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POWDERED OINTMENT BASE OF METHYL CELLULOSE AND SORBITOL

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1 Claim. (Cl. 167—63)

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This invention relates to new therapeutic preparations and more particularly refers to dry, stable therapeutic powders capable on addition of water of rapid transformation into gelatinous ointments or ointment vehicles.

It is well known in the pharmaceutical field that the formulation, storage, and dispensing of drugs in water-miscible solid vehicles has presented such extraordinary difficulties that hydrophilic ointments have been very little used. Wet jellies such as starch paste and colloidal suspensions of the soluble proteins and vegetable gums not only are bulky and tend to "leak" as a result of syneresis, but often give rise to various forms of microbial deterioration. Moreover, they tend to dry out, thus defeating the purpose for which they were compounded. Once dried, it is well known that such ointment bases are not easily rehydrated to give jellies having the proper texture.

Notwithstanding the foregoing difficulties, ointment bases of hydrophilic character have been demonstrated repeatedly to be useful in releasing medicaments for absorption through the skin, when applied to local areas of the body. For example, extensive experiments in the use of sulfa drugs have indicated the superiority of water-dispersible preparations for the application of these compounds. In the same manner, clinical tests have demonstrated the value of hydrophilic ointments as a means of bringing powerful antibiotics into contact with surfaces of the body. A special problem in this connection is removal of necrotic tissue from the site of burned tissue. The removal of such tissue is important to avoid infection and permit granulation of new tissue which protects and heals the wound. In the past, mechanical debridement of burns by scrubbing or surgery was common, but it caused considerable pain and increased the danger from shock. In addition, it has been found to damage or remove residual islands of epithelial cells capable of regenerating new tissue.

In an endeavor to avoid the disadvantages of the customary mechanical debridement treatment for burns, attempts have been made to remove necrotis tissue therefrom by chemical means. G. Connor and S. C. Harvey (Ann. Surgery 120, 362 (1944)) found that jells containing organic acids such as pyruvic acid or succinic acids cause removal of slough in a single tough pellicle, leaving a clean granulating surface. Connor and Harvey used cornstarch paste containing pyruvic acid in a sufficient concentration to yield a jelly having a pH of 1.9. Serious objections, however,

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were encountered in the general use of such an ointment since the prepared paste was biologically unstable and it was troublesome to prepare it in fresh condition as needed.

From the foregoing it is evident that despite the great need for hydrophilic ointments, the difficulty of storing them or preparing them when needed has been such that these ointments have not received the widespread use which their effectiveness warrants. This is true not only for ointments which are particularly adapted for the treatment of burns but also for hydrophilic ointments generally as vehicles for the application of medicaments to the skin.

It is an object of this invention to produce an entirely new class of easily wettable therapeutic ointment powders. It is a further object to produce ointments in powder form that are compact, biologically and chemically stable, and easily and quickly convertible on addition of water into therapeutically active jellies suitable for the treatment of wounds. A still further object is to produce an ointment vehicle in powder form having the aforesaid properties, to which may be added whatever medicament is desired at the time of use. Additional objects will become apparent from a consideration of the following description and claims.

These objects are attained in accordance with the present invention by mixing a cellulose ether with a wetting agent and finely comminuting the mixture either before or after incorporation therein of the desired medicament. In a more restricted sense this invention is concerned with dry, stable therapeutic powders which speedily dissolve in water to form jellies capable of producing an adherent coating over wounds comprising a finely comminuted cellulose ether throughout which is uniformly incorporated a wetting agent, and if desired, a medicament. In its preferred embodiment the cellulose ether is methyl cellulose and the wetting agent is sorbitol.

Ethers of cellulose have been found to be surprisingly satisfactory swelling agents for the powders of this invention since they are substantially unattacked by microorganisms, remain stable when stored under widely varying conditions, and form excellent jellies when dissolved in water. Unfortunately, cellulose ethers are notoriously slow in dissolving in water, as a result of which their application for therapeutic purposes has been seriously retarded. For instance, when a chemist wishes to make an aqueous solution of methyl cellulose he ordinarily soaks it in cold water in a refrigerator overnight. If one adds

sorbitol or some other wetting agent to the water the time required to dissolve the cellulose ether is not substantially lowered.

