(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 January 2011 (06.01.2011)

PCT

(10) International Publication Number
WO 2011/001165 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/GB2010/051038

(22) International Filing Date:
23 June 2010 (23.06.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0911213.7 30 June 2009 (30.06.2009) GB

(71) Applicant *(for all designated States except US)*: **SYNTOPIX GROUP PLC** [—/GB]; Institute of Pharmaceutical Innovation, University of Bradford, Bradford, Yorkshire BD7 1DP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JONES, Stephen Philip** [GB/GB]; c/o Syntopix Group Plc, Institute of Pharmaceutical Innovation, University of Bradford, Bradford, Yorkshire BD7 1DP (GB). **FITZGERALD, Daniel James** [GB/GB]; c/o Syntopix Group Plc, Institute of Pharmaceutical Innovation, University of Bradford, Bradford, Yorkshire BD7 1DP (GB). **SEVILLE, Scott** [GB/GB]; c/o Syntopix Group Plc, Institute of Pharmaceutical Innovation, University of Bradford, Bradford, Yorkshire BD7 1DP (GB). **PAKUNLU, Refika, I.** [TR/US]; c/o Syntopix Group Plc, Institute of Pharmaceutical Innovation, University of Bradford, Bradford, Yorkshire BD7 1DP (GB). **DESAi, Nayan, N.** [US/US]; c/o Syntopix Group Plc, Institute of Pharmaceutical Innovation, University of Bradford, Bradford, Yorkshire BD7 1DP (GB). **DAVIS, Adrian** [GB/GB]; c/o Syntopix Group Plc, Institute of Pharamcetical Innovation, University of Bradford, Bradford, Yorkshire BD7 1DP (GB).

(74) Agent: **BREWSTER, Andrea**; GREAVES BREWSTER LLP, Indigo House, Cheddar Business Park, Wedmore Road, Cheddar Somerset BS27 3EB (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2011/001165 A2

(54) Title: FORMULATIONS

(57) Abstract: Anti-acne formulation containing (i) 3.5% w/v or greater of a dialkyl sulpho succinate (DAS) such as a dioctyl sulpho succinate and (ii) salicylic acid or a derivative thereof (other than a halogenated salicylanilide), which is suitable for application as a topical leave-on formulation. The salicylic acid or derivative may be present at a concentration of 0.5% w/w. The formulation may contain, in addition to the DAS and the salicylic acid or derivative, (a) a polyoxyalkylene-based solubilising agent and (b) an organic solvent, in particular an alcohol, optionally together with a thickening agent and/or water. It may contain an antioxidant such as AO 2246 or AO 425. It may be applied once daily over a period of several weeks.

Formulations

Field of the invention

This invention relates to anti-acne formulations, in particular leave-on formulations.

Background to the invention

It is known to use dialkyl sulphosuccinates (DASs) as topical antibacterial and anti-acne agents – see WO-2008/146030, GB-2 449 973, WO-86/07258 and US-4,717,737. These documents describe formulations for use as skin cleansers or for the treatment of acne, but most show a preference for the use of relatively low DAS concentrations, typically 1% w/w or lower.

WO-01/08657 shows the use of dioctyl sodium sulphosuccinate (DOSS) as a lathering surfactant in a disposable cleansing pad intended for cleansing and conditioning the skin or hair.

DOSS, which is available for instance under the trade name Docusate™, is also known for use as a stabiliser and/or surfactant in formulations containing other active substances, including in anti-acne formulations containing peroxides such as benzoyl peroxide and/or antibiotics such as erythromycin – see GB-2 054 375, US-4,387,107, US-5,767,098, US-4,497,794 and US-2003/0044432 – and in anti-ageing formulations containing retinoids. Again, for these applications the sulphosuccinate tends to be used at concentrations of 1% w/w or typically much lower.

DASs are anionic surfactants. As such they can be expected to cause irritancy if left in contact with the skin for too long, hence the preference for relatively low DAS concentrations in existing anti-acne and skin care products. Skin care preparations containing higher concentrations of anionic surfactants are typically formulated as "rinse-off" as opposed to "leave-on" products; they are applied to the skin and then immediately rinsed away to avoid irritancy or local skin damage.

