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A mucoadhesive formulation containing a clathrate host that encloses water molecules provides an effective means for, not only providing moisture to, and maintaining moisture on, a mucosal surface, but also in maintaining a high concentration of a sugar alcohol in situ on the mucosal surface for extended periods of time.

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(54) Title: COMPOSITION FOR THE RELIEF OF DRY MOUTH

(57) Abstract: A mucoadhesive formulation containing a clathrate host that encloses water molecules provides an effective means for, not only providing moisture to, and maintaining moisture on, a mucosal surface, but also in maintaining a high concentration of a sugar alcohol in situ on the mucosal surface for extended periods of time.

# COMPOSITIONS OF CLATHRATE AND XYLITOL FOR THE RELIEF OF DRY MOUTH

## Field of the Invention

The present application pertains to the field of  
5 compositions for oral use to reduce discomfort related to  
xerostomia.

## Background of the Invention

Xerostomia, also referred to as Dry Mouth, is a  
10 chronic condition due to an inadequacy of saliva flow in the  
mouth. It in itself is not a disease but is a symptom  
associated with a wide variety of causes and conditions.

There are many causes of xerostomia, including the  
use of medications such as antihistamines, antidepressants,  
15 anticholinergics, anorexiant, antihypertensives,  
antipsychotics, anti-Parkinson agents, diuretics, sedatives,  
antiemetics, antianxiety agents, decongestants, analgesics,  
antidiarrheals, bronchodilators and skeletal muscle relaxants.

Another cause of xerostomia is as a secondary effect  
20 of a disease. The most common disease causing xerostomia is  
Sjögren's syndrome, a chronic inflammatory autoimmune disease.  
Chronic inflammatory diseases, such as sarcoidosis and  
amyloidosis, are also causes of xerostomia.

Systemic diseases that can cause xerostomia include  
25 rheumatoid arthritis, systemic lupus erythematosus,  
scleroderma, diabetes mellitus, hypertension, cystic fibrosis,  
bone marrow transplantation, endocrine disorders, nutritional  
deficiencies, nephritis, thyroid dysfunction, and neurological  
diseases such as Bell's palsy and cerebral palsy.  
30 Hyposecretory conditions, such as primary biliary cirrhosis,  
atrophic gastritis and pancreatic insufficiency, may also  
cause xerostomia.

Dehydration resulting from impaired water intake,  
emesis, diarrhea or polyuria can result in xerostomia.

Psychogenic causes, such as depression, anxiety, stress or fear, can also result in xerostomia. Alzheimer's disease or stroke may alter the ability to perceive oral sensations. Dry mouth is often exacerbated by activities such as

5 hyperventilation, breathing through the mouth, smoking, or drinking alcohol. Trauma to the head and neck area can damage the nerves supplying sensation to the mouth, impairing the normal function of the salivary glands. Additionally, xerostomia is the most common toxicity associated with

10 radiation therapy to the head and neck.

Although xerostomia occurs in people of all ages, it is an especially common complaint in elderly people, and is estimated to affect approximately twenty percent of the elderly. In people suffering from xerostomia, common

15 complaints secondary to the xerostomia include oral dryness when eating, the need to sip liquids in order to swallow dry foods, difficulty swallowing, and the perception of a dry mouth due to too little saliva.

Xerostomia is also responsible for secondary

20 effects, including an increased incidence of dental caries and demineralization of teeth, and increased risk of secondary infections such as candidiasis. Therefore, ancillary treatment for xerostomia often includes the use of fluoride therapy for caries control and antifungal medications such as nystatin.

For the treatment of xerostomia itself, artificial saliva or saliva substitutes can be used to replace moisture and lubricate the mouth. These substitutes are available in a variety of formulations including solutions, sprays, gels and lozenges. These artificial saliva substitutes may contain an

25 agent to increase viscosity, such as carboxymethylcellulose or hydroxyethylcellulose, minerals such as calcium and phosphate ions and fluoride, preservatives, and flavoring agents.

30

The most commonly utilized oral treatment for xerostomia is BIOTENE® (GlaxoSmithKline plc, United Kingdom).

BIOTENE® is available in oral rinse and spray formulations, as well as an oral gel formulation. All formulations of BIOTENE® contain water glycerin, xylitol, and a mucoadhesive polymer. The BIOTENE® gel formulation additionally contains a carbomer  
5 as a thickening agent, in addition to its mucoadhesive properties. The sugar alcohols xylitol and sorbitol are present in the BIOTENE® formulations in small amounts in order to provide sweetness.

