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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

A1

WO 97/28805

14 August 1997 (14.08.97)

PCT/US97/02028

7 February 1997 (07.02.97)

9 February 1996 (09.02.96)

US

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PRIORITY DATA:

50/011,483

APPOINTED FOR:

AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

PUBLISHED

With international search report.

THERAPEUTIC COMPOSITIONS CONTAINING A HEXAHYDRO-5-PYRIMIDINAMINE COMPOUND AND A MORPHOLINE-ETHER COMPOUND

A therapeutic composition containing an antimicrobial hexahydro-5-pyrimidinamine compound and an anesthetic morpholine-ether compound in a pharmaceutically acceptable carrier is disclosed. The composition may be an oral topical composition or a non-oral topical composition. The preferred hexahydro-5-pyrimidinamine composition is hexetidine. The preferred morpholine-ether composition is pramoxine(4-[[4-butyrophenoxy)prozyl]morpholine).
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TITLED
THERAPEUTIC COMPOSITIONS CONTAINING A
HEXAHYDRO-5-PYRIDINAMINE
COMPOUND AND A MORPHOLINE-ETHER COMPOUND

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a therapeutic composition containing an antimicrobial hexahydro-
5-pyrimidinamine compound and an anesthetic morpholine-ether compound in a
pharmaceutically acceptable carrier. The therapeutic composition has both antimicrobial
and anesthetic efficacy and may take the form of either an oral topical or non-oral topical
composition.

Description of the Related Art

Hexahydro-5-pyrimidinamine compounds (5-amino-hexahydropyrimidine), such as
hexetidine (1,3-bis(2-ethylhexyl)hexahydro-5-methyl-5-pyrimidinamine), are well known
in the art for their broad spectrum antimicrobial activity. These hexahydro-5-
pyrimidinamine compounds are used in aqueous-based compositions for topical
application to treat skin and body cavity infections. For example, these antimicrobial
compositions are used in the treatment of oral infections such as gingivitis, sore throat,
oral ulcers, periodontal disease, and for the control of mouth odor, and in the treatment of
other topical infections such as cervical vaginal infections, ear infections, nasal
pharyngitis, and epidermal phytoses.
Hexetidine, however, has long been known to lack stability. The hexahydro-5-
pyrimidinamine ring system in hexetidine can be cleaved thermally and hydrolytically
to produce the open-chain compound triamine and the condensed bicyclic
heterocycle hexedine, see G. Satzinger et al., *Analytical Profiles of Drug
hexetidine when combined with other active compounds is uncertain.

Combinations of hexahydro-5-pyrimidinamine compounds with other
pharmacologically active compounds are known. For example, British Patent
Application No. 1,468,557 discloses a pharmaceutical composition said to prolong
the antibacterial effect of hexetidine. The composition contains hexetidine, choline
salicylate and chlorobutanol in a pharmaceutically acceptable solvent. Choline
salicylate and chlorobutanol are reported to have analgesic properties. European
Patent Application No. 308,210 discloses a combination of a quaternary ammonium
antiseptic compound, an antiseptic compound containing iodine salts or complexes
thereof, at least one antiseptic and/or anesthetic compound which is a terpene (e.g.
menthol or eucalyptol), and a phenolic compound (e.g. thymol) or an alcohol,
dissolved in an organic skin penetrating solvent. The instability of hexetidine and
the uncertainty associated therewith is not addressed by these references.

International Patent Application No. 92/09283 discloses that the stability of
hexetidine compositions has been improved through the use of aqueous buffer
solutions. There is no disclosure or suggestion of including an anesthetic
compound, particularly a morpholine-ether compound, in this stabilized system.

Morpholine-ether compounds, such as pramoxine (4-[3-(4-butoxyphenoxo)propyl]-
morpholine), are well known in the art for their anesthetic activity, as disclosed in
U.S. Patent No. 2,870,151. These morpholine-ethers, or pharmaceutically
acceptable salts thereof, are used in compositions as topical anesthetics.
United States Patent No. 3,836,654 discloses a combination of hexetidine and 2-methyl-2-nitro-1,3-dimorpholinopropane, two known antimicrobial agents, as a useful antimicrobial combination. The combination is applied topically as a lotion, cream or ointment. Morpholine-ether compounds are not disclosed or suggested.

It would be commercially advantageous to enhance the usefulness of hexahydro-5-pyrimidinamine compositions by including an agent possessing anesthetic properties without deleteriously effecting the stability of the hexahydro-5-pyrimidinamine compound.

SUMMARY OF THE INVENTION

This invention is directed to a therapeutic composition comprising: (a) an antimicrobially effective amount of a hexahydro-5-pyrimidinamine compound; (b) an anesthetically effective amount of a morpholine-ether compound; and (c) a pharmaceutically acceptable carrier.

Preferably the hexahydro-5-pyrimidinamine compound is hexetidine, a pharmaceutically acceptable salt thereof or a mixture thereof. The morpholine-ether compound is preferably 4[3-(4-butoxyphenoxy)propyl]morpholine, a pharmaceutically acceptable salt thereof or a mixture thereof. The compositions of this invention are advantageously stable compositions that provide both antimicrobial and anesthetic efficacy.
DETAILED DESCRIPTION OF THE INVENTION

This invention relates to the discovery that hexahydro-5-pyrimidinamine compounds can form stable therapeutic compositions with morpholine-ether compounds. Ester and amide containing anesthetic compounds are reactive, and are thus, believed to be incompatible with antimicrobial hexahydro-5-pyrimidinamine compounds. The incompatibility of hexahydro-5-pyrimidinamine compounds was also found to extend to various non-ester and non-amide anesthetic compounds, highlighting the unpredictability of hexetidine stability. Despite such unpredictability, the combination of morpholine-ether compounds with hexahydro-5-pyrimidinamine compounds has been found to provide therapeutic compositions that are stable for extended periods of time.

The hexahydro-5-pyrimidinamine compounds employed in this invention have antimicrobial efficacy. Any non-toxic, antimicrobial hexahydro-5-pyrimidinamine compound or pharmaceutically acceptable salt of a hexahydro-5-pyrimidinamine compound may be employed. Suitable non-toxic, antimicrobial hexahydro-5-pyrimidinamine compounds and their pharmaceutically acceptable salts are disclosed in United States Patent Nos. 2,837,463 and 4,141,968, the disclosures of which are incorporated by reference herein. The hexahydro-5-pyrimidinamine compounds are commercially available or may be readily prepared by one of ordinary skill in the art.

The preferred antimicrobial hexahydro-5-pyrimidinamine compound is hexetidine (1,3-bis(2-ethylhexyl) hexahydro-5-methyl-5-pyrimidinamine), and its pharmaceutically acceptable acid addition salts. Hexetidine is represented by the formula set forth below:
Hexetidine has an unusual affinity for tissue. When applied topically, hexetidine adheres to tissue and is not eliminated prematurely from the site of action either physiologically or by pathological secretions. Hexetidine has a broad antibacterial spectrum which makes it very useful in preparations for topical application to skin and body cavity infections.

The preferred pharmaceutically acceptable salts of hexetidine are the hydrochloride, hydrobromide, acetate, terphthalate, 4-sulfamylbenzoate, 4-hydroxybenzoate, 2-aminobenzoate, 4-aminobenzoate, 4-aminosalicylate, and 5-sulfosalicylate salts, similar salts, and mixtures of these salts.

A therapeutically effective amount of an antimicrobial hexahydro-5-pyrimidinamine compound is present in the therapeutic composition of this invention. In a preferred embodiment, the hexahydro-5-pyrimidinamine compound is present in the therapeutic composition in an amount from about 0.025% to about 1.0%, preferably from about 0.035% to about 0.5%, and more preferably from about 0.05% to about 0.25%, by weight of the therapeutic composition.

The morpholine-ether compounds employed in this invention have anesthetic efficacy. Any non-toxic, anesthetic morpholine-ether compound or pharmaceutically acceptable salt of a morpholine-ether compound may be employed. Suitable non-toxic, antiseptic morpholine-ether compounds and their pharmaceutically acceptable salts are disclosed in U.S. Patent No. 2,870,151, the
disclosure of which is incorporated by reference herein. The morpholine-ether compounds are commercially available or may be readily prepared by one of ordinary skill in the art.

The morpholine-ether compounds used in this invention may be represented by the formula:

![Chemical structure diagram]

or a pharmaceutically acceptable salt thereof, wherein: n is 2 to 5, x is 1 to 5, and R is independently selected from the group consisting of lower alkoxy having 1 to 6 carbon atoms, lower alkyl having 2 to 6 carbon atoms, lower alkenyl having 2 to 6 carbon atoms, chloro, fluoro, bromo and iodo.