There are a number of publications which refer to the irritant properties of surfactants, in particular anionic surfactants: see for example Effendy et al (1996), "Surfactants and experimental irritant contact dermatitis", *Contact Dermatitis*, Oct; 35(4): 264-5; Wilhelm et al (1993), "Surfactant-induced stratum corneum hydration in vivo: Prediction of the irritation potential of anionic surfactants", *Journal of Investigative Dermatology*, 101: 310-315; Imokawa G et al (1997), "Cumulative effect of surfactants on cutaneous horny layers: Lysosome labilising action", *Contact Dermatitis*, 5(3): 151-162; Tavss et al (1988), "Anionic detergent-induced skin irritation and anionic detergent-induced pH rise of bovine serum albumin", *J Soc Cosmet Chem*, 39: 267-272; Rieger et al (1997), *Surfactants in Cosmetics: Surfactant Science*, Sv68, Marcel Dekker Ltd; Leyden et al (2002), *Cosmetic Science and Technology Series*, volume 25: "Skin moisturisation", Marcel Dekker Inc; Chew et al (2006), *Irritant Dermatitis*, Springer (see page 249 onwards); Imokawa G (1980), "Comparative study on the mechanism of irritation by sulfate and phosphate type of anionic surfactants", *J Soc Cosmet Chem*, 31 (Mar-Apr): 45-66; Wilhelm et al (1994), "Surfactant-induced skin irritation and skin repair. Evaluation of the acute human irritation model by noninvasive techniques", *J Am Acad Dermatol*, Jun, 30(6): 944-9; and Bárány et al (1999), "Biophysical characterization of skin damage and recovery after exposure to different surfactants", *Contact Dermatitis*, 40: 98-103. Deepika and Tyagi in *J Oleo Sci*, Vol 55, No 9: 429-439 (2006) distinguish between mono- and diester sulphosuccinates, describing the diesters as more irritating and hence "rarely used in personal care products".

In *International Journal of Toxicology*, 17(Suppl. 4): 1-20, 1998, the Cosmetic Ingredient Review classed DOSS as a "cumulative irritant", and cautioned against prolonged contact with the skin. Many other surfactants are known to be cumulative irritants: prolonged contact with them can cause increased skin damage due to impairment of the skin barrier function.

Another known anti-acne agent is salicylic acid (2-hydroxybenzoic acid). It is a keratolytic which is widely used to unblock pores to help prevent whiteheads and blackheads becoming inflamed (Waller JM, Dreher F, Behnam S, Ford C, Lee C, Tiet T, Weinstein GD, Maibach HI, "'Keratolytic' properties of benzoyl peroxide and retinoic acid resemble salicylic acid in man", *Skin Pharmacol Physiol* 2006;19: 283-9).

The keratolytic action of salicylic acid is concentration dependent and it is often necessary to combine it with other actives to increase efficacy, especially against inflammatory lesions (see for example Touitou E, Godin B, Shumilov M, Bishouty N, Ainbinder D, Shouval R, Ingber A, Leibovici V, "Efficacy and tolerability of clindamycin phosphate and salicylic acid gel in the treatment of mild to moderate acne vulgaris", *J Eur Acad Dermatol Venereol* 2008; 22: 629-31). There is therefore a need to find alternative anti-acne formulations in which the activity of salicylic acid can be boosted by the presence of a second active ingredient, ideally one which can also act as an antibacterial agent against *P. acnes*, the bacteria which are implicated in inflammatory acne. Salicylic acid alone has weak antibacterial activity that is almost certainly insufficient to manifest against *P. acnes* on skin as typically formulated at concentrations of 2% w/v or less.

However, salicylic acid is also a potential irritant, particularly at higher concentrations: according to the Cosmetic Ingredient Review published in *International Journal of Toxicology*, 22(Suppl. 3): 1-108, 2003, the acid and its salts need to be "formulated to avoid skin irritation". They would not therefore be thought suitable for combining with another potentially irritating anti-acne active such as a DAS.

