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(54) **EMULSIVE COMPOSITION CONTAINING DAPSONE**

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(57) **ABSTRACT**

The present invention relates to a topical, emulsive composition containing Dapsone or its derivative. The inventive composition incorporates emollients and Dapsone or its derivative in a stable emulsion. The stability is achieved through the use of a combination of certain surfactant mixtures and an enhancer providing solubility of the Dapsone.

EMULSIVE COMPOSITION CONTAINING DAPSONE

STATEMENT OF PRIORITY

[0001] This application is a Continuation Under 35 U.S.C. § 1.111(a) of International Application No. PCT/US2004/026447, filed Aug. 13, 2004 and published in English as WO 2005/016296 on Feb. 24, 2005, which claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/494,912 filed Aug. 13, 2003, which applications are incorporated herein by reference.

BACKROUND OF THE INVENTION

[0002] DDS or 4,4'-diaminodiphenyl sulfone has the USP name, Dapsone, and is a well-known medicament possessing several beneficial medicinal activities. Dapsone is typically administered as one of the medicinal agents used in the treatment of leprosy. Dapsone and its derivatives are also effective for treatment of bacterial infections, protozoanal infections such as malaria, *pneumocystis carinii*, and plasmonic infections such as toxoplasmosis. Some of the early publications describing Dapsone and its derivatives include a 1938 French patent (FR829,926) and U.S. Pat. No. 2,385,899. These references explain that Dapsone has an inhibiting effect on the growth of bacteria, mycobacteria, an plasmodia. According to the 2001 Physicians Desk Reference, Dapsone is commercially available in tablet form from Jacobus Pharmaceutical Company. Dapsone also used as a cross-linking agent for epoxy resins.

[0003] Dapsone is also known to be useful as an anti-inflammatory agent. It has been used to treat skin diseases characterized by the abnormal infiltration of neutrophils, such as Dermatitis herpetiformis, linear IgA dermatosis, pustular psoriasis, pyoderma gangrenosum, acne vulgaris, and Sweet's Syndrome.

[0004] In all of these applications including topical applications, Dapsone treatment is systemic and the drug is administered orally. No topical formulation of Dapsone is commercially available for local treatment of skin disease and references describing topical administration of Dapsone are not common. Of the few scientists considering topical administration, Osborne (U.S. Pat. Nos. 5,863,560 and 6,060,085) is one providing a topical formulation of Dapsone. He describes a dermatological gel composition containing Dapsone.

[0005] One reason for the lack of commercial topical formulations rests upon the solubility character of Dapsone and its derivatives. Dapsone and many of its derivatives are soluble in ethanol, methanol, acetone and dilute, aqueous HCl but are practically insoluble in water and in oils such as petroleum gel, wax and vegetable oils. Consequently, topical formulations of Dapsone in water or oils are difficult to develop. Those topical formulations of Dapsone that have been developed typically include salt formers and solubilizing agents that enable formation of a single phase aqueous solution or gel. The solubilizing agents are water miscible and include such organic liquids as ethylene diglycol monoethyl ether and ethanol.

[0006] However, use of such topical formulations of Dapsone [illegible] oils and natural skin softeners from the skin thus causing it to be dry, itch and crack. Inclusion of exogeneous skin emollients, oils and the like, however, causes phase separation and precipitation of Dapsone. Use of typical emulsifiers does not solve the Dapsone precipitation owing to the lowered Dapsone solubility and conflicting physical characteristics of the phases of the resulting composition.

[0007] Therefore, there is a need to formulate a stable, aqueous based, emulsive Dapsone composition that will not dry or crack the skin. There is a further need to formulate such a composition with pharmaceutically acceptable ingredients. There is also a need to include exogeneous oils, emollients and the like in such an emulsion without causing separation or precipitation of the Dapsone.

SUMMARY OF THE INVENTION

[0008] These and other needs are achieved by the present invention which provides a stable, emulsive composition containing Dapsone or a derivative thereof. The emulsive composition enables the use of a wide variety of oil phase components as vehicles for the topical (skin or mucosa) delivery of Dapsone or a derivative thereof. The emulsive composition of the invention also provides for the use of polar phase components for the augmented delivery and enhancement of Dapsone or a derivative thereof on the skin or mucosa.

