Xylitol for treatment of vaginal infections

Abstract

A vaginal treatment composition that employs a therapeutic agent to inhibit and/or treat vaginal infection is provided. The therapeutic agent is capable of inhibiting and/or killing *Gardnerella* (e.g., *Gardnerella vaginalis*), *Candida* (e.g., *Candida albicans*), and/or *Trichomonas* (e.g., *Trichomonas vaginalis*) pathogens. Desirably, such antimicrobial efficacy is achieved without substantially inhibiting the growth of Lactobacillus acidophilus. For instance, sugars and/or sugar alcohols may be employed in the present invention as a therapeutic agent for inhibiting and/or treating vaginal infection. In one particular embodiment, D-xylitol is used as the therapeutic agent.

Classifications

A61K31/7004 Monosaccharides having only carbon, hydrogen and oxygen atoms

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Claims (32)

1. A method for treating bacterial vaginosis caused by *Gardnerella vaginalis*, the method comprising topically administering to the vagina of a female in need thereof a vaginal treatment composition comprising:

from about 0.1 wt/vol % to about 10 wt/vol % of at least one therapeutic agent that includes xylitol, and

from about 0.05 wt/vol % to about 5 wt/vol % of at least one gelling agent that includes gellan gum,

wherein the vaginal treatment composition has an osmolarity of from about 270 to about 310 milliosmoles per liter and a pH of from about 2.5 to about 5.0, and

wherein the treatment composition forms a gel after application to the vagina.

2. The method of claim 1, wherein the vaginal treatment composition comprises from about 0.2 wt/vol % to about 5.0 wt/vol % of xylitol.

3. The method of claim 1, wherein the vaginal treatment composition comprises from about 0.5 wt/vol % to about 4.5 wt/vol % of xylitol.

4. The method of claim 1, wherein the vaginal treatment composition has an osmolarity of from about 280 to about 300 milliosmoles per liter.

5. The method of claim 1, wherein the vaginal treatment composition is substantially free of tonicity agents other than xylitol.

6. The method of claim 1, wherein the therapeutic agent consists of xylitol.

7. The method of claim 1, wherein the vaginal treatment composition has a pH of from about 3.0 to about 4.5.

8. The method of claim 1, wherein the vaginal treatment composition further comprises a pH modifier.

9. The method of claim 8, wherein the pH modifier is a carboxylic acid.

10. The method of claim 8, wherein the pH modifier is lactic acid.

11. The method of claim 8, wherein the pH modifier is gallic acid.

12. The method of claim 1, wherein the gelling agent is present in the composition in an amount of from about 0.1 wt/vol % to about 1 wt/vol %.

13. The method of claim 1, wherein the composition is substantially free of monovalent and divalent salts.

14. The method of claim 1, wherein the gelling agent includes low acyl gellan gum.

15. The method of claim 1, wherein the vaginal treatment composition inhibits the growth of *Gardnerella vaginalis*.

16. The method of claim 1, wherein the vaginal treatment composition does not substantially inhibit the growth of *Lactobacillus acidophilus*.

17. A method for treating trichomonas vaginitis caused by *Trichomonas vaginalis*, the method comprising topically administering to the vagina of a female in need thereof a vaginal treatment composition comprising:

from about 0.1 wt/vol % to about 10 wt/vol % of at least one therapeutic agent that includes xylitol, and

from about 0.05 wt/vol % to about 5 wt/vol % of at least one gelling agent that includes gellan gum,

wherein the vaginal treatment composition has an osmolarity of from about 270 to about 310 milliosmoles per liter and a pH of from about 2.5 to about 5.0, and

wherein the treatment composition forms a gel after application to the vagina.

18. The method of claim 17, wherein the vaginal treatment composition comprises from about 0.2 wt/vol % to about 5.0 wt/vol % of xylitol.

19. The method of claim 17, wherein the vaginal treatment composition comprises from about 0.5 wt/vol % to about 4.5 wt/vol % of xylitol.

20. The method of claim 17, wherein the vaginal treatment composition has an osmolarity of from about 280 to about 300 milliosmoles per liter.

21. The method of claim 17, wherein the therapeutic agent consists of xylitol.

22. The method of claim 17, wherein the vaginal treatment composition has a pH of from about 3.0 to about 4.5.

23. The method of claim 17, wherein the vaginal treatment composition further comprises a pH modifier.

24. The method of claim 17, wherein the pH modifier is a carboxylic acid.

25. The method of claim 23, wherein the pH modifier is lactic acid.

26. The method of claim 23, wherein the pH modifier is gallic acid.

27. The method of claim 17, wherein the gelling agent is present in the composition in an amount of from about 0.1 wt/vol % to about 1 wt/vol %.

28. The method of claim 17, wherein the composition is substantially free of monovalent and divalent salts.

29. The method of claim 17, wherein the gelling agent includes a low acyl gellan gum.

30. The method of claim 17, wherein the vaginal treatment composition inhibits the growth of *Trichomonas vaginalis*.

31. The method of claim 17, wherein the vaginal treatment composition does not substantially inhibit the growth of *Lactobacillus acidophilus*.

32. The method of claim 17, wherein the vaginal treatment composition is substantially free of tonicity agents other than xylitol.

Description

RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. application Ser. No. 10/987,463, filed on Nov. 12, 2004 now abandoned. The present application is also a continuation-in-part of U.S. application Ser. No. 11/091,206, filed on Mar. 28, 2005 now abandoned.

BACKGROUND OF THE INVENTION

The female vagina is naturally colonized by a variety of bacteria, yeast, and microorganisms. For example, a normal vagina generally contains more than about 10^4 lactobacilli per milliliter of vaginal fluid. Under normal conditions, the vagina flora provides a mildly acidic environment that helps guard against the invasion of pathogenic microbes. Unfortunately, this vaginal balance may be easily upset by a variety of external factors that ultimately lead to vaginal infection. Vaginal infection is a clinical syndrome and exists in three primary forms, i.e., bacterial vaginosis, candidal vaginitis ("yeast"), and trichomonas vaginitis ("trich").

Bacterial vaginosis, for example, is a polymicrobial vaginal infection believed to be caused by an increase in the number of anaerobic organisms with a concomitant decrease in lactobacilli in the vagina. The decrease in the number of lactobacilli in the vagina has the dual effect of decreasing competition for nutrients and decreasing the amount of lactic acid present (i.e., increasing the pH). This allows for the multiplication of opportunistic pathogens in the vagina, whose growth is normally suppressed by the lactobacilli and the acidic pH of the vagina. The principal pathogen associated with bacterial vaginosis is believed to be *Gardnerella vaginalis*. Symptoms of bacterial vaginosis generally include an unpleasant smell, an elevated vaginal pH greater than about 5.0, a thin homogeneous discharge, and the presence of *Gardnerella* clue cells (i.e., vaginal epithelial cells coated with small Gram-variable rods). Current treatment regimens for bacterial infection of the vagina involve the use of various broad spectrum antibiotics, such as metronidazole. However, antibiotics are often undesirable because they may kill a broad range of the normal bacterial flora in the vagina, including the beneficial lactobacilli. This may cause secondary complications, because the lactobacilli keep various opportunistic pathogens in the vagina in check. The treatment may then necessitate a further treatment regimen, such as the ingestion of cultured dairy products to replace the lactobacilli in the body, as well as treatment by antifungal agents. Moreover, a rise in the level of anaerobes due to a lack of lactobacilli could further complicate the infection. Additionally, antibiotics, when used frequently within the vagina, may cause systemic toxicity through absorption from the vagina.

In addition, trichomonas vaginitis (or "trich") is one of the most common vaginal infections and is considered a sexually transmitted disease. Symptoms of trichomonas vaginitis include vulvar itching and odorous vaginal discharge. *Trichomonas vaginitis* is caused by *Trichomonas vaginalis*, a single-celled protozoan parasite not normally found in the flora of the genitourinary tract. *Trichomonas vaginalis* is a flagellate protozoa that is pear-shaped and about the size of a white blood cell. These motile cells have four flagellae and a single nucleus. Like bacterial vaginosis, this pathology is generally treated with metronidazole.

Further, the yeast *Candida albicans* causes the disease known as candidiasis (or "thrush"), as well as vulvitis (or "vulval" infection). *Candida albicans* is present in most humans as a harmless commensal organism. Problems arise, however, when a person experiences a loss of normal bacterial flora. In severely immune compromised patients, for example, *Candida albicans* infection may spread throughout the body and cause systemic infections. Candidiasis is usually treated with fluconazole, but this may have serious side effects and is not recommended for use during pregnancy.

As such, a need currently exists for an improved vaginal treatment composition.

SUMMARY OF THE INVENTION

In accordance with one embodiment of the present invention, a method for inhibiting and/or treating vaginal infection is disclosed. The method comprises topically administering a vaginal treatment composition to the vagina of a female. The vaginal treatment composition comprises an effective amount of at least one therapeutic

agent selected from the group consisting of sugars and sugar alcohols. In addition, the vaginal treatment composition also has an osmolarity of from about 270 to about 310 milliosmoles per liter.

