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METHOD OF PREPARING A TETRACYCLINE TYPE ANTIBIOTIC-CONTAINING WOUND DRESSING

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1 Claim. (Cl. 167—84)

This invention relates to a wound dressing satisfactory for surface wounds, for example burns, abrasions, skin grafting sites, or after surgery. We have prepared a sterile dressing consisting of a broad-spectrum tetracycline type antibiotic in an anhydrous ointment base, which forms a water-in-oil emulsion, on a gauze dressing or other backing and which can be applied directly to a wound, and may be stored, ready for instant use, in a sealed sterile container. Our invention also includes the method of preparation of the dressing, and the container for the dressing.

In the past it has been frequently customary to spread a petroleum jelly on a sterile gauze for application to a wound such as a burn. Unfortunately petroleum jelly does not absorb moisture and is incompatible with aqueous fluids, and causes maceration. A wound has small accumulations of moisture that support bacterial growth and interfere with healing underneath the dressing and as a result the dressing must be changed and healing is retarded.

We have prepared a sterile, sealed package containing a carrier for an ointment, which ointment is essentially anhydrous. The ointment is a special type which, on admixture with water, forms a water-in-oil emulsion, thereby providing a wound dressing which (1) keeps the wound dry, (2) minimizes maceration, (3) releases a broad-spectrum tetracycline type antibiotic over a long period, and (4) minimizes the adherence of the dressing to the wound. Because plasma or other aqueous fluid is absorbed into the emulsion to form a cream and is removed from the wound, the wound is kept sterile, clean, and dry, and therefore heals more rapidly than has been possible with previously known types of dressings.

The backing or carrier for our ointment may be a surgical gauze of cotton, nylon, cellulose acetate, etc., or may be a more tightly woven cloth, or may be an absorbent cotton, preferably felted, or other unwoven fabric, or may be of a plastic material, as for example, an oil resistant synthetic rubber or porous plastic or other material. It is preferred that the mesh be fairly fine to reduce the possibility of tissue growth through the interstices. We normally prefer a cotton gauze with about a 44 x 36 inch thread count because it has met with the greatest acceptance by the medical profession, is a standard commercial item and is very economical. Such a gauze is very soft and flexible and may be removed from the wound with a minimum of lint being left. Whereas we prefer such gauze, it is to be understood that other types of carriers may be used where desired.

Whereas most dispersing agents tend to produce an oil-in-water type of emulsion, we have found that we can obtain a reversed type of emulsion by using anhydrous lanolin, preferably acid washed lanolin, and a dispersing agent such as glyceryl monostearate or a cholesterol ester. Glyceryl monostearate is economical and available, but other glyceryl mono-esters of long chain fatty acids are good dispersing agents. Glyceryl monolaurate is another useful commercially available such dispersing agent. The glyceryl monostearate and anhydrous lanolin should be

suspended in an oil base. We prefer a mixture of white or yellow petrolatum and mineral oil together with a wax such as ceresin wax or beeswax or paraffin wax. Agar plate tests show that broad-spectrum tetracycline type antibiotics in the ointment diffuse slightly more rapidly when ceresin wax is used rather than beeswax or paraffin wax. The ratios of the petrolatum, the mineral oil and the wax should be chosen so that when combined with the dispersing agent and the anhydrous lanolin, there is obtained an ointment base which is fluid at just slightly above body temperatures. The preparation may melt between about 33 and 44° C. and preferably between 37 and 43° C. Those skilled in compounding can adjust the proportions of the mineral oil, the petrolatum and the wax so that the melting point is within this desired range.

