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## TOPICAL THERAPEUTIC COMPOSITION

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This invention relates to improved topical therapeutic compositions and particularly to compositions useful in treatment of disorders of the pilosebaceous apparatus. The invention also relates to a method of making such compositions.

Certain dermatoses, such as for example acne, involve disorders in the oil glands associated with hair follicles, the so called "pilosebaceous apparatus." These diseases are characterized by inflammation of the hair follicles and/or sebaceous glands and in some instances are marked by disfiguring papules, pustules, nodules or crusts. These diseases are frequently chronic and in many individuals are highly resistant to cure.

Many medicinals have been used in the treatment of such disorders of the pilosebaceous apparatus. Among the most effective remedial agents are resorcinol and resorcinol monoacetate which function by virtue of their keratolytic and/or keratoplastic effect, the particular effect depending principally on the concentration of the active ingredient. Dermatological preparations including resorcinol, resorcinol monoacetate or other phenolic compounds are frequently supplied as ointments in oleaginous bases, usually petrolatum with or without fats and waxes and may or may not include anodynes, such as for example bismuth subnitrate, zinc oxide, talc, etc. The effectiveness of resorcinol or other hydroxy aromatic compounds in treatment of disorders of the pilosebaceous system is reduced by the presence of oleaginous material therewith since such oleaginous material interferes with the activity of the therapeutic component of the composition. Accordingly, resorcinol is frequently employed in the form of a dilute solution or lotion when used to treat certain dermatoses. However, the use of flowable preparations for the purpose is highly undesirable particularly when the face is the site of the disorder treated because drippings of the medicament from said site can be unpleasant if not noxious, particularly to the hair, eyes, mouth or clothing of the patient. Hence, hydroxy aromatic therapeutic agents are advantageously applied in thickened systems. Ideally the therapeutic agent is incorporated in a hydrophilic base whereby the composition resists flow unless sufficient mechanical force is applied thereto. An advantage inherent in the use of a gel is that the total quantity of treating material topically applied to any cutaneous site is susceptible to control. Resorcinol preparations including a variety of hydrophilic colloids as the vehicle have been used in medicinals. However, the efficacy of resorcinol in such preparations as have been heretofore available is essentially that of the resorcinol in the absence of said colloid.

Accordingly, it is a principal object of the subject invention to provide a novel therapeutic composition of matter suitable for topical application to the skin in treatment of acne which combines in improved and more efficacious form the remedial and soothing effects of certain known therapeutic materials whereby the individual effects of each of those materials are enhanced and unexpectedly improved by the combination and conjoint application thereof.

Another object of the instant invention is to provide novel therapeutic compositions and techniques for the treatment of acne with a view to avoiding disadvantages of medicaments or modes of treatment heretofore employed.

A more particular object of the invention is the provision of a thickened hydrophilic therapeutic composition in which the thickening agent improves the ability of the principal medicament to combat certain skin disorders.

Still another object is the provision of a composition of the character described which is characterized by a remarkable degree of efficacy in the treatment of acne; that is substantially free of adverse side effect when used by the patient in the prescribed manner.

The invention combines in synergistic form and effect certain therapeutic materials which in combination effectively heal, soothe and improve acne, which is a disease involving disorders of the pilosebaceous apparatus. Preferred compositions of the invention have the property of existing as stable gels or highly thickened systems which turn to a dry composition after a period of controlled residence on the skin. The dry mass, and particularly the mineral component of said powder, has the property, inter alia, of permitting the primary active agent to function for prolonged periods without introduction to the site of the disorder of deleterious foreign matter, such as for example certain body oils. Said compositions have numerous advantages over ointments, lotions, or solutions heretofore suggested for use in treatment of acne.