In accordance with another embodiment of the present invention, a method for inhibiting and/or treating trichomonas vaginitis is disclosed. The method comprises topically administering a vaginal treatment composition to the vagina of a female. The vaginal treatment composition comprises an effective amount of at least one therapeutic agent that inhibits the growth of *Trichomonas vaginalis*, the therapeutic agent being selected from the group consisting of pentose sugars and pentose alcohols.

In accordance with still another embodiment of the present invention, a method for inhibiting and/or treating bacterial vaginosis is disclosed. The method comprises topically administering a vaginal treatment composition to the vagina of a female. The vaginal treatment composition comprises an effective amount of at least one therapeutic agent that inhibits the growth of *Gardnerella vaginalis*, the therapeutic agent being selected from the group consisting of pentose sugars and pentose alcohols.

Other features and aspects of the present invention are discussed in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

A full and enabling disclosure of the present invention, including the best mode thereof, directed to one of ordinary skill in the art, is set forth more particularly in the remainder of the specification, which makes reference to the appended figure in which:

FIG. 1 shows representative pictures of zone-of-inhibition testing plates obtained in Example 1 for the growth of *Gardnerella vaginalis* (left) and *Lactobacillus acidophilus* (right);

FIG. 2 shows representative pictures of testing plates obtained in Example 3 for the growth of *Gardnerella vaginalis* after 6 hours treatment (A—negative control; B—1% xylitol; C—5% xylitol);

FIG. 3 presents optical density data obtained at λ=600 nm in Example 2 that shows the effects of xylitol on *Gardnerella Vaginalis* after 2, 4, 6, and 24 hours treatment (n=4, * represents P<0.05);

FIG. 4 presents optical density data obtained at λ=600 nm in Example 2 that shows the effects of xylitol on *Lactobacillus acidophilus* after 2, 4, 6, and 24 hours treatment (n=4);

FIG. 5 is a light scattering analysis obtained in Example 6 for a solution containing only KELCOGEL®;

FIG. 6 is an overlay plot of Differential Molar Mass obtained in Example 4 for samples containing KELCOGEL® and xylitol, with and without acetic acid;

FIG. 7 is an overlay plot of Differential Molar Mass obtained in Example 4 for samples containing KELCOGEL®, with and without acetic acid;

FIG. 8 is an organism count obtained in Example 10 that shows the effect of xylitol on *Trichomonas vaginalis* after 24 hours at concentrations of 0.5%, 3.0%, and 5.0%;

FIG. 9 is an organism count obtained in Example 10 that shows the effect of xylitol on *Trichomonas vaginalis* after 48 hours at concentrations of 0.5%, 3.0%, and 5.0%;

FIG. 10 is an optical density reading obtained at λ=595 nm in Example 11 that shows the effect of certain sugars and sugar derivatives on *Candida albicans* after 24 hours;

FIG. 11 is a plate count number obtained in Example 12 that shows the effect of xylitol on *Candida albicans* after 24 hours; and

FIG. 12 is an optical density reading obtained at λ=595 nm in Example 13 that shows the effect of certain sugars and sugar derivatives on *Gardnerella vaginalis* after 24 hours.

DETAILED DESCRIPTION OF REPRESENTATIVE EMBODIMENTS Definitions

As used herein, the term "vagina" generally refers to the internal structure of the female reproductive tract extending from the cervix of the uterus to the vestibule. The term is also intended to include the external genitalia (e.g., labia majora, labia minora, and clitoris).

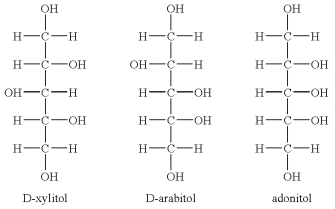
As used herein, the term "inhibit" generally means to reduce by a measurable amount or to prevent entirely.

As used herein, the term "treat" generally means to block at least one symptom that characterizes a pathologic condition in an animal threatened by or afflicted with the condition.

Detailed Description

Reference now will be made in detail to various embodiments of the invention, one or more examples of which are set forth below. Each example is provided by way of explanation of the invention, not limitation of the invention. In fact, it will be apparent to those skilled in the art that various modifications and variations may be made in the present invention without departing from the scope or spirit of the invention. For instance, features illustrated or described as part of one embodiment, may be used on another embodiment to yield a still further embodiment. Thus, it is intended that the present invention covers such modifications and variations as come within the scope of the appended claims and their equivalents.

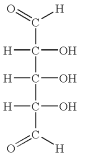
The vaginal treatment composition of the present invention employs a therapeutic agent to inhibit and/or treat vaginal infection. More specifically, the therapeutic agent is capable of inhibiting and/or killing *Gardnerella* (e.g., *Gardnerella vaginalis*), *Candida* (e.g., *Candida albicans*), and/or *Trichomonas* (e.g., *Trichomonas vaginalis*) pathogens. Desirably, such antimicrobial efficacy is achieved without substantially inhibiting the growth of *Lactobacillus acidophilus*. In this regard, the present inventors have discovered that certain sugar alcohols exhibit the desired selective inhibition and/or treatment of vaginal infection. Sugar alcohols, also known as polyols or polyhydric alcohols, are hydrogenated forms of sugars that may be modified into compounds that retain the basic configuration of saccharides, but with different functional groups. Suitable sugar alcohols may include pentose alcohols (e.g., D-xylitol, D-arabitol, meso-ribitol (adonitol), and isomers thereof) and hexose alcohols (e.g., glycerol, meso-galacitol (dulcitol), inositol, D-mannitol, D-sorbitol, and isomers thereof). Pentose alcohols, for instance, have the same linear structure as pentoses, but are modified with one on or more alcohol groups. As an example, the Fischer open chain structures of D-xylitol, D-arabitol, and adonitol are set forth below:

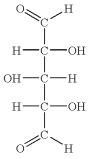


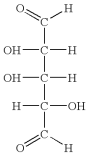
In one particular embodiment, the vaginal treatment composition employs D-xylitol as the therapeutic agent. Exogenous xylitol is metabolized to glucose and glucogen or pyruvate and lactate in the liver. Nevertheless, many bacteria are unable to utilize xylitol as an energy source, and as such, its presence may be harmful to some bacteria

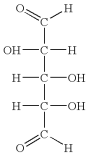
despite the availability of an alternative energy source, such as glucose. For instance, it is known that xylitol may reduce the growth of *Streptococcus mutans, Streptococcus salivarius, Streptococcus sanguis, Lactobacillus casei* and some strains of *Escherichia coli, Saccharomyces cerevisae* and *Salmonella typhii*. Although the anti-microbiological mechanism of xylitol is not fully understood, the present inventors believe that xylitol may be transported into a pathogen to disrupt its metabolic process and/or gene expression capabilities. For instance, xylitol may be phosphorylated through the constitutive fructose phosphotransferase system that regulates many metabolic processes and gene expression in bacteria. In addition, because bacteria adhere to host cells through carbohydrate-binding proteins, extracellular xylitol may also disturb the binding process by acting as a receptor analogue for the host cell, which could result in decreased adherence.

Besides sugar alcohols, certain sugars are also believed to provide the desired selective inhibition and/or treatment of vaginal infection. For instance, pentoses (e.g., five carbon-based sugars) having the general structure, $C_5H_{10}O_5$, may be used in some embodiments of the present invention. Exemplary pentoses include D-ribose, D-ribulose, D-arabinose, D-xylose, D-xylulose, and D-lyxose, and isomers thereof. As an example, the Fischer open chain structures of D-ribose, D-xylose, D-lyxose, and D-arabinose are set forth below:


D-ribose


D-xylose


D-lyxose


D-arabinose

Of course, other sugars, such as hexoses (e.g., D-galactose, D-inositose, D-mannose, and isomers thereof) may also be used in the present invention.

The therapeutic agent is generally placed into contact with a vagina in an effective amount to achieve the desired therapeutic benefit. More particularly, an "effective amount" is an amount sufficient to inactivate, but not necessarily kill, pathogenic microorganisms responsible for vaginal infection. In fact, although not required, it may be desired to use a concentration that does not significantly affect or inhibit the growth characteristics of the normal vaginal flora or otherwise significantly irritate the vaginal tissue when used at inhibitory, noncytotoxic, or clinical concentrations. For example, the therapeutic agent(s) are desirably employed at a concentration of about 0.01 wt/vol % to about 20 wt/vol %, in some embodiments from about 0.1 wt/vol % to about 10 wt/vol %, in some embodiments from about 0.2 wt/vol % to about 5 wt/vol %, and in some embodiments from about 0.5 wt/vol % to about 4.5 wt/vol % . As used herein, the designation "wt/vol %" or "wt/vol" refers to the value obtained by dividing the weight of a substance (in grams) by the volume of the solution (in milliliters), and then multiplying by 100. It should be understood that the dosage may vary with the age, condition, and type of infection suffered by the patient, and may be readily determined by one of skill in the art.