Kawa, U.S. Patent Application No. 2008/0317703  
10 discloses an oral care product for xerostomia which contains a combination of polyvinyl pyrrolidone (PVP) or a vinyl pyrrolidone/vinyl acetate or vinyl alcohol copolymer in combination with an anionic mucoadhesive polymer. Kawa discloses that the anionic polymer has an affinity for mucous  
15 membranes of the oral cavity and provides good mouth coating. However, such polymers often are overly tacky and, therefore, have negative sensory characteristics. The combination of the PVP or copolymer with the mucoadhesive polymer overcomes the bad mouth feel of the composition due to the presence of the  
20 mucoadhesive polymer.

Kawa further discloses that the composition may contain additional excipients, one of which may be a humectant. If present, the humectant may be glycerin, sorbitol, xylitol, propylene glycol, polyethylene glycol, or a  
25 combination.

Soderling et al, Curr. Microbial., 56:382-385 (2008), discloses that xylitol inhibits the growth of *Streptococcus mutans*, an organism that is commonly found in the oral cavity and which is a significant contributor to the  
30 development of dental caries.

In 2012, Ashland Inc. (Covington, KY) announced the release of LUBRAJEL® BA for the treatment of dry mouth. LUBRAJEL® BA hydrogel is a clathrate of glycerin and polyacrylate that encloses water molecules via hydrogen

bonding and Van der Waals forces. Because it binds water and is a highly viscous gel, LUBRAJEL® BA was marketed as an ingredient to provide moisture to the mouth. Ashland further disclosed that formulations containing LUBRAJEL® BA perform  
5 similarly to saliva under varying oral conditions. Moreover, these formulations had better mucoadhesion than saliva, so that it is expected that, with formulations containing LUBRAJEL® BA, the mouth will maintain longer hydration and relief from dry mouth (xerostomia).

10 A significant need exists for an oral care product that contains xylitol at a concentration sufficiently high to inhibit the growth of *S. mutans* and which product maintains the concentration of xylitol in the mouth, and particular on the oral mucosa, for a time sufficient for the xylitol to  
15 inhibit the growth of *S. mutans* in the mouth.

#### Detailed Description of the Invention

It has been unexpectedly discovered that, even in the presence of a high water concentration, a mucoadhesive  
20 formulation containing a clathrate host that encloses water molecules and which is effective in holding water molecules in place on a mucosal surface is also effective in holding a sugar alcohol in place on the mucosal surface, and that the ability to hold the sugar alcohol is maintained even in the  
25 presence of high concentrations of water.

Based on this initial discovery, it has been further discovered that a mucoadhesive formulation containing a clathrate host that encloses water molecules provides an effective means for, not only providing moisture to, and  
30 maintaining moisture on, a mucosal surface, but also in maintaining a high concentration of a sugar alcohol in situ on the mucosal surface for extended periods of time. The sugar molecule is preferably xylitol and the concentration of

xylitol that remains in situ may be sufficiently high in order to inhibit the development of dental caries.

Accordingly, the present application discloses, in a first embodiment, a formulation for providing moisture and the adherence of a sugar alcohol, such as xylitol, to a mucosal surface such as the oral mucosa.

The mucoadhesive formulation contains a mucoadhesive polymer. Suitable mucoadhesive polymers include cellulose polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, saccharide gums such as xanthan gum, guar gum, gum Arabic, and tragacanth, polyacrylic acid polymers such as carbomers or acrylate/C<sub>10-30</sub> alkyl acrylate cross polymers, or other polymers such as polyvinyl pyrrolidone or chitosan. In a preferred embodiment, the mucoadhesive polymer is a polyacrylic acid or polyacrylate.

The mucoadhesive polymer is present in the mucoadhesive formulation in a concentration sufficient to provide adhesion of the formulation to the oral mucosa. For example, the concentration of the mucoadhesive polymer in the formulation may be from 0.1% to 25% w/w, with a preferred range of 0.5% to 10%, and a more preferred range of 1.0% to 7%.