Our ointment may be compounded with any of the broad-spectrum tetracycline type antibiotics, or mixtures of them, in a therapeutically useful form. The first discovered of the tetracycline type antibiotics were chlortetracycline and oxytetracycline. A broad-spectrum antibiotic such as chlortetracycline may be present as a salt with an acid, such as the hydrochloride salt or the sulfate, as a free base, or a salt with a metallic or nitrogen base or any other stable therapeutically effective form such as the lauryl sulfate or aluminum glycinate salts. We normally prefer to use chlortetracycline hydrochloride as it is readily available commercially and is a form of such a broad-spectrum antibiotic which may be easily and conveniently micropulverized, stored, and utilized. The exact degree of pulverization may vary but a satisfactory form of dispersion is found to be one in which approximately 35% by weight is within the range of 5 to 10 microns, approximately 60% within the range of 3 to 5 microns and approximately 5% less than 3 microns.

The ointment may be spread on the carrier, and the finished dressing, such as gauze with the ointment, stored in a suitable sterile container. We have found that an aluminum foil container which is laminated on the inside to a film of a copolymer of vinyl chloride and vinyl acetate by a suitable adhesive, provides a heat sealable coating on the inside of the foil and gives a readily sealable sterile envelope.

In the preparation of our product we prefer to use a surgical gauze, such as a boiled and bleached gauze of 44 x 36 thread count, which normally contains 6 or 7% of moisture. It may be placed in the aluminum foil envelope which is sealed on three sides and sterilized while open on one end at a temperature of approximately 110° C for 10 hours, which dries and sterilizes both the gauze and the envelope.

We prefer to mix the glyceryl monostearate, anhydrous lanolin and white petrolatum and ceresin wax, and if desired, a portion of the mineral oil, by blending them together in an ointment mill until they are thoroughly intermixed and then sterilize them at a temperature of 110° C. for 10 hours. Separately, chlortetracycline hydrochloride is micropulverized and homogenized with the mineral oil, or rest of the mineral oil, and the mixture sterilized at 110° C. for 10 hours. The two parts of the ointment may then be mixed under aseptic conditions so as to maintain their sterility, and the required amount of the sterile finished ointment is then applied to the sterile gauze in the aluminum foil envelope while maintaining sterility. The air may then be pressed out of the envelope and the envelope sealed along the open edge by a sealing machine at a suitable temperature, such as about 200° C. After the ointment is added to the gauze in the envelope and the envelope sealed, it may then be uniformly heated to about 50 to 60° C. and the envelope rolled while warm lightly but firmly once or twice at right angles so as to distribute the ointment uniformly over the gauze.

We also find that our ointment may be melted, and while maintained melted, the gauze or other carrier may be passed through the liquid so as to impregnate the carrier. The temperature of the liquid and speed with which the gauze or carrier is passed through, and the nature of the carrier determines the amount of ointment on the carrier. A fine mesh gauze will carry more ointment than a coarse mesh gauze. A doctor blade or squeegee may be used to assist in the control of the amount applied. These operations should be carried out sterilely so that the continuous gauze strip thus formed may be cut into segments and packed sterilely into containers.

The final product is sterile and gives a chlortetracycline-containing ointment which may be used to treat a wound. As the chlortetracycline is released into the tissue fluid, the ointment base permits the diffusion of aqueous fluids. Any ointment which remains after use of the dressing can be removed from the surface of the wound by washing with water.

It is found that the inhibition of bacterial growth on an agar plate with our dressing is much greater than that obtained by conventional types of dressings, as our dressing permits diffusion of the antibiotic to a far greater extent than conventional dressings.

Our product may be maintained at 56° C. for two weeks without appreciable destruction of the chlortetracycline. This corresponds to between two and three years aging under normal storage conditions and proves that the product is storage stable under normal commercial conditions of use.

The exact composition of the burn dressing ointment may vary over rather wide limits. For example, the glyceryl monostearate may be present in proportions from 1 to 10%, the lanolin from 5 to 20%, the petrolatum from 10 to 30%, the wax from 5 to 20%, the mineral oil from 30 to 60% and the chlortetracycline from 0.1 to 5%. The variation in the various components is such that the sum total is 100% and the melting point is between 33 and 44° C., preferably between 37 and 43° C. Adjusting the quantity of wax is particularly effective in adjusting the melting point to the desired limits.

