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Over-the-counter sialagogues: pH, enamel dissolution, and biocompatibility

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Abstract

Background: Patients with xerostomia use products made to stimulate salivary flow. This study measured and compared pH of readily available sialagogues and their resulting effects on enamel dissolution and biocompatibility.

Methods: A wide variety of commercially available palliative sialagogues were examined for effects on hard tooth tissue as well as cells. Enamel surfaces were digitally scanned, exposed to the palliative sialagogues, and then re-scanned. Mouse fibroblasts were exposed to product diluents for 72h to test biocompatibility using the MTT assay.

Results: Both product and contact time significantly affected vertical enamel loss. Interestingly, the product having the lowest pH did not exhibit the greatest enamel loss. Most products showed decreased MTT activity at 1:1 dilution with complete media. Upon further dilution, MTT activity increased for all products, except for one.

Conclusions: Both lozenge and rinse forms of sialagogues demonstrate significant enamel loss with some products having low pH values. Many of the products demonstrate significant cell effects, which improves with dilution.

Practical implications: Over-the-counter palliative sialagogues can result in significant enamel loss and changes in cellular viability. Any sialagogue referred to the patient should be advised based on scientific evidence to avoid causing damage potential.

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Introduction

With an ever-increasing population age and skyrocketing levels of medication usage, dentists are seeing more and more patients who suffer from xerostomia. This malady is defined as a dry mouth resulting from reduced or absent salivary flow and is frequently encountered in older patients for a multitude of reasons: polypharmacy, autoimmune disease, head and neck radiation and chemotherapy, and more [1,2]. A distinction between xerostomia and other causes of dry mouth, such as salivary gland hypofunction, is needed to understand differences between the conditions; the comorbidity of both conditions is 2-6% [1,2]. Literature reports that xerostomia incidence ranges from 10-46%, with women more commonly afflicted [2,3].

The practical implications of xerostomia can be devastating to a patient's ability to communicate, eat, sleep, and swallow resulting in poor nutrition and oral health as well as social isolation. Individuals reporting with symptoms of xerostomia are 2.3 to 4.9 times more likely to experience a negative impact to their general health than are control groups [4] and are at a greater risk for experiencing dental problems, such as caries and erosion [5]. To alleviate the symptoms accompanying a lack of saliva, patients may initially purchase over-the-counter palliative sialagogues, whose purposes are to stimulate salivary gland production, but without addressing the underlying cause of the condition. Such salivary stimulants are available as lozenges, mouth sprays, or rinses. Often, some of these products contain acidic components, likely because tart/sour flavors are potent inducers of stimulating salivary flow [5]. Thus, the potential for dental erosion should be of particular importance for clinicians with patients using such palliative sialagogue treatments.

Dental erosion occurs from the presence of weak acids adjacent to tooth structures when the hydrogen ion of the acid group attacks hydroxyl apatite in enamel or dentin [6]. In addition, the anion from the weak acid may complex with calcium liberated from the crystal. Not every acid is capable of this "double action" but, those that do can be extremely dangerous to tooth structure (such as citric acid, commonly found in medications and food products) [6,7]. Tooth dissolution is correlated with solution pH and pKa values of the active acid groups, but the process is also dependent on concentrations of calcium and phosphate present in the solution [7]. Several studies demonstrate that addition of calcium to a solution significantly reduces the erosive potential of the product [7,8]. These variations in redox chemistry can also be related to cell vitality and regeneration, because human keratinocytes and fibroblasts demonstrate decreased cell migration in acidic environments [9].

In a patient having a normal salivary flow, the function of saliva is multifold and its composition is complex. The average pH values of healthy human saliva is 6.78 +/- 0.04 and a long-term drop of pH below 5.5 in the oral cavity is generally regarded as initiating enamel demineralization [10]. Saliva also modulates oral pH and thus helps to regulate the tooth demineralization and remineralization cycle. The presence of, or even the mere thought of an acidic liquid, initiates an immediate and increased level of salivary flow in healthy individuals [11,12].

The consequences of dry mouth are manifest in many ways, such as dental caries, cheilosis, and more [13,14]. For these reasons, it is necessary that clinicians inquire about salivary flow at every appointment and correlate those findings with the patient's medical history. A xerostomatic patient may be unaware of their condition, and in patients with decreased salivary flow, appropriate and immediate treatment is necessary in order to prevent dental problems and encourage optimal quality of life [6].