Briefly, the subject invention is the result of our surprising discovery that the clay mineral attapulgite, and particularly colloidal attapulgite, has the ability to cooperate with certain hydroxylated aromatic compounds to effectively arrest acne when said attapulgite and said hydroxylated aromatic compound in intimate association with each other, and preferably in the absence of oleaginous material, are applied to the site of such a disorder. When the mineral has colloidal properties liquid dispersions thereof provide suitable hydrophilic thickened or gelled systems which function as ideal carriers for the hydroxylated aromatic compound and such other auxiliary therapeutic agents as may be included in formulations. We are cognizant of the fact that various clays have been topically applied by primitive peoples and that healing qualities have been imputed to the clays. Nevertheless it is recognized by competent dermatologists that the acute inflammatory cutaneous disorders with which we are concerned fail to respond to topical application of attapulgite or other clays, sorptive or non-sorptive. Furthermore, in vivo observations show that bentonitic clays used in lieu of attapulgite in compositions of our invention fail to enhance the therapeutic value of the hydroxy aromatic compound when used therewith in the treatment of acne.

Clays are naturally-occurring crystalline or semi-crystalline hydrous aluminum silicates frequently associated in nature with minor amounts of impurities such as feldspar, quartz or other impurities. In some clays aluminum is replaced in the lattice of the crystal by magnesium, calcium and/or small amounts of alkali metals. Clay species vary considerably in such physical characteristics as lattice orientation, substitution of aluminum by alkaline earth or alkali metal constituents, quantity and physical state of water associated with the clay and imponderables such as origin of the clay. Kaolinitic clay, for example, is a hydrous aluminum silicate which in its raw state comprises as the chief mineral constituent hexagonal platelets of kaolinite, nacrite or dickite. Kaolinitic clays have very low sorptivity for water or other fluids and fail to gel in water or other fluids or otherwise exhibit colloidal properties. On the other hand, clays having as the chief constituent a montmorillonite mineral have layer-like structures and exhibit physical characteristics markedly different from those of kaolinitic clays. Furthermore, the properties of individual species of montmorillonite minerals or clays including a substantial portion of such minerals differ considerably inter se. For example, bentonite,

of which the major component is montmorillonite, exists as a sodium-type montmorillonite which swells in water and as a calcium-type which is non-swelling.

Montmorillonite is a layer-like mineral in which the bonding between sheets is weak so that water or other polar molecules can penetrate between sheets and be sorbed. In the case of sodium montmorillonites, the sheets can be swelled apart to the point where the sheets can be colloiddally dispersed in the swelling medium. The term fuller's earth usually refers to non-swelling sorptive clays and encompasses both calcium-montmorillonites and clays comprising the mineral attapulgite. Attapulgus clay, sometimes called "Attapulgus fuller's earth," contains in addition to a major portion of attapulgite minor amounts of montmorillonite minerals, sepiolite, quartz or feldspar. The morphology of attapulgite, an aluminum-magnesium silicate mineral, differs considerably from that of the layer-like montmorillonite minerals and from the hexagonal platelets of kaolinite. The shape of the ultimate particles of attapulgite is acicular and the mineral occurs in a state in which the needles or fibers occur in packets of close-packed fibers. These fibers are relatively short, ranging from about 0.5 to 2.0 micron in length and from about 20 to 60 millimicrons in width. The mineral in its colloidal and non-colloidal states is distinguished for its high sorptivity for water and other media. Attapulgite, unless heated to about 600-1000° F. can be dispersed to colloidal size particles (0.1 to 0.5 micron) in water or other polar liquids to form thickened gelatinous systems exhibiting a high degree of thixotropy. High shear is required to bring out the colloidal properties of attapulgite particularly when associated with small quantities of non-colloidal impurities.

More specifically, our invention is practiced by preparing a thickened system including a vaporizable innocuous liquid having attapulgite dispersed therein and incorporating into the thickened system a hydroxy aromatic compound which when applied to the site of certain dermatoses has a keratolytic or keratoplastic effect. Compositions of our invention comprise a hydroxy aromatic compound, preferably resorcinol or resorcinol monoacetate, in a liquid thickened by dispersion of attapulgite therein, said attapulgite being present in amount at least equal to and preferably at least double that of the hydroxy aromatic compound. Auxiliary therapeutic agents such as for example certain anodynes, humectants, antiseptic and antibiotics may be included in the composition. Pursuant to a preferred embodiment of the invention, the thickened system is a gel whereby particulate insoluble material may be included in stable formulations by being suspended by the gel.