In the formulation of the product, the broad-spectrum tetracycline type antibiotic may be ground to the desired particle size before it is mixed with the mineral oil, or it may be ground in the mineral oil.

The broad-spectrum tetracycline type antibiotics, such as chlortetracycline hydrochloride, seem to control undesired bacterial growth and it has been demonstrated clinically that the use of our ointment in a dressing causes the destruction of hemolytic organisms responsible for delaying the healing of wounds and for preventing the take of skin grafts. The dressing may be either used on a wound which has present such bacterial growth to control the growth, or as a prophylactic measure on clean wounds to inhibit and prevent undesired bacterial growth. Such materials as the alkyl esters of para-hydroxybenzoic acid may be incorporated with the broad-spectrum antibiotic if the growth of monilia is a problem.

Unlike so many of the sulfa drugs and previously used materials, the broad-spectrum tetracycline type antibiotics do not interfere with wound healing or epithelialization. The effect of the broad-spectrum tetracycline type antibiotics, such as chlortetracycline hydrochloride, is most amazing and the increased speed of wound healing may be in fact partly due to the antibiotic itself. The dressing usually does not adhere to the wound even if left for one or two weeks without being disturbed and during this time maintains a high concentration of the antibiotic. With chlortetracycline, a concentration is obtained which is sufficient to control the growth of even such resistance organisms as Proteus.

The quantity of the ointment used on the dressing may vary over wide limits. We find that from 15 to 20 milliliters of the ointment provides a very satisfactory coating for an 8 x 12 inch single layer surgical gauze bandage. A much lesser amount may be used for thinner bandages or less serious wounds, and a greater quantity may be used with a multiple layer bandage or where the impregnated layer forms part of a multiple layer bandage.

We find that a single layer bandage prepared in accordance with our invention may be removed from its sterile container and placed in contact with the surface of the wound and then backed by surgical sponges or multiple layers of gauze bandages, and then wrapped with an elastic bandage to serve as a pressure dressing. Such a dressing on even deep burns may be left in place for a week or two and at the end of that time most wounds will have been found to have completely healed.

By way of illustration, but not limitation, certain examples of our invention are herewith set forth.

EXAMPLE 1

Ointment

5 grams of glyceryl monostearate, 10 grams of anhydrous lanolin, U. S. P., 20 grams of white petrolatum, U. S. P., and 15 grams of refined ceresin wax be mixed in an ointment mill at a temperature of 100° C. until a smooth, thin, homogeneous mixture is obtained. The mixture may then be heated at 110° C. for 10 hours.

Separately, there is prepared a mixture of 49 grams of mineral oil U. S. P. and 1 gram of chlortetracycline hydrochloride which has been micropulverized. The chlortetracycline hydrochloride is mixed with the mineral oil, then sterilized at 110° C. for 10 hours.

The two sterile mixtures are mixed under aseptic conditions at room temperature until a smooth, homogeneous ointment is obtained. The ointment is stored sterilely and handled sterilely throughout.

EXAMPLE 2

Complete dressing

A single layer 8 x 12 inch gauze dressing of a 44 x 36 thread count may be folded in accordance with usual procedures and fitted into a 3 x 4 inch envelope prepared from a thermosealing plastic-lined aluminum foil sealed together on three sides. The folded gauze in the envelope is sterilized at 110° C. for 10 hours which dries and sterilizes both the gauze and the envelope. Aseptically there may be then added 15 milliliters of the ointment prepared in accordance with the preceding example. The envelope is then sealed along the open edge.

The ointment may be evenly dispersed throughout the dressing by heating the sealed envelope to 55° C. and rolling twice in each direction with a rolling pin. The ointment in the dressing as thus prepared is evenly dispersed and the dressing is ready for application to a burn or other wound. The envelope may be stored until needed for use. At the time of use the foil envelope should be torn open and the bandage removed under sterile conditions and applied to the wound.

