Helps regulate fluid balance and osmotic pressure in cells. Chloride ions in saliva substitutes contribute to maintaining electrolyte balance and hydration in oral tissues. *Magnesium:* Necessary for enzyme function and energy production. Magnesium ions in saliva substitutes can support overall oral health and help maintain normal cellular function. These electrolytes are typically included in saliva substitutes to mimic the natural ionic composition of saliva, ensuring optimal hydration, pH balance, and overall oral health maintenance.
7.	Flavors and sweeteners	Flavors and sweeteners	Flavors: *Mint:* Commonly used for its refreshing and cooling sensation. *Fruit flavors (e.g., berry, citrus):* Provides a fruity taste profile. *Vanilla:* Adds a creamy and sweet flavor. *Cinnamon:* Offers a warm and spicy taste. *Bubblegum:* Provides a sweet and nostalgic flavor. *Herbal flavors (e.g., chamomile, green tea):* Offers natural and soothing tastes. Sweeteners: *xylitol:* Besides its role in stimulating saliva production and preventing cavities, xylitol also serves as a sweetener.

8.	Preservatives	Prevent microbial growth and extend the product's shelf life.	Preservatives are used in saliva substitutes to prevent microbial growth, maintain product stability, and extend shelf life. Here are some common types of preservatives used in saliva substitutes: *Benzoates (e.g., sodium benzoate):* Effective against yeasts, molds, and certain bacteria. Sodium benzoate is widely used in oral care products due to its safety profile and effectiveness. *Parabens (e.g., methylparaben, propylparaben):* Broad-spectrum preservatives that inhibit the growth of bacteria, yeast, and mold. They are often used in combination to provide a synergistic effect and ensure product safety. *Phenoxyethanol:* A glycol ether used as a preservative against bacteria, molds, and yeasts. It is considered safe for use in oral care products when used within regulatory limits. *Ethylhexylglycerin:* A synthetic compound used as a preservative enhancer and skin conditioning agent. It is often used in combination with other preservatives to boost efficacy. *Sorbic acid:* An organic acid that inhibits the growth of molds and yeasts. It is commonly used in oral care products for its effectiveness and safety profile. *Citric acid:* While primarily used as an acidulant and pH adjuster, citric acid also exhibits preservative properties by lowering the pH and creating an environment less conducive to microbial growth. These preservatives are carefully selected and used in appropriate concentrations to ensure the microbiological stability and safety of saliva substitutes throughout their shelf life and during use.
9.	Antimicrobial agents	Help reduce bacterial growth and maintain oral health.	Antimicrobial agents used in saliva substitutes help to reduce bacterial growth and maintain oral health. These agents are important in preventing infections and maintaining the integrity of oral tissues. Here are some common types of antimicrobial agents used in saliva substitutes: *Chlorhexidine:* A broad-spectrum antimicrobial agent effective against bacteria, fungi, and some viruses. It is commonly used in oral care products due to its strong antimicrobial activity and ability to reduce plaque formation. *Cetylpyridinium Chloride (CPC):* An antimicrobial agent with activity against bacteria and fungi. CPC is often used in oral care products for its ability to reduce oral bacteria and inhibit plaque formation. *Xylitol:* Besides its role in stimulating saliva production and preventing cavities, xylitol also has antimicrobial properties and can help reduce the growth of oral bacteria. *Essential oils:* Natural oils, such as tea tree oil, eucalyptus oil, and thymol have antimicrobial properties and are used in oral care products for their ability to reduce bacteria and freshen breath. *Silver nanoparticles:* Nanoparticles of silver have antimicrobial properties and can inhibit the growth of bacteria and fungi. They are used in oral care products for their antimicrobial efficacy and safety. *Triclosan:* An antimicrobial agent effective against a wide range of bacteria. Triclosan is used in oral care products for its ability to reduce plaque and gingivitis. These antimicrobial agents are incorporated into saliva substitutes to help maintain oral hygiene, reduce the risk of oral infections, and promote overall oral health. They are chosen based on their efficacy, safety profile, and compatibility with other ingredients in saliva substitute formulations.

Table 2. Examples of marketed saliva substitutes.