To avoid adverse physiological effects, the vaginal treatment composition is generally "isotonic" in that it has an osmolarity that is substantially similar to vaginal mucosa (i.e., about 290 milliosmoles per liter ("mOsm/L")). For example, an isotonic vaginal treatment composition may have an osmolarity of from about 270 to about 310 mOsm/L, in some embodiments from about 280 to about 300 mOsm/L, and in one embodiment, about 290 mOsm/L. The osmolarity of the vaginal treatment composition may be estimated using the following equation:

$$O_{composition}=\Sigma O_{species}$$

wherein,

$O_{species}$ is the osmolarity of a species in the composition. The osmolarity of a particular species is likewise determined using the following equation:

$$O_{species}=[c/m]\times n\times\varphi\times 1000$$

wherein,

c is the concentration of the species, in grams per liter;

m is the average molecular weight of the species;

n is the number of particles that dissociate from the molecule;

φ is the osmotic coefficient of the species.

One particularly beneficial aspect of the present invention is that the sugar or sugar-based therapeutic agent may provide the desired osmolarity without the need for additional tonicity agents. For example, xylitol may be particularly effective in achieving both the desired osmolarity and the desired biological activity. Such dual functionality provides a variety of benefits to the resulting composition, including the elimination of unnecessary components that would otherwise increase production complexity and costs. Nevertheless, a tonicity agent may be employed in some embodiments of the present invention to help achieve the desired osmolarity. Suitable tonicity agents may include ionic salts, such as sodium chloride, potassium chloride, and calcium chloride; nonionic agents, such as dextrose, glycerin, propylene glycol, mannitol, sorbitol, xylitol, trehalose, and sucrose; and so forth. When utilized, any effective amount of the tonicity agent(s) may be employed in the vaginal treatment composition to achieve the desired osmolarity. For example, the tonicity agent(s) may be present in an amount from about 0.01 wt/vol % to about 5 wt/vol %, in some embodiments from about 0.05 wt/vol % to about 2 wt/vol %, and in some embodiments, from about 0.1 wt/vol % to about 1 wt/vol % of the vaginal treatment composition.

The pH of the treatment composition may also be controlled within a range that is considered more biocompatible. For instance, it is typically desired that the pH be maintained at a mildly acidic level to correspond to normal vaginal conditions. For example, the pH may be within a range of from about 2.5 to about 5.5, in some embodiments from about 2.5 to about 5.0, and in some embodiments, from about 3.0 to about 4.5. Such a low pH may also provide other benefits. For instance, when the composition is configured to form a gel, such as described below, a low pH level may also improve the gelation rate and gel strength to reduce the likelihood of leakage just after insertion of the composition into the vagina.

If desired, various pH modifiers may be utilized in the vaginal treatment composition to achieve the desired pH level. Some examples of pH modifiers that may be used in the present invention include, but are not limited to, mineral acids, sulfonic acids (e.g., 2-[N-morpholino]ethane sulfonic acid), carboxylic acids, and polymeric acids. Specific examples of suitable mineral acids are hydrochloric acid, nitric acid, phosphoric acid, and sulfuric acid. Specific examples of suitable carboxylic acids are lactic acid, acetic acid, citric acid, glycolic acid, maleic acid, gallic acid, malic acid, succinic acid, glutaric acid, benzoic acid, malonic acid, salicylic acid, gluconic acid, and mixtures thereof. Specific examples of suitable polymeric acids include straight-chain poly(acrylic) acid and its copolymers (e.g., maleic-acrylic, sulfonic-acrylic, and styrene-acrylic copolymers), cross-linked polyacrylic acids having a molecular weight of less than about 250,000, poly(methacrylic) acid, and naturally occurring

polymeric acids such as carageenic acid, carboxymethyl cellulose, and alginic acid. Basic pH modifiers may also be used in some embodiments of the present invention to provide a higher pH value. Suitable pH modifiers may include, but are not limited to, ammonia; mono-, di-, and tri-alkyl amines; mono-, di-, and tri-alkanolamines; alkali metal and alkaline earth metal hydroxides; alkali metal and alkaline earth metal silicates; and mixtures thereof. Specific examples of basic pH modifiers are ammonia; sodium, potassium, and lithium hydroxide; sodium, potassium, and lithium meta silicates; monoethanolamine; triethylamine; isopropanolamine; diethanolamine; and triethanolamine.

Apart from simply providing the desired pH level, the present inventors have discovered that certain pH modifiers may also synergistically improve the inhibition and/or treatment of vaginal infection when used in combination with the sugar or sugar-based therapeutic agent. For instance, a phenolic acid may be employed that imparts both antimicrobial efficacy and the desired pH level to the vaginal treatment composition. Exemplary phenolic acids may include, for instance, p-hydrobenzoic acid, protocatechuic acid, vanillic acid, chlorogenic acid, caffeic acid, ferulic acid, gallic acid, sinapic acid, syringic acid, coumaric acid, cinnamic acid, gentisic acid, saliclic acid, veratric acid, anisic acid, crotonic acid, hydroxy benzoic acid, hydroxy phenyl acetic acids, and derivatives and isomers thereof. In one particular embodiment, for example, gallic acid (i.e., trihydroxybenzoic acid) helps inhibit the growth of *Gardnerella vaginalis* and to impart a pH level of between about 3.0 to about 4.5.

When utilized, the pH modifier may be present in any effective amount needed to achieve the desired pH level. In some embodiments, the pH modifier(s) are present in an amount between about 0.001 wt/vol % to about 5 wt/vol %, in some embodiments between about 0.005 wt/vol % to about 1 wt/vol %, and in some embodiments, between about 0.01 wt/vol % to about 0.25 wt/vol % of the vaginal treatment composition.

Besides the ingredients mentioned above, the vaginal treatment composition may also contain one or more additional ingredients to impart a variety of different benefits to the composition. For example, the vaginal treatment composition may contain a preservative or preservative system to inhibit the growth of microorganisms over an extended period of time. Suitable preservatives for use in the present compositions may include, for instance, alkanols, disodium EDTA (ethylenediamine tetraacetate), EDTA salts, EDTA fatty acid conjugates, isothiazolinone, benzoic esters (parabens) (e.g., methylparaben, propylparaben, butylparaben, ethylparaben, isopropylparaben, isobutylparaben, benzylparaben, sodium methylparaben, and sodium propylparaben), benzoic acid, propylene glycols, sorbates, urea derivatives (e.g., diazolindinyl urea), and so forth. Other suitable preservatives include those sold by Sutton Labs, such as "Germall 115" (amidazolidinyl urea), "Germall II" (diazolidinyl urea), and "Germall Plus" (diazolidinyl urea and iodopropynyl butylcarbonate). Another suitable preservative is Kathon CG®, which is a mixture of methylchloroisothiazolinone and methylisothiazolinone available from Rohm & Haas; Mackstat H 66 (available from McIntyre Group, Chicago, Ill.). Still another suitable preservative system is a combination of 56% propylene glycol, 30% diazolidinyl urea, 11% methylparaben, and 3% propylparaben available under the name GERMABEN® II from International Specialty Products of Wayne, N.J. In one particular embodiment of the present invention, benzoic acid is employed as a preservative due to its broad efficacy against a wide variety of organisms, lack of odor, and optimal performance at the low pH values often employed for the vaginal treatment composition (e.g., from about 2.5 to about 5.5).

When utilized, the amount of the preservative or preservative system utilized in the vaginal treatment composition may generally vary depending on the relative amounts of the other components present within the composition. For example, in some embodiments, preservative(s) are present in the composition in an amount from about 0.001 wt/vol % to about 5 wt/vol %, in some embodiments from about 0.001 wt/vol % to about 1 wt/vol %, and in some embodiments, from about 0.1 wt/vol % to about 0.15 wt/vol % of the composition.

Further, other therapeutics agents may also be employed in the present invention to provide additional therapeutic benefits. Examples of such therapeutic agents include, for instance, antimicrobial agents, antiparasitic agents, antibiotics, antihistamines, decongestants, antipruritics, antimetabolites, antiglaucoma agents, anti-cancer agents, antiviral agents, antifungal agents, antimycotics, anti-inflammatory agents, anti-diabetic agents, anesthetic agents, anti-depressant agents, analgesics, anti-coagulants, opthalmic agents, angiogenic factors, immunosuppressants, anti-allergic agents, spermicides, humectants and emollients, hormones, and so forth. Numerous such compounds are known to those of skill in the art and described, for example, in *The Pharmacological Basis of Therapeutics*, Hardman, Limbird, Goodman & Gilman, McGraw-Hill, New York, (1996), as well as U.S. Pat. No. 6,419,913 to Niemiec, et al.; U.S. Pat. No. 6,562,363 to Mantelle, et al.; U.S. Pat. No. 6,593,292 to Rothbard, et al.; U.S. Pat. No. 6,567,693 to Allen, Jr.; and U.S. Pat. No. 6,645,181 to Lavi, et al., all of which are incorporated herein in their entirety by reference thereto for all purposes. One particularly useful class of therapeutic agents for vaginal applications is anti-inflammatory agents that reduce pain, swelling, stiffness, inflammation, etc. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) may be utilized. Examples of NSAIDs include, but are not limited to, aspirin, ibuprofen, indomethacin, phenylbutazone, bromfenac, sulindac, nabumetone, ketorolac, mefenamic acid, and naproxen. Other suitable anti-inflammatory drugs are COX-2 inhibitors, such as celecoxib, meloxicam, rofecoxib, and flosulide. These drugs inhibit the production of the COX-2 (cyclooxygenase-2) enzyme induced by pro-inflammatory stimuli in migratory cells and inflamed tissue.