Hydroxy aromatic compounds capable of effectively influencing the cure of pilosebaceous disorders include resorcinol, resorcinol monoacetate, hexylresorcinol, cresol and metacresyl acetate. Resorcinol and resorcinol monoacetate are preferred species because of their outstanding efficacy. Phenol has been used as a desquamating agent, however, the toxicity and irritating effects of phenol make it less desirable for the purpose of treating pilosebaceous disorders than resorcinol. An important advantage of resorcinol, particularly when the resorcinol-attapulgite ratio is low, is that its high water solubility promotes homogeneous distribution of the compound throughout the composition. Resorcinol monoacetate, on the other hand, is only slightly soluble in water, although readily soluble in alcohol. Accordingly, distribution of resorcinol monoacetate in the composition is facilitated by use of alcohol as the principal fluid in which the attapulgite is dispersed or in admixture with the water used for the purpose. In general, from about 2 to 10 percent by weight of resorcinol or the monoacetate thereof is used in formulations of the invention. At lower levels the benefits are minimal. At levels higher than about 10 percent the irritating effect of the ingredient will usually be excessive. However, it will be understood

that in the treatment of disorders in some individuals less than 2 percent and more than about 10 percent of resorcinol or resorcinol monoacetate is indicated.

The carrier for the hydroxy aromatic compound is a thickened system, preferably sufficiently bodied to be a gel, and which is formed by the dispersion of colloidal attapulgite in an innocuous liquid which is substantially vaporizable under ambient conditions of temperature and humidity.

It will be understood that the term "attapulgite" as used herein refers to the pure mineral or to a clay in which attapulgite is the chief mineral constituent, such as so called "Attapulgus clay." A typical chemical analysis of an Attapulgus clay expressed in terms of the oxides present is tabulated below on a volatile-free basis.

	Percent
SiO <sub>2</sub> -----	67.0
Al <sub>2</sub> O <sub>3</sub> -----	12.5
MgO -----	11.0
Fe <sub>2</sub> O <sub>3</sub> -----	4.0
CaO -----	2.5
Others -----	3.0

The liquid or liquid mixture is preferably one in which the hydroxy aromatic compound has good solubility so that uniform distribution of that compound in the formulation and into the interstices of the attapulgite is facilitated. Furthermore, the liquid should be sufficiently polar to permit satisfactory dispersion of the attapulgite therein. Particularly useful liquids include water (preferably distilled), ethanol, isopropanol, and mixtures thereof. However, propanol and C-4 alcohols may be used. The ultimate choice in liquid composition will be predicated on the determination of desirable rate of evaporation of liquid from the composition after topical application. A particularly useful liquid mixture when resorcinol is used is a 50-50 mixture of water and ethanol. When the evaporation of the liquid is to be restricted, a humectant, such as for example glycerol, ethylene glycol or sorbitol may be added to the liquid. The total liquid is ordinarily about 50 percent by weight of the ultimate formulation, although the quantity will vary somewhat with variations in consistency of the composition and use, if any, of a particulate insoluble anodyne such as for example, zinc oxide, sulfur or talc.