[0009] Accordingly, the present invention is directed to an emulsive composition of the following components: a) Dapsone or its derivative (hereinafter collectively termed Dapsone), b) a solvation medium (polar phase component) for Dapsone c) an emulsifier system, d) an oil phase component, e) optional water and f) optional gelation or thickening agents. Excipients as well as other additives and colorants may also be included as additional compounds in the solvation medium (polar phase) and oil phase components. Each of the components of the emulsive composition (except the optional water) can be composed of one or more individual compounds falling within the component description.

[0010] The solvation medium (polar phase) may be an organic solvent that ranges in water solubility from moderately soluble (for example having from 2% to 10% by weight solubility in water) to completely miscible in water in all proportions. The solvation medium will at least partially, and preferably will completely dissolve Dapsone. When optional water is combined with the solvation medium, the combination also at least partially, and preferably completely, dissolves the Dapsone. In either aspect, the solvation medium or solvation medium plus water dissolves or disperses the Dapsone as a stable solution or dispersion. When the combination of solvation medium and water are employed, that combination is the polar phase (an aqueous polar phase) and the solvation medium preferably enhances the solubility of the Dapsone in this aqueous polar phase. Preferred organic solvents that function as the solvation medium either alone or in combination with water include a polyglycol, a polyol, a polyglycol ether, a polyol ether, a polyglycol monoether or a polyol monoether or a combination thereof.

[0011] The oil phase component includes any pharmaceu[illegible]

dermis. Waxes, oils, fatty acids, polyols, and esterified fatty acids are some examples of the oil phase component.

[0012] The emulsifier system has both ionic and nonionic properties so that it stabilizes the emulsive composition of the invention and prevents Dapsone separation. Preferably, the ionic properties are anionic properties. The combination of these properties can be achieved by a mixture of surfactant and a saturated and/or unsaturated fatty alcohol. In particular, a blend of a C10 to C24 saturated and/or unsaturated fatty alcohol, and any one of more of a C8 to C24 saturated and/or unsaturated fatty alcohol phosphate ester or diester, a C8 to C24 saturated and/or unsaturated fatty alcohol sulfate ester or diester, a C8 to C24 saturated and/or unsaturated fatty alcohol carbonate ester or diester as well as derivatives of such saturated and/or unsaturated fatty alcohol phosphate, sulfate and/or carbonate esters may serve as the emulsifier system according to the invention. Preferably, the emulsifier system is a combination of a C12 to C18 fatty alcohol, a phosphate diester of a C12 to C18 fatty alcohol and a phosphate monoester of an unsaturated C12 to C18 fatty alcohol.

[0013] According to the invention, the concentrations of the components by weight relative to the total weight of the emulsive composition are as follows:

[0014] a) Dapsone may range from about 0.005 percent to about 30 percent, preferably about 0.1 percent to about 25 percent, more preferably about 0.1 percent to about 15 percent, especially more preferably about 0.1 percent to about 10 percent, very especially more preferably about 0.2 percent to about 8 percent, and most preferably about 0.5 to about 5 percent by weight of the emulsive composition, with such percentages as 1, 2, 5 and 7.5 being especially preferred embodiments thereof;

[0015] b) The solvation medium may range from about 0.5 percent to about 99 percent, preferably about 0.5 percent to about 50 percent, more preferably about 5 percent to about 40 percent, especially more preferably about 5 percent to about 35 percent, most preferably about 5 percent to about 30 percent;

[0016] c) The emulsifier system may range from about 0.1 percent to about 30 percent, preferably about 0.5 percent to about 25 percent, more preferably about 1 percent to about 25 percent, most preferably about 5 percent to about 25 percent, most preferably about 5 percent to about 20 percent;

[0017] d) The oil phase may range from about 0.1 weight percent to about 75 percent, preferably about 0.1 to about 50 percent, more preferably about 1 to about 45 percent, most preferably about 2 to about 40 percent;

[0018] e) Water may range from 0 percent to about 99 percent, preferably from 0 to about 50 percent, more preferably from 0 to about 40 percent, most preferably from 0 to about 35 percent, i.e., water is optional;

[0019] f) The amounts are combined to equal 100 percent, and except for water, each of the components a-d is to be included. Each of the four ingredient components a-d may be composed of one or more

[0020] The emulsive composition of the invention provides therapeutic benefits such as, but not limited to, anti-inflammatory activity, antibacterial activity, anti-itch activity and emollient properties so that it is useful in the treatment of such dermatological disorders as psoriasis, dermatitis and the itch associated with healing or gealed burn wounds while maintaining skin and/or mucosal integrity, flexibility, stretch and moisturization.

