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SPRAYABLE COMPOSITION

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This invention relates to a sprayable ointment containing an antibiotic and/or other medicant which may be applied directly to tissue surfaces.

When the skin is irritated as for example by a burn or abrasion or other wound, it is frequently desirable to coat the surface with an ointment which contains an antibiotic. The antibiotic inhibits bacterial growth and assists in maintaining the body's defenses while tissue is being regenerated and a new skin being grown. The ointment may contain nutrients or other constituents which are useful to the body tissues in the process of regeneration, or an anesthetic to ease pain.

In the case of burns or some types of abrasive wounds, or in certain ulcerous conditions, the surface of the body is extremely tender and any spreading of an ointment may be extremely painful. Further, the spreading of an ointment may also spread contamination if present. It thus appears that the spraying of an ointment onto the surface would furnish an ideal method of application in that it is extremely convenient, prevents spreading of contamination, and is as gentle a method of application as is known.

The problem of providing a sprayable composition is quite complex. While the concept of using an ointment containing an antibiotic or other drug on the surface of a wound is quite ancient, the problem of providing a suitable composition has plagued inventors and doctors for a long time.

It has now been found that a pressurized sprayable composition may be used to coat wound surfaces. To spray well, the composition must have a viscosity which is low enough to be sprayable as an ointment at low temperatures. Propellant compositions expand on passing through a spray nozzle with a resultant cooling effect. If an ointment is used which becomes solid on such cooling or if the ointment has constituents which solidify on cooling, there is a tendency for such constituents to build up at the valve, clogging the valve and giving a distorted spray. Similarly, the ointment itself, freed from the propellant, must be sufficiently viscous to remain in place when sprayed on the skin surface. All other components in the composition must be either very soluble or very insoluble in the propellant ointment base mixture. The propellant itself affects the solubility of the components of the ointment in the pressurized spray container and in the ointment as sprayed. If any of the constituents are slightly soluble in either the ointment alone or in the ointment with the propellant, there is a tendency for such constituents to build up at the spray nozzle, clogging the nozzle. However, if the constituents are very soluble, they remain in solution or if they are very insoluble, they remain as solids without solution problems arising.

Solid components must be finely divided in order to pass through a spray orifice; and, at the same time, are preferably free from long needles which can mat or clog a spray orifice. Similarly, the solid components must not be subject to crystal growth in the propellant-ointment system. If the solid particles are subject to crystal growth during standing prior to use, the particle size may increase and at the time of use particles in the ointment-propellant composition may have become large enough to clog the valve.

All of the components must be compatible and not react or interact in such a fashion as to interfere with the therapeutic effect when used or the sprayability of the composition. Additionally, the ointment composition must consist of ingredients which are basically homogeneous and do not have variations in viscosity, at various places through the composition. Additionally, the propellant must be nontoxic.

The requirements thus can be seen to be quite rigorous and as such many problems not previously solved have risen in the preparation of sprayable ointment compositions.

In the past, antibiotics have been sprayed involving such techniques as that disclosed in U.S. Patent No. 2,782,975, J. F. Bird, "Sprayable Amorphous Antibiotic Composition, Pressurized Container With Same, and Method of Preparing," February 26, 1957. This patent discloses finely divided calcium chlortetracycline and calcium tetracycline in a pressurized dispenser using a haloalkane propellant, which may contain additional ingredients, and a local anesthetic. The same local anesthetics may be used in the present invention. Antibiotic containing ointments are disclosed in such references as U.S. Patent No. 2,804,421, Stirn and Carstensen, "Tetracycline Type Antibiotic Ointment," August 27, 1957.