The vaginal treatment composition is generally applied in the form of a douche formulation, spray, moisturizer, lotion, cream, jelly, liniment, ointment, salve, oil, foam, gel, film, wash, suppository, slow-releasing polymer, coating, liquid, vaginal capsule, vaginal tablet, vaginal film, vaginal sponge, vaginal ovule, etc. The composition may also be applied to a vaginal insert, tampon, wipe or pad, and then administered to the vagina.

In one particular embodiment of the present invention, for example, the vaginal treatment composition is configured to rapidly form a gel when applied to the vagina. A "gel" is a colloid in which a disperse phase combines with a dispersion medium to produce a jelly-like, solid or semi-solid material. The gel may form in less than about 1 hour, in some embodiments less than about 1 minute, and in some embodiments, less than about 30 seconds. Among other things, such rapid gelation reduces the likelihood of leakage during use. In addition, because the gel may form intravaginally, it is more likely to retain its structure and shape over an extended period of time. In this manner, the gel may provide the prolonged release of a therapeutic agent that inhibits and/or treats vaginal infection. For instance, the gel may remain within the vagina for about 2 to about 48 hours to provide the desired effect.

Although a variety of compounds may be employed, water is usually employed as the dispersion medium for the gel to optimize biocompatibility. Other possible dispersion mediums include non-aqueous solvents, including glycols, such as propylene glycol, butylene glycol, triethylene glycol, hexylene glycol, polyethylene glycols, ethoxydiglycol, and dipropyleneglycol; alcohols, such as ethanol, n-propanol, and isopropanol; triglycerides; ethyl acetate; acetone; triacetin; and combinations thereof. Typically, the dispersion medium (e.g., water) constitutes greater than about 75 wt/vol %, in some embodiments greater than about 90 wt/vol %, and in some embodiments, from about 95 wt/vol % to about 99 wt/vol % of the vaginal treatment composition.

The disperse phase of the gel may be formed from any of a variety of different gelling agents, including temperature responsive ("thermogelling") compounds, ion responsive compounds, and so forth. Thermogelling systems, for instance, respond to a change in temperature (e.g., increase in temperature) by changing from a liquid to a gel. Generally speaking, the temperature range of interest is from about 25° C. and 40° C., in some embodiments from about 35° C. and 39° C., and in one particular embodiment, at the human body temperature (about 37° C.). Compositions that change state at about this temperature are useful because they will remain in a body cavity, for example, after they have been delivered. Any of a variety of thermogelling compounds that are capable of gelling when applied to the vagina may be used in the present invention. In some cases, thermogelling block copolymers, graft copolymers, and/or homopolymers may be employed. For example, polyoxyalkylene block copolymers may be used in some embodiments of the present invention to form a thermo-gelling composition. The term "polyoxyalkylene block copolymers" refers to copolymers of alkylene oxides, such as ethylene oxide and propylene oxide, which form a gel when dispersed in water in a sufficient concentration. Some suitable polyoxyalkylene block copolymers include polyoxybutylene block copolymers and polyoxyethylene/polyoxypropylene block copolymers ("EO/PO" block copolymers), such as described in U.S. Patent Application Publication No. 2003/0204180 to Huang, et al., which is incorporated herein in its entirety by reference thereto for all purposes. For instance, exemplary polyoxyalkylene block copolymers include polyoxyethylene/polyoxypropylene block copolymers (EO/PO block copolymers) having the following general formula:

$HO(CH_2CH_2O)_x(CH(CH_3)CH_2O)_y(CH_2CH_2O-)_zH$

wherein,

x, y, and z are each integers in the range of about 10 to about 150.

The polyoxyethylene chain of such block copolymers typically constitutes at least about 60 wt. %, in some embodiments at least about 70 wt. % of the copolymer. Further, the copolymer typically has a total average molecular weight of at least about 5000, in some embodiments at least about 10,000, and in some embodiments, at least about 15,000. Suitable EO/PO polymers for use in the vaginal treatment composition of the present invention are commercially available under the trade name PLURONIC® (e.g., F-127 L-122, L-92, L-81, and L-61) from BASF Corporation, Mount Olive, N.J.

Of course, any other thermogelling compound may also be used in the present invention. For example, other suitable thermogelling polymers may include homopolymers, such as poly(N-methyl-N-n-propylacrylamide), poly(N-n-propylacrylamide), poly(N-methyl-N-isopropylacrylamide), poly(N-n-propylmethacrylamide), poly(N-isopropylacrylamide), poly(N,n-diethylacrylamide); poly(N-isopropylmethacrylamide), poly(N-cyclopropylacrylamide), poly(N-ethylmethyacrylamide), poly(N-methyl-N-ethylacrylamide), poly(N-cyclopropylmethacrylamide), and poly(N-ethylacrylamide). Still other examples of suitable thermogelling polymers may include cellulose ether derivatives, such as hydroxypropyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, and ethylhydroxyethyl cellulose. Moreover thermogelling polymers may be made by preparing copolymers between (among) monomers, or by combining such homopolymers with other water-soluble polymers, such as acrylic monomers (e.g., acrylic or methacrylic acid, acrylate or methacrylate, acrylamide or methacrylamide, and derivatives thereof).

As stated, ion responsive compounds are also suitable for use in the present invention. Such compounds are generally well known in the art, and tend to form a gel in the presence of certain ions or at a certain pH. For instance, one suitable class of ion responsive compounds that may be employed in the present invention is anionic polysaccharides. Anionic polysaccharides may form a three-dimensional polymer network that functions as the disperse phase of the gel. Generally speaking, anionic polysaccharides include polysaccharides having an overall anionic charge, as well as neutral polysaccharides that contain anionic functional groups.

It is well known that vaginal mucosa contains certain monovalent and polyvalent cations, such as sodium (Na^+) and calcium (Ca^{2+}) ions. See e.g., Owen, D. H. and Katz, D. F., A Vaginal Fluid Simulant, Contraception, 59, 91-95(1999). Thus, such cations may be used to crosslink anionic polysaccharide molecules to form a three-dimensional network, i.e., a gel. The ability to form a gel based on the reaction with ions contained in vaginal mucosa provides a variety of benefits to the vaginal treatment composition. For example, due to their high molecular weight, most anionic polysaccharides will not be absorbed by the body such that their gel-like properties may be maintained while in the vagina. Still another benefit of saccharide-based gels is that they are generally biocompatible and biodegradable. Further, unlike compositions in which gel formation is induced by temperature (i.e., thermogels), the vaginal treatment composition of the present invention may be stored and transported at a variety of different temperatures without fear of premature gelation. It should be understood, however, that the composition may be partially or wholly gelled prior to application to the vagina in other embodiments of the present invention.

Any of a variety of anionic polysaccharides capable of forming a gel when contacted with vaginal mucosa may be used in the present invention. Such gel-forming anionic polysaccharides are typically stable over the normal acidic pH values found in the vagina (e.g., from about 2.5 to about 5.5). For instance, some suitable examples of gel-forming anionic polysaccharides include natural gums, such as gellan gum and alginate gums (e.g., ammonium and alkali metal of salts of alginic acid); chitosan; carboxymethylcellulose, pectins, carrageenan, xantham gum, and derivatives or salts thereof. The particular type of anionic polysaccharide selected will depend, in part, on the nature of the vaginal treatment composition and the other components used therein. For example, carrageenan is sensitive to particular types of cations, e.g., it typically gels in the presence of potassium but not sodium. Glycuronans, likewise, typically gel in the presence of divalent cations (e.g., Ca^{2+}), but not monovalent cations (e.g., Na^+). Xanthan gum may gel in the presence of divalent cations, but only at a relatively high pH.

Although any of the above-described anionic polysaccharides may be used in the present invention, gellan gum is particularly desired for use in the present invention, either alone or in combination with other gelling agents, because it is able to form a gel in the presence of a wide variety of different cations, including both monovalent and divalent cations. Gellan gum is produced from strains of the bacteria, Sphingomonas Elodea. Typically, the gum is produced as an extracellular product through the aqueous cultivation of the microorganisms in a medium containing appropriate carbon, organic and inorganic nitrogen, and phosphate sources. The fermentation is carried out under sterile conditions with strict control of aeration, agitation, temperature, and pH. When fermentation is complete, the resulting viscous broth is pasteurized to kill viable cells prior to recovery of the gum. The gum may be recovered in a variety of ways. For instance, direct recovery from the broth yields the gum in its native or "high acyl" form. On the other hand, recovery after deacylation (e.g., by treatment with a base) yields the gum in its "low acyl" form. The degree of deacylation (i.e., the percentage of acyl groups removed) may be controlled by varying the temperature (e.g., 25° C. to 85° C.), the amount of base (e.g., pH>7.0), the reaction time, etc. Regardless, the constituent sugars of gellan gum are glucose, glucuronic acid and rhamnose in the molar ratio of about 2:1:1. These sugars are linked together to give a primary structure having a linear tetrasaccharide repeat unit.