Definitions

[0021] As used herein, certain terms have the following meanings. All other terms and phrases used in this specification have their ordinary meanings as one of skill would understand. Such ordinary meanings may be obtained by reference to such technical dictionaries as *Hawley's Condensed Chemical Dictionary* 11th Edition, by Sax and Lewis, Van Nostrand Reinhold, New York, N.Y., 1987; *The Merck Index,* 11th Edition, Merck & Co., Rahway N.J. 1989; *The Physician's Desk Reference* (PDR), 2001 Edition, Medical Economics Company, Montvale, N.J.; *Stedman's Medical Dictionary,* 25th Edition, Williams & Wilkens, Baltimore, Md., 1990.

[0022] Dapsone is 4,4'-diaminodiphenyl sulfone. It has the chemical formula $C_{12}H_{12}N_2O_2S$ and is alternatively known as 4,4'-sulfonyldianiline or bis (4-aminophenyl)sulfone (also spelled sulphone). See the above-referenced Merck Index at entry no. 2820.

[0023] Derivatives of Dapsone refer to compounds that have a similar chemical structure and thus similar therapeutic potential to Dapsone. These include compounds with two organic substituents (R_1, R_2) at the two amino groups ($R_1R_2NC_6H_4SO_2C_6$ $H_4NR_1R_2$). R_1 and/or R_2 each may be hydrogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxyoyl as well as a substituted alkyl group of 1 to 6 carbons wherein the substituent may be hydroxyl, thio, alkoxy, halo, amido and similar polar or lipophilic substituents. Preferably, R_1 and R_2 are the same. When the R_1 and R_2 substitution is R═CHO, the compound formed is generically named diformylDapsone. It is alternatively known as bis (4-formaminophenyl-)sulfone and 4,4'-diformyldiaminodiphenyl sulfone. When the R_1 and R_2 substitution is R═COCH3, the compound formed is AceDapsone, alternatively named bis (4-acetamidophenyl)sulfone and 4,4'-diacetyldiaminodiphenyl sulfone. AceDapsone is a known prodrug of Dapsone. Other derivatives known to have antibacterial and/or anti-inflammatory effect are glucosulfone sodium, solapsone, diathymosulfone, acediasulfone, monoacetyl Dapsone, acetosulfone, succisulfone, aldesulfone sodium, and thiazolsulfone. Additional Dapsone derivatives are described in the following journal articles, the disclosures of which are incorporated herein by reference: M. D. Colman et al. *J. Pharm. Pharmacol.,* 1997, 49, 53-57; *J. Pharm. Phamracol.,* 1996, 48, 945-50; *Environmental Toxicology and Pharmacology,* 1996, 2, 389-395.

[0024] An emulsifying agent is a surfactant (defined separately below). However, not all surfactants are emulsifying agents. An emulsifying agent is typically a term used to describe an organic compound that stabilizes a uniform dispersion of one solvent in another where the two solvents are immiscible. Portions of the emulsifying agent dissolve in the different phases so that the dispersion is prevented from coalescing into two separate liquids.

groups such as halo, alkoxy of 1 to 6 carbons, alkyl keto of 2 to 6 carbons, alkoxycarbonyl of 2 to 6 carbons, alkyl amido of 2 to 6 carbons and alkye amine of 1 to 6 carbons optionally substituted with 1 or 2 alkyl groups of 1 to 4 carbons on the amine.

[0026] The terms "insoluble" and "immiscible", as applied to two liquids, mean that one liquid displays essentially no solubility in the second. While the measurable solubility need not be zero, for the practical purposes of formulating topical products, the level of solubility is insignificant if an ingredient is described as insoluble or immiscible in another.

[0027] The term "miscible" when used in connection with two liquids means that the two liquids are soluble in each other at all ratios.

[0028] A solution is a system at chemical equilibrium in which a solute (liquid, solid, or gas) is dissolved in a liquid solvent.

[0029] A surfactant or surface active agent is an organic compound that reduces the surface tension when dissolved in water or water solutions. In an emulsion, a surfactant will contain a hydrophilic portion and a lipophilic portion by which it functions to reduce the surface tension of the surfaces between immiscible phases. Functionally, in dermatological applications, surfactants include emulsifying agents, wetting agents, cleansing agents, foam boosters, and solubilizing agents. A surfactant is any nonionic, anionic, or cationic organic compound of moderate to high molecular weight (such as from about 100 to 300,000 daltons) for which a significant portion of the molecule is hydrophilic and a significant portion is lipophilic.