The mucoadhesive formulation contains a clathrate host that is capable of enclosing water. The clathrate host may be other than the mucoadhesive polymer. An example of a clathrate host that is suitable for the present invention, and which is not itself a mucoadhesive polymer, is a cyclodextrin. Examples of suitable cyclodextrins include  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, and  $\gamma$ -cyclodextrin, and derivatives of cyclodextrin such as methylated cyclodextrins, ethylated cyclodextrins, hydroxypropyl cyclodextrins, and hydroxyethyl cyclodextrins.

In a preferred embodiment, the mucoadhesive polymer and the clathrate host are the same, or the mucoadhesive

polymer is a component of the clathrate host. In a most preferred embodiment, the mucoadhesive polymer/clathrate host is a clathrate of glycerin and polyacrylate as sodium polyacrylate and polyacrylic acid that encloses water by hydrogen bonding and Van der Waals forces. This mucoadhesive polymer/clathrate host is marketed by Ashland Inc. (Covington, KY) as LUBRAJEL® BA. Additional minor components of LUBRAJEL® BA are butylene glycol, benzoic acid, and EDTA.

The mucoadhesive formulation contains water. As supplied by the manufacturer in the form of a hydrogel, LUBRAJEL® BA contains about 50% water w/w and about 50% non-water ingredients. The mucoadhesive formulation of the present application contains, in addition to the water that is provided by the LUBRAJEL® BA, a concentration of water that is at least as much as, and preferably several times higher than that of, the water concentration that is inherently in the LUBRAJEL® BA in the formulation. For purposes of this application, the water in the formulation that is not a component of the LUBRAJEL® BA in the formulation is referred to as "free water." If LUBRAJEL® BA is the clathrate host in the formulation, the free water in the formulation is the total water concentration in the formulation minus 50% of the concentration of LUBRAJEL® BA in the formulation.

As an illustrative example, the mucoadhesive formulation may contain LUBRAJEL® BA at a concentration of 10%. Of this, 50% is water and, therefore, 50% of the LUBRAJEL® BA is other than water. Therefore, the concentration of water that is inherent in a formulation containing 10% LUBRAJEL® BA is 5%. Therefore, if the concentration of free water in this example formulation is at least as high as that of the water that is a part of the LUBRAJEL® BA, the mucoadhesive formulation contains a concentration of free water of at least 5% and preferably higher than 5%.



Preferably, the concentration of free water in the mucoadhesive formulation is two or more times that of the concentration of water that is part of the LUBRAJEL® BA. In one preferred embodiment, the concentration of free water that is  
5 in the mucoadhesive formulation is 3 or more times that of the concentration of water that is part of the LUBRAJEL® BA. In a more preferred embodiment, the concentration of free water is at least 4 times, such as 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 11 times, 12 times, 13 times, 14 times, 15  
10 times, or even more than 15 times the concentration of water that is in the LUBRAJEL® BA of the formulation.

In the formulation, the concentration of free water is between 5% and 75%. Preferably, the concentration of free water in the formulation is less than 50%, such as between 10%  
15 and 42%. As disclosed below, it is preferred that concentration of other components, such as sugar alcohols, is higher than that of free water, and may be higher than that of free water plus water that is in the LUBRAJEL® BA. That is, preferably the total amount of free water in the formulation,  
20 from all sources, and most preferably the total amount of water including free water and water that is part of the LUBRAJEL® BA, is less than 50%.

The mucoadhesive formulation contains one or more sugar alcohols of 4 to 6 carbons. Examples of sugar alcohols  
25 of 4 to 6 carbons that are suitable for the mucoadhesive formulation include 4-carbon (C<sub>4</sub>) sugar alcohols such as erythritol and threitol, 5-carbon (C<sub>5</sub>) sugar alcohols such as arabitol, xylitol, and ribitol, and 6-carbon (C<sub>6</sub>) sugar alcohols such as nannitol, sorbitol, galactitol, fucitol,  
30 iditol, and inositol. In one preferred embodiment, the sugar alcohol is xylitol or sorbitol.

In a most preferred embodiment, the sugar alcohol is xylitol. Xylitol is preferred because, in addition to its use

as a sweetener, xylitol inhibits the growth of organisms that contribute to the development of dental caries.

The concentration of the sugar alcohol in the formulation is sufficient to provide the function for which is intended. Therefore, if used as a humectant or as a sweetener, the concentration of the sugar alcohol is sufficient to provide these functions. Concentrations of sugar alcohol sufficient as a humectant or to provide sweetness to a formulation are generally between 1.0% and 10%.

