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MEDICATED GELS

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This invention relates to gelled compositions. More particularly this invention relates to medicated gel compositions for oral administration and pressurized dispensing units containing the medicated gels. The medicament employed in the gel can be any water soluble vasoconstrictor, antihistamine, bronchodilator, sympathomimetic, or antitussive. The above medicaments can be used either singly or in various combinations.

Unit dosages for oral administration of the above classes of medicaments are usually administered in the form of tablets, capsules or syrups. Tablets and capsules are relatively slow-acting since they have to disintegrate and the active components solubilized in the stomach before being absorbed by the body. Also, in the solid dosages, differences in solubilities of the solid medicaments in the gastrointestinal tract affect the time when each medicament acts and the medicaments often do not act in unison. Syrups are messy and difficult to dispense, particularly in measured doses without spillage in a convenient unit dosage form such as a teaspoon. Also, the syrups comprise emulsion or suspension systems which are often unstable.

The primary object of this invention is to produce a gelled therapeutic composition containing one or more of the above enumerated classes of medicaments which does not produce deleterious side effects upon oral administration; which is rapidly and substantially simultaneously absorbed by the gastrointestinal tract; and which is stable.

A further object is to produce a medicated gel which can be dispensed from a pressurized container in a steady gelled stream wherein the gel is substantially clear and transparent. Additional objects appear in the specification.

The medicated gels of this invention are more rapidly assimilated by the body than the solid dosage forms. Also, since combinations of the medicaments are solubilized in the gel they are absorbed by the body at a more uniform rate. The gels are stable and it is easier to measure a convenient dosage such as a teaspoon of the gel than a syrup. Pressurized units containing the medicated gels are safer for storage in the home since children cannot easily evacuate the unit as in the case of simply removing a cap from a bottle. The gels have good stability and can be substantially clear and transparent.

By the term "gel" we mean the solid phase of a colloidal solution, as opposed to sol, the liquid phase.

The gels of this invention are produced by conventional techniques such as by admixing a water soluble medicament as hereinabove set forth, and specifically medicaments of the above classes such as phenylephrine hydrochloride, chlorpheniramine maleate, 7-beta hydroxypropyl theophylline, ephedrine sulfate or dextromethorphan hydrobromide and the gelling agent with water. Optionally additives such as buffers, flavors, coloring agents, humectants such as glycerine or sorbitol and sweetening agents can be added to the gel. The gel can contain up to about 900 grams of additives per liter and preferably up to about 400 grams of additives per liter of the gel. In all instances each liter of the gel contains a total of at least 50%, by weight, of water and preferably at least 65% of water. The maximum quantity of water is determined by the quantity of the other ingredients in the gel. Thus the quantity of water can be as high as about 98.9% of the gel.

As mentioned hereinabove the medicament used is water soluble. The medicament can be in either the acid form or salt, e.g. non-toxic pharmaceutically acceptable acid addition salts of base compounds. The term "water soluble" is intended to embrace even minute quantities of a medicament soluble in water, provided that such quantities, either alone or in combination with other medicaments in the formulation, are therapeutically effective. The quantity of each medicament can vary over a wide range within the minimum quantity which is therapeutically effective and the maximum quantity which will cause serious side effects. Since the composition is a viscous gel which is effectively dispensed on to a teaspoon having a 5 ml. capacity per unit dosage the quantity of medicament employed can be calculated to provide the acceptable quantity per teaspoon unit dosage. Illustratively such quantities can vary from about 5 to 1,500 milligrams per teaspoon (5 ml. dosage), and preferably from about 10 to 1,000 mg. per 5 ml. of the gel. A water soluble drug is one having a sufficient water solubility which is therapeutically effective. Also, the term "water soluble" includes the use of any aqueous medium containing a sufficient amount of a common solvent to solubilize a sufficient quantity of the medicament. The common solvent must be compatible in the gelled system. Illustrative of such common solvents there can be mentioned alcohols having from 1 to 6 carbon atoms such as the aliphatic monohydric, dihydric or polyhydric alcohols, e.g. ethanol. However, it is preferred that the medicaments do not require the use of a common solvent.