Formulations which are intended for application to the skin, for instance as disinfectants or cleansers, or indeed as anti-acne products, can be used as either "leave-on" or "rinse-off" products. Leave-on products are applied to the skin and then, rather than being rinsed away, left there for continued therapeutic or cosmetic effect. This mode of delivery is however clearly unsuitable for active substances which could cause irritation if left in contact with the skin for prolonged periods. Thus in WO-02/02073, for example, which relates to topical leave-on anti-sebum compositions, a preference is expressed for only low levels, if any, of surfactants. Dialkyl sulphosuccinates are specifically mentioned as surfactants which should be limited in or ideally excluded from the compositions to avoid skin damage.

For this reason, the person skilled in the art of preparing topical skin care formulations, including for antimicrobial or anti-acne use, would be likely to formulate a DAS as a rinse-off or "wash-off" product. The higher the concentration of the DAS in the product, the more likely this would be. If the DAS were to be combined with another

potentially irritating active substance, again the combination would be more suitably applied as a rinse-off rather than a leave-on product.

It has now surprisingly been found that the combination of a DAS and salicylic acid can cause less skin irritation than would have been expected from the properties of the individual substances alone, even when the combination is applied to the skin as a leave-on product, and even at relatively high concentrations of the two substances.

Statements of the invention

According to a first aspect of the present invention there is provided an anti-acne formulation containing (i) 3.5% w/v or greater of a dialkyl sulphosuccinate (DAS) and (ii) salicylic acid or a derivative thereof, wherein the formulation is suitable for application as a topical leave-on formulation, and provided that the salicylic acid derivative is not a halogenated salicylanilide. The formulation should thus be suitable and/or adapted and/or intended for topical application to the skin, in particular human skin.

In an embodiment, the concentration of the salicylic acid or derivative in the formulation is 0.5% w/v or greater.

As shown in the examples below, this combination of two relatively "harsh" active substances has surprisingly been found to be well tolerated on human skin, even when left in contact with the skin for prolonged periods of time. It is therefore suitable for, and indeed may be adapted and/or intended for, application as a topical leave-on formulation, as described in more detail below.

As used herein, the term "dialkyl sulphosuccinate" or "DAS" means a dialkyl ester of sulphosuccinic acid, in which the sulphonic acid group is present as $–S(O)_2–OH$. Such a compound may be used in the form of a derivative; suitable DAS derivatives can include salts such as metal salts, ammonium salts (in particular the NH_4^+ salt) and any form of the compound in which the sulphonic acid group is present as the sulphonate – $S(O)_2–O^-$, as well as solvates and so-called "prodrug" forms or protected forms which

revert to an active form of the compound at an appropriate time on or after administration.

Each of the two alkyl groups of the DAS may have for example up to 22 carbon atoms. It may have up to 20 or up to 18 or up to 16 or 14 or 12 or 10 carbon atoms. It may have 1 or more carbon atoms, or 2 or more carbon atoms, or 3 or 4 or 5 or 6 or more. Thus for example the alkyl groups may be C_1 to C_{22} or C_1 to C_{20} or C_1 to C_{18} alkyl groups, in particular C_2 to C_{12} or C_2 to C_{10} or C_2 to C_9 alkyl groups, such as C_6 to C_{10} and in particular C_8. They may be C_6 to C_{18} or C_7 to C_{18} or C_8 to C_{18} alkyl groups. In an embodiment of the invention, the DAS is a dioctyl sulphosuccinate. The alkyl groups may be substituted or unsubstituted, preferably the latter. If substituted, they may for example be mono-, di- or tri-substituted, and may suitably include one or more substituents selected from amido groups and ethers. They may be straight chain, branched or in cases cyclic. They may include one or more unsaturated carbon-carbon bonds. In an embodiment of the invention, the alkyl groups of the DAS are not substituted with ether groups. In an embodiment, the alkyl groups are not substituted with amido groups. In an embodiment, the alkyl groups do not include unsaturated carbon-carbon bonds.

