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HYDROUS GELS

Irving L. Ochs, Annapolis, and Preston L. Veltman, Severna Park, Md.

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This invention relates to compositions of use in a number of fields and particularly to gels carrying or having incorporated therein an active ingredient whereby such gel may be used as a reservoir or depot for said active ingredient, and to methods of producing and of utilizing said gels.

It is frequently desirable or necessary to maintain a concentration of an active ingredient in a particular locality or environment in order to secure a specific action which is caused or enhanced by such active ingredient. An example is in the use of acetic acid solutions in wet dressing for the treatment of skin infections, as for example in the treatment of burns and of infected wounds. Such wet dressing technique has not been satisfactory due to its many limitations, and also because often it is impracticable for a given situation. It is known that surfaces denuded of epithelium vary greatly in the amount of fluid exuded. To maintain the optimal concentration of acetic acid at the surface of the wound requires adjustment of the concentration of the acid in accordance with the degree of dilution of the exudate.

Wet dressings require that the part of the body, being treated be unclothed and immobilized. Further the solution requires replenishment at frequent intervals. This is troublesome and impractical with an ambulant patient. In addition, gauze carrying the solution for a wet dressing is irritating to the raw area to which it is applied due to its abrasive or other physical action. Furthermore, the healing wound often grows through the interstices of the gauze and when removed necessarily traumatizes the area being treated with consequent regression in the healing process. The gauze also acts as a wick favoring the evaporation of solution supplied by capillarity and body fluids, which in turn, results in a concentration of electrolytes which may act as irritants because of the resulting change in osmotic balance. Nor is there certainty of control over the concentration of medicament, when, of necessity, the area must be kept open with consequent solution (water) evaporation.

A wet dressing also requires frequent attention and the required care is not always available. Because of the inherent porosity of a wet dressing and the necessity for keeping the area accessible, contamination and secondary infection by air-borne organisms often occurs. Also, it is difficult to keep a continuous liquid phase in contact with raw tissue. Or, considering the treatment of corneal ulcers, the use of solutions is disadvantageous in that it is impossible to immobilize the eye due to the necessity of frequently applying drops or solutions to maintain an effective concentration of medicament. In addition, the movement of the eye-lid over the ulcer is painful and healing is inhibited by mechanical irritation, thus slowing the process of epithelization. Further, in the treatment of body cavities or fistulae, whose location is such that they are drained by gravity, solutions can not be applied effectively.

Besides therapeutic utilizations, there are many other situations in which it is desired to maintain a source of

supply of a given reagent or reactant, or of an acid or base to maintain given conditions of acidity or pH. Intermittent or continuous introduction of solutions offers a number of the same difficulties referred to above in the use of wet dressings.

Among the objects of the present invention is the production of hydrous gels containing an active ingredient which gel thus serves as a reservoir or depot supply for said active ingredient to a particular environment.

Further objects include such hydrous gels carrying a lower fatty acid such as acetic acid in effective concentrations for the utilization desired as for example in therapeutic amounts when used for therapeutic purposes.

Other objects include methods of producing such gels and their utilization.

Still further objects and advantages of the present invention will appear from the more detailed description set forth below, it being understood that such more detailed description is given by way of illustration and explanation only, and not by way of limitation, since various changes therein may be made by those skilled in the art without departing from the scope and spirit of the present invention.

In accordance with the present invention, a hydrous gel is used as a carrier for an active ingredient so that such hydrous gel carrying said ingredient may be placed at the locality to which the active ingredients is to be supplied, and the gel will serve as a reservoir or depot supply for the active ingredient which is continuously supplied therefrom to the locality. Whether used therapeutically, or in chemical or physical processes, such hydrous gels carrying active ingredients may be used effectively to maintain a source of supply of active ingredient without requiring constant attention. The invention is particularly useful in therapeutic application and may well be illustrated by the use of hydrous gels carrying organic acids, such as acetic acid.