Illustrative of vasoconstrictors there can be mentioned: 1-methylamino-2-phenylpropane hydrochloride, (phenylpropylmethyl amine hydrochloride); m-methylaminoethanolphenol hydrochloride, (phenylephrine hydrochloride); 1-phenyl-2-methylaminopropanol lactate, (ephedrine lactate); 2-methyl-6-methylamino-2-methylheptene, (isometheptene); ephedrine hydrochloride; 2-(1-napthylmethyl)imidazoline hydrochloride, (naphazoline hydrochloride); 2-aminoheptane sulfate, (tuaminoheptane sulfate); 1-cyclopentyl-2-methylaminopropane hydrochloride, (cyclopentamine hydrochloride); 2-amino-1-(2,5-dimethoxyphenyl)-1-propanol hydrochloride, (methoxamine hydrochloride); 2-(1,2,3,4-tetrahydro-1-naphthyl)-2-imidazoline HCl, (tetrahydrozoline hydrochloride); and 2-(4'-tert.-butyl-2',6'-dimethylphenylmethyl)imidazoline HCl, (xylometazoline hydrochloride). The preferred vasoconstrictor is phenylephrine hydrochloride.

Illustrative of antihistamines there can be mentioned: n-(2'-dimethylamino-2'-methylethylphenothiazine hydrochloride, (promethazine HCl); 2-(benzhydryloxy)-N,N-dimethylethylamine HCl, (diphenhydramine hydrochloride); bromodiphenhydramine; 2-dimethylaminoethylphenylmethyl-2-picoline succinate, (doxylamine succinate); 2-[benzyl(2-dimethylaminoethyl)amino] pyridine, (tripelennamine hydrochloride); 2-[(2-dimethylaminoethyl)(p-methoxybenzyl) amino]pyridine maleate, (pyrilamine maleate); trans-2-[3-(1-pyrrolidinyl)-1-tolylpropenyl]pyridine HCl, (triprolidine HCl); dimethyl-prindene maleate; 2-(dimethylaminoethoxy)diphenylmethane, (phenyltoloxamine dihydrogencitrate) maleate and 1-(p-chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane (chlorpheniramine maleate).

Illustrative of bronchodialators there can be mentioned: b-(o-methoxyphenyl)isopropylmethylamine HCl, (methoxyphenamine hydrochloride); 2-amino-1-phenyl-1-propanol HCl, (phenylpropanolamine HCl); and 7-beta-hydroxypropyl theopylline.

Illustrative of sympathomimetics there can be mentioned: epinepherine bitartrate; isoproterinol; mephentermine sulfate; phenylephrine hydrochloride; 2-methyl-

aminoheptane; methoxamine hydrochloride; and ephedrine sulfate.

Illustrative of antitussives or expectorants there can be mentioned: dextromethorphan hydrobromide; codein phosphate; potassium citrate; dihydrocodeinone bitartrate; dimethoxinate; carbetapentane citrate; caramiphen ethanedisulfonate; benzononatine HCl; glyceryl guaiacolate; ammonium chloride; and sodium citrate. The more detailed names of medicaments, when not given herein, can be found in the Merck Index, Seventh Edition.

Illustrative of the gelling agents there can be mentioned: the propylene glycol ester of alginic acid, polyvinylpyrrolidone, hydroxyethylcellulose (HEC) and vegetable gums. The particular gelling agent employed is not critical and any non-toxic gelling agent which is compatible with the active ingredients can be used. However, the above enumerated gelling agents are preferred since they produce stable substantially clear transparent gels whose viscosity is not greatly affected by changes in temperature. Hydroxyethylcellulose is particularly preferred as the gelling agent since it produces stable substantially clear transparent gels over a wide range of conditions. Thus, hydroxyethylcellulose is unaffected by water soluble salts and ions in solution; is stable over a wide pH range such as that of about 3 to 12 and particularly from about 3.5 to 7; has good temperature stability; and does not require warm water for dispersion to attain maximum viscosity. The good temperature stability of HEC is particularly an advantageous feature since substanitally constant dosages of the gel can be administered over a wide variation in temperature. A number of gelling agents although operable are not well suited for the compositions of this invention. Thus gelatin has a wide viscosity fluctuation over a narrow temperature range when the concentration of gelatin is sufficient to form a gel which can be dispensed from a pressure pack such as those which employ an inert gas such as nitrogen as the propellant. Starches are not well suited as the gelling agent since the resultant composition is not clear. Citrus pectin is also not well suited as the gelling agent due to wide viscosity fluctuations over a narrow temperature range.

The viscosity of the medicated gel can vary from about 5,000 cps. to about 200,000 cps. at 25° C. and atmospheric pressure, preferably from about 10,000 to 100,000 cps. and particularly from about 35,000 to 70,000 cps. The viscosity values are determined by standard methods such as the use of a Brookfield viscosimeter using a No. 4 spindle at 20 r.p.m. in a 400 cc. beaker. The gel has sufficient cohesion to itself and a sufficient adhesion to a conventional metal teaspoon so that it will not fall out of the spoon when the spoon is inverted. The quantity of gelling agent can vary over wide limits provided it is sufficient to impart the required viscosity. Preferably the quantity of gelling agent can vary from about 1.0% to about 10.0%, by weight, based on the entire composition, and particularly from about 1.5% to about 3% by weight of the entire composition.