[0030] The term "pharmaceutically active agent" is used to refer to a chemical material or compound that is suitable for topical administration and induces a desired physiological effect.

[0031] The term "topical administration" means the delivery of a composition or active agent to the skin or to mucosal tissue. A topical composition is one that is suitable for topical administration.

[0032] The term "about" means a variation of 10 percent of the value specified; for example about 50 percent carries a variation from 45 to 55 percent.

DETAILED DESCRIPTION OF THE INVENTION

[0033] The present invention solves the formulation and treatment problems associated with topical administration of Dapsone and its derivatives (hereinafter collectively termed Dapsone). These compounds are aromatic, are substituted with diamino groups and are difficult to formulate as aqueous based topical compositions. The compounds themselves readily separate and/or precipitate from such aqueous based compositions. When solvation enhancers are used, the resulting compositions typically cannot include desirable, oil-based skin conditioning agents. Such skin conditioning agents, however, are common formulation ingredients for topical compositions because without them, topical compositions often dry, redden and are detrimental to the skin.

[0034] According to the invention, it has been discovered [illegible] positions that include oil-based skin conditioning agents. In particular, the emulsive composition of the invention includes Dapsone, a solvation medium, an emulsifier system and one or more oil-based skin conditioning agents. An alternative emulsive composition of the invention includes water with the solvation medium so as to provide an aqueous polar phase.

[0035] The emulsive composition of the present invention may display a consistency and feel characteristic of products suitable to application to the skin or a mucous membrane. The consistency of the composition may be a freely-flowing liquid. Such a consistency allows for a rapid spreading on the skin and an ease of application. Alternately, the consistency of the composition may range to a stiff or firm, semi-solid. A stiff consistency may be suitable for a heavier application of the composition to a limited site on the skin or on a mucous membrane. Further, a stiff consistency resulting from a high oil phase may contribute to the occlusive property of the composition on the skin or a mucous membrane. The feel of the composition on the skin may range from a thin, wet feel to a stiff, waxy feel. With the adjustment of the various ingredients the composition can be formulated to display a consistency and feel optimal for the delivery of the Dapsone for an intended indication.

Composition of the Invention

[0036] Many dermatological products are described as emulsions but the two immiscible phases forming such products often do not form colloidal mixtures. Instead, the internal phases are dispersed as droplets within the continuous phases to create temporarily stable systems. The chemical equilibria in such systems are toward the separation of the immiscible phases.

[0037] A system may be said to be at chemical equilibrium when it is stable theoretically forever as a result of random molecular movement. In contrast, a physically stable topical emulsion system often involves a practical and limited stability. An emulsion may be classified as physically stable when it displays no or insignificant change in the phase dispersion over a defined period of time. For a dermatological emulsion product, a physically stable system typically is a system that shows no or insignificant change in the phase dispersion over the period of a marketable self-life.

[0038] In dermatological or topical products, common emulsions are oil-in-water emulsions and water-in-oil emulsions. In the former, the oil phase is the internal phase dispersed in the continuous water phase. In the latter, the oil phase may be the continuous phase. More complex emulsion systems have been described and formulated as dermatological products. Water-in-oil-in-water emulsions and other complex combinations may be formed between immiscible phases.

[0039] In many topical emulsions, an internal oil phase contains oily or fatty excipients that are solid at room temperature, thereby raising a point of confusion over the definition of an emulsion as a liquid-in-liquid dispersion. This point is clarified by the understanding that at the time of formation, the emulsion is a liquid-in-liquid dispersion because the oil phase may have been heated or otherwise manipulated by make it a liquid. It may also be noted that at the water/oil interface the precise nature of the physical state [illegible]

[0040] The oil phase of a topical emulsion may contain oily or fatty materials that are miscible or compatible with each other but that have no or insignificant miscibility or solubility in water. As many oil phase excipients are solids at standard temperature, the miscibility is commonly evaluated with the excipients in their liquid states.

[0041] In topical or dermatological products, the water phase, or aqueous phase, often contains an amount of water and optionally a variety of liquids or solids that are soluble, miscible, or dispersed in the water.

[0042] Many of these properties are present in the emulsive composition of the present invention. However, water need not be present in combination with the solvation medium according to the invention.

[0043] In the following discussion, use of the term "Dapsone" shall mean Dapsone or its derivative unless otherwise stated.