If oral palliative sialagogues successfully alleviate symptoms in the short-term, it is likely that the patient will continue to use these products over a long period of time, because there is currently no known cure for the condition. Furthermore, there is limited literature demonstrating the efficacy of non-prescription sialogogues [15-17]. No data were found comparing the effect of short-or long-term contact with palliative sialagogues, regarding their potential to demineralize enamel. Because these sialagogues also come in contact with the oral mucosa, it is important to assess their interaction with living cells. However, no literature was found comparing the biocompatibility of these products. The need for long-term use of over-the-counter palliative sialagogues indicates that such information would be extremely useful to both patients and clinicians.

Thus, the purpose of this study was to measure and compare the human enamel dissolution potential of a wide variety of commercial, non-prescription, over-the-counter sialagogue products, compared to a control of phosphate buffered saline. In addition, the effect of these products on cellular viability was examined using the MTT test, against the negative control: PBS. The research hypotheses tested were that oral palliative sialagogues having an overall pH less than 5.5 will result in (1) significantly greater enamel dissolution, and (2) significantly lower cellular viability than those with higher pH values.

Table 1: Product ingredients.

Product	Abbreviation	Ingredients on Label
TheraBreath Dry Mouth Oral Rinse [18]	TBOR	Aqua, glycerin, peg-40 hydrogenated castor oil, xylitol, sodium benzoate, menthapiperita oil, parfum, citrus limon peel oil, lysozyme, amylase, papain, amyloglucosidase, serralysin, lactoferrin, maltodextrin, spilanthesacmella flower extract, propylene glycol, sodium citrate
Mouth Kote Spray [19]	MKS	Water, xylitol, sorbitol, Yerba Santa, citric acid, natural lemon-lime flavor, ascorbic acid, sodium benzoate, sodium saccharin
MedActive Oral Relief Lozenges, Orange Crème Flavor [20]	ORL	isomalt, water, poloxamer 338, citric acid, acesulfame potassium, dimethicone, flavor (includes Spilanthes Extract), malic acid, pectin, sucralose, FD&C Yellow No. 5
Ludens-Pectic Lozenges, Kiwi Strawberry Flavor [21]	LL	Active: pectin (2.8 mg); Inactive: ascorbic acid, citric acid, corn syrup, FD&C blue no. 1, FD&C yellow no. 5, flavors, malic acid, sucrose, water
Hylamint (Hyaluronic Acid) Lozenge [22]	HAL	Xylitol, "Natures Moisturizer Blend" (hyaluronic acid, pectin, slippery elm bark, cranberry extract), natural peppermint, spearmint flavor, vegetable magnesium stearate, citric acid, sodium bicarbonate, Stevia.
MighTeaFlow Lozenge [23]	MTFL	Xylitol, sorbitol, natural flavors, green tea (leaf), acadia gum, jaborandi extract (leaf), magnesium stearate, silicon dioxide, sucralose.

Methods

Sample preparation

The pH values of a wide variety of non-prescription, over-the-counter, commercial oral palliative sialagogue products (2 liquid* and 4 lozenge** delivery systems) were measured in triplicate (Accumet AR20, Fisher Scientific, Waltham, WA, USA): TheraBreath Oral Rinse* (TBOR); Mouth Kote Spray* (MKS); MedActive Oral Relief Lozenges**, Orange Crème Flavor (ORL); Ludens-Pectic Lozenges**, Kiwi Strawberry Flavor (LPL); Hylamint (Hyaluronic Acid) Lozenge** (HAL); Migh Tea Flow Lozenge** (MTFL); and phosphate buffered saline (PBS, control). Liquid products were tested as received. Lozenges were prepared via dissolution in deionized water (one part lozenge to five parts deionized water). All solutions were centrifuged at 2000 rpm for five minutes to remove any particulate prior to pH measurement. Products and their listed ingredients are provided in Table 1.