S.N.	Name of the Saliva Substitutes	Description	Ingredients and Role
1.	Biotène	Available as a gel, spray, and rinse, Biotène products contain enzymes and humectants to provide long-lasting moisture and protection for dry mouths.	Biotène products come in various formulations like mouthwash, toothpaste, gel, and spray. The ingredients may differ slightly between these products, but common ingredients include:
2.	Biotène oral rinse		*Water:* The primary component for hydration. *Glycerin:* Moisturizer and humectant. *Sorbitol:* Sweetener and humectant. *Propylene glycol:* Moisturizer. *Poloxamer 407:* Surfactant. *Xylitol:* Sweetener and salivary stimulant. *Sodium benzoate:* Preservative. *Methylparaben:* Preservative. *Propylparaben:* Preservative. *Sodium phosphate:* Buffering agent. *Disodium phosphate:* Buffering agent. *Flavor:* For taste enhancement.
3.	Biotène dry mouth toothpaste		*Glycerin:* Moisturizer and humectant. *Water:* The primary component for hydration. *Hydrated silica:* Mild abrasive. *Sorbitol:* Sweetener and humectant. *PEG-8:* Humectant. *Xylitol:* Sweetener and salivary stimulant. *Cocamidopropyl betaine:* Surfactant. *Sodium methyl cocoyl taurate:* Surfactant. *Cellulose gum:* Thickening agent. *Flavor:* For taste enhancement. *Sodium benzoate:* Preservative. *Zinc chloride:* Anti-bacterial agent. *Sodium saccharin:* Sweetener.
4.	Biotène moisturizing gel		*Water:* The primary component for hydration. *Glycerin:* Moisturizer and humectant. *Xylitol:* Sweetener and salivary stimulant. *Carbomer:* Thickening agent. *HEC:* Thickening agent. *Sodium hydroxide:* pH adjuster. *Methylparaben:* Preservative. *Propylparaben:* Preservative.
5.	Biotène mouth spray		*Water:* The primary component for hydration. *Glycerin:* Moisturizer and humectant. *Xylitol:* Sweetener and salivary stimulant. *Propylene glycol:* Moisturizer. *PEG-60 hydrogenated castor oil:* Emulsifier. *Sodium benzoate:* Preservative. *Sucralose:* Sweetener. *Zinc gluconate:* Anti-bacterial agent. *Sodium citrate:* Buffering agent. *Citric acid:* pH adjuster. *Flavor:* For taste enhancement.
6.	Oasis	A mouth spray designed to lubricate and soothe dry oral tissues with glycerin and natural flavors.	*Water:* The primary component for hydration. *Glycerin:* A humectant that helps retain moisture.

		Oasis Moisturizing Mouth Spray is designed to provide relief from dry mouth symptoms. Selected to provide moisture, lubrication, and protection to help relieve symptoms of dry mouth.	*Xylitol:* A natural sweetener that also helps to stimulate saliva production. *Propylene glycol:* A moisturizer and solvent. PEG-40 hydrogenated castor oil: An emulsifier to help blend ingredients. *Potassium sorbate:* A preservative to prevent microbial growth. *Sodium benzoate:* Another preservative to maintain product stability. *Flavor:* To improve taste and user experience. *Sodium saccharin:* A sweetener. *Citric acid:* To adjust the pH level of the product. *Zinc gluconate:* An ingredient that can help reduce oral bacteria and improve oral health.
7.	Mouth Kote	A spray that uses natural Yerba santa extract, xylitol, and other ingredients to provide moisture and stimulate saliva production. Mouth Kote is a mouth spray designed specifically to relieve dry mouth symptoms. The typical ingredients found in Mouth Kote spray include: These ingredients work synergistically to provide moisture, lubrication, and relief from dry mouth symptoms. Mouth Kote is often recommended for individuals experiencing xerostomia (dry mouth) due to various causes, including medication side effects or medical conditions.	*Water:* The base ingredient for hydration. *Xylitol:* A sugar alcohol that helps stimulate saliva production and prevents dental cavities. *Yerba santa:* A natural herbal extract known for its moisturizing and soothing properties. *Carbomer homopolymer type B:* A thickening agent that helps to create a gel-like consistency. *Sodium benzoate:* A preservative to prevent microbial growth. *Potassium sorbate:* Another preservative for product stability. *Sodium hydroxide:* Used as a pH adjuster. *Flavor:* Typically added to enhance taste and improve user experience.
8.	Salivart	Salivart: An aerosol spray that delivers immediate moisture relief with a glycerin base. Salivart is an aerosol spray used to relieve dry mouth symptoms. The typical ingredients found in Salivart spray include:	*Water:* The base ingredient for hydration. *Glycerin:* A humectant that helps retain moisture. *Xylitol:* A natural sweetener that can stimulate saliva production and prevent dental cavities. *Sorbitol:* Another humectant that helps retain moisture and provides a smooth texture. *Potassium thiocyanate:* An enzyme that may help to enhance saliva production. *Lysozyme:* An enzyme that can help break down bacterial cell walls. *Lactoferrin:* A protein that has antimicrobial properties and may help maintain oral health. *Lactoperoxidase:* An enzyme that can help control bacteria in the mouth. *Glucose oxidase:* Another enzyme that can help control bacteria and improve oral hygiene. *Aloe vera gel:* Known for its soothing and moisturizing properties. *Sodium benzoate:* A preservative to prevent microbial growth. *Potassium thiocyanate:* An enzyme that may help to enhance saliva production. *Lysozyme:* An enzyme that can help break down bacterial cell walls. *Lactoferrin:* A protein that has antimicrobial properties and may help maintain oral health.