In the case of xylitol, because of its anti-caries effects in addition to providing sweetness, it is preferred to have a concentration in the mucoadhesive formulation of at least 10%, so as to be capable of providing its anti-caries effect. More preferably, the concentration of xylitol in the mucoadhesive formulation is at least 15%, such as at least 20% or at least 25%. In one preferred embodiment, the concentration of xylitol in the mucoadhesive formulation is at least 30%, such as at least 35% or at least 40%. If desired, concentrations of xylitol higher than 40% may be used, such as 42%, 45%, or higher.

When the formulation contains xylitol as the sugar alcohol, it is preferred that the concentration of xylitol in the formulation be at least 25% of the concentration of the free water in the formulation. For example, the concentration of xylitol in the formulation may be at least 33% of the concentration of the free water, or at least 50% of the concentration of the free water, in the formulation. More preferably, the concentration of xylitol in the formulation is at least 75% that of the free water. Most preferably, the concentration of xylitol in the formulation is equal to or higher than that of the free water. In one particularly preferred embodiment, xylitol is the component that is in the highest concentration of all components in the mucoadhesive

formulation. Thus, it is particularly preferred that the free water concentration of the formulation be less than 50% w/w.

An optional additional component of the mucoadhesive formulation is glycerin (glycerol). Glycerin is a sugar alcohol commonly used in oral preparations as a humectant. Although glycerin is a sugar alcohol, it is discussed separately in this application because it is often used in oral preparations in addition to other sugar alcohols and, unlike xylitol, glycerin is not known to have an anti-carries effect.

If present in the formulation, glycerin is at a concentration less than that of the C<sub>4</sub> to C<sub>6</sub> sugar alcohol such as xylitol. Preferably, the concentration of glycerin is less than half of the concentration of the sugar alcohol such as xylitol. More preferably, the concentration of glycerol is less than 35% that of the concentration of the sugar alcohol such as xylitol, and most preferably less than 25% that of the sugar alcohol such as xylitol.

Generally, if present, the concentration of glycerin in the formulation is less than 25%, preferably less than 20%, and most preferably less than 15%. In a most preferred embodiment, glycerin is present in a concentration less than 12%, such as 10% or less.

The mucoadhesive formulation may optionally contain other ingredients, such as flavoring agents, preservatives, buffering agents, antioxidants, decay preventing compounds such as fluorides like sodium fluoride, stannous fluoride, and sodium monofluorophosphate, and non-aqueous vehicles such as propylene glycol. Preferably, the mucoadhesive formulation is free of alcohols other than sugar alcohols.

The mucoadhesive formulation may be in any form that is useful for delivery to the oral mucosal surface, such as a liquid like a rinse or mouthspray, or as a semi-solid like a gel or a paste. Generally, similar formulations may be used as

either rinse or mouthspray. Gel and paste formulations contain a thickening agent in an amount sufficient to render the formulation in the form of a semi-solid.

In another embodiment, the invention is a method for providing and preferably maintaining a sugar alcohol, such as xylitol, in situ on the oral mucosal surface and additionally providing moisture to the oral mucosal surface. In accordance with this embodiment, the mucoadhesive formulation described above in the form of a liquid, as in a rinse or mouthspray, or as a semi-solid, as in a gel or paste, is administered into the oral cavity of an individual. The formulation may be administered by any practical means, such as by rinsing, spraying, or applying into the mouth.

Preferably, the individual maintains the formulation in the oral cavity for a period of time sufficient to permit the formulation to adhere to the oral mucosa. This may be achieved by means such as gargling or by merely holding the formulation in the mouth. The time required for the formulation to adhere to the mouth may, in some cases, be instantaneous. In such situations, merely administering the formulation into the oral cavity would be sufficient for such adherence.

Because of its anti-caries effects, the sugar alcohol that is preferred for this embodiment of the invention is xylitol. Thus, as disclosed above, it is preferred that xylitol is the component that is in the highest concentration in the mucoadhesive formulation, with the possible exception of water.