The preferred anesthetic morpholine-ether compound is pramoxine (4-[3-(4-butoxyphenoxy)propyl]morpholine), and its pharmaceutically acceptable acid addition salts. Pramoxine has broad anesthetic properties and low toxicity which make it very useful in preparations for application to skin and body cavity surfaces.

The preferred pharmaceutically acceptable salts of pramoxine are the hydrochloride, hydrobromide, acetate, terphathalate, 4-sulfamylbenzoate, 4-hydroxybenzoate, 2-aminobenzoate, 4-aminobenzoate, 4-aminosalicylate, and 5-sulfosalicylate salts, similar salts, and mixtures of these salts.

Pramoxine has the chemical formula set forth below:

![Chemical structure diagram]

The amount of anesthetic morpholine-ether compound present in the therapeutic composition is a therapeutically effective amount. In a preferred embodiment, the morpholine-ether compound is present in the therapeutic composition in an amount
from about 0.1% to about 10.0%, preferably from about 0.25% to about 5.0%, and more preferably from about 0.5% to about 2.0%, by weight of the therapeutic composition.

The therapeutic composition may be used or formulated with pharmaceutically acceptable carriers such as topical vehicles (non-oral and oral) and ingestible vehicles to prepare a wide variety of topical and ingestible pharmaceutical compositions to suit particular applications. Non-oral topical compositions employ non-oral topical vehicles, such as creams, gels, foams, ointments and sprays, which are intended to be applied to the skin or body cavity and are not intended to be taken by mouth. Oral topical compositions employ oral vehicles such as mouthwashes, rinses, oral sprays, suspensions, and dental gels, which are intended to be taken by mouth but are not intended to be ingested. Ingestible compositions employ ingestible or partially ingestible vehicles such as confectionery bulking agents which include hard and soft confectionery such as lozenges, tablets, toffees, nougats, suspensions, chewy candies, and chewing gums.

In one embodiment of the invention, the therapeutic composition includes a non-oral topical vehicle and may take the form of a cream, gel, foam, ointment, spray, and the like. Non-toxic non-oral topical vehicles known in the pharmaceutical arts may be used in the present invention. The preferred non-oral topical vehicles are water and pharmaceutically acceptable water-miscible organic solvents such as ethyl alcohol, isopropyl alcohol, propylene glycol, glycerin, and the like, and mixtures of these solvents. Water-alcohol mixtures are particularly preferred and are generally employed in a weight ratio from about 1:1 to about 20:1, preferably from about 3:1 to about 20:1, and most preferably from about 3:1 to about 10:1, respectively.

Such non-oral topical therapeutic compositions may also contain conventional additives normally employed in those products. Conventional additives include humectants, emollients, lubricants, stabilizers, dyes, and perfumes, providing the
additives do not interfere with the antimicrobial and anesthetic properties of the pyrimidinamine and morpholine-ether compounds.

Suitable humectants useful in the non-or oral topical therapeutic compositions include glycerin, propylene glycol, polyethylene glycol, sorbitan, fructose, and the like, and mixtures thereof. Humectants, when employed, may be present in amounts from about 10% to about 50%, by weight of the topical therapeutic composition.

The coloring agents (colors, colorants) useful in the non-or oral topical therapeutic composition are used in amounts effective to produce the desired color. These coloring agents include pigments which may be incorporated in amounts up to about 6% by weight of the non-or oral topical therapeutic composition. A preferred pigment, titanium dioxide, may be incorporated in amounts up to about 2%, and preferably less than about 1%, by weight of the non-or oral topical therapeutic composition. The coloring agents may also include natural food colors and dyes suitable for food, drug and cosmetic dyes and lakes. The materials acceptable for the foregoing uses are preferably water-soluble. Illustrative nonlimiting examples include the indigoid dye known as F.D.&C. Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye know as F.D.&C. Green No. 1 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-(N-ethyl-p-sulfoniumbenzylamino)diphenylmethene]-[1-(N-ethyl-N-p-sulfoniumbenzyl)-delta-2,5-cyclohexadieneimine]. A full recitation of all F.D.&C. coloring agents and their corresponding chemical structures may be found in the Kirk-Other Encyclopedia of Chemical Technology, 3rd Edition, in volume 5 at pages 857-884, which text is incorporated herein by reference.

In accordance with this invention, antimicrobially and anesthetically effective amounts of the therapeutic components of the present invention may be admixed with a non-or oral topical vehicle to form a topical therapeutic composition. These amounts are readily determined by those skilled in the art without the need for undue experimentation. In a preferred embodiment, the non-or oral topical therapeutic
composition comprises the therapeutic components, i.e., the hexahydro-5-pyrimidinamine compound and the morpholine-ether compound, in a total amount from about 0.125% to about 5%, and a non-oral topical vehicle in a quantity sufficient to bring the total amount of composition to 100%, by weight of the non-oral topical therapeutic composition. In a more preferred embodiment, the non-oral topical therapeutic compositions will comprise the antimicrobial and anesthetic therapeutic components in a total amount from about 0.25% to about 2.5% and a non-oral topical vehicle in a quantity sufficient to bring the total amount of composition to 100%, by weight of the non-oral topical therapeutic composition.

In another embodiment of the invention, the therapeutic composition includes an oral topical vehicle and may take the form of a mouthwash, rinse, oral spray, suspension, dental gel, and the like. Typical non-toxic oral vehicles known in the pharmaceutical arts may be used in the present invention. The preferred oral vehicles are water, ethanol, and water-ethanol mixtures. The water-ethanol mixtures are generally employed in a weight ratio from about 1:1 to about 20:1, preferably from about 3:1 to about 20:1, and most preferably from about 3:1 to about 10:1, respectively. The pH value of the oral vehicle is generally from about 4 to about 7, and preferably from about 5 to about 6.5. An oral topical vehicle having a pH value below about 4 is generally irritating to the oral cavity and an oral vehicle having a pH value greater than about 7 generally results in an unpleasant mouth feel.

Such oral topical therapeutic compositions may also contain conventional additives normally employed in those products. Conventional additives include a fluorine providing compound, a sweetening agent, a flavoring agent, a coloring agent, a humectant, a buffer, and an emulsifier, providing the additives do not interfere with the antimicrobial and anesthetic properties of the hexahydro-5-pyrimidinamine and morpholine-ether compounds.
The coloring agents and humectants, and the amounts of these additives to be employed, set out above as useful in the non-oral topical therapeutic composition may be used in the oral topical therapeutic composition.

Fluorine providing compounds may be fully or slightly water soluble and are characterized by their ability to release fluoride ions or fluoride containing ions in water and by their lack of reaction with other components in the composition. Typical fluorine providing compounds are inorganic fluoride salts such as water-soluble alkali metal, alkaline earth metal, and heavy metal salts, for example, sodium fluoride, potassium fluoride, ammonium fluoride, cuprous fluoride, zinc fluoride, stannic fluoride, stannous fluoride, barium fluoride, sodium fluoroaluminate, ammonium fluorosilicate, sodium fluorozirconate, sodium monofluorophosphates, aluminum mono- and difluorophosphates and fluorinated sodium calcium pyrophosphate. Alkali metal fluorides, tin fluoride and monofluorophosphates, such as sodium and stannous fluoride, sodium monofluorophosphate and mixtures thereof, are preferred.

The amount of fluorine providing compound present in the oral topical therapeutic compositions of this invention is dependent upon the type of fluorine providing compound employed, the solubility of the fluorine compounds, and the nature of the final oral therapeutic composition. The amount of fluorine providing compound used must be a nontoxic amount. In general, the fluorine providing compound when used will be present in an amount up to about 3%, preferably from about 0.001% to about 2.0%, and most preferably from about 0.01% to about 1.5%, by weight of the oral topical therapeutic composition.