As stated, the gellan gum may be either high or low acyl gellan. In the high acyl (or "native") form, two acyl substituents, acetate and glycerate, are present. Both substituents are located on the same glucose residue and, on average, there is one glycerate per repeat unit and one acetate per every two repeat units. In the low acyl form, the acyl groups may be wholly or partially removed through deacylation. The degree of deacylation of deacylated gellan gums may be at least about 20%, in some embodiments at least about 50%, and in some embodiments, at least about 75% . Alternatively, the low acyl gellan gum may simply be "nonacylated" in that it is formed without acyl groups by genetically engineered bacteria. Regardless of the manner in which they are formed, low acyl gellan gums generally have a gelation temperature within the range 30° C. to 50° C. depending on the nature and concentration of the cations present. In contrast, most high acyl gellan gums have a gelation temperature of above 50° C. For this reason, a low acyl gellan gum may be desired so that it may gel at body temperatures of about 37° C., but remain stable at typical storage and transportation temperatures of about 25° C. In addition, low acyl gellan gums are also firm and elastic, and thus may retain their shape after delivery to the vaginal cavity.

Of course, other types of gellan gums may also be used in the present invention. In fact, the term "gellan gum" is intended to encompass any form of gellan, including native gellan, clarified gellan, deacylated gellan, nonacylated gellan (e.g., produced from genetically engineered bacteria), clarified gellan (the polysaccharide is fully or partially removed from the bacterial debris), chemically modified gellan, etc. Various types of gellan gums and methods for forming such gums are described in U.S. Pat. Nos. 4,326,052; 4,326,053 to Kang, et al.; U.S. Pat. Nos. 4,377,636; 4,385,123; 4,563,366 to Baird. et al.; U.S. Pat. No. 5,190,927 to Chang. et al.; as well as U.S. Patent Application Publication No. 2003/0100078 to Harding, et al., all of which are incorporated herein in their entirety by reference thereto for all purposes. Gellan gums are commercially available from a variety of different sources. For example, GELRITE™ gellan gum is available from Sigma-Aldrich Chemical Co. of St. Louis, Mo., and is produced from a naturally occurring polysaccharide after deacylation and clarification. Deacylated gellan is also available from CP Kelco U.S., Inc. of Chicago, Ill. under the name KELCOGEL®.

Regardless of the type selected, the gelling agent(s) are generally present in the vaginal treatment composition in an amount sufficient to form a self-supporting gel upon application to the vagina. This amount may vary depending on a variety of factors, such as the nature of the gelling agent(s), the conditions of intended use, the nature of other components in the vaginal treatment composition, and so forth. In most embodiments, however, the gelling agent(s) are present in an amount of from about 0.01 wt/vol % to about 10 wt/vol %, in some embodiments from about 0.05 wt/vol % to about 5 wt/vol %, and in some embodiments, from about 0.1 wt/vol % to about 1 wt/vol % of the vaginal treatment composition.

If desired, a gelling vaginal treatment composition may be provided in any desired form (e.g., liquid, powder, etc). In fact, one particular benefit of the composition is that it may be administered as a liquid, which allows for the selection of a wider variety of administration techniques than would otherwise be available for a solid or semi-solid gel. One technique that may be employed includes dispensing the composition through a liquid applicator, such as a syringe or tube, into the vaginal cavity. The administered volume of the composition may constitute a single dose or two or more doses. Although not necessarily required, the vaginal treatment composition of may also be sterilized prior to administration. Sterilization may be accomplished by any technique known in the art, such as using a gas (e.g., ethylene oxide), radiation (e.g., gamma), or heat (autoclaving). If desired, the composition may be subjected to one or more filtration steps prior to sterilization to help remove contaminants.

The present invention may be better understood with reference to the following examples.

Microorganisms and Culture Media

Gardnerella vaginalis was obtained from the American Type Culture Collection (ATCC #14018). The culture medium was Casman's medium base (BD 229010) with 5% rabbit blood (ATCC medium 70).

Trichomonas vaginalis was obtained from the American Type Culture Collection (ATCC #30001). The culture medium was LYI-S-2 medium (ATCC medium 2154).

Candida albicans was obtained from the American Type Culture Collection (ATCC), catalog number 96113. The culture medium was YM medium (ATCC medium 200).

Lactobacillus acidophilus was obtained from the American Type Culture Collection (ATCC #4356). The culture medium was Lactobacilli MRS broth (ATCC medium 416).

EXAMPLE 1

A microorganism culture of 10^5cfu (colony forming units)/ml in a 1× phosphate buffered saline (PBS) solution (diluted from 10× PBS LIQUID CONCENTRATE from VWR Cat. No. EM-6507] was used. One milliliter of the solution was plated on proper agar plates, depending on which microorganism was being tested. The agar plates were incubated at 35° C. for 4 hours. Three 4-millimeter diameter wells were then punched in each agar plate. A test sample of 100 microliters of 5% xylitol in sterilized 2-N-morpholino ethane sulfonic buffer (0.1 M 2-[morpholino]-ethanesulfonic acid, 0.9% NaCl, pH 4.7, prepared from BupH™ MES Buffer Saline Pack from Cat. No. 28390, Pierce Biotechnology, Inc., Rockford, Ill.) was added to one well of each plate. Into each of the other two wells were added MES buffer and 1% benzyl quats (diluted from BARDAC® 205M, from Lonza Inc., Fair Lawn, N.J.) as negative and positive controls, respectively. The plates were incubated overnight at 35° C.

The following day, the "zone of inhibition" for each sample was then measured for *Gardnerella vaginalis* and *Lactobacillus acidophilus* activity. The "zone of inhibition" is a circular zone formed around the agar plate in which the growth of the microorganism is inhibited. Absent treatment with an effective antimicrobial agent, the bacterial cells would normally produce an opaque lawn of growth. However, when growth is inhibited, a clear zone is observed. The diameter of this clear zone may thus be used as an indicator of antimicrobial effectiveness. The results are set forth below in Table 1 and shown in FIG. 1.

TABLE 1

Effect of xylitol on *G. vaginalis* and *L. acidophilus*, n = 2.

Sample	*Gardnerella vaginalis*	*Lactobacillus acidophilus*
5% xylitol	4 mm	0 mm
1% benzyl quats	5 mm	15 mm
MES buffer	0 mm	0 mm

As shown, xylitol inhibited *Gardnerella vaginalis*, but did not affect the growth of *Lactobacillus acidophilus*. The positive control, 1% Benzyl Quats, inhibited both microorganisms, while MES buffer itself had no effect on either of the two microorganisms.

EXAMPLE 2

Test compounds were dissolved in culture media to form a suspension. Control or xylitol solutions (0.9 milliliters) were filtered and added into culture tubes, and to this was added 0.1 milliliter of either the *Gardnerella vaginalis* or *Lactobacillus acidophilus* suspension at a concentration of around 10^6 cfu/milliliter. The culture tubes were then incubated overnight at 37° C., whereafter the optical density was measured at 2, 4, 6 and 24 hours by pipetting 100 microliters of the control or sample solutions into 96-well microplates, and then using a ThermoMax Microplate Reader (Molecular Devices of Sunnyvale, Calif.) to obtain the optical density readings at 590 or 600 nm wavelengths. The results are shown in FIGS. 3 and 4. As shown in FIG. 3, xylitol exhibited significant inhibition on the growth of *Gardnerella vaginalis* as early as 2 hours after treatment. The inhibition effect remained evident throughout the 24-hour experimental period. In contrast, as shown in FIG. 4, xylitol did not exhibit any significant inhibition on the growth of *Lactobacillus acidophilus*.

EXAMPLE 3

Test compounds were dissolved in culture media to form a suspension. Control or xylitol solutions (0.9 milliliters) were filtered and added into culture tubes. To these solutions, 0.1 milliliter of the *Gardnerella vaginalis* or *Lactobacillus acidophilus* suspension was then added at a concentration of around 10^6 cfu/milliliter. The culture tubes were incubated at 37° C. for 6 hours. The samples in the culture tubes were then diluted at 1, 10 and 100 times, and 100 microliters of each dilution was plated onto agar plates with WASP (Whitely Automatic Spiral Plate) spiral plating equipment from Don Whitely Scientific Limited, USA. The plates were incubated overnight at 35° C., and the numbers of colonies were counted on each plate by either ProtoCol® from Synbiosis, Frederick, Md., USA Whitely Scientific Limited, USA or by hand count. The results are shown below in Tables 2-3 and in FIG. 2,

TABLE 2

Effect of xylitol on *G. Vaginalis*, n = 4

	Control	1% xylitol	2% xylitol	3% xylitol	4% xylitol	5% xylitol
Plate Count	2.32E+07	*1.24E+05	*1.64E+03	*4.63E+02	*1.03E+02	*1.98E+01

*represents $p < 0.05$ compared to control group

TABLE 3

Effect of xylitol on *L. acidophilus*, n = 4

	Control	1% xylitol	5% xylitol
Plate Count	3.85 ± 0.44 E+05	3.77 ± 0.49 E+05	3.97 ± 0.36 E+05

As indicated, all five concentrations exhibited significant inhibition of *Gardnerella vaginalis* growth compared to the control group. In contrast, xylitol did not exhibit any significant inhibition on the growth of *Lactobacillus acidophilus*.