We have found that by mixing sorbitol or other suitable wetting agent with the cellulose ether and finely comminuting the mixture in a hammer mill or other efficient grinding device, a dry, stable powder is obtained which dissolves in water almost instantaneously, in contrast with the inordinate periods formerly considered to be essential. In accordance with this invention, the powdered cellulose ether may be mixed in a dry form with a wetting agent to which has been added, if desired, a medicament, and the mixture thereafter finely comminuted by passing through a hammer mill or similar device. However, optimum results are obtained if the cellulose ether is first added to an aqueous solution of the wetting agent (with or without medicament) and the mixture stirred for a prolonged period until a homogeneous ointment is formed. Thereafter this ointment is dehydrated in thin layers, such as by spreading the mixture on sheets of glass in layers about one-half centimeter thick and drying for 24 hours in an oven at about 75° C. The dehydrated sheets thus produced are then finely comminuted in a pulverizing mill. The resulting powder has the surprising property of completely redissolving in water in approximately 1 minute, so that it can be converted to an ointment whenever needed, and if desired medicament may be added at the time of use.

By the unique methods referred to above we have succeeded for the first time in preparing dry, easily wettable, biologically stable, solid therapeutic ointment bases wherein the gelling agent is a cellulose ether. These powders may have the medicament incorporated therewith before comminution in the manner referred to previously, or if an all-purpose ointment vehicle is desired the medicament may be omitted, to be added at the time of use. Preparation of these powders with methyl cellulose, hydroxyethyl cellulose or other cellulose ethers as the gelling agents, imparts specific desirable characteristics to the resulting ointments. These agents have good body and cling to undersurfaces without tendency to flow. They are free from irritation and are inert towards microbial attack. Their viscosities may be varied within a wide range by varying the amount of wetting agent and the amount of water added thereto.

While methyl cellulose is a preferred cellulose ether, it has been found that ethyl cellulose, propyl cellulose, and related ethers may be employed. Likewise, substituted cellulose ethers such as hydroxyethyl cellulose and cellulose glycollic acid may be used. These cellulose ethers may be employed alone or in admixture with one another, and it is contemplated that other gelling agents may be added thereto although for optimum results it is preferred to employ only cellulose ethers for this purpose.

Sorbitol is the preferred wetting agent. However, other wetting agents may be employed and in particular those wetting agents commonly known as non-polar or non-ionic wetting agents. The non-ionic wetting agents may be illustrated by the well known polyhydric alcohols and their ethers and esters. Since sorbitol is a solid, nontoxic material it is ideally suited for employment as a wetting agent in the compounds of this invention.

The grinding operation which is essential to finely comminute the cellulose ether and wetting

agent may be carried out in a variety of standard mills such as the micropulverizer, the ball mill, the hammer mill, the burr mill, or the micronizer.

This invention may be more readily understood by a consideration of the following illustrative examples wherein the quantities, unless otherwise indicated, are stated in parts by weight.

Example 1

One hundred parts of methyl cellulose and 20 parts of an 85% aqueous solution of sorbitol was thoroughly mixed and passed several times through a hammer mill. The product was a fine white powder. Whereas the original methyl cellulose dissolved very slowly, it was found that the fine powder produced as aforesaid could be easily wetted in less than a minute.

Example 2

One hundred parts of methyl cellulose was incorporated with 20 parts of Xynomine (wetting agent) and 9.5 parts of pyruvic acid. The mixture was finely ground in a hammer mill until the whole mass would easily pass through a fine screen. The resulting fine white powder had a fluffy appearance and swelled rapidly in eight parts of water to give a sticky semitransparent paste of a proper consistency for application as an ointment. The acidity of the aqueous ointment measured pH 1.87. The ointment was found to be very effective when applied as a dressing for the debridement of thermal or chemical burns.

Example 3

One hundred parts of methyl cellulose, 20 parts of 85% sorbitol syrup, and 12.3 parts of pyruvic acid was thoroughly mixed and passed through a pulverizing mill. The resulting fine powder wetted with water in 2 minutes to give a clear jelly, having a pH of 2.28. Similarly, another acid debridement composition was prepared by substituting 16.7 parts of phosphoric acid for the pyruvic acid used above. The pH of this composition was 1.6.