			Lactoperoxidase: An enzyme that can help control bacteria in the mouth. *Glucose oxidase:* Another enzyme that can help control bacteria and improve oral hygiene.
9.	Xero-Lube	*Xero-Lube:* A gel that mimics natural saliva's lubricating properties using CMC. Xero-Lube is a gel designed to mimic the lubricating properties of natural saliva. The typical ingredients found in Xero-Lube gel include:	*Water:* The base ingredient for hydration. *Glycerin:* A humectant that helps retain moisture. *CMC:* A thickening agent that increases viscosity and provides lubrication. *Sodium CMC:* Another form of CMC used for its thickening properties. *Sodium benzoate:* A preservative to prevent microbial growth. *Methylparaben:* A preservative that helps to maintain product stability. *Propylparaben:* Another preservative to extend shelf life. *Disodium phosphate:* A buffering agent to maintain pH balance. *Propylene glycol:* A moisturizer and solvent. *Flavor:* Typically added to improve taste and user experience. These ingredients work together to provide lubrication, moisture, and relief from dry mouth symptoms, making it easier to swallow and speak comfortably.
10.	Aquarol	These ingredients work together to provide lubrication, moisture, and relief from dry mouth symptoms, making it easier to swallow and speak comfortably. *Aquoral:* A lipid-based spray that creates a protective barrier to retain moisture and reduce dry mouth symptoms. Aquoral is a lipid-based spray designed to provide relief for dry mouth symptoms. The typical ingredients found in Aquoral spray include:	*Water:* The base ingredient for hydration. *Glycerin:* A humectant that helps retain moisture. *Xylitol:* A natural sweetener that can stimulate saliva production and prevent dental cavities. *HEC:* A thickening agent that helps create a gel-like consistency. *Sodium hyaluronate:* A derivative of hyaluronic acid, known for its moisturizing and lubricating properties. *Potassium sorbate:* A preservative to prevent microbial growth. *Sodium benzoate:* Another preservative for product stability. *Sodium phosphate:* Used as a buffering agent. *Citric acid:* Added to adjust the pH level of the product. *Flavor:* Typically added to enhance taste and improve user experience. These ingredients are combined to provide long-lasting moisture, lubrication, and relief from dry mouth symptoms, helping to improve oral comfort and maintain oral health [17–21].

METHODOLOGY

Saliva substitutes, designed to relieve dry mouth (xerostomia), have distinctive pharmacokinetic and pharmacodynamic characteristics compared to traditional medications, as they act primarily within the oral cavity rather than systemically.

Below Is an Overview of Their Profiles

Pharmacokinetics

Absorption

Saliva substitutes are intended to function locally in the mouth, meaning they are not significantly absorbed into the bloodstream. Their components, such as lubricating agents, remain primarily in the oral cavity to provide moisture and lubrication.

Distribution

The distribution is confined to the oral cavity. The product spreads across the mucous membranes, teeth, gums, and tongue, forming a protective and lubricating layer.

Metabolism

Since saliva substitutes are not absorbed systemically, they do not undergo significant metabolic processes. Any minor components that might be swallowed are typically metabolized by the gastrointestinal tract like regular dietary components.

Excretion

The majority of the saliva substitute is not absorbed and is eventually swallowed or spit out. Swallowed components are excreted via the gastrointestinal tract, while the non-absorbed portion is removed through regular oral hygiene practices.