In a preferred form of the invention the gel is dispensed from a pressurized container. The propellant employed is preferably a non-toxic inert gas such as nitrogen, argon, helium, neon, carbon dioxide, nitrous oxide, etc. Nitrogen is preferred. Such gases do not liquify at room temperature (25° C.) and pressures of 30 to 115 p.s.i.g. in contradistinction to the conventional haloalkane propellants. Haloalkanes which are liquified at pressures of 30 to 115 p.s.i.g. at room temperature are not desirable in this invention since they produce excess foaming of the gelled product. Furthermore, the inert gasses are substantially insoluble in the gel in contrast to the haloalkanes. The pressures employed in the containers can vary from about 30 to 115 p.s.ig. and preferably from about 50 to 95 p.s.i.g. The pressurized containers are charged by conventional methods such as by

first placing the gelled product in a conventional aerosol can, leaving about 20% to 40% by volume of headspace in the can, crimping on a valve to seal the container and charging the can with the desired propellant. In addition to the use of inert gases, other means wherein the specified pressure is maintained on the gel, and wherein there is no sputtering or contamination can also be employed although such means are not preferred. Illustratively the use of a plastic bag under pressure within the container or a piston under substantially constant pressure are also operable.

The preferred medicaments of this invention are phenylephrine hydrochloride, chlorpheniramine maleate, 7-beta hydroxypropyl theophylline, ephedrine sulfate and dextromethorphan hydrobromide.

The invention is illustrated by the following examples of suitable compositions, although it is not intended that the compositions or dosages be limited by any of the proportions, amounts, specific medicaments or specific gelling agents set forth herein.

Example 1

A one liter quantity of a vasoconstrictor gel was prepared. The gel had the following composition per liter of gel:

	Grams
Phenylephrine hydrochloride	1.0
Sorbitol solution, 70% sorbitol in water	200.0
Glycerin	200.0
Sodium cyclamate	3.5
Potassium sorbate	1.0
Hydroxyethylcellulose (HEC)	15.0
Citric acid	0.55
Flavor	0.0003
FD & C Yellow #6	0.0343
Water, distilled	680.00

The viscosity of the above gel was 12,000 cps. at 25° C. The propellant employed was nitrogen at a pressure of 90 p.s.i.g.

Each teaspoon, i.e. a 5 ml. portion of the above gel contains 5 mg. of phenylephrine hydrochloride.

The composition of Example 1 was prepared in the following manner:

A glass-lined tank equipped with a Daysolver (Turbopeller) was charged with the water. There was dissolved in order: potassium sorbate, FD & C Yellow #6, phenylephrine hydrochloride, sodium cyclamate, and citric acid. Sorbo and flavor were then added, HEC was passed through a 50 mesh screen and mixed with glycerin. The ingredients were then added to a mixing kettle and agitated for 30 to 45 minutes to produce the gel. The gel was packed by purging a can with nitrogen, filling with product to approximately 65% of volume of can, crimping on the valve assembly and finally charging the unit through the valve with nitrogen.

Example 2

A one liter quantity of a combination vasoconstrictor and antihistamine gel was prepared. The gel had the following composition per liter.

	Grams
Phenylephrine hydrochloride	1.0
Chloropheniramine malate	0.2

Example 3

A one liter quantity of a combination vasoconstrictor and antihistamine gel was prepared by conventional techniques and packaged in a nitrogen pressurized unit. The gel had the following medicaments:

	Grams per liter of gel
Phenylephrine hydrochloride	2.0
Chloropheniramine maleate	0.2

Example 4

A one liter quantity of a combination vasoconstrictor and antihistamine gel was prepared by conventional techniques and packaged in the manner shown in Example 1. The gel contained the following medicaments:

	Grams
Phenylephrine hydrochloride	2.0
Chloropheniramine maleate	0.4

Example 5

A one liter quantity of a sympathomimetic and bronchodialator gel was prepared and packaged by the method shown in Example 1. The gel contained the following medicaments:

	Grams
7-beta hydroxypropyl theophylline	12.5
Ephedrine sulfate	2.0

Example 6

A one liter quantity of a combination vasoconstrictor, antihistamine and bronchodialator gel was prepared.