The DAS is conveniently used in the form of a salt in which the sulphonic acid group is present as the sulphonate $-S(O)_2-O^-$, such as in particular a metal salt or ammonium salt. Suitable metal salts include the alkali metal salts (for example the sodium or potassium salts, in particular the former) and the alkaline earth metal salts (for example the calcium salt). The DAS may be suitable for cosmetic use. It is suitably pharmaceutically acceptable.

In an embodiment of the invention, the DAS is used in the form of its sodium salt, for example dioctyl sodium sulphosuccinate (also known as dioctyl sulphosuccinate sodium or docusate sodium).

A DAS derivative may be a pharmaceutically acceptable derivative. It may be a free acid – ie an alkyl sulphosuccinnic acid – from which the sulphosuccinate can be derived. In an embodiment, however, the DAS is present in the form of the sulphosuccinate.

The concentration of the DAS in a formulation according to the invention is 3.5% w/v or greater. It may be 4% w/v or greater, or 4.5% w/v or greater. Its concentration might be up to 10% w/v, or up to 9 or 8 or 7 or 6 or 5% w/v. For example, its concentration might be in the range from 3.5 to 10% w/v, or from 3.5 to 8 or 6% w/v, or from 3.5 to 5% w/v, such as about 3.5 or 4 or 4.5 or 5% w/v.

The formulation of the invention also contains salicylic acid (2-hydroxybenzoic acid) or a derivative thereof. A salicylic acid "derivative" may be a salt, for example a metal salt or ammonium salt or vitamin salt. Suitable metal salts include the alkali metal salts (for example the sodium and potassium salts, in particular the former) and the alkaline earth metal salts (for example the calcium and magnesium salts, in particular the former). A metal salicylate may also be selected from bismuth salicylate, bismuth subsalicylate and transition metal salts such as zinc, copper or titanium salts. Other salicylate salts include MEA-salicylate and TEA-salicylate. Other salicylic acid derivatives include salicylic acid esters, in particular alkyl esters (of which the alkyl group may be either straight chain or branched, or may incorporate one or more cyclic groups), more particularly C_1-C_{20} or C_{12}-C_{15} or C_1-C_{10} or C_1-C_6 alkyl esters such as in particular methyl salicylate ("wintergreen"), capryloyl salicylic acid and homosalate (3,3,5-trimethylcyclohexyl 2-hydroxybenzoate). Further derivatives include benzyl salicylate and betaine salicylate. In cases they may include substituted salicylic acids and salts thereof, such as 4-aminosalicylic acid, thiosalicylic acid and their salts.

A salicylic acid derivative may be selected from 4-aminosalicylic acid and its salts; capryloyl salicylic acid; glucosamine salicylate; MEA-salicylate; TEA-salicylate; metal salicylates such as those listed above; thiosalicylic acid; benzyl salicylate; amyl (pentyl) and isoamyl (isopentyl) salicylates; azeloyl diethyl salicylate; betaine salicylate; butyloctyl salicylate; chitosan salicylate; dipropylene glycol and glycol salicylates; ethylhexyl (octyl) salicylate; hexanediol disalicylate; hexyl dodecylsalicylate; hexyl salicylate; isocetyl salicylate; isodecyl salicylate; menthyl salicylate; methyl salicylate; myristyl salicylate; niacinamide salicylate; phenyl salicylate; potassium methoxysalicylate; pyridoxine salicylate; silanediol salicylate; tridecyl salicylate; trimethylsilyl trimethylsiloxy salicylate; zinc thiosalicylate; 4-acetaminophenyl salicylate; cyclohexanol, 3,3,5- trimethyl-salicylate; sodium

ethylmercurithiosalicylate; C_{12}-C_{15} alkyl salicylates; isopropylbenzyl salicylate; zinc glycinate salicylate; and mixtures thereof.