A composition which meets the requirements of sprayability and therapeutic effectiveness and which is convenient to prepare in sterile form and economically practicable comprises an oil base such as mineral oil, isopropyl palmitate, isopropyl myristate or other pharmacologically acceptable oil, which contains a thixotropic hydrogenated vegetable oil, such as hydrogenated castor oil, and an antibiotic such as one of the insoluble tetracycline type antibiotics such as oxytetracycline, chlortetracycline, tetracycline, bromotetracycline, demethylchlortetracycline, or a pharmacologically acceptable salt thereof, or other antibiotics such as chloramphenicol, bacitracin, dihydrostreptomycin, erythromycin, penicillin, tyrothricin, etc., or one of the sulfonamides such as sulfadiazine, sulfamerazine, sulfamethazine, sulfamethoxypyridazine, etc.; and an enzyme such as streptokinase or streptodornase. Certain mixtures of oils and thixotropic agents are disclosed in Abrams U.S. Patent No. 2,157,379 and Veatch U.S. Patent No. 2,673,838. The composition may also contain other medicaments such as one or more of the steroids including triamcinolone as the alcohol, acetonide, diacetate, hemisuccinate, etc., cortisone, hydrocortisone, etc., and a local anesthetic and a haloalkane propellant.

The propellant needs to be one which has pressure temperature characteristics such that an economical container may be used, and, at the same time, has sufficient pressure to give a good dispersion to the ointment when in use. The haloalkanes are found to fullfill this requirement. Among the preferred haloalkanes are trichlorofluoromethane with a boiling point of about +24° C., dichlorodifluoromethane with a boiling point of about —30° C., dichlorofluoromethane with a boiling point of about +9° C., chlorodifluoromethane with a boiling point of about —41° C., 1,1,2 trichloro-1,2,2 trifluoroethane with a boiling point of about +48° C. and dichlorotetrafluoroethane with a boiling point of about +4° C. Other haloalkanes may be used. A pressure between 12 and 100 pounds per square inch gage at 25° C. gives good results.

A mixture of trichlorofluoromethane and dichlorodifluoromethane is particularly useful because the composition in a mixture of about 50–50 or 40–60 has good pressure characteristics for sprayability at room temperature and yet gives a composition which does not have an unduly high pressure with moderate temperature increases, nor does the composition lose its sprayability characteristics at moderately reduced temperatures such as en-

countered in cool weather. Higher pressure propellants such as dichlorodifluoromethane alone give good dispersion, but the spray container must be sturdy.

Compressed gases such as carbon dioxide or nitrogen can be used as a propellant when a solid stream rather than a spray is desired. For such gases, a sturdy container is required. Usually lower pressure propellants are more economical.

The mineral oil can vary from a thin to a thick oil. A medium viscosity refined mineral oil which meets pharmaceutical grade requirements is satisfactory and economical. A very thin mineral oil may require more of the thixotropic agent. A very thick mineral oil reduces the requirement for the thixotropic agent, but at the same time, tends to become less easily dispersible at lower temperatures. With the thinner mineral oils as much as 10% of hydrogenated castor oil may be used for effective viscosity control whereas with thicker mineral oils, particularly for thin ointments, as low as 1% of hydrogenated castor oil is satisfactory. With other oils, the amount of thixotropic agent used varies with the viscosity desired.

Whereas hydrogenated castor oil is a readily commercially available thixotropic agent, the same type of agent may be prepared from other sources. A considerable part of castor oil consists of ricinoleic acid, on hydrogenation the double bond becomes saturated.

Synthetic thixotropic agents such as solubilized polyethylene may be used. Such agents are disclosed in U.S. Patents 2,627,938, February 10, 1953, Frohmader and Archer, "Method of Making High Viscosity Products Having Petroleum Oil Base and Products of Such Method," and 2,628,187, February 10, 1953, Frohmader and Shoemaker, "Medicinal Mineral Oil Vehicle Thickened With Polyethylene."

Suitable thixotropic agents are those which cause the mineral oil in which dissolved to exhibit the property of thixotropy which has been defined as the property of certain gels to become fluid on shaking, and coagulating again when left at rest. The thixotropic agent in mineral oil gives an ointment composition which has very little change in viscosity with temperature and tends to set up on standing. This thixotropic property is extremely valuable in a sprayable composition used as an ointment.

A thicker oinment base is needed with suspended medicaments which are very light or very heavy, and thus tend to settle or rise in the spray dispenser.