Colloidal attapulgite is used in the formulation and serves at least a tri-fold function. First, by virtue of its colloidal properties, the attapulgite forms the gel or thickened system and provides a suitable flow-resistant vehicle for the hydroxy aromatic compound. Secondly, the attapulgite-bodied vehicle is a suspending agent for any materials present in the formulation in excess of their solubility or which are totally insoluble. Thirdly, and of utmost importance, the attapulgite enhances the ability of the medicinal to combat the dermatosis. The reason underlying the remarkable ability of the attapulgite to cooperate in such a manner with the medicinal ingredient is unknown. Although we do not wish to be bound in any manner to the hypothesis herein set forth, it is felt that the unusual sorptivity and ultimate particle shape of the attapulgite is responsible. Since the hydroxy aromatic compound is associated with the minute particles of attapulgite the penetration characteristics of the compound into the skin is probably profoundly different from what it would be in the absence of the attapulgite. Furthermore, after all or a substantial portion of the liquid is evaporated from the formulation subsequent to topical application, the attapulgite resident at the diseased site is available to sorb bacteria originating therein, deleterious foreign sebaceous matter or sebaceous exudate of which the inflamed area is the precursor. Furthermore, the attapulgite exerts a soothing cooling effect when present on the skin because of its hygroscopic nature.

From about 0.5 to about 5.0 percent by weight of the liquid phase of attapulgite is required for thickening the

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liquid whereas from about 5.0 to 20.0 percent by weight will produce gellation. For satisfactory formulations the weight ratio of attapulgite to hydroxyl aromatic material should be at least 1/1 and is more preferably about 2/1 or higher. When the quantity of attapulgite is more than can be satisfactorily dispersed in the liquid by high shear it may be agitated into the previously thickened system. The attapulgite may be used in its raw state after removal of grit. Preferably the mineral is washed to remove impurities and classified as wet or dry methods well-known to those skilled in the art. The attapulgite may be heat treated to effect sterilization although this step may be omitted when a disinfectant, suitably a halogenated organic compound is included in minor proportion in the formulation. Sterilization should be carried out at temperatures not to exceed about 400° F., and usually from about 225–400° F., since the gel-forming properties of the material will be reduced.

Pursuant to an embodiment of the invention, zinc oxide or other anodynes is included in the formulation in relatively large proportions. Colloidal sulfur may be used in lieu of or as a supplement to the zinc oxide. Particulate water-insoluble anodynes are especially desirable because they are retained at the site of application. The water-insoluble anodyne should be used in finely-divided form so that its retention on the skin is adequate and so that it is non-irritating when applied to the skin. Although relatively large quantities of insoluble anodynes may be used, they should not be used in amounts exceeding that capable of being stably suspended by the thickened system.

Small amounts of other active ingredients such as disinfectants, particularly halogenated disinfectants as exemplified by hexachlorophene and quaternary ammonium salts, may be included in formulations where their use is indicated. These additives may be soluble or insoluble in the liquid component in the system.

A preferred method of preparing the compositions of the instant invention includes the preliminary step of forming a thickened or gelled system comprising attapulgite in liquid by use of high shear technique. When the total quantity of mineral called for in a particular formulation exceeds that which is capable of being colloiddally dispersed in the liquid only a fraction of the total may be preliminarily dispersed. Suitable high shear equipment includes colloid mills, kinetic energy mills, 3-roll mills and ball mills. The resorcinol or other hydroxy aromatic compound is incorporated into the formulations by high shear technique, suitable by addition in the presence of additional quantities of liquid. The balance of the attapulgite, up to a total of 35 parts by weight, and any other comminuted insoluble material is then blended into the thickened system using a conventional mechanical mixing device.

The following examples are given only for the sake of further illustrating the invention and are not to be construed as limiting the scope thereof.

#### Example I

A pharmaceutical preparation demonstrated to be highly effective in the cure of acne was prepared. The composition of the preparation is as follows:

	Percent
Resorcinol -----	10
Zinc oxide -----	20
Hexachlorophene -----	1
Attigel 20 -----	20
Distilled water -----	25
Ethanol -----	24
	100

Attigel 20 is a purified colloidal form of attapulgite mined in Georgia and sold by Minerals & Chemicals Corporation of America. It can be dispersed to an average particle size of less than 0.1 micron. In the prepara-

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tion of the composition, the Attigel may be dispersed in the water and the alcohol and sheared in a Waring Blendor for about 10 minutes with intermittent stirring to prevent formation of shear planes. The resultant dispersion is a very stiff homogeneous gel. Hexachlorophene and resorcinol are incorporated into the stiff gel and homogenized therein in the Blendor. The resultant stiff gel is transferred to a low-speed mixer. The zinc oxide is then added to the mass and stirred into the composition at increasing rates of speed for about 30 minutes. The resultant product is a smooth creamy unctuous-feeling suspension.