Various types of gels may be employed including both organic and inorganic gels. Thus hydrous gels may be made from inorganic components such as of silica, alumina, ferric oxide, etc., or from organic components such as carboxymethyl cellulose and other carboxy alkyl celluloses, pectins, polyvinyl alcohol, gelatin, partially oxidized cellulose, agar, fibrin, albumin, starch, etc. Such gels may be prepared by conventional methods and the active ingredient incorporated into them, either after production of the gel or preferably during its preparation. Thus water soluble active ingredients may be incorporated into the water or aqueous solution used in preparing the sol from which the gel is formed. Desirably the gels used in accordance with the present invention are hydrous gels or hydrophilic gels since for therapeutic purposes, water transfer is an important desideratum. Further, it is a simple matter to prepare such gels with thixotropic properties by conventional methods so that upon shaking they may be reduced in viscosity sufficiently for application as a fluid, but promptly set up to a substantially rigid structure or shape.

The character of active ingredient may vary depending on the particular field of utilization for the product. The invention will be illustrated by the use of aliphatic acids as the active ingredient. Many of the these acids exhibit a sufficient germicidal action for utilization for therapeutic purposes including lower monobasic (fatty) acids such as formic, acetic, propionic, butyric, and valeric acids, hydroxy monobasic acids such as glycolic and lactic acids, and polybasic acids such as malonic, succinic, oxalic, aconitic, and citric acids. All of these acids exhibit substantial bactericidal action but it should be kept in mind that various factors govern the activity exhibited, and some of the acids are more effective against one type of bacteria than against another. For example, acetic acid

is less effective against *Staphylococcus aureus* than against *Pseudomonas aeruginosa, Eberthella typhosa,* or *Escherichia coli.* The same is true of citric acid. In general with monobasic acids, the bactericidal action decreases with molecular weight and introduction of hydroxy groups renders them from two to twelve times more effective. The undisassociated molecule plays a major role so that activity is not due merely to pH.

However, for present purposes, the water solubility of the acid is an important factor where use in a hydrous gel is employed. More soluble acids like acetic acid may desirably be utilized therefore and acetic acid will be referred to below in examples illustrating the invention.

The amount of active ingredient employed will depend on the utilization to which the product is put. When used for therapeutic purposes, the amount of active ingredient should be kept below that which will cause undesired irritation at the point of application. Thus for hydrous gels carrying acetic acid, used for therapeutic purposes, a therapeutic amount of acetic acid should be employed, i. e. an amount which will exhibit the desired effect. Ordinarily, this will not be more than 4 parts by weight per 100 parts of water in the hydrous gel, and usually will be much less as for example 1.25 parts per 100 parts of water in the hydrous gel. There is no particular lower limit since any proportions may be used, but amounts to give desired effects will usually be at least 0.01 to .25 part per 100 parts of water in the hydrous gel.

Similar amounts of the other acids may be used. Nor is it essential that all the acid present be in solution.

The proportions of water to gel-forming component may be anything to give a gel of the type desired. The gradation from sol to gel is a gradual one, and the gel may take various degrees of rigidity depending on the components and their proportions. Water transfer is an important characteristic of hydrogels, and the elastic organic hydrogels are superior to the inorganic hydrogels in that the former not only lose water in dry air, but the hydration process is reversible, whereas with the inorganic gels it is not. In general, satisfactory results will be obtained with the organic hydrous gel produced with from 5 to 30 parts of gel forming material to 100 parts of water, all parts being by weight.

The following examples illustrate the invention parts being by weight unless otherwise indicated.

I

This example illustrates a very desirable composition which is in the form of a hydrous, substantially immobile gel containing a small, but effective quantity of acetic acid.