The antibiotic or antibiotics or other medicaments to be added to the ointment base are largely a matter of choice depending on therapeutic requirements. As much as about 15% by weight may be added to the ointment base, but usually from 1 to 5% by weight of an antibiotic is a concentration preferred by the medical profession. The concentration of other medicaments varies more widely. Broad spectrum antibiotics are usually preferred. Open wounds may have a wide variety of microorganisms present and the wider the spectrum of the antibiotic the more effective. Particularly useful are the tetracycline antibiotics including chlortetracycline, oxytetracycline, bromotetracycline, and derivatives thereof.

The tetracycline type antibiotics may be present as acid salts such as a hydrochloride or hydrobromide or as a free base or as a metallic salt such as the calcium salt. Usually, the hydrochloride is found to be very effective. Additional antibiotics such as neomycin, which may be present as the sulfate salt or other acid salt or the free base are effective.

A neomycin salt of a tetracycline type antibiotic or a combination containing the same is effective. The sulfa drugs, etc. may be added. For human use, it is preferred that the composition as sold be sterile; for animal use, sterility is not as important, but it is desirable.

The composition may be prepared by simply stirring the ingredient together. More conveniently the hydrogenated castor oil or other thixotropic agent is added to part of the mineral oil, and preferably heated while being mixed. The antibiotics can be slurried in the remaining mineral oil and each part of the composition sterilized by heat and then mixed sterilely and filled. The final ointment may be heat sterilized. Less discoloration usually results if the antibiotics and other medicaments are separately sterilized and added to the sterile oil-thixotropic agent mixture. Discoloration is particularly apt to occur in the presence of water or other impurities.

In filling into the pressurized containers, the containers may be sterilized, and the ointment composition sterilized by heat or radiation. The container is filled, the container cooled, the cold haloalkane propellant added, and the container closed while at low temperature. Other filling cycles may be used such as mixing the ointment and the propellant and cold filling; or the composition may be pressure filled at higher temperatures; such methods of filling are conventional. The present composition may be filled by any of these procedures, thus being adapted to use by manufacturers who have different types of filling equipment.

Fortunately, the ointment base gives such viscosity to the contents of the pressurized dispenser that the various forms of antibiotics above-mentioned remain sufficiently uniformly dispersed throughout the dispenser that a comparatively uniform composition results. Any slight tendency towards settling of the antibiotic composition can be overcome by shaking the dispenser just prior to use.

The amount of propellant varies over a wide range. As much as 90% propellant or more of propellant gives a thin film and a well dispersed ointment. A very low propellant usage, such as 10%, gives a sprayable composition, but the spray is of much larger particles. By using a comparatively thick ointment and a small concentration of propellant, a jet of ointment can be dispensed, for uses where such a jet is considered desirable by the medical profession.

While the scope of the present invention is as defined in the appended claims, the following examples are given as illustration of certain of the preferred embodiments of the present invention.

Example 1

An ointment base is prepared by mixing 150 parts of hydrogenated castor oil and 2,850 parts by weight of pharmaceutical grade mineral oil of medium viscosity by heating at 90° C. with stirring until the solution is clear, and passing through an ointment mill as the mixture cools. To 188 parts of this ointment base is added 6 parts of neomycin sulfate ground to less than 15 microns average maximum diameter and 6 parts tetracycline hydrochloride ground to less than 15 microns average maximum diameter. The mixture is stirred at room temperature until homogeneous. 30 grams of the above composition is placed in a three ounce pressure spray dispenser, chilled, 70 grams of a cold mixture of 60% trichlorofluoromethane and 40% dichlorodifluoromethane is added, the container sealed, using standard techniques, and the mixture is allowed to come to room temperature and is shaken to uniformly disperse the ointment in the propellant. The composition sprays satisfactorily through a standard spray valve having a 0.025 inch spray orifice and when sprayed upon the surface of the skin gives a smoothe uniform homogeneous antibiotic containing ointment.