Enamel dissolution studies

Freshly extracted, non-restored, caries-free, human molars, previously stored in a supersaturated thymol solution were acquired. Teeth were individually embedded in epoxy resin (Epoxy Cure #1 and #2, Buehler, Lake Bluff, IL), with the lingual, coronal enamel surfaces exposed using sequential wet-grinding to a final 1000 grit SiC finish. Two 300 µm-deep dimples were made in the embedding epoxy, 10 mm apart and adjacent to the exposed, polished enamel surface. Pilot testing revealed that the set epoxy resin was not affected by any fluid in which the teeth were immersed. The dimples acted as constant-level indices of the horizontal epoxy surface, to which the ground tooth was coplanar, prior to immersion. Baseline surface profile scans were made (Form Talysurf Series 2, Model 50i, Taylor Hobson, Leicester, England), to include the two lateral dimples and the epoxy and enamel surface between them. The specimens (n=5/group) were immersed in their respective, prepared solutions for a 2-hour (short-term exposure) duration. During this immersion, the solutions were slightly agitated continuously (Model 260300F, Ocelot Orbital Shaker, Boekel Scientific, Feasterville, PA, USA). The specimens were then retrieved, rinsed, and air-dried. Surface scans were repeated through the same specimen areas. Specimens were re-immersed and agitated in solution for an additional 10 hours (accumulated 12 hour long-term exposure), followed by final surface scans. Surface scan data were imported into a spreadsheet program where they were further analyzed, and graphical overlays were made (Excel 2010. Microsoft Corporation, Redmond, WA, USA).Average vertical enamel loss (microns) over a 5 mm long enamel length between the dimples was determined using digital subtraction of the 2 and 12 hr immersed specimen (short- and long-term immersion) profiles from that of the pre-immersion baseline (Figure 1). Data were analyzed using a repeated measures, 2-factor ANOVA and the Tukey post-hoc test at a pre-set alpha of 0.05 (SigmaPlot V 11 for Windows, Systat Software, San Jose, CA, USA).

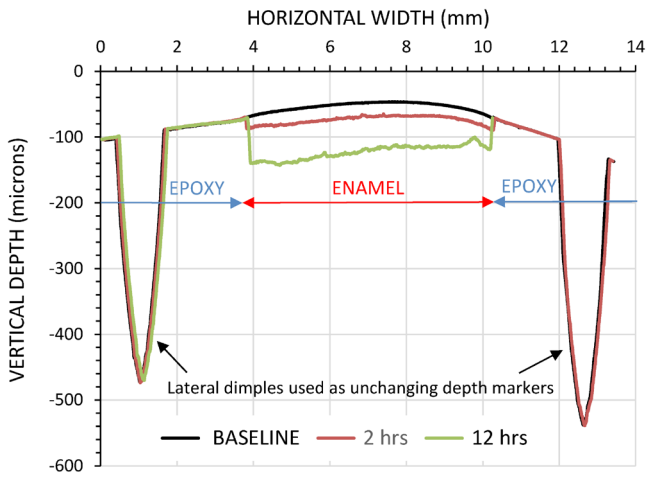

Figure 1: Graphical profile overlay for enamel loss as a function of immersion duration in fluid. The initial curve (black) shows relatedly flat specimen between two indensions. The curve after 2-hr immersion (red) shows much less verticle enamal loss than does the profile from the 12 hr profile (green).

Cellular biocompatibility using the MTT Assay (Succinate Dehydrogenase Activity)

The material elutes were tested for cytotoxicity on L929 fibroblasts (ATCC CCL1, NCTC clone 929) cultured in Dulbecco's Modification of Eagle's Medium (DMEM), 3% NuSerum, glutamine (2 mMol), gentamicin (10 ug/mL), penicillin (125 units/mL), streptomycin (125 ug/mL). The cells were plated at 8000 cells/cm^2 in 24-well format and incubated at 37°C in humidified 5% CO_2. Once the cells were near confluency, the cells were exposed to the warmed elutes of the material. To determine the presence of viable mitochondrial activity, an indicator of cellular viability, succinate dehydrogenase (SDH) activity was measured using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. This test uses a measure of the level of purple color in a test well as a positive indicator of cellular viability, arising from the ability of mitochondrial enzymes present in viable cells to reduce the tetrazolium dye (MTT) to an insoluble, purple-colored product.

The oral palliative sialagogue solutions were diluted at 1:1, 1:10, and 1:20 ratios with complete media and pH was measured. Dilutions were made to test the effects of the sialagogues in a manner simulating their lowered concentration when dissolving into saliva over time. Phosphate Buffered Saline (PBS) served as the control solution. Dilutions were applied to mouse fibroblast (L929) cells (ATCC, Manassas, VA USA) and incubated at 37˚C for 72 hours (n=6/product). Afterward, a 2% MTT solution in 0.25 M sodium succinate was added and formazan crystal formation was allowed to proceed for 1 hour. Cells were then formalin-fixed and solubilized in dimethylsulfoxide. The level of formazan production was quantified using absorbance spectroscopy at 562 nm (Synergy H1 Spectrophotometer, Biotek, USA). Cellular mitochondrial Succinate Dehydrogenase (SDH) activity (MTT testing) was expressed as a percentage of the appropriate PBS controls. Within a product, percent control values were compared using a 1-way, repeated measures ANOVA. Within a dilution level, percent control values were compared using a 1-way ANOVA. Pair-wise means comparisons were analyzed using the Tukey post-hoc test at a pre-set alpha of 0.05.