An unexpected discovery concerning the administration of the mucoadhesive formulation containing xylitol as described above to the oral mucosa is the ability of the formulation to "hold" xylitol in situ on the oral mucosa at high concentrations and for extended periods of time. For example, a formulation comprising water, xylitol,

and a clathrate of glycerin and polyacrylate was found to be held on the oral mucosa for several minutes in nearly identical concentration ratios as in the formulation itself. As described below in the Examples, this capability was found  
5 to be present in formulations in which the ratio in the formulation of the concentrations of free water and the water in the clathrate was more than 10 times and the concentration in the formulation of xylitol was six times that of the clathrate. This establishes that the clathrate in the  
10 formulation not only holds water, in dramatically high concentrations, but together with such high concentrations of water, simultaneously holds xylitol at high concentrations.

In another embodiment, the invention is a method for providing and retaining moisture in situ on the oral mucosal  
15 surface. In accordance with this embodiment, the mucoadhesive formulation described above in the form of a liquid, as in a rinse or mouthspray, or as a semi-solid, as in a gel or paste, is administered into the oral cavity of an individual. The formulation may be administered by any practical means, such  
20 as by rinsing, spraying, or applying into the mouth.

In accordance with this embodiment of the invention, it has been unexpectedly discovered that combining, in a formulation containing water, xylitol and a clathrate host that encloses water molecules and which is effective in  
25 holding water molecules in place on a mucosal surface provides for the holding of significantly more water than is obtained by use of the clathrate host without xylitol.

As discussed above, the clathrate host may be other than a mucoadhesive polymer, such as a cyclodextrin mentioned  
30 above, or the clathrate host may be a mucoadhesive polymer or have a mucoadhesive polymer as a component of the clathrate host. A preferred example of a clathrate host in which a mucoadhesive polymer is the clathrate host or a component of the clathrate host is a clathrate of glycerin and polyacrylate

as sodium polyacrylate and polyacrylic acid that encloses water by hydrogen bonding and Van der Waals forces, such as LUBRAJEL® BA.

In accordance with this embodiment of the invention,  
5 the relative concentrations w/w % of the clathrate host, such as LUBRAJEL® BA, and xylitol are preferably between 1:1 and 1:10, with a more preferred range between 1:2 and 1:8, and a most preferred range between 1:4 and 1:6.

Preferably, the concentration of xylitol in the  
10 formulation is at least 25% of the concentration of free water in the formulation. More preferably, the concentration of xylitol is at least 50% of the concentration of free water in the formulation. Even more preferably, the concentration of xylitol is at least 75% of the concentration of free water in  
15 the formulation. In a most preferred embodiment, the concentration of xylitol in the formulation is equal to or greater than the concentration of water in the formulation.

The invention is further illustrated in the following non-limiting examples.

20

Example 1 - Mucosal retention of xylitol by prior art liquid formulation

A prior art liquid formulation as disclosed in Kawa, U.S. Patent Application No. 2008/0317703, was evaluated for  
25 its ability to retain xylitol on a mucosal surface. The prior art formulation contained the following ingredients as shown in Table 1.

Ingredients	Concentration (w/w %)
Water	52.94
Glycerin	35.00
Xylitol	7.50
Vinyl pyrrolidone/vinyl acetate copolymer	1.00
PEG 60 hydrogenated castor oil	1.60
Flavor ingredients	0.81
Sodium benzoate	0.50
Xanthan gum	0.40
Methylparaben	0.10
Propylparaben	0.10
Cetylpyrindinium chloride	0.05

Table 1

Plastic microscope slides were coated with AVALURE™  
 5 UR 450 polymer (Lubrizol Corp., Wickliffe, OH), an artificial polyurethane membrane that mimics the oral mucosal surface. The coating was dried overnight at room temperature. After drying, the slides were soaked in de-ionized water for 25 minutes at which time the coating was determined to have  
 10 changed from clear to slightly opaque, indicating that moisture had been absorbed.

In order to determine the percent solids in the prior art formulation, the untreated slides were weighed and then coated with the prior art formulation of Table 1 using a  
 15 varnish brush. The amount of solution coated on the slides was determined by measuring weight loss from the original container. After coating, the slides were weighed and then left at a temperature of 37°C to dry and again reweighed. After coating, the slides were weighed and then left at a  
 20 temperature of 37°C to dry and again reweighed. It was

determined that the constant residual weight of the prior art formulation, that remaining after the volatile components evaporated, was 52.9%.