Pharmacodynamics

Mechanism of Action

- *Lubrication:* Saliva substitutes mimic the natural lubricating properties of saliva, reducing friction and discomfort in the mouth.
- *Moisture retention:* They contain humectants (e.g., glycerin, sorbitol) that attract and retain moisture, helping to keep the mouth hydrated.
- *pH balance:* Some formulations help maintain a neutral pH in the mouth, which can protect against dental decay and promote oral health.
- *Onset of action:* The onset of action is typically immediate upon application, providing rapid relief from the symptoms of dry mouth.
- *Duration of action:* The duration can vary depending on the product formulation and individual use. Some products may need to be reapplied frequently, while others offer longer-lasting effects. Generally, the effects last from a few hours to half a day, depending on factors, such as saliva flow, eating, and drinking.

Efficacy

The effectiveness of saliva substitutes varies based on individual needs and the severity of dry mouth. They are generally effective in providing temporary relief and improving the quality of life for individuals with xerostomia.

Side Effects

Most saliva substitutes are well-tolerated with minimal side effects. Potential minor side effects may include changes in taste, a slight burning sensation, or mild irritation. Saliva substitutes primarily exert their effects locally in the mouth, providing immediate and temporary relief from dry mouth without significant systemic absorption or metabolism. Their pharmacokinetic and pharmacodynamic profiles reflect their role as supportive treatments to improve oral comfort and health in individuals with xerostomia.

Ex Vivo Models for Studying Oral Friction

A lack of salivary lubrication significantly increases the friction coefficient between the tongue and tooth enamel, leading to discomfort and pain for patients. Lubricants play a crucial role in reducing

this friction through various mechanisms. To evaluate these lubricants' effectiveness, ex vivo tribological tests and models that replicate oral friction are essential. These models must accurately represent oral tissues and their functions, as well as the biomechanics of the entire oral cavity.

Few studies use actual oral biological tissues for tribological research. Instead, they often focus on whole-mouth saliva and saliva substitutes to reduce friction between hard enamel-like surfaces, such as silica discs, spheres, and smooth glass. Those that do use biological tissues often employ silicone balls or enamel friction models on porcine tongues, which resemble human tongues but have significant flaws, such as quick decomposition, complex surface chemistry, and variability between samples.

Due to these issues, researchers are exploring synthetic materials like PDMS (polydimethylsiloxane) as alternatives to biological tongue models. PDMS can be easily synthesized and modified in the lab to mimic the surface chemistry, topography, deformability, and wettability of biological tongues.

Given the difficulty of measuring oral friction in vivo, most studies focus on mouthfeel, where patients describe the texture of materials or foods in their mouths. Standard questions assess whether patients sip liquids to swallow food, wake up at night for a drink, have difficulty swallowing dry food, suck on candies to relieve dry mouth, or have too much or too little saliva.

Clinical Approaches for Studying Dry Mouth

Clinical evaluations may also involve objective measures like salivary flow rate tests, which assess the quantity of saliva produced. Additionally, assessments of oral health are conducted to identify any related issues, such as oral infections or cavities.

Treatment approaches are tailored based on the underlying cause of dry mouth and can include the use of saliva substitutes, medications to stimulate saliva production and lifestyle adjustments. Regular follow-ups are essential to monitor treatment efficacy and adjust strategies as needed. These combined methods provide a comprehensive understanding of dry mouth and guide effective management strategies for affected individuals.

In clinical settings, diagnosing dry mouth (xerostomia) involves gathering the patient's medical history, medications, symptom severity, and self-assessment of salivary flow. Clinicians may perform tests, such as having the patient swallow a dry biscuit or checking the adhesion of a dental mirror to the buccal mucosa. The most common diagnostic method is measuring the unstimulated whole-mouth salivary flow rate. Visual signs of severe xerostomia include tooth caries around the gum line and changes to the tongue's surface, such as depapillation or erythema. Palpation of the salivary glands and, occasionally, biopsies of minor salivary glands may also aid in diagnosis, particularly for conditions like Sjögren's syndrome.

Salivary flow rates can be measured in several ways: for unstimulated flow, patients may collect saliva into a graduated cylinder for 15 minutes or spit every 60 seconds. Stimulated salivary flow is measured after chewing unflavored gum for one minute, with collection over five minutes.