EXAMPLE 4

Sorbitol, glucose, and xylitol were tested as described in Example 1. The results are show below in Table 4.

TABLE 4

Effect on *G. vaginalis* and *L. acidophilus*

Sample	*Gardnerella vaginalis*	*Lactobacillus acidophilus*
10% xylitol	4 mm	0 mm
10% sorbitol	0 mm	0 mm
10% glucose	0 mm	0 mm
1% benzyl quats	5 mm	15 mm

TABLE 4

MES buffer	0 mm	0 mm

As indicated, xylitol exhibited an inhibitory effect on the growth of *Gardnerella vaginalis*, but not on *Lactobacillus acidophilus*.

EXAMPLE 5

Solutions were formed from xylitol and a gellan gum obtained from CP Kelco U.S., Inc. of Chicago, Ill. under the name KELCOGEL®. The solutions contained 0.7% (wt/vol) of the KELCOGEL® gum and 4.4% (wt/vol) xylitol, and were formed by dissolving 0.07 grams of the polymer powder and 0.44 grams of xylitol into 10 milliliters of water at a temperature between 70° C. to 80° C. After vortexing the solutions to help dissolve the solids, they were allowed to cool to room temperature. After cooling, the pH of the solutions was adjusted using varying amounts of either acetic acid or lactic acid.

The osmolarity of the solutions was estimated using the following equation:

$O_{composition}=\Sigma O_{species}$

wherein,

$O_{species}$ is the osmolarity of a species in the composition. The osmolarity of a particular species is likewise determined using the following equation:

$O_{species}=[c/m]\times n\times\varphi\times 1000$

wherein,

c is the concentration of the species, in grams per liter;

m is the average molecular weight of the species;

n is the number of particles that dissociate from the molecule;

φ is the osmotic coefficient of the species.

More specifically, the molecular weight of the KELCOGEL® gellan gum was approximately 500,000 grams per mole. Because gellan gum does not generally dissociate, it was considered to have an n value equal to 1. Xylitol has a molecular weight of 154.12 grams per mole and was also considered to have an n value equal to 1 due to its lack of dissociation. Lactic acid and acetic acid have molecular weights of 90.08 and 122.12 grams per mole, respectively. In addition, lactic acid and acetic acid dissociate into two (2) species (though not necessarily to completion) and thus were considered to have an n value equal to 2. With respect to the osmotic coefficient φ, it is well known that its value depends on its concentration and chemical properties of the particular molecule. Generally speaking, the value of φ for a solute approaches 1 as it becomes more dilute in solution. Thus, due to the low concentrations of KELCOGEL® gellan gum, xylitol, lactic acid, and acetic acid employed in the vaginal treatment composition, it was assumed that the value of φwas 1 for each species. From the above, it was determined that the solutions were isotonic, e.g., between about 270 to about 310 mOsm/L. The properties of the solutions are set forth below in Tables 5 and 6.

TABLE 5

Acetic Acid-Modified Compositions

Sample	Gum (wt/vol %)	Xylitol (wt/vol %)	Acetic Acid (microliters)	pH	Properties
1	0.7	—	10 (pure)	3.0	Gelled rapidly
2	0.7	—	10 (1:100 dilution)	4.8	Thickened, but did not gel
3	0.7	4.4	50 (1:100 dilution)	4.5	Thickened, but did not gel
4	0.7	4.4	240 (1:100 dilution)	4.0	Very loose gel (after 24 hours)
5	0.7	4.4	1700 (1:100 dilution)	3.6	Very loose gel (after 24 hours)
6	0.7	4.4	4000 (1:100 dilution)	3.4	Self-supporting gel after ~20 minutes

TABLE 6

Lactic Acid-Modified Compositions

Sample	Gum (wt/vol %)	Xylitol (wt/vol %)	Lactic Acid (microliters)	pH	Properties
7	0.7	—	50 (pure)	3.0	Immediately formed strong gel
8	0.7	—	10 (pure)	3.7	Gelled
9	0.7	—	10 (1:100 dilution)	5.4	—
10	0.7	—	20 (1:100 dilution)	4.6	Thickened, but did not gel
11	0.7	4.4	25 (1:100 dilution)	4.7	Thickened, but did not gel
12	0.7	4.4	40 (1:100 dilution)	4.5	Thickened, but did not gel (after 24 h.)
13	0.7	4.4	120 (1:100 dilution)	4.0	Very loose gel (after 24 hours)
14	0.7	4.4	540 (1:100 dilution) and 12 (pure)	3.5; 3.4	Self-supporting gel (after 24 hours)
15	0.7	4.4	15 (pure)	3.3	Gelled rapidly (self-supporting in a few minutes)
16	0.7	4.4	40 (1:100 dilution)	4.5	Thickened, but did not gel

As indicated, xylitol did not appear to negatively impact the gelation ability of the polymer, nor did it appear to affect the gelation time. Further, the solutions of lower pH typically formed self-supporting gels slightly faster, but all solutions appeared to form self-supporting gels in the vials within one minute. An interesting discovery during initial experimentation with the pH modifiers was that a very small amount of highly concentrated or pure acid rapidly and completely gelled the solution. Thus, the strength of the gel may be tunable via adjustment of acid strength and concentration.

EXAMPLE 6

The ability to sterilize the vaginal treatment composition was demonstrated. Nine solutions were initially formed as set forth below in Table 7.

TABLE 7

Composition of Solutions

Sample	Gum (wt/vol %)	Xylitol (wt/vol %)	Starting pH	Acetic Acid (microliters, 1:100 dilution)	Ending pH
1	0.7	4.4	5.2	240	4.1
2	0.7	4.4	5.1	280	4.1
3	0.7	4.4	5.3	—	5.3
4	0.7	—	5.9	240	4.1
5	0.7	—	5.8	280	4.1
6	0.7	—	5.9	—	5.9
7	—	4.4	5.3	240	3.9
8	—	4.4	5.2	240	3.8
9	—	4.4	5.4	—	5.4

One pH-modified and one non-modified sample were then autoclaved in a liquid cycle for 20 minutes. After autoclaving, the solutions appeared to undergo a reduction in viscosity. As this could have been a result of the intense heat, the solutions were cooled and observed 72 hours later for comparison to un-autoclaved counterparts. The un-autoclaved samples formed very loose gels over the 72-hour period, while the autoclaved solutions remained ungelled. To ensure that the extreme heat of the autoclave did not alter the pH of the solutions (e.g., through volatilization of acetic acid), the pH of each solution was determined in a laminar flow hood using colorpHast® pH indicator strips (available from EMD Chemicals, Inc.). All solutions maintained their pre-autoclave pH values. After checking that the pH remained unchanged in the autoclaving process, 500 microliters of each solution was mixed with 150 microliters of SVF and the gelation behavior was observed.

Upon analysis, it was determined that only the solutions that were pH-modified and then autoclaved did not form gels. In addition, the solutions that were not pH modified were observed to exhibit the same behavior as the un-autoclaved, pH-modified control. This suggested that the reason for the change in gelation behavior was somehow related to the effect of heat and acid on the polymer. Although certainly not intending to be limited by theory, one possibility was that the heated acid cut the polymer chains, resulting in a chain length that was too small to form the physical entanglements needed for ion-induced gelation. To test this theory, Samples 1, 3, 4, 6, 7, and 9 were subjected to light scattering molecular weight analysis. The results are set forth in FIGS. 5-7. In particular, FIG. 5 provides the spectra for KELCOGEL®, while FIGS. 6-7 illustrate the molecular weight differences between Samples 1 and 4 (FIG. 6) and Samples 2 and 5 (FIG. 7). The analysis revealed a decrease in molecular weight of the KELCOGEL® polymer when the acid was present during autoclaving.

EXAMPLE 7

A solution was formed from 0.07 grams KELCOGEL®, 0.44 grams xylitol, and 0.0075 grams gallic acid by adding 10 milliliters of hot water (70 to 80° C.) to the powders and vortexing to dissolve. When cooled, the pH was measured and found to be about 4.0. 500 microliters of this solution was then reacted with 150 microliters of SVF and monitored for gelation behavior. The solution was also autoclaved and the gel test with SVF repeated. Upon analysis, the gallic-acid containing solution was observed to exhibit a low viscosity and a gelation rate in a glass vial of 10 seconds. After autoclaving, however, the solution did not gel with SVF.

EXAMPLE 8

The ability of the vaginal treatment composition of the present invention to inhibit and/or treat vaginal infection was demonstrated. Initially, eight (8) solutions were formed as set forth below in Table 8.

TABLE 8

Solution Composition

Sample	KELCOGEL ® (wt/vol %)	Xylitol (wt/vol %)	Gallic Acid (wt/vol %)	pH
Control	—	—	—	6
1	0.7	—	—	6
2	0.7	4.4	—	6
3	0.7	4.4	0.075	4
4	0.7	—	0.075	4
5	—	4.4 (in water)	—	6
6	—	—	0.075	4
7	—	4.4 (in growth medium)	—	6

Samples 1-2 were prepared by dissolving the KELCOGEL® (0.07 grams) and/or xylitol (0.44 grams) into 10 milliliters of water heated to between 70° C. to 80° C. Samples 3-4 and 6 were formed by first autoclaving a gallic acid stock solution (0.75 grams of gallic acid/20 mL water), autoclaving, and then adding 200 microliters of sterile gallic acid (0.0075 grams) to each sterile solution. Sample 5 was formed by dissolving 0.44 grams of xylitol in deionized water, followed by autoclaving. Sample 7 was formed by dissolving 0.44 grams of xylitol in sterilized growth medium for *Gardnerella vaginalis* and then filtering. The amount of xylitol was selected to yield isotonic solutions. After vortexing the solutions to help dissolve the solids, they were allowed to cool to room temperature.