In an embodiment of the invention, a salicylic acid derivative may be selected from metal salicylates; alkyl salicylates of chain length C_{10} or greater; betaine salicylates; TEA-salicylate; MEA-salicylate; and mixtures thereof.

In an embodiment, component (ii) of the invented formulation is selected from salicylic acid, metal salicylates and mixtures thereof. In an embodiment, it is salicylic acid.

In an embodiment, the component (ii) is not a salicylanilide, for example a halogenated salicylanilide of the type referred to in GB-2 456 376. In an embodiment, the component (ii) is not an alkyl salicylate, in particular not a C_1 to C_9 alkyl salicylate, more particularly not methyl salicylate.

A derivative of salicylic acid is preferably a pharmaceutically acceptable derivative. It may be for example a salt, ester, complex or solvate or a so-called "prodrug" form or protected form which reverts to an active form of the relevant compound at an appropriate time on or after administration. In an embodiment, however, the salicylic acid is present in the form of the free acid (which, dependent on the pH of the formulation, may be present in dissociated form, typically as salicylate anions and protons).

The salicylic acid (or any derivative thereof) may be either naturally or synthetically derived. It may for example be obtained from a natural source such as willow herb.

The concentration of the salicylic acid or derivative in a formulation according to the invention might suitably be 0.1 or 0.2 or 0.5% w/v or greater, for example 1 or 1.5 or 2% w/v or greater. Its concentration might be up to 5% w/v, or up to 3 or 2 or 1% w/v. In an embodiment of the invention, the concentration of the salicylic acid or derivative is from 0.5 or 1 to 5% w/v, or from 0.5 or 1 to 3% w/v, or from 0.5 or 1 to 2% w/v, such as about 1 or 2% w/v. In cases, for example in chemical peels for use against acne, its concentration might be up to 10 or 20 or even 30% w/v.

In addition to the DAS and the salicylic acid or derivative, a formulation according to the invention may also contain an antioxidant. The antioxidant may for example be Antioxidant 2246 (AO 2246) or Antioxidant 425 (AO 425).

In an embodiment of the invention, the formulation contains, in addition to the DAS and the salicylic acid or derivative, the following components:

(a) a polyoxyalkylene-based solubilising agent; and

(b) an organic solvent, in particular an alcohol.

The combination of components (a) and (b) has been shown to be effective for formulating DASs for topical antimicrobial and anti-acne use, in particular in aqueous gels, as described in WO-2008/146030. It has moreover been shown, in an aqueous gel containing a thickening agent and water, to be effective as an anti-acne agent, in particular against non-inflamed acne lesions (again see WO-2008/146030). The examples below also show its suitability for use as a vehicle in a leave-on product containing a DAS and salicylic acid.

The solubilising agent (a) is polyoxyalkylene-based, for example polyoxyethylene (polyethylene glycol, PEG)-based. It may comprise a derivative of a polyoxyalkylene, for example an ether or more particularly an ester. It may for example be selected from (1) polyalkoxylated esters, other than polyalkoxylated sorbitan esters and (2) polyalkoxylated alkyl ethers. More particularly it may be selected from (1) polyethoxylated esters, other than polyethoxylated sorbitan esters and (2) polyethoxylated alkyl ethers. It is suitably nonionic.

A polyalkoxylated ester may be a polyalkoxylated fatty acid ester. The fatty acid component may be a C_{10} to C_{20} group or a C_{12} to C_{18} group, for example stearic acid (C_{18}) or 12-hydroxystearic acid. It may in particular be a hydroxyl-substituted fatty acid group. Suitable such solubilising agents are commercially available as Myrj™ 45 (PEG 400-monostearate) and Solutol® HS 15 (PEG-15-hydroxystearate, also known as PEG 660 12-hydroxystearate and Macrogol-15-hydroxystearate).

Solutol® HS 15 is a nonionic solubilising agent available from BASF AG. It consists primarily of polyglycol mono- and di-esters of 12-hydroxystearic acid (the lipophilic part of the molecule) and of about 30% of free polyethylene glycol (the hydrophilic part). It is prepared by reacting 15 moles of ethylene oxide with one mole of 12-hydroxystearic acid.