When sweetening agents (sweeteners) are used, those sweeteners well known in the art, including both natural and artificial sweeteners, may be employed. The sweetening agent used may be selected from a wide range of material including water-soluble sweetening agents, water-soluble artificial sweetening agents, water-soluble sweetening agents derived from naturally occurring water-soluble...
sweetening agents, dipeptide based sweetening agents, and protein based
sweetening agents, including mixtures thereof. Without being limited to particular
sweetening agents, representative categories and examples include:

(a) water-soluble sweetening agents such as monosaccharides, disaccharides and
polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose,
fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and
glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids,
dihydrochalcones, monellin, steviosides, and glycyrrhizin, and mixtures thereof;

(b) water-soluble artificial sweeteners such as soluble saccharin salts, i.e., sodium
or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt
of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide, the potassium salt of
3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-2,2-dioxide (Acesulfame-K), the free acid
form of saccharin, and the like;

(c) dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as
L-aspartyl-L-phenylalanine methyl ester (Aspartame) and materials described in
United States Patent No. 3,492,131, L-alpha-aspartyl-N-(2,2,4,4-tetraethyl-3-
thietanyl)-D-alanine-amide hydrate (Alitame), methyl esters of L-aspartyl-L-
phenylglycine and L-aspartyl-L-2,5-dihydrophenyl-glycine, L-aspartyl-2,5-dihydro-
L-phenylalanine; L-aspartyl-L-(1-cyclohexen)-alanine, and the like;

(d) water-soluble sweeteners derived from naturally occurring water-soluble
sweeteners, such as chlorinated derivatives of ordinary sugar (sucrose), e.g.,
chlorodeoxysugar derivatives such as derivatives of chlorodeoxysucrose or
chlorodeoxygalactosucrose, known, for example, under the product designation of
Sucralose; examples of chlorodeoxysucrose and chlorodeoxygalacto-sucrose
derivatives including but not limited to: 1-chloro-1'-deoxysucrose; 4-chloro-4-
deoxy-alpha-D-galacto-pyranosyl-alpha-D-fructofuranose, or 4-chloro-4-
deoxygalactosucrose; 4-chloro-4-deoxy-alpha-D-galacto-pyranosyl-1-chloro-1-
deoxy-beta-D-fructo-furanoside, or 4,1'-dichloro-4,1'-dideoxyagalactosucrose; 1',6'-
dichloro-1',6'-dideoxysucrose; 4-chloro-4-deoxy-alpha-D-galacto-pyranosyl-1,6-
dichloro-1,6-dideoxy-beta-D-fructo-furanoside, or 4,1',6'-trichloro-4,1',6'
trideoxygalacto-sucrose; 4,6-dichloro-4,6-dideoxy-alpha-D-galacto-pyranosyl-6-
chloro-6-deoxy-beta-D-fructofuranoside, or 4,6,6'-trichloro-4,6,6'
trideoxyagalactosucrose; 6,1',6'-trichloro-6,1',6'-trideoxysucrose; 4,6-dichloro-4,6-
dideoxy-alpha-D-galacto-pyranosyl-1,6-dichloro-1,6-di-deoxy-beta-D-
fructofuranoside, or 4,6,1',6'-tetrachloro-4,6,1',6'-tetradeoxyagalacto-sucrose; and
4,6,1',6'-tetrachloro-4,6,1',6'-tetradeoxy-sucrose; and

(e) protein based sweeteners such as thaumaoccus danielli (Thaumatin I and II).

In general, an effective amount of sweetening agent is utilized to provide the level
of sweetness desired in the particular oral topical therapeutic composition, and this
amount will vary with the sweetener selected and the final oral therapeutic product
desired. The amount of sweetener normally present is in the range from about
0.0025% to about 90%, by weight of the oral topical therapeutic composition,
depending upon the sweetener used. The exact range of amounts for each type of
sweetener is well known in the art and is not the subject of the present invention.

The flavoring agents (flavors, flavorants) which may be used include those flavors
known to the skilled artisan, such as natural and artificial flavors. Suitable flavoring
agents include mints, such as peppermint, citrus flavors such as orange and lemon,
artificial vanilla, cinnamon, various fruit flavors, both individual and mixed, and the
like.

The amount of flavoring agent employed in the oral topical therapeutic composition
is normally a matter of preference subject to such factors as the type of final oral
therapeutic composition, the individual flavor employed, and the strength of flavor
desired. Thus, the amount of flavoring may be varied in order to obtain the result
desired in the final product and such variations are within the capabilities of those
skilled in the art without the need for undue experimentation. The flavoring agents, when used, are generally utilized in amounts that may, for example, range in amounts from about 0.05% to about 6%, by weight of the oral topical therapeutic composition.

In a preferred embodiment of this invention, the therapeutic composition comprises (a) an antimicrobially effective amount of a hexahydro-5-pyrimidinamine compound, (b) an anesthetically effective amount of a morpholine-ether compound, (c) a sufficient amount of a buffer solution to maintain the pH of the therapeutic composition between about 5 and about 7, and (d) a non-ionic surfactant in a pharmaceutically acceptable carrier.

Buffer solutions are solutions to which limited amounts of a strong acid or strong base may be added without causing a significant change in the pH value of the solution. Buffer solutions usually contain two components, such as a weak acid and a salt of a weak acid, a mixture of an acid salt with the normal salt, or a mixture of two acid salts.

The buffer solutions in the preferred embodiment of this invention are solutions which are capable of maintaining the pH value of the therapeutic composition, which contain therapeutically effective amounts of the hexahydro-5-pyrimidinamine compound and the morpholine-ether compound, between about 5 and about 7, and preferably about 6. The buffer solution must not induce degradation of the hexahydro-5-pyrimidinamine compound, the morpholine-ether compound, or otherwise adversely affect the antimicrobial and anesthetic activity of these compounds, respectively. Suitable buffer solutions in the present invention include citric acid-sodium citrate solution, phosphoric acid-sodium phosphate solution, and acetic acid-sodium acetate solution. The buffer solution is preferably selected from the group consisting of citric acid-sodium citrate solution, phosphoric acid-sodium phosphate solution, and mixtures thereof, and more preferably, the buffer solution is citric acid-sodium citrate solution. The exact ratio of components in the buffer
solution to obtain a specific pH value is well known in the art and is not the subject of the present invention.

Surfactants (surface active agent) are compounds which reduce surface tension when dissolved in water or which reduce interfacial tension between two liquids or a liquid and a solid. Surfactants can aid in the dispersion of a composition over the skin and throughout the oral cavity.

The surfactants in the preferred invention are compounds which will solubilize therapeutically effective amounts of hexahydro-5-pyrimidinamine and morpholine-ether compounds in water such as the buffer solutions in the present invention. The surfactant must not induce degradation of these compounds or otherwise adversely affect their activity. The surfactant is preferably a nonionic surfactant.

Nonionic surfactants useful in the present invention include polyoxyethylene sorbitan fatty acid esters (polysorbates, polyethylene oxide sorbitan esters), which are the condensates of sorbitol esters of fatty acids with ethylene oxide. Polysorbates are available commercially as "Tweens," a trademark of ICI United States, Inc. Particularly preferred polysorbates are Polysorbate 20 (sorbitan, monododecanoate, poly(oxy-1,2-ethanediyl) derivative, polyoxyethylene 20 sorbitan monolaurate, Tween 20) and Polysorbate 80 (sorbitan, mono-9-octadecanoate, poly(oxy-1,2-ethanediyl) derivative, polyoxyethylene 20 sorbitan monooleate, Tween 80). Both Polysorbate 20 and Polysorbate 80 are yellow oily liquids, and have a characteristic odor and a warm somewhat bitter taste. Polysorbates are stable to weak acids and weak bases and are well tolerated, practically non-irritating, and have very low toxicity.

Other suitable nonionic surfactants useful in the present invention include polyoxyethylene castor oil derivatives which are ethoxylated hydrogenated castor oils. These surfactants are prepared by hydrogenating castor oil and treating the hydrogenated product with from about 10 to about 200 moles of ethylene glycol.
These ethoxylated hydrogenated castor oils are known by the non-proprietary name of Polyethylene glycol (PEG) hydrogenated castor oils, in accordance with the dictionary of the Cosmetics, Toiletries and Fragrance Association, 3rd Edition, which name is used in conjunction with a numeric suffix to designate the degree of ethoxylation of the hydrogenated castor oil product, i.e., the number of moles of ethylene oxide added to the hydrogenated castor oil product. Suitable PEG hydrogenated castor oils include PEG 16, 20, 25, 30, 40, 50, 60, 80, 100, and 200. A preferred PEG hydrogenated castor oil surfactant is Cremophor RH 60, a commercially available product from BASF-Wyandotte, Parsippany, New Jersey.

In a preferred embodiment, the nonionic surfactant is selected from the group consisting of polyethylene oxide sorbitan esters, polyethylene glycol hydrogenated castor oils, and mixtures thereof. In a more preferred embodiment, the nonionic surfactant is selected from the group consisting of polysorbate 80 (polyethylene oxide sorbitan ester 80, Tween 80) and PEG 60 (polyethylene glycol hydrogenated castor oil 60, Cremophore RH 60), and mixtures thereof. In a most preferred embodiment, the nonionic surfactant is polysorbate 80 (polyethylene oxide sorbitan ester 80).