Example 2

300 grams of the ointment composition containing the neomycin sulfate tetracycline hydrochloride mixture in the preceding example is chilled and mixed cold with 700 parts of a 60–40 propellant mixture of trichlorofluoromethane and dichlorodifluoromethane. The cool mixture is filled into spray dispensers, the dispenser sealed and allowed to attain room temperature. The spray dispenser thus filled dispenses a satisfactory ointment spray.

Example 3

Example 1 is repeated except that only 1% each of

neomycin sulfate and tetracycline hydrochloride are added to the composition. The composition is a thoroughly satisfactory ointment spray having a comparatively low antibiotic content. The color of the ointment is not very pronounced but the ointment sprays well and spreads evenly over the surface of the wound.

Example 4

The procedure of Example 1 is followed except that only 50 grams of the propellant mixture is added. An easily sprayable composition results. The ointment when sprayed appears to have a few bubbles in it.

Example 5

An ointment composition is prepared by dissolving 175 grams of hydrogenated castor oil and 9,825 grams of mineral oil by heating to 90° C. and stirring until uniform and cooling to room temperature. To this ointment base is added 3% tetracycline hydrochloride and 3% tetracycline neomycin sulfate. This mixture is then passed through a Manton-Gaulin homogenizer. 30 grams of the antibiotic containing ointment and 20 grams of a 60–40 trichlorofluoromethane and dichlorodifluoromethane propellant is added cold to a dispenser. A glass dispenser having a metering valve is used as the container. A comparatively coarse ointment spray is formed which is easily and conveniently applied to the surface of the wound.

Example 6

2½% by weight of hydrogenated castor oil is incorporated in mineral oil. To this base is added 5% chlortetracycline hydrochloride and 5% neomycin sulfate, both of the antibiotics being finely divided. The composition is filled into dispensing containers, chilled and thereto added an equal weight of the 60–40 propellant composition above-mentioned; the dispenser is closed and allowed to attain room temperature, and then shaken to insure uniform dispersion of the ointment and antibiotics in the propellant. The resulting container dispenses a uniform ointment spray which is easily applied to the surface of the wound.

Example 7

The preceding experiment is repeated using 40% by weight of dichlorodifluoromethane alone as the propellant. The spray and ointment are satisfactory.

Example 8

7 kilograms of mineral oil is heated to 90° C. and thereto is added 495 grams of hydrogenated castor oil. The mixture is stirred and then heated to 120° C. for 10 hours, then cooled with agitation. 1270 grams of mineral oil is mixed with 94.5 grams of tetracycline hydrochloride and 140.5 grams of finely divided neomycin sulfate. The composition is heated at 110° C. for 10 hours. The two compositions are blended together under sterile conditions and aseptically filled into sterile pressure dispenser containers. 30 grams are filled into each container. The container is chilled, and 70 grams of the 60–40 propellant above referred to is introduced and the can sealed. A satisfactory sprayable composition and dispenser is obtained resulting in a smooth uniform dispersion of the antibiotic containing ointment.

Example 9

A composition is prepared using 5% hydrogenated castor oil in mineral oil base with 5% of O,O-dimethyldithiophosphate of diethyl mercaptosuccinate, 5% of sorbitan mono-oleate, 0.3% of Dodge & Olcott #40R 4770 deodorant and 1% of cedar pine oil.

The composition is chilled and 30 grams of ointment are mixed with 70 grams of a 50–50 mixture of trichlorofluoromethane, dichlorodifluoromethane and filled into cans. A satisfactory spray is dispersed after warming to room temperature and shaking.

Example 10

100 parts by weight of sesame oil is mixed with 2.5 parts of hydrogenated castor oil at 90° C. and after thorough mixing, cooled to room temperature with agitation. An additional 100 parts of sesame oil is homogenized with 5 parts rotenone, 10 parts of iodochlorohydroxyquinoline, 11 parts of tetracycline hydrochloride, 5.5 parts neomycin sulfate, 5.0 parts of benzocaine, and 0.3 part of mixed tocopherols. After blending, the two compositions are mixed together and diluted to 500 parts by volume with sesame oil. 25 grams of the ointment and 75 parts of a mixture of 60% trichlorofluoromethane and 40% dichlorodifluoromethane are filled into pressurized spray dispensers by filling the ointment first chilling and then adding the cold propellant, sealing and allowing the sealing dispenser to warm up after which it is shaken.