Water	100
Carboxymethyl cellulose	20
Glacial acetic acid	1.25

The carboxymethyl cellulose was "Hercules Type 70" and of low viscosity. The acetic acid and water were mixed and the carboxymethyl cellulose added slowly with efficient stirring to produce a smooth, uniform, gelatinous mass. It is desirable to employ vigorous mixing to avoid lumps and the product may be somewhat opaque due to occluded air. The mass may be heated to drive out the air, as for example for 30 minutes at approximately 200° F. (short periods of time below the boiling point of water) without breaking down the gel structure, to produce a clear gel useful in treating infected tissue enabling the progress of healing to be observed. The content of carboxymethyl cellulose may be increased to produce a stiff plastic mass, as for example by using up to 30 parts. Compositions containing 15 parts of the carboxymethyl cellulose have a moderate degree of mobility and may be used for specific applications. The acetic acid content may be increased or decreased as for example up to 4 parts by weight which compositions have been successfully employed. Acetic acid concentrations greater than approximately 1.25 parts are mildly painful when placed on raw tissue, although, generally, the acetic acid acts as an anesthetic and the sensation of pain disappears quickly. Small concentrations approaching a few hundredths of one per cent are effective and notably bactericidal in these compositions.

II

Water	100
Pectin powder	10
Glacial acetic acid	1.25

The acetic acid and water were mixed and the powdered pectin added with good agitation to avoid lumping. The mass was then warmed as for example to approximately 200° F. for about 30 minutes to complete the hydration of the pectin. On cooling, a gelatinous mass was obtained which exhibited bactericidal properties and promotes healing of diseased tissue. Variations in proportions as to pectin and acetic acid may be made as described above under Example I. Experience has shown that the above given composition is notably effective in general use; however, where fluid exudation is copious, the acid concentration is optimally increased.

III

Water	100
Polyvinyl alcohol	5
Glacial acetic acid	1.25

The polyvinyl alcohol may be "Du Pont's Elvanol 71–24." The water and acetic acid were mixed and the powdered polyvinyl alcohol added with efficient mixing to form a gelatinous mass. To remove entrapped air, the mass may be heated as at about 200° F. for approximately 30 minutes. Upon heating, the viscosity may be reduced and greater fluidity developed. Increasing the polyvinyl alcohol content makes a firmer composition capable of absorbing greater quantities of body fluids without becoming undesirably mobile.

IV

Water	100
Gelatin	10
Glacial acetic acid	1.25

The water and acetic acid were mixed, heated to about 200° F., and the powdered gelatin dissolved therein with efficient stirring. The mass was cooled to a clear gelatinous therapeutic composition. Proportions may be varied as set forth above but the acid content most generally useful is approximately 1.25.

V

Water	100
Partially oxidized cellulose	10
Glacial acetic acid	1.25

The gel may be made by dissolving the cellulose material in the water acid solution following the procedures of other examples as set forth above. The partially oxidized cellulose is oxycellulose of which the Parke Davis & Co. product was used.

Various grades of carboxymethylcellulose may be used including low viscosity 25 to 50 cps., medium viscosity 400 to 600 cps., and high viscosity approximately 2000 cps., all measured in 2% solution. Various grades of polyvinyl alcohols may be used including low viscosity 4 to 6 cps., medium viscosity 20 to 28 cps., and high viscosity 35 to 120 cps., all measured in 4% solution.

Adjuvants of various types may be included for example, lanolin, mineral oil, anesthetics, perfumes, coloring matter or dyes, for any particular purposes. A small but effective amount of preservatives such as sodium benzoate, phenol, or hydroxyquinoline may be included in the product. Acetic acid solutions of various concentrations may be used in lieu of glacial acetic acid. Mixtures

of gel-forming components may be employed, and mixtures of active ingredients may be utilized.