The amount of nonionic surfactant present in the therapeutic composition is an amount sufficient to solubilize therapeutically effective amounts of the antimicrobial hexahydro-5-pyrimidinamine compound and the anesthetic morpholine-ester compound. In general, the nonionic surfactant will be present in the therapeutic composition in an amount from about 0.2% to about 2.0%, preferably from about 0.4% to about 1.5%, and more preferably about 0.5% to about 1%, by weight of the composition.

Suitable buffer solutions useful in the oral topical therapeutic compositions include citric acid-sodium citrate solution, phosphoric acid-sodium phosphate solution, and acetic acid-sodium acetate solution in amounts up to about 1%, and preferably from about 0.05% to about 0.5% by weight of the oral topical therapeutic composition.
As noted previously, therapeutically effective amounts of the antimicrobial and anesthetic therapeutic components of the present invention may be admixed with an oral topical vehicle to form an oral topical therapeutic composition. These amounts are readily determined by those skilled in the art without the need for undue experimentation. In a preferred embodiment, the oral topical therapeutic compositions will comprise the antimicrobial and anesthetic therapeutic components, i.e., the hexahydro-5-pyrimidinamine compound and the morpholine-ether compound in a total amount from about 0.125% to about 5% and an oral topical vehicle in a quantity sufficient to bring the total amount of composition to 100%, by weight of the oral topical therapeutic composition. In a more preferred embodiment, the oral topical therapeutic compositions will comprise the antimicrobial and anesthetic therapeutic components in a total amount from about 0.25% to about 2.5% and an oral topical vehicle in a quantity sufficient to bring the total amount of composition to 100%, by weight of the oral topical therapeutic composition.

The oral topical therapeutic composition is prepared by admixing a therapeutically effective amount of the antimicrobial and anesthetic therapeutic components of the present invention and an oral topical vehicle. The final compositions are readily prepared using standard methods and apparatus generally known by those skilled in the pharmaceutical arts. The apparatus useful in accordance with the present invention comprises mixing apparatus well known in the pharmaceutical arts, and therefore the selection of the specific apparatus will be apparent to the artisan.

In a preferred embodiment, an oral topical therapeutic composition is made by first dissolving coloring agents, sweetening agents, and similar additives in water. The antimicrobial and anesthetic therapeutic components are then admixed with the aqueous solution. Then sufficient water or ethanol, or mixtures of water and ethanol, are added to the solution with mixing until the final solution volume is reached. In a more preferred embodiment, the antimicrobial and anesthetic
therapeutic components are added to the solution as the final ingredient. The final oral topical therapeutic compositions are readily prepared using methods generally known in the pharmaceutical arts.

The oral therapeutic composition may also be in the form of dental gel. As used herein, the term "gel" means a solid or semisolid colloid which contains considerable quantities of water. The colloid particles in a gel are linked together in a coherent meshwork which immobilizes the water contained inside the meshwork.

The dental gel compositions of the present invention may contain the conventional additives set out above for oral topical therapeutic compositions such as mouthwashes, rinses, oral sprays, and suspensions and, in addition, may contain additional additives such as a polishing agent, a desensitizing agent, and the like, providing the additional additives do not interfere with the antimicrobial properties of the hexahydro-5-pyrimidinamine compound and the anesthetic properties of the morpholine-ether compound.

In a dental gel composition, the oral vehicle generally comprises water, typically in an amount from about 10% to about 90%, by weight of the dental gel composition. Polyethylene glycol, propylene glycol, glycerin, sorbitol solution and mixtures thereof may also be present in the vehicle as humectants or binders in amounts from about 10% to about 50%, by weight of the dental gel composition. Particularly preferred oral vehicles comprise mixtures of water with polyethylene glycol or water with glycerin and polypropylene glycol.

The dental gels of the present invention include a gelling agent (thickening agent) such as a natural or synthetic gum or gelatin. Gelling agents such as hydroxyethyl cellulose, methyl cellulose, glycerin, carboxypolymethylene, and gelatin and the like, and mixtures thereof may be used. The preferred gelling agent is hydroxyethyl cellulose. Gelling agents may be used in amounts from about 0.5% to about 5%,
and preferably from about 0.5% to about 2%, by weight of the dental gel composition.

The dental gel compositions of the present invention may also include a polishing agent. In clear gels, a polishing agent of colloidal silica and/or alkali metal aluminosilicate complexes is preferred since these materials have refractive indices close to the refractive indices of the gelling systems commonly used in dental gels. In non-clear gels, a polishing agent of calcium carbonate or calcium dihydrate may be used. These polishing agents may be used in amounts up to about 75%, and preferably in amounts up to about 50%, by weight of the dental gel composition.

The dental gel may also contain a desensitizing agent such as a combination of citric acid and sodium citrate. Citric acid may be used in an amount from about 0.1% to about 3%, and preferably from about 0.2% to about 1%, by weight, and sodium citrate may be used in an amount from about 0.3% to about 9%, and preferably from about 0.6% to about 3%, by weight of the dental gel composition.

In accordance with this invention, therapeutically effective amounts of the antimicrobial and anesthetic therapeutic components of this invention may be admixed into the dental gel compositions. These amounts are readily determined by those skilled in the art without the need for undue experimentation. In a preferred embodiment, the dental gel compositions will comprise the antimicrobial and anesthetic therapeutic components, i.e., the hexahydro-5-pyrimidinamine compound and the morpholine-ether compound, in a total amount from about 0.125% to about 5% and an oral topical vehicle in a quantity sufficient to bring the total amount of composition to 100%, by weight of the dental gel composition. In a more preferred embodiment, the dental gel compositions will comprise the antimicrobial and anesthetic therapeutic components in a total amount from about 0.25% to about 2.5% and an oral topical vehicle in a quantity sufficient to bring the total amount of composition to 100%, by weight of the dental gel composition.
The dental gel composition is prepared by admixing therapeutically effective amounts of the antimicrobial and anesthetic therapeutic components of the present invention and an oral topical vehicle. The final compositions are readily prepared using methods generally known by those skilled in the dental and pharmaceutical arts. The apparatus useful in accordance with the present invention comprises mixing apparatus well known in the pharmaceutical arts, and therefore the selection of the specific apparatus will be apparent to the artisan.

In yet another embodiment of the invention, the therapeutic composition includes an ingestible vehicle as the pharmaceutically acceptable carrier. The ingestible vehicle may be a confectionery bulking agent in the form of lozenges, tablets, toffees, nougats, suspensions, chewy candies, chewing gums, and the like. The ingestible vehicle may be prepared from a wide range of materials including, but not limited to, diluents, binders and adhesives, lubricants, disintegrants, coloring agents, bulking agents, flavoring agents, sweetening agents and miscellaneous materials such as buffers and adsorbents that may be needed in order to prepare a particular therapeutic confection.

The preparation of confectionery formulations is historically well known and has changed little through the years. Confectionery items have been classified as either "hard" confectionery or "soft" confectionery. The antimicrobial and anesthetic therapeutic components of this invention can be incorporated into confectionery compositions by admixing the inventive composition into conventional hard and soft confections.

As used herein, the term confectionery material means a product containing a bulking agent selected from a wide variety of materials such as sugar, corn syrup, and in the case of sugarless bulking agents, sugar alcohols such as sorbitol and mannitol and mixtures thereof. Confectionery material may include such exemplary substances as lozenges, tablets, toffee, nougat, suspensions, chewy candy, chewing gum and the like. The bulking agent is present in a quantity sufficient to bring the
total amount of composition to 100%. In general, the bulking agent will be present in amounts up to about 99.98%, preferably in amounts up to about 99.9%, and more preferably in amounts up to about 99%, by weight of the ingestible therapeutic composition.

Lozenges are flavored medicated dosage forms intended to be sucked and held in the mouth. Lozenges may be in the form of various shapes such as flat, circular, octagonal and biconvex forms. The lozenge bases are generally in two forms: hard boiled candy lozenges and compressed tablet lozenges.

Hard boiled candy lozenges may be processed and formulated by conventional means. In general, a hard boiled candy lozenge has a base composed of a mixture of sugar and other carbohydrate bulking agents kept in an amorphous or glassy condition. This amorphous or glassy form is considered a solid syrup of sugars generally having from about 0.5% to about 1.5% moisture. Such materials normally contain up to about 92% corn syrup, up to about 55% sugar and from about 0.1% to about 5% water, by weight of the final composition. The syrup component is generally prepared from corn syrups high in fructose, but may include other materials. Further ingredients such as flavoring agents, sweetening agents, acidulants, coloring agents and the like may also be added.