Plastic microscope slides were weighed and coated  
5 with the UR 450 polymer and allowed to dry. The slides were  
then weighed to the nearest 0.001g. The slides were coated  
with the formulation of Table 1 and weighed when wet. The  
slides were then placed in Drip Flow Biofilm Reactor Model DFR  
110 (BioSurface Technologies Corporation, Bozeman MT) at a 10  
10 degree slope for one hour and exposed to a drip flow of water  
at a rate of 0.35 ml/min in order to mimic the flow of saliva.  
The slides were removed from the Reactor, allowed to dry, and  
were re-weighed to the nearest 0.001 g. The residual amount of  
wet coating was determined using the calculation of solids as  
15 described above.

After the one-hour drip flow treatment, it was  
determined that there was no residual coating of the prior art  
formulation on the slides, indicating that none of the solids,  
including xylitol, remained on the in-vitro oral mucosal  
20 substitute surface.

As a control, slides coated with the UR 450 polymer  
only were placed in the drip flow reactor and treated in the  
same manner as the slides coated with the prior art  
formulation. The weight of the slides was determined to be the  
25 same before placing in the drip flow reactor and following the  
one hour treatment with subsequent drying.

#### Example 2 - Mucosal retention of xylitol by liquid formulation of the invention

30 The study of Example 1 was repeated except that a  
liquid formulation as shown below in Table 2 was used in place  
of the prior art formulation of Table 1.



Ingredients	Concentration (w/w %)
Water	40.85
Glycerin	10.00
Xylitol	42.00
LUBRAJEL® BA hydrogel	7.00
Flavor ingredients	0.15

Table 2

The dry weight of the liquid formulation was determined to be 45.8%, composed primarily of the xylitol and the hydrogel. The original weights of coating on the slides before drying and before drip flow treatment were 0.097 g and 0.113 g and the residual weights after treatment and subsequent drying were 0.020 g and 0.031 g, respectively.

By dividing the residual weight by the original weight multiplied by the percent dry weight, the dry weight residual percent retained on the slides was determined. This results in 45.0% and 59.9% of the formulation being retained for each sample, respectively.

This study established that the liquid formulation of the invention maintains xylitol in contact with oral mucosa for over one hour in the presence of a rate of flow of liquid that is typically found in an individual suffering from a dry mouth condition.

Example 3 - Mucosal retention of xylitol by prior art gel formulation

The study of Example 1 was repeated except that a gel formulation of the prior art (BIOTENE® ORAL BALANCE® Dry Mouth Moisturizing Gel, GlaxoSmithKline, Philadelphia, PA) was used in place of the prior art liquid formulation of Table 1. The prior art gel formulation contained the following ingredients. The concentration of the ingredients was not

determined. BIOTENE® ORAL BALANCE® Dry Mouth Moisturizing Gel contains glycerin, water, sorbitol, xylitol, carbomer, hydroxyethyl cellulose, sodium hydroxide, and propylparaben.

The dry weight of the prior art gel formulation was determined to be 70.1%. The original weights of coating on the slides before drying and before drip flow treatment were 0.526 g and 0.248 g and the residual weights after treatment and subsequent drying were 0.219 g and 0.077 g, respectively.

By dividing the residual weight by the original weight multiplied by the percent dry weight, the dry weight residual percent retained on the slides was determined. This results in 49% and 37% of the formulation being retained for each sample, respectively.

Example 4 - Mucosal retention of xylitol by gel formulation of the invention

The study of Example 3 was repeated except that a gel formulation as shown below in Table 3 was used in place of the prior art formulation of Example 3.

Ingredients	Concentration (w/w %)
Water	40.35
Glycerin	5.00
Xylitol	43.00
LUBRAJEL® BA hydrogel	10.00
Carboxymethyl cellulose 7HSF	1.50
Flavor ingredients	0.15

Table 3

The dry weight of the gel formulation was determined to be 55.9% solids, composed primarily of the xylitol and the

hydrogel. The original weights of coating on the slides before drying and before drip flow treatment were 0.150 g and 0.129 g and the residual weights after treatment and subsequent drying were 0.033 g and 0.037 g, respectively.

5 By dividing the residual weight by the original weight multiplied by the percent dry weight, the dry weight residual percent retained on the slides was determined. This results in 39% and 51% of the formulation being retained for each sample, respectively.