The Clinical Oral Dryness Score (CODS) is a standardized test that provides a consistent way to evaluate xerostomia severity. It includes various qualitative assessments, such as the adhesion of a dental mirror to the tongue and buccal mucosa, the presence of frothy saliva, and condition of the oral mucosa. The CODS ranks dryness severity on a scale from 1 to 10.

Lubricating Saliva Substitutes

Lubricating saliva substitutes are designed to aid individuals with reduced or altered saliva production by providing moisture and lubrication to oral surfaces. This helps alleviate symptoms of

xerostomia, such as difficulty swallowing and speaking. These substitutes contain various ingredients: hydrophilic macromolecules for lubrication, active molecules like malic and tartaric acids to stimulate saliva production, buffering agents to regulate pH and ionic balance, and artificial flavoring agents.

Membrane Permeation of Saliva Substitutes

Membrane permeation in the context of saliva substitutes refers to how these substitutes interact with and penetrate biological membranes, such as the mucosal layers in the oral cavity. This interaction is crucial for effective lubrication and therapeutic efficacy. Here's an overview of key concepts and considerations regarding membrane permeation of saliva substitutes:

Importance of Membrane Interaction

- *Mucoadhesion:* For a saliva substitute to be effective, it must adhere to the mucosal surfaces in the oral cavity. This is often achieved through mucoadhesive properties, where the substitute forms a strong bond with mucosal tissues, providing prolonged relief from dryness.
- *Penetration:* The substitute needs to permeate the mucosal membrane to deliver hydration and lubrication effectively. This involves diffusion through the mucus layer and interaction with epithelial cells.

Saliva substitutes are medications designed to relieve dry mouth, which is primarily absorbed within the oral cavity. They act primarily within the mouth, providing moisture and lubrication. They are not absorbed systemically, meaning they do not undergo significant metabolic processes. The majority of the saliva substitute is excreted through the gastrointestinal tract, while the non-absorbed portion is removed through oral hygiene. Saliva substitutes mimic the natural lubricating properties of saliva, reducing friction and discomfort in the mouth. They contain humectants that attract and retain moisture, helping to maintain a neutral pH in the mouth. The onset of action is typically immediate, and the duration can vary depending on the product formulation and individual use. The effectiveness of saliva substitutes varies based on individual needs and the severity of dry mouth. Ex vivo tribological tests and models that replicate oral friction are essential for evaluating their effectiveness. Researchers are exploring synthetic materials like PDMS as alternatives to biological tongue models.

Evaluation of Saliva Substitutes

Saliva substitutes are evaluated based on their effectiveness, safety, and suitability for individual needs. The main criteria include effectiveness, safety, palatability, stability, ease of use, patient feedback, quality of life, clinical efficacy, cost, and accessibility. The evaluation process involves assessing the product's moisture ability, duration of effect, consistency, texture, consistency, spreadability, adhesion, pH level, stability, appearance, and density.

Effectiveness is determined by its moisturizing ability, duration of effect, consistency, feel, safety, toxicity, palatability, stability, ease of use, patient feedback, quality of life, clinical efficacy, cost, and accessibility. The product's texture, consistency, spreadability, adhesion, pH level, stability, appearance, and density are all evaluated to ensure they closely resemble natural saliva and provide a comfortable mouthfeel. Safety is monitored for allergic reactions, irritation, and toxicity risks. The product's stability is assessed under various conditions to ensure long-term effectiveness and safety.

In Vitro Kinetic Release

In vitro kinetic release studies of saliva substitutes typically involve analyzing how the active ingredients are released over time. The data obtained from these studies can be fitted to various kinetic models to understand the release mechanism. Here's an overview of common kinetic models used in these studies, along with their equations:

Zero-Order Kinetics

Definition: The release rate of the active ingredient is constant over time, independent of its concentration.

Equation: $Q(t) = Q_0 + k_0 \cdot t$.

Q(t) = Amount of active ingredient released at time t.
Q_0 = Initial amount of the active ingredient.
k_0 = Zero-order release rate constant.
t = Time.

Characteristics: The plot of Q(t) versus time is linear.

First-Order Kinetics
Definition: The release rate is proportional to the concentration of the active ingredient remaining.

Equation: $Q(t) = Q_0 \cdot (1 - e^{-k}{}_1 \, . \, t)$.

Q(t) = Amount of active ingredient released at time t.
Q_0 = Total amount of active ingredient.
k1 = First-order release rate constant.
t = Time.