Boiled candy lozenges may also be prepared from non-fermentable sugars such as sorbitol, mannitol, and hydrogenated corn syrup. Typical hydrogenated corn syrups are Lycasin, a commercially available product manufactured by Roquette Corporation, and Hystar, a commercially available product manufactured by Lonza, Inc. The candy lozenges may contain up to about 95% sorbitol, a mixture of sorbitol and mannitol in a ratio from about 9.5:0.5 up to about 7.5:2.5, and hydrogenated corn syrup up to about 55%, by weight of the solid syrup component.
Boiled candy lozenges may be routinely prepared by conventional methods such as those involving fire cookers, vacuum cookers, and scraped-surface cookers also referred to as high speed atmospheric cookers.

Fire cookers involve the traditional method of making a boiled candy lozenge base. In this method, the desired quantity of carbohydrate bulking agent is dissolved in water by heating the agent in a kettle until the bulking agent dissolves. Additional bulking agent may then be added and cooking continued until a final temperature of 145°C to 156°C is achieved. The batch is then cooled and worked as a plastic-like mass to incorporate additives such as flavors, colorants and the like.

A high-speed atmospheric cooker uses a heat-exchanger surface which involves spreading a film of candy on a heat exchange surface, the candy is heated to 165°C to 170°C in a few minutes. The candy is then rapidly cooled to 100°C to 120°C and worked as a plastic-like mass enabling incorporation of the additives, such as flavors, colorants and the like.

In vacuum cookers, the carbohydrate bulking agent is boiled 125°C to 132°C, vacuum is applied and additional water is boiled off without extra heating. When cooking is complete, the mass is a semi-solid and has a plastic-like consistency. At this point, flavors, colorants, and other additives are admixed in the mass by routine mechanical mixing operations.

The optimum mixing required to uniformly mix the flavoring agents, coloring agents and other additives during conventional manufacturing of boiled candy lozenges is determined by the time needed to obtain a uniform distribution of the materials. Normally, mixing times of from 4 to 10 minutes have been found to be acceptable.

Once the boiled candy lozenge has been properly tempered, it may be cut into workable portions or formed into desired shapes. A variety of forming techniques may be utilized depending upon the shape and size of the final product desired. A
general discussion of the composition and preparation of hard confections may be found in H.A. Lieberman, *Pharmaceutical Dosage Forms: Tablets*, Volume 1 (1980), Marcel Dekker, Inc., New York, N.Y. at pages 339 to 469, the disclosure of which is incorporated by reference herein.

The apparatus useful in accordance with the present invention comprises cooking and mixing apparatus well known in the confectionery manufacturing arts, and therefore the selection of the specific apparatus will be apparent to the artisan.

In contrast, compressed tablet confections contain particulate materials and are formed into structures under pressure. These confections generally contain sugars in amounts up to about 95%, by weight of the composition, and typical tablet excipients such as binders and lubricants as well as flavoring agents, coloring agents and the like.

In addition to hard confectionery materials, the lozenges of the present invention may be made of soft confectionery materials such as those contained in nougat. The preparation of soft confections, such as nougat, involves conventional methods, such as the combination of two primary components, namely (1) a high boiling syrup such as a corn syrup, hydrogenated starch hydrolysate or the like, and (2) a relatively light textured frappe, generally prepared from egg albumin, gelatin, vegetable proteins, such as soy derived compounds, sugarless milk derived compounds such as milk proteins, and mixtures thereof. The frappe is generally relatively light, and may, for example, range in density from about 0.5 to about 0.7 grams/cc.

The high boiling syrup, or "bob syrup" of the soft confectionery is relatively viscous and has a higher density than the frappe component, and frequently contains a substantial amount of carbohydrate bulking agent such as a hydrogenated starch hydrolysate. Conventionally, the final nougat composition is prepared by the addition of the "bob syrup" to the frappe under agitation, to form the basic nougat
mixture. Further ingredients such as flavoring agents, additional carbohydrate bulking agent, coloring agents, preservatives, medicaments, mixtures thereof and the like may be added thereafter also under agitation. A general discussion of the composition and preparation of nougat confections may be found in B.W. Minifie, 


The procedure for preparing the soft confectionery involves known procedures. In general, the frappe component is prepared first and thereafter the syrup component is slowly added under agitation at a temperature of at least about 65°C., and preferably at least about 100°C. The mixture of components is continued to be mixed to form a uniform mixture, after which the mixture is cooled to a temperature below 800 C., at which point, the flavoring agent may be added. The mixture is further mixed for an additional period until it is ready to be removed and formed into suitable confectionery shapes.

The therapeutic compositions of this invention may also be in the form of a pharmaceutical suspension. Pharmaceutical suspensions of this invention may be prepared by conventional methods long established in the art of pharmaceutical compounding. Suspensions may contain adjunct materials employed in formulating the suspensions of the art. The suspensions of the present invention can comprise:

(a) preservatives such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), benzoic acid, ascorbic acid, methyl paraben, propyl paraben, tocopherols, and the like, and mixtures thereof. Preservatives are generally present in amounts up to about 1%, and preferably from about 0.05% to about 0.5%, by weight of the suspension;

(b) buffers such as citric acid-sodium citrate, phosphoric acid-sodium phosphate, and acetic acid-sodium acetate in amounts up to about 1%, and preferably from about 0.05% to about 0.5% by weight of the suspension;
(c) suspending agents or thickeners such as cellulosics like methylcellulose, carrageenans like alginic acid and its derivatives, xanthan gums, gelatin, acacia, and microcrystalline cellulose in amounts up to about 20%, and preferably from about 1% to about 15%, by weight of the suspension;

(d) antifoaming agents such as dimethyl polysiloxane in amounts up to about 0.2%, and preferably from about 0.01% to about 0.1%, by weight of the suspension;

(e) sweetening agents such as those sweeteners well known in the art, including both natural and artificial sweeteners. Sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, glycyrrhizin, and sugar alcohols such as sorbitol, mannitol, maltitol, hydrogenated starch hydrolysates and mixtures thereof may be utilized in amounts up to about 60%, and preferably from about 20% to about 50%, by weight of the suspension. Water-soluble artificial sweeteners such as soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (Acesulfame-K), the free acid form of saccharin, and the like may be utilized in amounts from about 0.001% to about 5%, by weight of the suspension;

(f) flavoring agents such as those flavors well known to the skilled artisan, such as natural and artificial flavors and mints, such as peppermint, menthol, citrus flavors such as orange and lemon, artificial vanilla, cinnamon, various fruit flavors, both individual and mixed and the like may be utilized in amounts from about 0.5% to about 5%, by weight of the suspension;

(g) coloring agents such as pigments which may be incorporated in amounts up to about 6%, by weight of the suspension. A preferred pigment, titanium dioxide, may be incorporated in amounts up to about 2%, and preferably less than about 1%, by weight of the suspension. The coloring agents may also include natural food colors and dyes suitable for food, drug and cosmetic
applications. These colorants are known as F.D. & C. dyes and lakes. The materials acceptable for the foregoing uses are preferably water-soluble. Such dyes are generally present in amounts up to about 0.25%, and preferably from about 0.05% to about 0.2%, by weight of the suspension;

(h) decolorizing agents such as sodium metabisulfite, ascorbic acid and the like may be incorporated into the suspension to prevent color changes due to aging. In general, decolorizing agents may be used in amounts up to about 0.25%, and preferably from about 0.05% to about 0.2%, by weight of the suspension; and

(i) solubilizers such as alcohol, propylene glycol, polyethylene glycol, and the like may be used to solubilize the flavoring agents. In general, solubilizing agents may be used in amounts up to about 10%, and preferably from about 2% to about 5%, by weight of the suspension.

The pharmaceutical suspensions of the present invention may be prepared as follows:

(A) admix the thickener with water heated from about 40°C to about 95°C, preferably from about 40°C to about 70°C, to form a dispersion if the thickener is not water soluble or a solution if the thickener is water soluble;

(B) admix the sweetening agent with water to form a solution;

(C) admix the antimicrobial and anesthetic therapeutic components, i.e., the hexahydro-5-pyrimidinamine compound and the morpholine-ether compound, with the thickener-water admixture to form a uniform thickener therapeutic composition;

(D) combine the sweetener solution with the thickener therapeutic composition and mix until uniform; and

(E) admix the optional adjunct materials such as coloring agents, flavoring agents, decolorants, solubilizers, antifoaming agents, buffers and additional water with the mixture of step (D) to form the suspension.
The ingestible therapeutic compositions of this invention may also be in chewable form. To achieve acceptable stability and quality as well as good taste and mouth feel in a chewable formulation several considerations are important. These considerations include the amount of active substance per tablet, the flavoring agent employed, the degree of compressibility of the tablet and the organoleptic properties of the composition.