Example 11

An ointment base is prepared by mixing 500 grams of hydrogenated castor oil and 6,700 grams of isopropyl myristate, heating to 90° C. with agitation until the solution is clear, allowing the solution to cool to 30° C. and adding slowly, with agitation 1000 grams methylsalicylate, 500 grams eugenol, 100 grams menthol, and 1500 grams ethyl aminobenzoate, having a particle size not greater than 15 microns. The mixture is passed through a homogenizer. Thirty grams of the mixture is placed in a three ounce aerosol container, seventy grams of a cold mixture of 60% trichlorofluoromethane and 40% dichlorodifluoromethane added, and the container sealed using standard techniques. The container is allowed to come to room temperature and shaken prior to usage to insure uniform dispersion.

Example 12

An ointment is prepared by mixing 100 grams of hydrogenated castor oil and 870 grams of isopropyl palmitate, heating to 90° C. with agitation, cooling to 30° C., and slowly with agitation, adding 10 grams triamcinolone acetonide and 20 grams pyrilamine maleate, both having particle size of less than 15 microns. The mixture is stirred until homogeneous and passed through a homogenizer. 20 grams of the mixture is filled in a container and 80 grams of a cold mixture of 40% dichlorodifluoromethane and 60% dichlorotetrafluoroethane is added. The container is sealed and allowed to come to room temperature. A good spray is obtained from the dispenser for wound or burn treatment.

Example 13

An excellent sterile ointment for use on wounds or burns is prepared by adding 50 grams of hydrogenated castor oil to 870 grams of light liquid petrolatum and heating to 110° C. for 10 hours, then sterilely cooling. 30 grams of demethylchlorotetracycline and 50 grams of chloroprocaine both having a particle size of less than 15 microns are mixed, then sterilized using ethylene oxide gas and added aseptically to the cooled ointment base at 30° C. Containers are sterilized by heating at 110° C. for 10 hours. The valves are ethylene oxide sterilized. 30 grams of the ointment is filled aseptically into the sterile containers and 70 grams of a cold, sterile filtered mixture consisting of 50% trichloromonofluoromethane and 50% dichlorodifluoromethane added, and the container sealed with a sterile valve under aseptic conditions. A sterile spray, suitable for open wounds, is obtained.

Example 14

57 grams of mineral oil and 40 grams of solubilized polyethylene are mixed together and heated to 110° C. for 10 hours. Under sterile conditions, 3 grams of sterile demethylchlortetracycline as the free base is added to the sterile mineral oil-polyethylene mixture at room temperature. The mixture is passed through a homogenizer and filled into sterile aerosol containers. 30 grams of the composition is placed in each sterile container. The con-

tainer is chilled, then 70 grams of a cold sterile mixture of 50% dichlorodifluoromethane and 50% trichloromonofluoromethane is added. A valve, sterilized with ethylene oxide, is placed on the container and sealed thereto. The sealed container is allowed to reach room temperature and then shaken to disperse the ointment in the propellant. A sterile demethylchlortetracycline ointment spray suitable for open wounds is obtained.

Example 15

5.5 parts of hydrogenated castor oil and 91.5 parts of light liquid petrolatum are placed in a stainless steel drum equipped with baffles, the drum is closed, and rotated in an oven at 110° C. for 10 hours and then allowed to cool to room temperature with the drum constantly rotating. Under sterile conditions, the lid is removed from the drum and 1.5 parts of sterile tetracycline hydrochloride ground to less than 5 microns particle size is added. 1.5 parts of neomycin sulfate also sterile and ground to a particle size of less than 5 microns is added. The drum is closed and rotated for one hour on a drum tumbler and 4 hours on a drum roller. Under sterile conditions the ointment is passed through a homogenizer at 3,000 pounds per square inch and then aseptically filled into aerosol dispenser containers. 34 grams is filled into each container. The containers are sterilized by heating before filling. A 60–40% mixture of trichlorofluoromethane and dichlorodifluoromethane is chilled, passed through a bacterial filter, and filled into the cooled cans. 73 grams are filled into each can.