Results

Enamel dissolution studies

Figure 1 provides an example of profiles of the same surface at baseline (black), after 2hr in solution (red), and after 12 hr immersion (green).

Figure 2 graphically displays the trends of vertical enamel loss with respect to the different products and durations of immersion. Enamel loss for TBOR, HAL, and MTFL were lowest and did not statistically differ within or between immersion time elements or from the PBS control. The products TBOR and MTFL yielded pH values nearing that or above a neutral pH (9.7 and 6.3, respectively), whereas HAL demonstrated a pH value of 4.4. The product MKS (pH 2.7) showed the highest enamel loss, both at 2 and 12 hour immersion times. The enamel loss resulting from a 2 hour immersion time in MKS did not significantly differ from those of ORL and LL at 2 hours, but was significantly higher at the 12 hour immersion time. Only MKS statistically differed from the PBS control at both 2 and 12 hour immersion times. Enamel loss for 2 hour and 12 hour immersion times for MKS, ORL, and LL were significantly different within each brand, with the 12 hr value being significantly greater than that at 2 hrs. Enamel loss in LL (pH 2.2) and ORL (pH 2.3) was statistically greater than the control at the 12 hour immersion time. However, neither enamel values statistically differed at the 2 hour immersion time. The vertical enamel loss at 2 hour and 12 hour immersion times for LL and ORL were significantly different, with LL showing significantly greater loss than ORL at the 12 hr duration time. Enamel loss at the 2-hour immersion time point was nearly identical between these products.

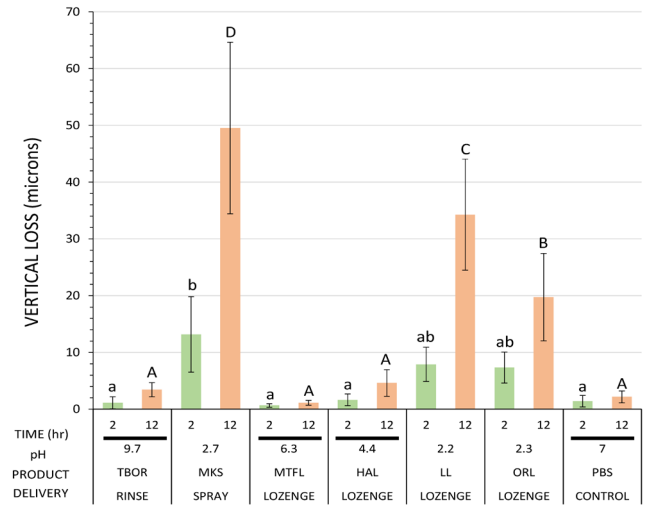

Figure 2: Enamel loss resulting from immersion in palliative sialagogue medications after 2- and 12-h. Values of groups identified using similar letters above bars (lower case 2-hr, upper case 12-hr immersion times) were not significantly different. Horizontal bars in the "TIME" row indicate enamel loss values between time intervals that or not significantly different. (n=5 condition, error bar= +/- stdev).

pH testing

Figure 3 demonstrates the pH values as the medicaments were diluted in complete media. All products approached neutral pH when diluted using media. The product TBOR was the only medicament indicating a decrease in pH with media dilution; all other medicaments, as well as the PBS control, increased in pH with dilution factor. The products LL and ORL demonstrated nearly identical pH values at 1 and 1:1 dilutions; at the 1:10 and 1:20 dilutions the pH increased quickly to near physiologic level (~7). All other medicaments demonstrated regular increments of pH increase with dilution factor.