#### Example II

The preparation of the composition of Example I is repeated except that resorcinol is used in the amount of 2.5 percent, based on the total weight of the composition. Such a preparation is preferred to a 10 percent resorcinol composition when the latter produces in a particular patient severe exfoliation or other adverse effects.

One hundred patients were treated with compositions of Example I or II over a period of from one to eight months in private practice and in institutions under the supervision of competent dermatologists. Over ninety percent of these patients, many of whom failed to respond to competent treatment with various commonly used modalities, showed satisfactory improvement, with remarkable improvement being noted in many of the cases of acne. Disorders treated comprised severe cystic acne, congestive nodular acne, rosacea, verruca plana juvenilis. Bentonite used in lieu of attapulgite in formulations otherwise identical did not produce the outstanding benefits when used as a control.

It will be understood that the invention is susceptible to variation without departing from the spirit and scope thereof.

We claim:

1. A thickened hydrophilic therapeutic composition suitable for topical application to the skin in treatment of acne consisting essentially of at least one liquid selected from the group consisting of water, ethanol and isopropanol, from 2 to 10 percent by weight of a hydroxyl aromatic material selected from the group consisting of resorcinol and resorcinol monoacetate, and colloidal attapulgite dispersed in said liquid in an amount at least substantially equal to the weight of said hydroxyl aromatic material, said composition being substantially devoid of oleaginous matter.

2. A thickened hydrophilic therapeutic composition suitable for topical application to the skin in treatment of acne consisting essentially of water, from 2 to 10 percent by weight of resorcinol, and colloidal attapulgite dispersed in said water in an amount within the range of from 2 to 35 percent by weight and at least substantially equal to the weight of said resorcinol, said composition being substantially devoid of oleaginous matter.

3. A thickened hydrophilic therapeutic composition suitable for topical application to the skin in treatment of acne consisting essentially of a liquid consisting of water and ethanol, from 2 to 10 percent by weight of resorcinol, and colloidal attapulgite dispersed in said liquid in an amount within the range of from 2 to 35 percent by weight and at least substantially equal to the weight of said resorcinol, said composition being substantially devoid of oleaginous matter.

4. A hydrophilic therapeutic gel suitable for topical application to the skin in treatment of acne consisting essentially of at least one material selected from the group consisting of water, ethanol and isopropanol, from 2 to 10 percent by weight of resorcinol, and colloidal attapulgite dispersed in said liquid in an amount within the range of from about 5 to 20 percent by weight and at least substantially equal to the weight of said resorcinol, said composition being substantially devoid of oleaginous matter.

5. A hydrophilic therapeutic gel suitable for topical

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application to the skin in treatment of acne consisting of about 50 percent by weight of a water-ethanol mixture, from 2 to 10 percent by weight of resorcinol, and about 20 percent by weight of colloidal attapulgite dispersed in said water-ethanol mixture, the balance being finely divided zinc oxide.

6. A hydrophilic therapeutic gel suitable for topical application to the skin in treatment of acne consisting of about 50 percent by weight of a 50-50 water-ethanol mixture, from 2 to 10 percent by weight of resorcinol, about 20 percent by weight of colloidal attapulgite dispersed in said water-ethanol mixture, and about 1 percent of hexachlorophene, the balance being finely divided zinc oxide.

7. A hydrophilic therapeutic gel suitable for topical application to the skin in treatment of acne comprising as essential ingredients about 50 percent by weight of a water-ethanol mixture, from 2 to 10 percent by weight of resorcinol, and about 20 percent by weight of colloidal attapulgite dispersed in said water-ethanol mixture, the balance being finely divided sulfur.

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