Upon formation, 1 milliliter of each control or sample solution was then added into a culture tube, followed by the addition of 0.8 milliliters of growth medium for *Gardnerella vaginalis*. To this mixture was added 0.2 milliliters of a *Gardnerella vaginalis* suspension (at a concentration of around 10^6 cfu/ml; diluted from 10^8 cfu/ml stock). The tubes were incubated in culture tubes at 37° C. After 24 and 48 hours, the optical density was measured for each sample at wavelengths of 450 and 595

nanometers. The 24-hr solution samples were then diluted at 0.001× and 0.0001×. 3 milliliters of growth medium were then added into the 24-hour composition samples, followed by 1 hour of shaking at 30° C. Solution was then taken from well-shaken test tubes and diluted at 0.001× and 0.0001×. "WASP" (Whitely Automatic Spiral Plate) spiral plating equipment from Don Whitely Scientific Limited was used to plate 100 microliters of the above solutions onto agar plates. The plates were incubated overnight at 35° C. The number of colonies on each plate was counted using ProtoCol® software from Synbiosis of Frederick, Md. All samples were plated in triplicate. The results are shown in Table 9.

TABLE 9

Average Plate Counts

Sample	Average Plate Count	St. Dev.
Growth media control	1.81×10^8	6.36×10^6
Kelcogel ®	1.37×10^8	3.82×10^7
Kelcogel ® + xylitol	5.91×10^5	4.95×10^4
Kelcogel ® + xylitol + gallic acid	2.01×10^5	2.12×10^4
Kelcogel ® + gallic acid	4.14×10^7	4.03×10^6
Xylitol	1.56×10^4	5.66×10^2
Gallic acid	3.43×10^4	2.12×10^3
Xylitol in growth media	2.40×10^4	2.83×10^3

As indicated, the presence of KELCOGEL® did not significantly inhibit or increase the growth of *Gardnerella vaginalis*. On the other hand, xylitol exhibited significant inhibition for *Gardnerella vaginalis* growth, both in solutions (growth medium and D.I water) and in the KELCOGEL® compositions. Further, the solution containing both xylitol and gallic acid exhibited even better inhibition for *Gardnerella vaginalis* growth than the solution containing only xylitol. It should also be noted that the inhibition of *Gardnerella vaginalis* growth, though very effective, appeared to be less for the KELCOGEL®-based solutions than for the compounds in growth media or water. This was most likely due to the fact that the therapeutic agent needed to first diffuse from the gel before contacting the bacteria.

EXAMPLE 9

The ability to form a vaginal treatment composition with a preservative was demonstrated. Initially, a solution was formed that contains 0.7% KELCOGEL®, 4.4% (wt/vol) xylitol, and 0.1% (wt/vol) benzoic acid by measuring out the appropriate powders and adding hot water (approx. 70° C.). After the solution had cooled to room temperature, the pH was adjusted to approximately 4.0 using a 1:50 solution of lactic acid so that its final concentration in solution was 0.1% (wt/vol). A larger batch (300 milliliters) was also created by adding hot water to ingredients using a high shear mixer. The 1:50 lactic acid was again added to bring the final concentration in solution to 0.1% (wt/vol). Solutions were mixed with SVF. It was observed that both the small and large-batch solutions formed self-supporting gels within 1 minute of contact with SVF.

EXAMPLE 10

A sterile LYI-S-2 medium was prepared according to the manufacturer's instructions, and the pH of this medium was adjusted to pH 6.0 using 1 N HCl. Xylitol was then dissolved into the LYI-S-2 medium at concentrations of 0.5%, 3.0%, and 5.0% (wtvol). 0.9 milliliters of xylitol and culture medium (as control) were also added into different culture tubes. Thereafter, 0.1 milliliter of *Trichomonas vaginalis* culture suspension (concentration of 1×10^6/milliliter) was added to each of the culture tubes, and then incubated at 35° C. on a 15 degree horizontal slant. The viable *Trichomonas vaginalis* cells in each tube were counted under a microscope after 24 and 48 hours. The above procedure was repeated four times for each concentration of xylitol and the control. The results are shown in FIGS. 8-9. As shown, xylitol significantly reduced the *Trichomonas vaginalis* cell count after 24 hours in comparison to the control group (FIG. 8). After 48 hours, xylitol had an even more significant inhibitory effect on the *Trichomonas vaginalis* cell count (FIG. 9). No live *Trichomonas vaginalis* cells were observed in the 3% and 5% xylitol treatment groups, while around 1.6 million *Trichomonas vaginalis* cells were counted in the control group.

EXAMPLE 11

A YM culture medium was prepared according to the manufacturer's instructions, and the pH of this medium was adjusted to pH 6.0 using 1 N HCl. D-ribose (99%, Calbiochem), adonitol (99%, Alfa Aesar), and xylitol (98%, Danisco) were then dissolved into the YM medium at concentrations of 1.0% and 5.0% (wt/vol). 0.9 milliliters of the culture medium was also added into a different culture tube as a control. Thereafter, 0.1 milliliter of *Candida albicans* culture suspension (concentration of 1×10^6/milliliter) was added to each of the culture tubes, and then incubated overnight at 37° C. The viable *Candida albicans* cells in each tube were counted under a microscope after 24 hours. The above procedure was repeated four times for each concentration of the samples and the control. Thereafter, the optical density was measured for each sample at a wavelength of 590 nanometers. This was accomplished by pipetting 100 microliters of the control or sample solutions into 96-well agar plates, and then using a ThermoMax Microplate Reader from Molecular Devices of Sunnyvale, Calif. to obtain the optical density readings. The results are shown in FIG. 10. As shown, the sugar and sugar-based compounds reduced the *Candida albicans* cell count after 24 hours in comparison to the control group.

EXAMPLE 12

A YM culture medium was prepared according to the manufacturer's instructions, and the pH of this medium was adjusted to pH 6.0 using 1N HCl. Xylitol was then dissolved into the YM medium at concentrations of 1%, 2%, 3%, 4%, and 5.0% (wt/vol). 0.9 milliliters of the culture medium were also added into a different culture tube as a control. Thereafter, 0.1 milliliter of *Candida albicans* culture suspension (concentration of 1×10^6/milliliter) was added to each of the culture tubes, and then incubated at 37° C. The viable *Candida albicans* cells in each tube were counted under a microscope after 24 hours. The above procedure was repeated four times for each concentration and the control. The results are shown in FIG. 11. As shown, xylitol significantly reduced the *Candida albicans* cell count after 24 hours in comparison to the control group.

EXAMPLE 13

A growth medium for *Gardnerella vaginalis* was prepared according to the manufacturer's instructions, and the pH of this medium was adjusted to pH 6.0 using 1N HCl. D-ribose (99%, Calbiochem), D-arabinose (98%, Alfa Aesar), D-xylose (Aldrich), D-lyxose (99%, Avovado), D-arabitol (97%, Alfa Aesar), adonitol (99%, Alfa Aesar), xylitol (99%, Alfa Aesar), xylitol (98%, Danisco), and xylitol (98%, Aldrich) were then dissolved into the growth medium at a concentration of 1.0% (wt/vol). 0.9 milliliters of the culture medium was also added into a different culture tube as a control. Thereafter, 0.1 milliliter of *Garnerella vaginalis* culture suspension (concentration of 1×10^6/milliliter) was added to each of the culture tubes, and then incubated overnight at 37° C., and the optical density was then measured after 24 hours at a wavelength of 595 nanometers. This was accomplished by pipetting 100 microliters of the control or sample solutions into 96-well microplates, and then using a ThermoMax Microplate Reader from Molecular Devices of Sunnyvale, Calif. to obtain the optical density readings. The results are depicted in FIG. 12. As shown, xylitol and D-ribose significantly reduced the *Gardnerella vaginalis* cell count after 24 hours in comparison to the control group. Although the remaining compounds did not have a significant effect on the *Gardnerella vaginalis* cell count in this example, it is nevertheless believed that such compounds may be effective under other conditions, such as at higher concentrations.

While the invention has been described in detail with respect to the specific embodiments thereof, it will be appreciated that those skilled in the art, upon attaining an understanding of the foregoing, may readily conceive of alterations to, variations of, and equivalents to these embodiments. Accordingly, the scope of the present invention should be assessed as that of the appended claims and any equivalents thereto.