Chewable therapeutic candy is prepared by procedures similar to those used to make soft confectionery. In a typical procedure, a boiled sugar-corn syrup blend is formed to which is added a frappe mixture. The boiled sugar-corn syrup blend may be prepared from sugar and corn syrup blended in parts by weight ratio of about 90:10 to about 10:90. The sugar-corn syrup blend is heated to temperatures above about 120°C to remove water and to form a molten mass. The frappe is generally prepared from gelatin, egg albumin, milk proteins such as casein, and vegetable proteins such as soy protein, and the like, which is added to a gelatin solution and rapidly mixed at ambient temperature to form an aerated sponge-like mass. The frappe is then added to the molten candy mass and mixed until homogenous at temperatures between about 65°C and about 120°C.

The antimicrobial and anesthetic therapeutic components of the instant invention can then be added to the homogeneous mixture as the temperature is lowered to about 65°C - 95°C whereupon additional ingredients can then be added such as flavoring agents and coloring agents. The formulation is further cooled and formed into pieces of desired dimensions.

A general discussion of the lozenge and chewable tablet forms of confectionery may be found in H.A. Lieberman and L. Lachman, *Pharmaceutical Dosage Forms: Tablets* Volume 1, Marcel Dekker, Inc., New York, N.Y. at pages 289 to 466, the disclosure of which is incorporated by reference herein.
In accordance with this invention, therapeutically effective amounts of the antimicrobial and anesthetic therapeutic components of this invention may be admixed into the hard and soft confectionery products. These amounts are readily determined by those skilled in the art without the need for undue experimentation.

In a preferred embodiment, the ingestible therapeutic composition will comprise the antimicrobial and anesthetic therapeutic components, i.e., the hexahydro-5-pyrimidinamine compound and the morpholine-ether compound, in a total amount from about 0.125% to about 5% and an ingestible vehicle, that is a pharmaceutically acceptable carrier, in a quantity sufficient to bring the total amount of composition to 100%, by weight of the therapeutic composition. In a more preferred embodiment, the ingestible composition will comprise the antimicrobial and anesthetic therapeutic components in a total amount from about 0.25% to about 2.5% and an ingestible vehicle in a quantity sufficient to bring the total amount of composition to 100%, by weight of the ingestible therapeutic composition.

An ingestible therapeutic composition may be prepared by admixing therapeutically effective amounts of the antimicrobial and anesthetic therapeutic components with a pharmaceutically-acceptable carrier. The apparatus useful in accordance with the present invention comprises mixing and heating apparatus well known in the confectionery arts, and therefore the selection of the specific apparatus will be apparent to the artisan. The final ingestible therapeutic compositions are readily prepared using methods generally known in the confectionery arts.

The therapeutic compositions of this invention also include chewing gums. In this form of the invention, the chewing gum composition contains a gum base, a bulking agent, the antimicrobial and anesthetic therapeutic components, and various additives.

The gum base employed will vary greatly depending upon various factors such as the type of base desired, the consistency of gum desired and the other components used in the composition to make the final chewing gum product. The gum base
may be any water-insoluble gum base known in the art, and includes those gum bases utilized for chewing gums and bubble gums. Illustrative examples of suitable polymers in gum bases include both natural and synthetic elastomers and rubbers. For example, those polymers which are suitable as gum bases include, without limitation, substances of vegetable origin such as chicle, crown gum, nispero, rosadinha, jelutong, perillo, niger gutta, tunu, balata, gutta-percha, lechi-capsi, sorva, gutta kai, mixtures thereof and the like. Synthetic elastomers such as butadiene-styrene copolymers, polyisobutylene, isobutylene-isoprene copolymers, polyethylene, mixtures thereof and the like are particularly useful.

The gum base may include a non-toxic vinyl polymer, such as polyvinyl acetate and its partial hydrolysate, polyvinyl alcohol, and mixtures thereof. When utilized, the molecular weight of the vinyl polymer may range from about 2,000 to and including about 94,000.

The amount of gum base employed will vary greatly depending upon various factors such as the type of base used, the consistency of the gum desired and the other components used in the composition to make the final chewing gum product. In general, the gum base will be present in amounts from about 5% to about 94%, by weight of the final chewing gum composition, and preferably in amounts from about 15% to about 45%, and more preferably in amounts from about 15% to about 35%, and most preferably in amounts from about 20% to about 30%, by weight of the final chewing gum composition.

The gum base composition may contain conventional elastomer solvents to aid in softening the elastomer base component. Such elastomer solvents may comprise terpinene resins such as polymers of alpha-pinene or beta-pinene, methyl, glycerol or pentaerythritol esters of rosins or modified rosins and gums, such as hydrogenated, dimerized or polymerized rosins or mixtures thereof. Examples of elastomer solvents suitable for use herein include the pentaerythritol ester of partially hydrogenated wood or gum rosin, the pentaerythritol ester of wood or gum
rosin, the glycerol ester of wood rosin, the glycerol ester of partially dimerized wood or gum rosin, the glycerol ester of polymerized wood or gum rosin, the glycerol ester of tall oil rosin, the glycerol ester of wood or gum rosin and the partially hydrogenated wood or gum rosin and the partially hydrogenated methyl ester of wood or rosin, mixtures thereof, and the like. The elastomer solvent may be employed in amounts from about 5% to about 75%, by weight of the gum base, and preferably from about 45% to about 70%, by weight of the gum base.

A variety of traditional ingredients may be included in the gum base in effective amounts such as plasticizers or softeners such as lanolin, palmitic acid, oleic acid, stearic acid, sodium stearate, potassium stearate, glyceryl triacetate, glyceryl lecithin, glyceryl monostearate, propylene glycol monostearate, acetylated monoglyceride, glycerine, mixtures thereof, and the like may also be incorporated into the gum base to obtain a variety of desirable textures and consistency properties. Waxes, for example, natural and synthetic waxes, hydrogenated vegetable oils, petroleum waxes such as polyurethane waxes, polyethylene waxes, paraffin waxes, microcrystalline waxes, fatty waxes, sorbitan monostearate, tallow, propylene glycol, mixtures thereof, and the like may also be incorporated into the gum base to obtain a variety of desirable textures and consistency properties. These traditional additional materials are generally employed in amounts up to about 30%, by weight of the gum base, and preferably in amounts from about 3% to about 20%, by weight of the gum base.

The gum base may include effective amounts of mineral adjuvants such as calcium carbonate, magnesium silicate, talc, tricalcium phosphate, dicalcium phosphate and the like as well as mixtures thereof. These mineral adjuvants may serve as fillers and textural agents. These fillers or adjuvants may be used in the gum base in various amounts. Preferably the amount of filler when used will be present in an amount up to about 60%, by weight of the chewing gum base.
The chewing gum base may additionally include the conventional additives of coloring agents, antioxidants, preservatives and the like. For example, titanium dioxide and other dyes suitable for food, drug and cosmetic applications, known as F.D. & C. dyes, may be utilized. An anti-oxidant such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, and mixtures thereof, may also be included. Other conventional chewing gum additives known to one having ordinary skill in the chewing gum art may also be used in the chewing gum base.

The gum composition may include effective amounts of conventional additives selected from the group consisting of sweetening agents (sweeteners), plasticizers, softeners, emulsifiers, waxes, fillers, bulking agents, mineral adjuvants, flavoring agents (flavors, flavorings), coloring agents (colorants, colorings), antioxidants, acidulants, thickeners, mixtures thereof and the like. Some of these additives may serve more than one purpose. For example, in sugarless gum compositions, the sweetener, e.g., sorbitol or other sugar alcohol or mixtures thereof, may also function as a bulking agent. Similarly, in sugar containing gum compositions, the sugar sweetener can also function as a bulking agent.

The plasticizers, softeners, mineral adjuvants, colorants, waxes and antioxidants discussed above as being suitable for use in the gum base may also be used in the gum composition. Examples of other conventional additives which may be used include emulsifiers, such as lecithin and glyceryl monostearate, thickeners, used alone or in combination with other softeners, such as methyl cellulose, alginates, carrageenan, xanthum gum, gelatin, carob, tragacanth, locust bean, and carboxy methyl cellulose, acidulants such a malic acid, adipic acid, citric acid, tartaric acid, fumaric acid, and mixtures thereof, and fillers, such as those discussed above under the category of mineral adjuvants. The fillers when used will be utilized in an amount up to about 60%, by weight of the gum composition.