Characteristics: The plot of ln(Q0 − Q(t)) versus time is linear.

Higuchi Model
Definition: Describes the release of drugs from a matrix system based on diffusion principles.

Equation: $Q(t) = k_H \cdot t^{1/2}$.

Q(t) = Amount of active ingredient released at time t.
k_H = Higuchi release rate constant.
t = Time.

Characteristics: The plot of Q(t) versus $t^{1/2}$ is linear.

Korsmeyer-Peppas Model
Definition: A semi-empirical model used to describe the release of drugs from polymeric systems, incorporating both diffusion and erosion.

Equation: $Q(t)/Q\infty = k_{KP} \cdot t^n$.

Q(t) = Amount of active ingredient released at time t.
$Q\infty$ = Total amount of active ingredient.
k_{KP} = Korsmeyer-Peppas release rate constant.
t = Time.
n = Release exponent, indicating the release mechanism (e.g., Fickian diffusion, non-Fickian transport).

Characteristics: The plot of $Q(t)/Q\infty$ versus t is linear when n is constant.

Weibull Model
Definition: A flexible model that can describe a range of release behaviors, from exponential to more complex patterns.

Equation: $Q(t) = Q\infty \cdot (1 - e^{-(t/\tau)\beta})$.

Q(t) = Amount of active ingredient released at time t.
Q∞ = Total amount of active ingredient.
τ = Time constant.
β = Shape parameter.

Characteristics: The Weibull model can fit various release profiles depending on the values of τ and β.

Data Analysis

Fitting models: Fit the release data to the above equations using regression analysis to determine the best-fit model.

Parameter estimation: Extract kinetic parameters, such as release rate constants and exponent values.

Goodness of fit: Evaluate the goodness of fit using statistical measures like R^2 or residual analysis to ensure the model accurately describes the release profile.

In vitro kinetic release studies with these models provide insights into how a saliva substitute releases its active ingredients over time. By fitting the release data to these models, you can better understand the release mechanism and optimize the formulation for desired performance.

Bioequivalence Study

Historical Overview

Artificial saliva has been studied since the late 19th century, with the development of a multistage system simulating the oral cavity using natural saliva. Over time, it evolved into more sophisticated systems, such as the computer-controlled Multiple Artificial Mouth (MAM) in the 1990s. Early research focused on mercury toxicity from amalgam fillings, and later on, the Fusayama formula refined artificial saliva composition for corrosion studies. Today, artificial saliva is used in various biological tests, including dental material research, whitening and treatment, xerostomia and drug delivery, and nutrient bioavailability studies. This standardization and advancements in technology have led to the development of various artificial saliva formulas for various research needs [21–23].

RESULTS

Xerostomia, or dry mouth, is a condition caused by inadequate oral lubrication and can significantly impact the quality of life. It is primarily caused by polypharmacy, radiation therapy, and Sjögren's syndrome. Saliva plays a crucial role in lubrication, and various methods for assessing oral lubrication and xerostomia are discussed. Artificial saliva formulations, including proteins, glycoproteins, biopolymers, synthetic polymers, lipids, and phospholipids, have been explored for treatment. However, developing effective substitutes is challenging due to the need to balance objective metrics with subjective qualities. Future research is needed to develop new materials to alleviate symptoms and improve patient quality of life.

DISCUSSION

Saliva substitutes are used to manage xerostomia, a condition that affects quality of life. They provide lubrication to reduce discomfort, improve oral health, enhance drug efficacy, and improve quality of life. However, they may have potential adverse drug reactions (ADRs), including allergic reactions, taste alterations, mucosal irritation, and overuse effects. Saliva substitutes are generally safe for oral use, but considerations include ingredient safety, long-term use, and regulatory standards. A 60-year-old female with xerostomia was prescribed a gel-based saliva substitute, which provided significant relief, improved oral health, and decreased discomfort. No long-term adverse effects were observed, and regular check-ups were scheduled to monitor effectiveness and potential side effects.

CONCLUSIONS

Artificial saliva formulations range from simple solutions to complex mixtures with multiple ingredients. Key components include salts, buffers, and preservatives, with pH ranging from 5.0 to 7.3. Saliva substitutes are crucial for managing xerostomia and maintaining oral health. However, they must consider potential adverse reactions and long-term ingredients safety. Case studies emphasize personalized treatment plans and ongoing monitoring.

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