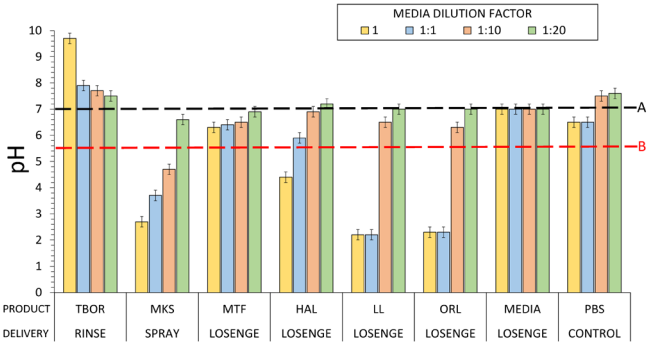

Figure 3: Pallilative sialagogue medication pH in dilutions of complete media. Errors bars= +/- 1 stdev. N=3, Dashed horizontal black line (A) represents neutral pH, red line (B) represents pH below which enamel is known to dissolve.

Biocompatibility testing (MTT Assay)

The various products demonstrated significant differences in biocompatibility among dilutions (Figure 4). The activity of TBOR at the 1:1 dilution differed significantly from the 1:10 and 1:20 dilution factors, but the 1:10 and 1:20 dilution activities were not significantly different. The products MKS, MTFL, LL, and ORL differed significantly in their MTT activity at all dilution factors. The only product whose MTT activity did not differ significantly at any dilution factor was HAL, which also did not significantly differ from the PBS control values at any given dilution.

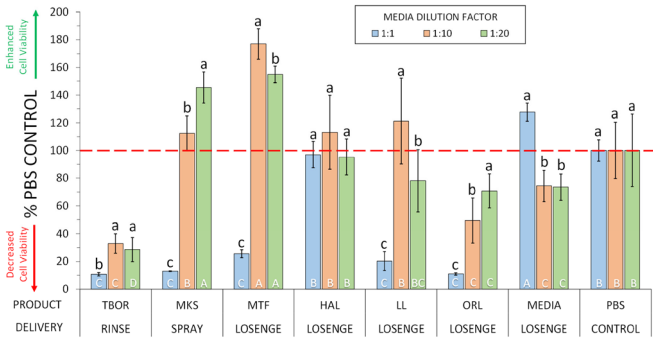

Figure 4: MTT activity in L929 cells treated with pallilative sialagogues when diluted with media. Values (above bars) of groups identified using similar lower case letters are not significantly different with in each material, among dilutions. Values of groups identified using similar upper case, white letters (bottoms of bars) are not significantly different at a given dilution, among products. (n=6 condition, verticle bar = +/- 1 stdev).

At the 1:1 dilution, all solutions (with exception of HAL) demonstrated MTT activity that was significantly below the PBS control. At the 1:10 dilution, only MKS and HAL did not differ significantly from the PBS control. The MTFL 1:10 dilution demonstrated increased MTT activity compared to the PBS control, while TBOR, The needs to be the, and media yielded decreased MTT activity compared to the PBS control. At the 1:20 dilution, TBOR demonstrated the lowest MTT activity, significantly different from all other solutions. The second lowest MTT activity was noted with ORL and media, which was significantly different from all other solutions. The MTT activity of LL was also not significantly different from the PBS control, HAL, ORL, and media at the 1:20 dilution. At 1:20 dilution, some MTT values decreased relative to the 1:10 value: MTFL, LPL, and HAL, with MKS and MTFL significantly exceeding control value.

Discussion

The first research hypothesis, that oral palliative sialagogues with a pH of less than 5.5 will demineralize enamel while products having a neutral to basic pH will show no demineralization, was proven. Both product and contact time significantly affected vertical enamel loss, but the results were product-dependent, as shown in Figure 2. The products MTFL, TBOR, and HAL demonstrated the lowest enamel losses (pH > 6.44, Figure 3), and for each product, there was no significant effect of immersion time. There was no significant difference in enamel loss between these products and the PBS control. The 2 hour enamel loss of MKS was not significantly different from those of ORL or LL, but was greater than all others. Twelve-hour enamel losses for MKS were highest, followed by LL and ORL. For pH values < 6.44 (those near 2.5-3.0), enamel loss started to become apparent. Interestingly, the product with the lowest pH value (ORL) did not exhibit the highest enamel loss.

The second research hypothesis, that oral palliative sialagogues having an overall pH of less than 5.5 will impair cell vitality as measured using their MTT activity while palliative sialagogues with a neutral to basic pH will have not demonstrate any significant effect, was disproven (Figure 4). All solutions, except for HA (original pH 4.4), showed significantly decreased MTT activity at the 1:1 ratio. At dilutions of 1:10 and 1:20, MTT activity increased for all products, except for TBOR (initial pH 9.7; (7.9, 7.7, and 7.5 with dilutions, respectively)). Some products demonstrated higher MTT activity than control, notably at the 1:10 dilution. Interestingly, some products stimulated mitochondrial activity (>100 of the PBS control) and The Most Basic Solutions (TBOR) maintained low MTT values, even after dilution.