Bulking agents (carriers, extenders) suitable for use in chewing gums include sweetening agents, selected from the group consisting of monosaccharides,
disaccharides, poly-saccharides, sugar alcohols, and mixtures thereof; polydextrose; maltodextrins; minerals, such as calcium carbonate, talc, titanium dioxide, dicalcium phosphate, and the like. Bulking agents may be used in amounts up to about 90%, by weight of the final gum composition, with amounts from about 40% to about 70%, by weight of the gum composition being preferred, with from about 50% to about 65%, by weight, being more preferred and from about 55% to about 60%, by weight of the chewing gum composition, being most preferred.

The sweetening agent used may be selected from a wide range of materials including water-soluble sweeteners, water-soluble artificial sweeteners, water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, dipeptide based sweeteners, and protein based sweeteners, including mixtures thereof. Without being limited to particular sweeteners, representative categories and examples include:

(a) water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribulose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, glycyrhrhizin, and sugar alcohols such as sorbitol, mannitol, maltitol, hydrogenated starch hydrolysates and mixtures thereof;

(b) water-soluble artificial sweeteners such as soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3,-oxathiazine-4-one-2,2-dioxide (Acesulfame-K), the free acid form of saccharin, and the like;

(c) dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (Aspartame) and materials described in United States Patent No. 3,492,131, L-alpha-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alanin-amide hydrate (Alitame), methyl esters of
L-aspartyl-L-phenylglycine and L-aspartyl-L-2,5-dihydrophenyl-glycine, L-aspartyl-2,5-dihydro-L-phenylalanine; L-aspartyl-L-(1-cyclohexen)-alanine, and the like;
(d) water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as chlorinated derivatives of ordinary sugar (sucrose), known, for example, under the product designation of Sucralose; and
(e) protein based sweeteners such as thaumatin I and II (Thaumatin I and II).

In general, an effective amount of sweetener is utilized to provide the level of bulk and/or sweetness desired, and this amount will vary with the sweetener selected. This amount of sweetener will normally be present in amounts from about 0.0025% to about 90%, by weight of the gum composition, depending upon the sweetener used. The exact range of amounts for each type of sweetener is well known in the art and is not the subject of this invention. The amount of sweetener ordinarily necessary to achieve the desired level of sweetness is independent from the flavor level achieved from flavor oils.

Preferred sugar based-sweeteners are sugar (sucrose), corn syrup and mixtures thereof. Preferred sugarless sweeteners are the sugar alcohols, artificial sweeteners, dipeptide based sweeteners and mixtures thereof. Preferably, sugar alcohols are used in the sugarless compositions because these sweeteners can be used in amounts which are sufficient to provide bulk as well as the desired level of sweetness. Preferred sugar alcohols are selected from the group consisting of sorbitol, xylitol, maltitol, mannitol, and mixtures thereof. More preferably, sorbitol or a mixture of sorbitol and mannitol is utilized. The gamma form of sorbitol is preferred. An artificial sweetener or dipeptide based sweetener is preferably added to the gum compositions which contain sugar alcohols.

The color agents useful in the gum compositions are used in amounts effective to produce the desired color. These coloring agents include pigments which may be incorporated in amounts up to about 6% by weight of the gum composition. A
preferred pigment, titanium dioxide, may be incorporated in amounts up to about 2%, and preferably less than about 1% by weight of the composition. The colorants may also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as F.D. & C. dyes and lakes. The materials acceptable for the foregoing uses are preferably water-soluble. Illustrative nonlimiting examples include the indigoid dye known as F.D. & C. Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as F.D. & C. Green No. 1 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-(N-ethyl-p-sulfoniumbenzylamino) diphenylmethylen]-[1-(N-ethyl-N-p-sulfoniumbenzyl)-delta-2,5-cyclohexadieneimine]. A full recitation of all F.D. & C. colorants and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Edition, in volume 5 at pages 857-884, which text is incorporated herein by reference.

Suitable oils and fats usable in gum compositions include partially hydrogenated vegetable or animal fats, such as coconut oil, palm kernel oil, beef tallow, lard, and the like. These ingredients when used are generally present in amounts up to about 7%, by weight, and preferably up to about 3.5%, by weight of the gum composition.

In accordance with this invention, therapeutically effective amounts of the antimicrobial and anesthetic therapeutic components of this invention may be admixed into a chewing gum. These amounts are readily determined by those skilled in the art without the need for undue experimentation. In a preferred embodiment, the final chewing gum composition will comprise the antimicrobial and anesthetic therapeutic components, i.e., the hexahydro-5-pyrimidinamine compound and the morpholine-ether compound in a total amount from about 0.125% to about 5% and a chewing gum composition in a quantity sufficient to bring the total amount of composition to 100%, by weight of the chewing gum composition. In a more preferred embodiment, the final chewing gum composition will comprise the antimicrobial and anesthetic therapeutic components in an amount from about
0.25% to about 2.5% and an oral vehicle in a quantity sufficient to bring the total amount of composition to 100%, by weight of the chewing gum composition.

The antimicrobial and anesthetic therapeutic components may be incorporated into an otherwise conventional chewing gum composition using standard techniques and equipment known to those skilled in the art. The apparatus useful in accordance with the present invention comprises mixing and heating apparatus well known in the chewing gum manufacturing arts, and therefore the selection of the specific apparatus will be apparent to the artisan.

For example, a gum base is heated to a temperature sufficiently high enough to soften the base without adversely effecting the physical and chemical make up of the base. The optimum temperatures utilized may vary depending upon the composition of the gum base used, but such temperatures are readily determined by those skilled in the art without undue experimentation.

The gum base is conventionally melted at temperatures that range from about 60°C to about 120°C for a period of time sufficient to render the base molten. For example, the gum base may be heated under these conditions for a period of about thirty minutes just prior to being admixed incrementally with the remaining ingredients of the base such as the plasticizer, fillers, the bulking agent and/or sweeteners, the softener and coloring agents to plasticize the blend as well as to modulate the hardness, viscoelasticity and formability of the base. The chewing gum base is then blended with the antimicrobial and anesthetic therapeutic components of the present invention which may have been previously blended with other traditional ingredients. Mixing is continued until a uniform mixture of gum composition is obtained. Thereafter the gum composition mixture may be formed into desirable chewing gum shapes.

The present invention is further illustrated by the following examples which are not intended to limit the effective scope of the claims. All parts and percentages in the
examples and throughout the specification and claims are by weight of the final composition (also denoted as "% w/w") unless otherwise specified.

EXAMPLE 1

A therapeutic composition was prepared containing 0.1% w/w hexetidine, and 1.0% w/w pramoxine HCl, 10% w/w ethanol, 1% w/w Tween 80 (a nonionic surfactant, Polysorbate 80 available from ICI United States, Inc.) and a sodium citrate/citric acid buffer to adjust pH to about 6.0.

COMPARATIVE EXAMPLES 1-5

A set of five hexetidine/anesthetic compositions were prepared in a manner similar to Example 1 with the exception that five different anesthetics (benzyl alcohol, benzocaine, phenol, dyclonine HCl and menthol) were substituted for pramoxine HCl in the amounts set forth in Table 1. The comparative compositions and the therapeutic composition of Example 1 were evaluated for their initial visual appearance as illustrated in Table 1 below.
### TABLE 1

**HEXETIDINE/ANESTHETIC COMPOSITIONS**

<table>
<thead>
<tr>
<th>COMPOSITION</th>
<th>ANESTHETIC</th>
<th>CONCENTRATION</th>
<th>VISUAL APPEARANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex. 1</td>
<td>Pramoxine HCl</td>
<td>1.0% w/w</td>
<td>Clear</td>
</tr>
<tr>
<td>Comp. Ex. 1</td>
<td>Benzyl Alcohol</td>
<td>1.0% w/w</td>
<td>Clear</td>
</tr>
<tr>
<td>Comp. Ex. 2</td>
<td>Benzocaine</td>
<td>1.0% w/w</td>
<td>Opaque/Cloudy</td>
</tr>
<tr>
<td>Comp. Ex. 3</td>
<td>Phenol</td>
<td>1.0% w/w</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Comp. Ex. 4</td>
<td>Dyclonine HCl</td>
<td>0.5% w/w</td>
<td>Clouds on Standing</td>
</tr>
<tr>
<td>Comp. Ex. 5</td>
<td>Menthol</td>
<td>0.06% w/w</td>
<td>Opaque/Clouds on Standing</td>
</tr>
</tbody>
</table>

As shown in Table 1, only benzyl alcohol and pramoxine HCl gave initially clear solutions with hexetidine. The opaque or cloudy appearance of the other solutions is believed to be an indication of incompatibility.

### COMPARATIVE EXAMPLES 6-8

A set of three compositions were prepared in a manner similar to Comparative Examples 2-4 with the exception that the anesthetic was reduced to 0.1% w/w.