[0044] The present invention provides a physically stable emulsive composition containing Dapsone in a solvation medium (polar phase) in combination with at least one oil phase component (oil phase) and an emulsifying system. The solvation medium (polar phase) includes an organic solvent for solvating the Dapsone. Optionally, the solvation medium may contain additional compounds such as common excipients, coloring agents and the like. Also optionally, the solvation medium may form a combination with water to act as the polar phase.

[0045] The emulsifying system may be a combination of a fatty alcohol and a surfactant.

[0046] The emulsive composition can be formulated into a range of topical compositions, from light, non-greasy lotions to heavy, emollient creams.

[0047] According to the invention, the concentration of Dapsone may be any amount that provides effective antibacterial and/or anti-inflammatory properties to the emulsive composition. In particular, the concentration of Dapsone in the emulsive composition of the invention may range from about 0.05 percent to about 30 percent by weight of the emulsion formulation. Preferably, this concentration may be from about 0.1 percent to about 25 percent, more preferably about 0.1 percent to about 15 percent, especially more preferably about 0.1 percent to about 10 percent, very especially more preferably about 0.2 percent to about 8 percent, and most preferably about 0.5 to about 5 percent by weight of the emulsive composition. The Dapsone concentration of especially preferred embodiments may be such percentages as 1, 2, 5 and 7.5.

[0048] According to the invention, the solvation medium may be an organic solvent that is moderately soluble to miscible with water and dissolves Dapsone or enables dissolution of Dapsone in the combination of solvation medium and optional water. The solvation medium or its combination with water acts as the polar phase of the emulsive composition.

[0049] Preferably, in either alternative, namely, use of an organic solvent or solvents alone as the solvation medium or use of the combination of the organic solvent or solvents and the water enables the complete dissolution of Dapsone in the

tration of organic solvent in the combination of water and solvation medium may also enable partial dissolution of the Dapsone in the emulsive composition. In the latter situation, the portion of Dapsone not dissolved in the solvation medium or combination may be suspended as a dispersion of microparticles or micronized particles and the like in the emulsive composition. Alternatively, the portion of Dapsone not dissolved may be suspended as a dispersion of crystalline Dapsone. The size of the suspended particles of Dapsone may be controlled by the preparation of the Dapsone raw material or by the process by which the emulsive composition is compounded. The size of the suspended particles may range from below 10 microns (microparticles or micronized particles) to palpable particles above about 100 microns. The emulsifying system participates in the maintenance of this dispersion. Alternatively, the undissolved portion of Dapsone may be dissolved in the oil phase of the emulsive composition when it is formed by combination of the solvation medium, the oil phase and the emulsifying system.

[0050] Partial dissolution of Dapsone may be the result of any one or more of a number of formulation designs. First, the organic solvent may not enable complete dissolution of the desired concentration of Dapsone in the solvation medium even though lower amounts of Dapsone will be completely dissolved. Second, the volume of the oil phase may be insufficient to dissolve this portion of Dapsone not dissolved in the solvation medium. Third, the formation of the emulsive composition may decrease the solubility of Dapsone in the solvation medium because of interaction of the oil phase, the emulsifying system and the solvation medium.

[0051] Notwithstanding the dissolution characteristics of Dapsone in the salvation medium and in the emulsive composition, in a preferred embodiment of the invention, the amounts of Dapsone and organic solvent are selected to fully dissolve Dapsone in the neet organic solvent. Although the dissolution of Dapsone in organic solvent may be complete, subsequent formation of the emulsive composition may result in partial precipitation of Dapsone or maintain complete dissolution of Dapsone. Both possibilities are within the invention.

[0052] According to the invention, the concentration of the solvation medium as the organic solvent alone relative to the total weight of the emulsive composition ranges from about 0.5 percent to about 99 percent by weight. More preferably the concentration of solvation medium is from about 0.5 percent to about 50 percent by weight. Especially more preferably the concentration of solvation medium is from about 5 percent to about 40 percent, very especially more preferably about 5 percent to about 35 percent by weight, and most preferably about 5 percent to about 30 percent by weight of the emulsion composition.

[0053] When water is combined with an organic solvent or solvents as the solvation medium, the concentration of solvation medium relative to the weight of the water plus solvation medium ranges from 0.005 weight percent to 98 weight percent. The ingredients in this instance are the organic solvent or solvents and water.

[0054] The concentration of the organic solvent in the

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