Valves are sterilized with an ethylene oxide-carbon dioxide mixture and held sterile until ready for assembly. Each container is closed with a sterile valve and the valve is sealed onto the container. The sealed container is allowed to attain room temperature and shaken to uniformly disperse the ointment in the propellant. The sealed containers can be tested by placing in a water bath at about 150° F. for 3 minutes to check for leakers. If tested for leakers by immersing in water, the containers are dried before use. The dispensers are found to deliver a soft, finely divided spray suitable as a sterile covering for a burn or open wound.

Inasmuch as the above examples are given by way of illustration and not by way of limitation, it is to be understood that a wide variation of antibiotic concentrations may be used and local anesthetics or other therapeutic agents may be added providing that such agents are either soluble in the propellant ointment composition or completely insoluble in the same, and dispersed in finely divided form, so that the particles will pass through spray valves without clogging.

We claim:

1. A pressurized dispenser container having therein from 10 to 90% of a haloalkane propellant, said haloalkane having not more than 4 carbon atoms, and the halogens selected from the group consisting of fluorine and chlorine, an ointment base containing from 0.5% to 10% of hydrogenated castor oil in mineral oil and from 1 to 15% of the ointment base weight of at least one antibiotic selected from the group consisting of the free base antibiotics tetracycline, chlortetracycline, bromotetracycline, demethylchlortetracycline, bacitracin, neomycin and a therapeutically effective salt of the free base.

2. A pressurized dispensing container having therein a lower haloalkane propellant, said haloalkane having not more than 4 carbon atoms, and the halogens selected from the group consisting of fluorine and chlorine, a hydrogenated castor oil-mineral oil ointment base, and a finely divided therapeutically effective antibiotic.

3. The dispenser of claim 2 in which the antibiotic is a mixture of tetracycline hydrochloride and neomycin sulfate.

4. The dispenser of claim 2 in which the antibiotic comprises demethylchlortetracycline.

5. A pressurized dispensing container containing from 10 to 90% of a propellant consisting of dichlorodifluoromethane and trichloromonofluoromethane; mineral oil, hydrogenated castor oil, and from 1 to 15% by weight of the sum of the oils of a finely divided antibiotic.

6. A pressurized dispenser container having therein from 10 to 90% of a lower haloalkane propellant, said haloalkane having not more than 4 carbon atoms, and the halogens selected from the group consisting of fluorine and chlorine, an ointment base consisting essentially of mineral oil and a thixotropic agent selected from the group consisting of hydrogenated castor oil and polyethylene, and from 1 to 15% of the ointment base weight of a steroid.

7. The dispenser of claim 6 in which the steroid is triamcinolone in a therapeutically effective form.

8. A method of preparing a pressurized dispenser containing a sterile, sprayable, therapeutically-effective antibiotic ointment which comprises: mixing approximately 50 parts of hydrogenated castor oil and approximately 870 parts of light liquid petrolatum and heating to about 110° C. for at least 10 hours, and then sterilely cooling; separately mixing approximately 30 parts of demethylchlortetracycline and 50 parts of chloroprocaine having a particle size of less than 15 microns, and sterilizing the mixture using ethylene oxide gas; separately sterilizing the containers by heating; separately sterilizing the valves by ethylene oxide; under sterile conditions mixing the chloroprocaine - demethylchlortetracycline mixture with the petrolatum containing the hydrogenated castor oil, sterilely filling the ointment composition thus formed into the sterile containers and sterilely adding at the ratio of approximately 70 parts of propellant to 30 parts of ointment a sterile, filtered mixture of trichloromonofluoromethane and dichlorodifluoromethane, while cold, and inserting and sealing the sterile valve into the container, thereby forming a pressurized dispenser containing a sterile composition which dispenses a sterile antibiotic-containing ointment.

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