Possible causes for the solution and MTT activity effects include the presence of specific types of acidic groups in the products. Citric acid is a listed component of MKS, ORL, and LL, ascorbic acid is present in LL and MKS, and malic acid is seen in ORL and LL. The presence of these ingredients may be responsible for the observed increase in enamel loss. In addition, because enamel loss during short- and long-term immersion in these products was significantly different from each other, it is suspected that the continued usage of the product *in vivo* would result in further tooth erosion.

The presence of different acids and their effects are very much dependent on the amount and the presence of other neutralizing ingredients. A titration curve for each solution and its dilution would have been helpful to observe how the presence of the other ingredients participated in the acid availability. Titratable acidity may in fact be a better indicator of the erosive potential of the different products [24]. However, at the time of writing, adding this technique to the paper is impossible because one of the products tested is no longer available. Therefore, it is difficult to ascertain which ingredients contribute to the low pH, or how much of each ingredient is responsible, because the exact compositions of the products are not known. Nevertheless, it likely that the result is a product of both acid concentration as well as the presence of other neutralizing ingredients in combination with the strength of the acid itself. The pKa of the respective acids is valuable information to determine the potential causative ingredients responsible for enamel loss. While malic, citric, and ascorbic acid are all considered weak acids in nature, their pKa values vary (3.51 and 5.03 for malic acid, 2.79 for citric acid, and 4.7 for ascorbic acid) [25]. The pKa value is dependent on the reactivity of certain portions of the acid molecule. The lower the pKa values the more reactive these molecules become as the pH of the solution decreases thus causing more tooth dissolution [24,26].

Regarding the overall solution pH values, LL and MKS, the citric and malic acids would not have been 100% dissociated, but the ascorbic would have been deprotonated at the solutions pH. The product HAL also contains citric acid and demonstrates an acidic pH, although slightly higher than those of ORL, MKS, and LL. The slightly higher pH is likely due to the presence of another basic pH component neutralizing the acid. Additionally, citric acid is one of the last components listed as an ingredient (suggesting a lower amount) in HAL, while this acid appears in the top five ingredients of MKS, ORL, and LL.

A major limitation of this study was that it was an *in vitro* investigation. The dental pellicle and saliva normally help neutralize acids and result in less than expected enamel loss. However, in saliva-compromised individuals, this protection is greatly diminished. In reality, the rinses and lozenges would not be used for 2 h or 12 h continuously and some remineralization may occur following consumption of the product intraorally. However, patients may also use these products more than their prescribed limits if the products are perceived to lessen symptoms. It is also important to note that several of the palliative sialagogues contain sugar (ORL contains corn syrup and LL contains sucrose). Thus, it is not unreasonable to imagine that the presence of sugars in a low pH oral environment could contribute to further enamel loss than the conditions imposed in this bench top study.

Palliative sialagogues only treat the symptoms of dry mouth, and not the root cause. Several therapies are being studied to improve salivary flow through systemic medications and possibly *via* gene therapy/tissue engineering [27]. However, the palliative sialagogues are conservative treatment of the symptoms. Any lack of salivary flow should be thoroughly diagnosed initially, and observation over time needs to occur to arrive at a definitive diagnosis for a specific individual. Subsequent dental appointments should monitor patient compliance and saliva flow perception, while the actual measurement of flow needs to be determined. If decreased flow is due to salivary gland damage or disease, palliative sialagogues might be prescribed with warning to patients about the potential for tooth or mucosa damage arising from continuously consuming these products.

Summary

1. Within the limitations imposed, the following conclusions can be made: Certain over-the-counter palliative sialagogues (either in spray, rinse, or lozenge form), can result in significant enamel loss when in contact with human enamel for as little as 2 hours. The enamel loss effect with sialagogues is product-dependent, and seems to occur with greater magnitude in products having a pH value near 3 or less.

2. Biocompatibility of over-the-counter palliative sialagogues varies significantly and does not correlate with initial pH of the solutions. Over-the-counter palliative sialagogues can result in significantly lower cellular activity, especially at only a 1:1 dilution. The decrease in cellular activity does not always correspond with solution pH.

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