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US10183076B2	2005-05-16	2019-01-22	Resdevco Research And Development Co. L	Topical compositions for treatment of irritation of mucous membranes
Family To Family Citations				
CN101175503B *	2005-04-27	2012-12-12	深圳福诺生物技术有限公司	Composition and method for regulating and remaining vaginal flora and vaginal acidity be normal
US7786176B2 *	2005-07-29	2010-08-31	Kimberly-Clark Worldwide, Inc.	Vaginal treatment composition containing xylitol
US20070048358A1 *	2005-08-31	2007-03-01	Schorr Phillip A	Antimicrobial substrates
US20070048344A1 *	2005-08-31	2007-03-01	Ali Yahiaoui	Antimicrobial composition
US20070048356A1 *	2005-08-31	2007-03-01	Schorr Phillip A	Antimicrobial treatment of nonwoven materials for infection control
US20070048345A1 *	2005-08-31	2007-03-01	Kimberly-Clark Worldwide, Inc.	Antimicrobial composition
US20070083175A1 *	2005-10-11	2007-04-12	Kimberly-Clark Worldwide, Inc.	Transparent/translucent absorbent composites and articles
US7745685B2 *	2005-10-31	2010-06-29	Kimberly-Clark Worldwide, Inc.	Absorbent articles with improved odor control
US20070129697A1 *	2005-12-02	2007-06-07	Soerens Dave A	Articles comprising flexible superabsorbent binder polymer composition
US7619131B2 *	2005-12-02	2009-11-17	Kimberly-Clark Worldwide, Inc.	Articles comprising transparent/translucent polymer composition
US8399012B2	2006-04-17	2013-03-19	Kimberly-Clark Worldwide, Inc.	Degradable therapeutic delivery device
US8338659B2 *	2007-04-30	2012-12-25	Kimberly-Clark Worldwide, Inc.	Absorbent article featuring leakage warning
FR2917291B1 *	2007-06-14	2009-09-18	Cooperative Bretonne D Insemin	Microcapsules containing spermatozoa of mammals, insemination dose containing and porcede for obtaining them
US20090123628A1 *	2007-11-09	2009-05-14	Shinya Ikeda	Low acyl gellan gels with reduced thermal hysteresis and syneresis
KR100862211B1 *	2008-04-23	2008-10-09	신라대학교 산학협력단	Composition for preventing and treating comprising an extract of laminaria japonica for preventing and treating diseases of vagina as antibacterial agent
US8044258B2 *	2008-06-27	2011-10-25	Kimberly-Clark Worldwide, Inc.	Absorbent article featuring leakage warning
GB0905677D0 *	2009-04-01	2009-05-20	Yes Syzygy Ltd	Intimate lubrication kit
US9408868B2	2009-10-19	2016-08-09	Won Seog Choi	Skin external composition comprising a combination of sodium chloride and glucose as active ingredients for treating vaginosis and the use thereof
KR101133723B1 *	2009-10-19	2012-04-09	최원석	Composition comprising salt and sugar for protecting and treating vaginosis disease and the use thereof
US9433641B2	2009-10-19	2016-09-06	Won Seog Choi	Skin external composition comprising a salt and sugar as active ingredients for preventing and treating vaginosis and the use thereof
NL1037411C *	2009-10-23	2011-04-27	Pk Peters Krizman Sa	A composition comprising anisic acid, a derivative thereof and / or a pharmaceutically acceptable salt thereof and an acidic buffer, as well as a dosage form, and uses thereof.
ITFI20110241A1 *	2011-11-03	2013-05-04	Lo Li Pharma Srl	Formulations to improve the chances of fertilization and the number of pregnancies
CN102600288B *	2012-04-20	2014-03-05	广西源安堂药业有限公司	Compound yellow pine gel medicament for treating vaginitis and preparation method thereof
NL2009407C *	2012-09-03	2014-03-04	Dutch Renewable Energy B V	Antimicrobial composition.
KR101470282B1 *	2013-10-01	2014-12-05	최원석	Pharmaceutical Composition comprising a combination of a salt and sugar for proventing or treating lax vagina syndrome or colpoxerosis disease and the use thereof

* Cited by examiner, † Cited by third party, ‡ Family to family citation

Similar Documents

Publication	Publication Date	Title
Krithikadatta et al.	2007	Disinfection of dentinal tubules with 2% chlorhexidine, 2% metronidazole, bioactive glass when compared with calcium hydroxide as intracanal medicaments
US6355684B1	2002-03-12	Antimicrobial treatment for herpes simplex virus and other infectious diseases
US20060051385A1	2006-03-09	Cationic antiseptic compositions and methods of use
US6537538B2	2003-03-25	Method for the prevention, inhibition, or treatment of vaginitis and/or bacterial vaginosis using polystyrene sulfonate

US20090226541A1	2009-09-10	Methods of reducing microbial contamination
US20060052452A1	2006-03-09	Phenolic antiseptic compositions and methods of use
US20050249818A1	2005-11-10	Polycationic antimicrobial therapeutic
LeBlanc	2010	Advances in the Diagnosis and Treatment of Chronic Infectious and Post–Mating-Induced Endometritis in the Mare
US20050058673A1	2005-03-17	Antimicrobial compositions and methods
US7521064B2	2009-04-21	Non-hormonal vaginal contraceptive
US6440949B1	2002-08-27	Method for promoting the growth of gram-positive bacilli and increasing the acidity in vagina
US20060204557A1	2006-09-14	Water-based personal moisturizers and lubricants, in particular vaginal lubricants, and uses thereof
Andriole et al.	1962	Factors influencing experimental candidiasis in mice. I. Alloxan diabetes
US20050271711A1	2005-12-08	Therapeutic antimicrobial compositions and methods
US20090191288A1	2009-07-30	Composition to Treat Herpes, Pseudomonas, Staph, Hepatitis and Other Infectious Diseases
US20050095245A1	2005-05-05	Pharmaceutical delivery system
US20040115160A1	2004-06-17	Quaternary ammonium esters for disinfection and preservation
Wolinsky	1959	Chemotherapy and pathology of experimental photochromogenic mycobacterial infections
US5778886A	1998-07-14	Vaginal compositions combining a spermicidal agent and a peroxygen compound
WO2006001766A1	2006-01-05	Composition comprising lactic acid and lactoferrin
US6913759B2	2005-07-05	Gel composition and method for treatment of vaginal infections
Collier et al.	1959	Further Observations on the Biological Properties of Dequalinium (Dequadin) and Hedaquinium (Teoquel)
Raz et al.	1995	Intravenous administration of gentamicin once daily versus thrice daily in adults
Whatley et al.	1991	Azithromycin vs doxycycline in the treatment of non-gonococcal urethritis
Singh et al.	2014	Microbicides for the treatment of sexually transmitted HIV infections

Priority And Related Applications

Parent Applications (2)

Application	Priority date	Filing date	Relation	Title
US10/987,463	2004-11-12	2004-11-12	Continuation-In-Part	Compound and method for prevention and/or treatment of vaginal infections
US11/091,206	2005-03-28	2005-03-28	Continuation-In-Part	Method for preventing and/or treating trichomonas vaginitis

Priority Applications (3)

Application	Priority date	Filing date	Title
US10/987,463	2004-11-12	2004-11-12	Compound and method for prevention and/or treatment of vaginal infections
US11/091,206	2005-03-28	2005-03-28	Method for preventing and/or treating trichomonas vaginitis
US11/194,039	2004-11-12	2005-07-29	Xylitol for treatment of vaginal infections

Applications Claiming Priority (6)

Application	Filing date	Title
US11/194,039	2005-07-29	Xylitol for treatment of vaginal infections
EP05818781A	2005-11-09	Sugars and/or sugar alcohols for inhibiting and/or treating vaginal infection
DE200560024160	2005-11-09	Sugar and / or sugar alcohols for prevention and / or treatment of vaginal infections
PCT/US2005/040842	2005-11-09	Sugars and/or sugar alcohols for inhibiting and/or treating vaginal infection
MX2007005678A	2005-11-09	Sugars and/or sugar alcohols for inhibiting and/or treating vaginal infection.
KR1020077010710A	2005-11-09	Sugars and/or sugar alcohols for inhibiting and/or treating vaginal infection

Legal Events

Date	Code	Title	Description
2005-10-19	AS	Assignment	**Owner name**: KIMBERLY-CLARK WORLDWIDE, INC., WISCONSIN **Free format text**: ASSIGNMENT OF ASSIGNORS INTEREST;ASSIGNORS:YANG, SHU-PING;HUANG, LEI;MARTIN, STEPHANIE M.;AND OTHERS;REEL/FRAME:017110/0100;SIGNING DATES FROM 20050927 TO 20051005
2010-12-14	CC	Certificate of correction	
2013-03-14	FPAY	Fee payment	**Year of fee payment**: 4
2015-02-03	AS	Assignment	**Owner name**: KIMBERLY-CLARK WORLDWIDE, INC., WISCONSIN **Free format text**: NAME CHANGE;ASSIGNOR:KIMBERLY-CLARK WORLDWIDE, INC.;REEL/FRAME:034880/0742 **Effective date**: 20150101
2017-06-30	REMI	Maintenance fee reminder mailed	
2017-12-18	LAPS	Lapse for failure to pay maintenance fees	**Free format text**: PATENT EXPIRED FOR FAILURE TO PAY MAINTENANCE FEES (ORIGINAL EVENT CODE: EXP.)
2018-01-09	FP	Expired due to failure to pay maintenance fee	**Effective date**: 20171117

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