EXAMPLE 3

3 grams of crystalline chlortetracycline hydrochloride may be ground in 30 grams of mineral oil until the chlortetracycline hydrochloride is pulverized to a particle size predominantly between about 3 and 10 microns. The pulverized material in the mineral oil is heated at 110° C. for 10 hours. A second sterile mixture may be prepared containing 5 grams of glyceryl monostearate, 10 grams of anhydrous lanolin, 20 grams of white petrolatum, 15 grams of ceresin wax and 27 grams of mineral oil. This mixture is ground in an ointment mill until homogeneous and then sterilized at 110° C. for 10 hours. The two sterile mixtures are combined under aseptic conditions at room temperature to provide a smooth homogeneous sterile ointment. The ointment may be heated to 50° C. and therethrough passed a continuous surgical gauze approximately 4" wide. The amount of ointment on the gauze may be controlled by passing the dressing between

rolls. The ointment may be applied at the rate of approximately 1 milliliter to each 5 square inches of the dressing. The dressing may be then stored in a sterile jar until ready for use.

EXAMPLE 4

5 grams of glyceryl monostearate, 10 grams of anhydrous lanolin, 20 grams of white petrolatum and 15 grams of refined ceresin wax may be mixed in an ointment mill until a smooth homogeneous mixture is obtained, and then sterilized at 110° C. for 10 hours. Separately, there may be sterilely prepared a mixture of 47 grams of sterile mineral oil and 3 grams of sterile oxytetracycline hydrochloride which has been micropulverized. The oxytetracycline is mixed with the mineral oil and to this sterile mixture there is sterilely added the mixture above recited. The sterile mixture may then be added to a gauze dressing at the rate of ¼ of a milliliter per square inch and the dressing stored in a sterile container until ready for use.

EXAMPLE 5

1,650 grams of micropulverized chlortetracycline hydrochloride are suspended in about 20 liters of mineral oil in a colloid mill set at 0.002". The mixture may then be heated to sterilize it. A second mixture may be prepared containing 11,550 grams of anhydrous lanolin, 17,325 grams of ceresin wax, 23,100 grams of white petrolatum, 5,775 grams of glyceryl monostearate and the remainder of sufficient light liquid petrolatum so that a total of 90,600 grams are present in both mixtures, the mixture stirred until homogeneous, and then sterilized. The two mixtures may then be blended, preferably at room temperature and applied to surgical gauze at the rate of approximately ⅛ of a milliliter per square inch. The thus prepared gauze may be cut into individual bandages, sterilely inserted into foil containers and the individual foil containers sealed. The thus prepared wound dressing may be sterilely stored in the hermetically sealed foil containers until ready for use.

The ointment itself is described in greater detail and claimed in our co-pending application, Serial No. 222,729 filed April 24, 1951.

Where percentages are specified in the appended claim, such percentages are based upon the final ointment composition which is applied to the carrier.

As our invention we claim:

The method of preparing an anhydrous, storage stable, sterile, broad-spectrum antibiotic-containing wound dressing which comprises mixing from 1 to 10% of glyceryl monostearate, from 5 to 20% of anhydrous lanolin, from 10 to 30% of petrolatum, from 5 to 20% of wax, and from 0% to about 25% mineral oil, and sterilizing the mixture by heating, separately mixing and sterilizing by heating from 0.1 to 5% of a micropulverized broad-spectrum tetracycline type antibiotic in sufficient mineral oil so that a total of from 30 to 60% of mineral oil is present, the proportions being such that the melting point of the final mixture is between 33° and 44° C., sterilely mixing together the two thus prepared sterile mixtures, inserting a folded gauze carrier in a sealable foil envelope under non-sterile conditions, heat sterilizing said folded gauze carrier in said envelope together with the envelope, adding the sterile mixture sterilely to said sterile sealable foil envelope having therein said sterile gauze carrier, sealing said envelope, and dispersing the mixture uniformly over said carrier.

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