The gel contained the following medicaments:

	Grams
7-beta hydroxypropyl theophylline	12.5
Ephedrine sulfate	2.0
Phenyltoloxamine dihydrogen citrate	3.5

Example 7

A one liter quantity of a combination vasoconstrictor, antihistamine, bronchodialator and antitussive gel was prepared. The gel contained the following medicaments:

	Grams
7-beta hydroxypropyl theophylline	12.5
Ephedrine sulfate	2.0
Phenyltoloxamine dihydrogen citrate	3.5
Glyceryl guaiacolate	20.0

This application is a continuation-in-part of our copending application Serial No. 847,913, filed October 22, 1959, now U.S. Patent No. 3,051,621.

What is claimed is:

1. A pressurized dispensing unit containing a medicated gel and a non-toxic gaseous propellant under a pressure of from about 30 to 115 p.s.i.g. in contact with said gel, said gel having a viscosity of from about 5,000 cps. to about 200,000 cps. at 25° C. and comprising: (*a*) as the essentially sole therapeutic component a therapeutically effective quantity of a water soluble soluble medicament selected from the group consisting of a vasoconstrictor, antihistamine, bronchodilator, sympathomimetic, an antitussive and mixtures thereof; (*b*) from about 1% to 10%, by weight of a gelling agent; and (*c*) at least 50%, by weight, of water.

2. The pressurized composition of claim 1 wherein the propellant is nitrogen.

3. The pressurized composition of claim 1 wherein the medicament is a vasoconstrictor.

4. The pressurized composition of claim 1 wherein the medicament is an antihistamine.

5. The pressurized composition of claim 1 wherein the medicament is a sympathomimetic.

6. The pressurized composition of claim 1 wherein the medicament is a bronchodilator.

7. The pressurized composition of claim 1 wherein the medicament is an antitussive.

8. A pressurized dispensing unit containing a substantially clear medicated gel and a non-toxic gaseous propellant under a pressure of from about 50 to 95 p.s.i.g. in contact with said gel, said gel having a viscosity of about 10,000 cps. to about 100,000 cps. at 25° C., said gel comprising as the essentially sole therapeutic component a water soluble medicament selected from the group consisting of a vasoconstrictor, antihistamine, bronchodilator, sympathomimetic, an antitussive and mixtures thereof; from about 1% to 10%, by weight, of hydroxyethylcellulose, and at least 65%, by weight, of water, said gel being substantially free of liquified propellant.

9. A pressurized dispensing unit containing a medicated gel under a pressure of about 30 to 115 p.s.i.g., said gel comprising as the essentially sole therapeutic component a therapeutically effective quantity of a water soluble medicament selected from the group consisting of a vasoconstrictor, antihistamine, bronchodilator, sympathomimetic, an antitussive and mixtures hereof at least 50%, by weight, of water; and a sufficient quantity of a gelling agent to impart a viscosity of about 5,000 to 200,000 cps. at 25° C.

10. A pressurized dispensing unit containing a clear substantially transparent medicated gel and a non-toxic gaseous propellant under a pressure of from about 50 to 95 p.s.i.g., said gel having a viscosity of from about 35,000 to 70,000 cps. at 25° C. and being substantially free of liquified propellant, said gel comprising as the essentially sole therapeutic component a therapeutically effective quantity of a water soluble medicament selected from the group consisting of a vasoconstrictor, antihistamine, bronchodilator, sympathomimetic, an antitussive and mixtures thereof; a sufficient quantity of a gelling agent selected from the group consisting of the propylene glycol ester of alginic acid, polyvinylpyrrolidone, and hydroxyethylcellulose to impart a viscosity of 35,000 to 70,000 cps. at 25° C. to the gel and at least 65%, by weight, of water.

11. The pressurized dispensing unit of claim 10 wherein the gelling agent is hydroxyethylcellulose.

12. The pressurized dispensing unit of claim 11 wherein the propellant is nitrogen.

13. The pressurized dispensing unit of claim 12 wherein the medicament is a vasoconstrictor.

14. The pressurized dispensing unit of claim 13 wherein the vasoconstrictor is phenylephrine hydrochloride.

15. The pressurized dispensing unit of claim 12 wherein the medicament is a sympathomimetic.

16. A pressurized dispensing unit containing a medicated gel and a non-toxic gaseous propellant in contact with said gel, said propellant being gaseous at room temperature and pressures of about 30 to 115 p.s.i.g., said gel having a viscosity of from about 5,000 cps. to 200,000 cps. at 25° C. and comprising: (*a*) as the essentially sole therapeutic component, a therapeutically effective quantity of a water-soluble medicament selected from the group consisting of a vasoconstrictor, antihistamine, bronchodilator, sympathomimetic, antitussive, and mixtures thereof; (*b*) a gelling agent; and (*c*) water.

17. A pressurized dispensing unit according to claim 16 wherein said gelling agent is hydroxyethylcellulose.

References Cited in the file of this patent

UNITED STATES PATENTS

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