Example 4

One hundred parts of high viscosity hydroxyethyl cellulose was formulated with 8.9 parts of pyruvic acid and 25 parts of Arlacel C (wetting agent). After thorough grinding in a pulverizing mill the mixture dissolved to a clear jelly in a matter of a few minutes as compared with several hours for the untreated hydroxylethyl cellulose.

Example 5

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of water were mixed with a mechanical stirrer until a homogenous mixture was obtained. One hundred and nine parts of colloidal sulfur was thoroughly incorporated in the gel, and the smooth paste was dried on glass plates in thin layers at 75° C. for twenty-four hours. The dry film was ground to a fine powder to form a medicated base that could be quickly wetted with the calculated amount of water to form a five per cent sulfur ointment.

Example 6

Fifty parts of methyl cellulose, ten parts of sorbitol, and six hundred and sixty-seven parts of water were mixed with a mechanical stirring device until a homogenous gel was formed. Three and six-tenths parts of local anesthetic, procaine-hydrochloride, was added and mixed thor-

oughly with the gel. After drying in thin layers at 75° C. for twenty-four hours, the mass was finely pulverized. The resultant dry powder speedily wetted with water to form an ointment wtih local anesthetic properties.

Example 7

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of water were mixed with a mechanical stirring device until a homogenous gel was formed. Ten and nine-tenths parts of ephedrine hydrochloride dissolved in three hundred parts of water was added and mixed thoroughly with the gel. The mass was dried in thin layers at 75° C. for twenty-four hours and then finely pulverized. On wetting with water, the powder dissolved rapidly to form a clear ointment with vasoconstrictor properties.

Example 8

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of water were mixed in a power driven mixer until a homogenous gel was formed. Two hundred and eighteen parts of finely powdered salicylic acid and one hundred and nine parts of finely powdered benzoic acid were added and mixed thoroughly with the gel. The mass was dried in a stream of warm air 100° C. until a dry film was obtained and then finely pulverized. The resultant dry powder was easily wettable with water to form an ointment useful for treatment of skin diseases.

Example 9

One hundred parts of methyl cellulose, twenty parts of sorbitol, one thousand three hundred and thirty-three parts of water were mixed with a mechanical stirring device until a homogenous gel was formed. Seventy-two parts of finely powdered yellow mercuric oxide were added and mixed thoroughly with the gel. The mass was dried in thin layers at 75° C. for twenty-four hours and then finely pulverized.

Example 10

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of water were mixed with a mechanical stirring device until a homogenous gel was formed. Twenty-one and eight-tenths parts of lactic acid was added and mixed thoroughly with the gel. The mass was dried in thin layers at 75° C. for twenty-four hours and then finely pulverized. The resultant dry powder speedily wetted with water to form an ointment with contraceptive properties.

Example 11

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of water were thoroughly mixed over a period of time sufficient to swell and uniformly incorporated them into a homogenous gel. One hundred and nine parts of argyrol dissolved in five hundred parts of water were added and mixed thoroughly with the gel. The mass was dried and then finely pulverized. The resultant dry powder readily wetted with water to form an ointment with antiseptic properties.

Example 12

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of water were mixed with a mechanical stirring device until a homogenous gel was

formed. A solution of one hundred and nine parts of mercurochrome in five hundred parts of water was added and mixed thoroughly with the gel. The mass was dried in a stream of warm air for twenty-four hours and then finely pulverized. The resultant dry powder speedily wetted with water to form an ointment with antiseptic properties.

Example 13

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of distilled water were mixed with a mechanical stirring device until a homogenous gel was formed. A solution of ten and nine-tenths parts of silver nitrate dissolved in one thousand parts of water was added and mixed thoroughly with the gel. The mass was dried in thin layers at 75° C. for twenty-four hours and then finely pulverized. The resultant dry powder speedily wetted with water to form an ointment with antiseptic properties.

Example 14

To one hundred parts of finely powdered hydroxyethyl cellulose (high viscosity) was added with thorough mixing a solution of twenty-five parts of Arlacel C (wetting agent) and four and eighty-five hundredths parts of pyruvic acid in five hundred parts of acetone. The acetone was then evaporated from the mixture, and the residual mass was ground to a fine powder in a hammer mill. One part of this powder wetted readily with three parts of water to yield an ointment of pH 2.50 suitable for use in the debridement of burns.