The compositions of Example 1 and Comparative Examples 1 and 6-8 were assayed by gas chromatography for initial hexetidine content. The results, expressed as a decimal fraction of the hexetidine detected by gas chromatography, are set out in Table 2.
TABLE 2
HEXETIDINE/ANESTHETIC STABILITY

<table>
<thead>
<tr>
<th>COMPOSITION</th>
<th>ANESTHETIC</th>
<th>CONCENTRATION</th>
<th>FRACTION PRESENT**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex. 1</td>
<td>Pramoxine HCl</td>
<td>1% w/w</td>
<td>0.96</td>
</tr>
<tr>
<td>Comp. Ex. 1</td>
<td>Benzyl Alcohol</td>
<td>1% w/w</td>
<td>0.44</td>
</tr>
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<td>Comp. Ex. 6</td>
<td>Benzocaine</td>
<td>0.1% w/w</td>
<td>0.838</td>
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<tr>
<td>Comp. Ex. 7</td>
<td>Phenol</td>
<td>0.1% w/w</td>
<td>0.835</td>
</tr>
<tr>
<td>Comp. Ex. 8</td>
<td>Dyclonine HCl</td>
<td>0.1% w/w</td>
<td>0.637</td>
</tr>
<tr>
<td></td>
<td>Control*</td>
<td></td>
<td>0.93</td>
</tr>
</tbody>
</table>

*Control - contained the same ingredients as Example 1 without the anesthetic
** measured by Gas Chromatography

Note that Comparative Example 1 containing benzyl alcohol, though giving the appearance of a clear solution, had a significant loss of hexetidine in solution, i.e., about 56%.

The therapeutic compositions of Example 1 containing pramoxine HCl was divided into three equal samples. The first sample was stored at room temperature (RT), the second sample was stored at 37°C, and the third sample was stored at 45°C. The samples were observed for a period of two months and assayed monthly by gas chromatography to determine the amount of hexetidine remaining in solution. The results of the stability studies of the hexetidine/pramoxine compositions over the two-month testing period, expressed as a decimal fraction of the hexetidine detected by gas chromatography, are set out in Table 3.
TABLE 3
STABILITY OF HEXETIDINE/PRAMOXINE COMPOSITIONS
(Fraction of Hexetidine Present)

<table>
<thead>
<tr>
<th>Month</th>
<th>RT</th>
<th>370°C</th>
<th>450°C</th>
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<tbody>
<tr>
<td>1 month</td>
<td>1.03</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>2 months</td>
<td>0.912</td>
<td>1.004</td>
<td>0.931</td>
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The test results illustrate that hexetidine remained stable over the testing period when in combination with pramoxine HCl, even at elevated temperatures.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.
CLAIMS:

1. A therapeutic composition comprising:
   (a) an antimicrobially effective amount of a hexahydro-5-pyrimidinamine
   compound;
   (b) an anesthetically effective amount of a morpholine-ether compound;
   and
   (c) a pharmaceutically acceptable carrier.

2. A therapeutic composition according to Claim 1 wherein the morpholine-
   ether compound is represented by the formula:

   \[
   \begin{align*}
   &\text{O} \quad \text{(CH}_2\text{)}_n \quad \text{N} \quad \text{O} \\
   &\text{R}_x
   \end{align*}
   \]

   or a pharmaceutically acceptable salt thereof, wherein: \( n \) is 2 to 5, \( x \) is 1 to 5, and \( R \)
   is independently selected from the group consisting of lower alkoxy having 1 to 6
   carbon atoms, lower alkyl having 2 to 6 carbon atoms, lower alkenyl having 2 to 6
   carbon atoms, chloro, fluoro, bromo and iodo.

3. A therapeutic composition according to Claim 2 wherein the hexahydro-5-
   pyrimidinamine compound is selected from the group consisting of hexetidine,
   pharmaceutically acceptable salts of hexetidine, and mixtures thereof.

4. A therapeutic composition according to Claim 3 wherein the morpholine-
   ether compound is selected from the group consisting of 4-[3-(4-
   butoxyphenoxy)propyl] morpholine, pharmaceutically acceptable salts of 4-[3-4-
   butoxyphenoxy)propyl]morpholine, and mixtures thereof.

5. A therapeutic composition according to Claim 1 wherein the morpholine
   ether compound is present in the amount of about 0.1% to about 10% by weight of
   the composition.
6. A therapeutic composition according to Claim 5 wherein the morpholine-ether compound is present in the amount of about 0.25% to about 5% by weight of the composition.

7. A therapeutic composition according to Claim 6 wherein the morpholine ether compound is present in an amount from about 0.5% to about 2.0% by weight of the therapeutic composition.

8. A therapeutic composition according to Claim 1 wherein the hexhydro-5-pyrimidinamine compound is present in an amount from about 0.025% to about 1.0% by weight of the therapeutic composition.

9. A therapeutic composition according to Claim 8 wherein the hexhydro-5-pyrimidinamine compound is present in an amount from about 0.035% to about 0.5% by weight of the therapeutic composition.

10. A therapeutic composition according to Claim 9 wherein the hexhydro-5-pyrimidinamine compound is present in an amount from about 0.05% to about 0.25% by weight of the therapeutic composition.

11. A therapeutic composition according to Claim 1, further comprising a sufficient amount of an aqueous buffer solution to maintain a pH of the therapeutic composition between about 5 and about 7.

12. A therapeutic composition according to Claim 11 further comprising a nonionic surfactant.

13. A therapeutic composition according to Claim 11, wherein the buffer solution is selected from the group consisting of citric acid-sodium citrate solution, phosphoric acid-sodium phosphate solution, and mixtures thereof.
14. A therapeutic composition according to Claim 13, wherein the buffer solution is citric acid-sodium citrate solution.

15. A therapeutic composition according to Claim 11, wherein the buffer solution is present in an amount to maintain the pH of the therapeutic composition at about 6.

16. A therapeutic composition according to Claim 12, wherein the nonionic surfactant is selected from the group consisting of polyethylene oxide sorbitan esters, polyethylene glycol hydrogenated castor oils, and mixtures thereof.

17. A therapeutic composition according to Claim 16, wherein the nonionic surfactant is Polysorbate 80.

18. A therapeutic composition according to Claim 12, wherein the nonionic surfactant is present in an amount from about 0.02% to about 2.0%, by weight of the therapeutic composition.

19. A therapeutic composition comprising:

(a) hexetidine or a pharmaceutically acceptable salt thereof in an amount from about 0.025% to about 1%, by weight of the therapeutic composition;

(b) 4-[3-(4-butoxyphenoxy)propyl]morpholine or a pharmaceutically acceptable salt thereof in an amount from about 0.1% to about 10%, by weight of the therapeutic composition;

(c) a sufficient amount of buffer to maintain the pH of the therapeutic composition between about 5 and about 7;

(d) a nonionic surfactant; and

(e) a pharmaceutically acceptable carrier.
20. An oral topical therapeutic composition comprising a therapeutic composition comprising:

(a) an antimicrobially effective amount of a hexahydro-5-pyrimidinamine compound;

(b) an anesthetically effective amount of a morpholine-ether compound; and

(c) a pharmaceutically acceptable carrier.

21. An oral topical therapeutic composition according to Claim 20, wherein the antimicrobial hexahydro-5-pyrimidinamine compound is selected from the group consisting of hexetidine, pharmaceutically acceptable salts of hexetidine, and mixtures thereof.

22. An oral topical therapeutic composition according to Claim 21, wherein the hexahydro-5-pyrimidinamine compound is present in an amount from about 0.025% to about 1% by weight of the orally therapeutic composition.

23. An oral topical therapeutic composition according to Claim 21, wherein the morpholine-ether compound is selected from the group consisting of 4[3-(4-butoxyphenoxy)propyl]morpholine, pharmaceutically acceptable salts of 4[3-(4-butoxyphenoxy)propyl]morpholine, and mixtures thereof.

24. An oral topical therapeutic composition according to Claim 23, wherein the morpholine-ether compound is present in an amount from about 0.1% to about 10% by weight of the orally therapeutic composition.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER


According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
<td>US 3 836 654 A (HODGE E) 17 September 1974 cited in the application</td>
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<td>US 2 870 151 A (H. B. WRIGHT ET AL) 20 January 1959 cited in the application</td>
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Patent family members are listed in annex.

- Special categories of cited documents:
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  - E: earlier document but published on or after the international filing date
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  - O: document referring to an oral disclosure, use, exhibition or other means
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Date of the actual completion of the international search: 23 April 1997

Date of mailing of the international search report: 15.05.97

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Fax: (+31-70) 340-3016

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Herrera, S
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