The hydrous gels carrying acetic acid are particularly useful for therapeutic purposes. It is not necessary to immobilize the patient nor keep the part undergoing treatment, exposed. The gel acts as a reservoir and continued source of therapeutic substance, by permitting diffusion of the active agent to the surface of the diseased tissue. The gelatinous mass also serves to absorb and maintain any body exudate in a liquid state. This prevents crusting over of the wound and in addition reduces the chance of infection. The reservoir action makes frequent attention to the infected area unnecessary. The physical quality of softness makes the gelatinous mass nonirritating mechanically and there are no fixed or rigid elements in the gel structure to become enmeshed with the healing tissue. The compositions of this invention favor the absorption of body fluids and electrolytes and the outer surface of the gel may be covered with an impermeable membrane to keep sterility and also dynamic equilibrium with the body fluids. Fluid from burns may enter the gel and return to the body from the gel just as from a sponge. The use of the compositions of the present invention eliminate or materially reduce the possibility of contamination by air-borne organisms while the gelatinous mass provides complete protection for the wound by eliminating air pockets and unprotected areas. In applications where a reservoir of therapeutic agent is desired along with immobilization of any part, the compositions of the present invention may desirably be used.

In specific applications, compositions described herein may be enclosed in surgical wounds of infected or contaminated areas and may subsequently be absorbed by the body tissues. The adhesive nature of the materials of this invention permit them to adhere strongly to tissue surfaces even when the latter are wet and consequently these compositions may be used effectively in body cavities and fistulae regardless of gravity effects. Compositions of this invention when transparent are particularly useful in permitting a visual check of the healing process without disturbing the wound or the therapeutic agent.

The compositions of this invention may be used by treating any infected or potentially infected body tissues. By potentially infected tissue is meant areas whose epithelium which normally protects the body against bacterial invasion is disrupted by heat, cold, or physical injury. Compositions of this invention have been successfully used in treating a wide variety of diseased tissue due to bacteriacidal action and they also promote healing by maintaining a sterile and epithelization promotion medium at the surface of the wound.

These compositions are particularly effective against gram negative bacilli. Burns of varying degree of severity can be successfully treated for optimum results. A primary burn of a mild type requires medication for safe healing and the treating composition may be selected to provide a gelatinous covering that will retain its therapeutic power in accordance with the amount of exudate issuing from the wound. One skilled in treatment may estimate with accuracy the amount of body fluid to be expected and the best suited and balanced composition applied accordingly. When the amount of exudate is small, a composition containing a minimum concentration of acetic acid may be used in the hydrous gel containing only a small reserve capacity before becoming undesirably mobile. If the wound is severe and copious amounts of fluid are expected, a concentration containing acetic acid is desirably selected along with a hydrous gel specifically compounded to absorb large quantities of body fluids without becoming undesirably mobile. Thus the concentration of gelling agent should be proportioned to the amount of exudate. Compositions of the present invention have been particularly successful in treating infections of the outer ear. The adhesive is ideal in that the material remains in position even in the upper parts which it is quite impossible to treat with prior art fluid medicaments. The potent bactericidal action of the sustained low concentration of acetic acid provided by the compositions of this invention have notably been successful in applications of this character. Numerous low order of infections of the hands, feet and scalp yield to treatment by compositions disclosed herein.

Having thus set forth our invention, we claim:

1. A topical therapeutic immobile hydrous gel to promote healing by controlling infection without injuring tissue, consisting essentially of water 100 parts, gel forming material from 5 to 30 parts, and acetic acid, the acid being not over 4 parts, all parts being by weight, said gel forming material being selected from the group consisting of carboxymethyl cellulose, pectin powder, polyvinyl alcohol, gelatin and partially oxidized cellulose.

2. A topical therapeutic immobile hydrous gel to promote healing by controlling infection without injuring tissue, consisting essentially of water 100 parts, gel forming material from 5 to 30 parts, and acetic acid, the acid being not over 4 parts, all parts being by weight, said gel forming material being a carboxyalkylcellulose.

3. A topical therapeutic immobile hydrous gel as set forth in claim 1, said gel forming material being carboxymethyl cellulose.

4. A topical therapeutic immobile hydrous gel as set forth in claim 1, said gel forming material being pectin powder.

5. A topical therapeutic immobile hydrous gel as set forth in claim 1, said gel forming material being polyvinyl alcohol.

6. A topical therapeutic immobile hydrous gel as set forth in claim 1, said gel forming material being gelatin.

7. A topical therapeutic immobile hydrous gel as set forth in claim 1, said gel forming material being partially oxidized cellulose.

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