Example 15

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of water were mixed with a mechanical stirring device until a homogenous gel was formed. One hundred and nine parts of sulfathiazole, finely powdered, was added and mixed thoroughly with the gel. The mass was dried in thin layers at 75° C. for twenty-four hours and then finely pulverized. The resultant dry powder readily wetted with water to form an ointment useful for treatment of infections. A similar ointment was prepared in a like manner from methyl cellulose, sorbitol, and sulfadiazine.

Example 16

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of water were mixed with a mechanical stirring device until a homogenous gel was formed. One hundred and nine parts of sulfanilamide, finely powdered, was added and mixed thoroughly with the gel. The mass was dried in thin layers at 75° C. for twenty-four hours and then finely pulverized. The resultant dry powder readily wetted with water to form an ointment useful for treatment of infections.

Example 17

One hundred and fifty parts of methyl cellulose, thirty parts of sorbitol, and two thousand parts of warm water containing one hundred and nine parts boric acid were mixed until a homogenous gel was formed. The mass was dried in layers and pulverized. The powder readily formed on addition of water an antiseptic ointment.

It is to be understood that the individual components and the amounts thereof referred to in the preceding examples may be varied widely

without departing from the scope of this invention. As mentioned previously, other cellulose ethers, as well as other wetting agents, may be employed in the above examples in lieu of methyl cellulose and sorbitol. Likewise, mixtures of cellulose ethers or wetting agents may be used. The amount of cellulose ether is of course substantially larger than the amount of wetting agent. As a general rule, for 100 parts by weight of cellulose ether approximately 10 to 40 parts by weight of wetting agent is sufficient.

When the medicament is to be added to the ointment base at the time of preparation thereof any desired concentration necessary for the particular purpose to which the ointment is to be applied may be used. As a general rule, the medicament will vary from less than 1% to as high as 10 or 15% by weight of the ointment base, although larger amounts may be used if desired.

A wide variety of medicaments or mixtures thereof may be employed. Where the medicament is to be added to the ointment base when the latter is prepared it is of course advisable that it be stable on storage. If a medicament is unstable under the conditions of storage then it should be added to the ointment vehicle at the time the latter is dissolved in water, just prior to application to the wound.

A representative group of medicaments which may be incorporated in the ointment bases of the present invention includes mercurochrome, sulfapyridine, sulfathiazole, sulfadiazine, bichloride of mercury, silver nitrate, argyrol, boric acid, phosphoric acid, pyruvic acid; anesthetic agents such as procaine and butycaine; vasoconstrictors such as epinephrine and cocaine; antiseptics such as salicylic and benzoic acids and derivatives, zinc and mercury oxides, calamine, phenol, and cresol; oxidizing agents such as the more stable peroxides and chloramines; counter irritants such as mustard oil, menthol, eucalyptol, and camphor; coal tar products commonly used as parasiticides and for dermatitis; spermacides and contraceptive agents such as thymol and its derivatives, hexylresorcinol and hydroxyquinolines; colloidal silver proteins and protamines for treatment of infectious diseases; hormones such as testosterone and estrin for topical application, etc.

By means of the present invention an important class of new hydrophilic ointments and ointment bases has been made available for

therapeutic purposes. These ointments and ointment bases are free from the many disadvantages which have heretofore precluded the use of water-miscible, solid vehicles in the pharmaceutical industry. They are dry, stable powders which may be stored for long periods, but which dissolve readily in water when needed to produce an ointment or ointment vehicle of the desired characteristics.

As many apparently widely different embodiments of this invention may be made without departing from the spirit and scope hereof, it is to be understood that the invention is not limited to the specific embodiments hereof except as defined in the appended claim.

We claim:

A biologically and chemically stable ointment base in the form of a dry powder comprising a finely comminuted mixture of methyl cellulose and sorbitol containing from 10 to 40 parts by weight of sorbitol for each 100 parts by weight of methyl cellulose, said powder being readily soluble in water in approximately one minute.

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