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#### Example 5 - Moisture retention

Moisture retention was determined by applying 0.4 g of each product in a 37°C gravity flow incubator for 2 hours and then re-weighing the amount of product remaining after that time. This test was run in a first trial comparing BIOTENE® Dry Mouth Spray (containing the ingredients shown in Table 1), SPRY RAIN with Xylitol (containing water, xylitol, aloe vera concentrate, glycerin, flavoring, calcium glycerophosphate, cellulose gum, and grapefruit seed extract as a preservative), and the liquid formulation of Example 2. This test was run in a second trial comparing BIOTENE® Dry Mouth Spray, the liquid formulation of Example 2, and a formulation similar to that of Example 2 but without xylitol (58% water, 35% glycerin, and 7% LUBRAJEL® BA hydrogel. The results are shown below in Tables 4 and 5.

TEST FORMULATION	% Moisture Loss
BIOTENE® Dry Mouth Spray	31.7%
SPRY RAIN with Xylitol	39.5%
Example 2 Liquid Formulation	18.8%

Table 4

TEST FORMULATION	% Moisture Loss
BIOTENE® Dry Mouth Spray	38.3%
Example 2 Liquid Formulation	22.0%
Example 2 Liquid Formulation without xylitol	33.5%

Table 5

5           The results of Tables 4 and 5 establish that the inclusion of xylitol in a formulation containing a clathrate host that encloses water, such as LUBRAJEL® BA, unexpectedly provides a dramatic increase in the moisture retention capabilities of the formulation containing the clathrate host.

10           While preferred embodiments of the invention have been described in detail, it will be apparent to those skilled in the art that the disclosed embodiments may be modified. It is intended that such modifications be encompassed in the invention. Therefore, the foregoing description is to be  
15 considered to be exemplary rather than limiting, and the scope of the invention is that defined by the following claims.

**THE EMBODIMENTS OF THE INVENTION FOR WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:**

1. A mucoadhesive formulation comprising a clathrate host that is capable of enclosing water, wherein the clathrate host comprises a mucoadhesive polymer which is polyacrylate; and the clathrate host is formed from glycerin and the polyacrylate, free water at a concentration less than 75%, wherein the free water is at a concentration that is at least as high as the concentration of water from the aqueous clathrate host composition, and xylitol at a concentration at least 25% of the concentration of free water in the formulation and at least 20% of the formulation, wherein the amount of the mucoadhesive polymer and the clathrate in the formulation is sufficient to hold the sugar alcohol in situ when the formulation is applied to oral mucosa.
2. The mucoadhesive formulation of claim 1 wherein the concentration of xylitol is at least 50% of the concentration of free water in the formulation.
3. The mucoadhesive formulation of claim 1 wherein the concentration of xylitol is at least equal to the concentration of free water in the formulation.
4. The mucoadhesive formulation of claim 1 wherein the concentration of xylitol is higher than 35% of the formulation.
5. The mucoadhesive formulation of claim 1 wherein the relative concentration w/w % of the clathrate and the xylitol is between 1:1 and 1:10.
6. The mucoadhesive formulation of claim 1 wherein the xylitol is the component that is in the highest concentration of all components in the mucoadhesive formulation.
7. The mucoadhesive formulation of claim 1 that further comprises glycerin that is other than the glycerin that is part of the clathrate of glycerin and polyacrylate.

8. The mucoadhesive formulation of claim 7 wherein the concentration of glycerin that is other than the glycerin that is part of the clathrate of glycerin and polyacrylate is less than half the concentration of xylitol in the formulation.

9. The mucoadhesive formulation of claim 1 which is a liquid or a semi-solid.

10. The mucoadhesive formulation of claim 9 wherein the liquid is a mouth rinse or a mouth spray and the semi-solid is a gel or a paste.

11. The mucoadhesive formulation of claim 1 which comprises xylitol, water, a clathrate of glycerin and polyacrylate, and glycerin that is other than the glycerin that is part of the clathrate of glycerin and polyacrylate.

12. The mucoadhesive formulation of claim 11 wherein the concentration of xylitol in the formulation is at least 75% of the concentration of the free water in the formulation.

13. The mucoadhesive formulation of claim 12 wherein the concentration of xylitol is higher than 35% of the formulation.

14. Use of the mucoadhesive formulation as defined in any one of claims 1 to 13 for moisturizing the oral mucosa, wherein the formulation is formulated for application to the oral mucosa.

15. Use of the mucoadhesive formulation as defined in any one of claims 1 to 13 to provide xylitol to the oral mucosa, wherein the formulation is formulated for application to the oral mucosa.