A polyalkoxylated ester may be a polyalkoxylated glyceryl ester (also known as a polyalkoxylated glyceride), which is a glyceride ester of a polyalkylene glycol (typically PEG). It may contain mono-, di- or tri-glycerides, partial glycerides or mixtures thereof. It may for example be formed by esterification of a polyalkylene glycol with a glyceride oil of an appropriate chain length. The glyceride components may for example contain from 6 to 20 or from 8 to 18 carbon atoms. Suitable such solubilising agents are commercially available as Glycerox™ and Labrasol™. Glycerox™ esters, for example, are PEG-based products which are commercially available from Croda Inc in a number of grades reflecting the molecular weight of the PEG, for example PEG-6, PEG-7, PEG-8 (L8) and PEG-15 (L15). Of these, the PEG-6 version may be preferred. Glycerox™ esters are sold for use as emollients, for example in bath products, skin cleansers and shampoos, and as solubilisers, superfatting agents, dispersing agents and emulsifiers. Labrasol™ is a mixture of caprylic and capric glycerides of PEG-8 and is commercially available from Gattefosse, France.

A glyceride solubilising agent may for example be Glycerox™ 767 (polyoxyethylene (6) glyceryl monocaprylate/caprate, a mixture of caprylic and capric glycerides of PEG-6) or Glycerox™ HE, which is a PEG-7 glyceryl cocoate. It may be a Labrasol™ solubilising agent.

A polyalkoxylated alkyl ether may be a polyalkoxylated ether of a fatty alcohol such as a C_{12} to C_{20} or C_{14} to C_{20} alcohol, for example cetyl (C_{16}), stearyl (C_{18}) or oleyl ($C_{18:1}$). It may in particular be a polyethoxylated alkyl ether, also known as a macrogol ether. Suitable such solubilising agents are commercially available as Brij™ 97 (PEG-monooleyl ether) and Cremophor™ A 25 (a mixture of stearic and cetyl ethers).

In general, the polyalkylene glycol element of a solubilising agent (a) used in the present invention may have any appropriate molecular weight.

The solubilising agent (a) may in particular be a polyethoxylated ester, more particularly a fatty acid ester or a polyethoxylated glyceride. It may be a polyethoxylated glyceride. Solutol® HS 15, Glycerox™ 767 and Labrasol™ have been found to be suitable solubilising agents for use in the present invention.

The organic solvent (b) used in the formulation of the invention is suitably an alcohol, for example methanol, ethanol, isopropanol, octanol, a fatty acid alcohol (for example a C10 to C20 fatty acid alcohol) or phenoxyethanol. It may be selected from methanol, ethanol, isopropanol and mixtures thereof, preferably from methanol, ethanol and mixtures thereof. In an embodiment of the invention the organic solvent is ethanol.

The formulation of the invention may also contain water. In particular, it may be in the form of an aqueous gel. In an embodiment of the invention, the formulation is a gel, which may for example have a viscosity of from 25,000 to 300,000 cps, or from 50,000 to 200,000 cps. In an embodiment, it is in the form of a micro-emulsion.

A formulation according to the invention may contain a thickening agent, which may be any thickening agent suitable for topical application. It is suitably a gelling agent. It may in particular be a cellulose-based thickening agent such as ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose or a carboxymethyl cellulose. Such agents may be used in the form of a (preferably pharmaceutically acceptable) salt such as for instance the sodium salt. The thickening agent may be a polymeric thickening agent such as a carbomer, which will typically be a homopolymer of acrylic acid, cross-linked with an allyl ether.

In an embodiment, the thickening agent is hydroxyethyl cellulose. In another embodiment, it is hydroxypropyl cellulose. Thus, the thickening agent may be for example a Klucel™ thickener such as Klucel™ HF, which is a hydroxypropyl cellulose thickener commercially available from Hercules, USA.

A solubilising agent (a) may be present at a concentration of 1 or 2 or 3 or 4 or 5% w/w or greater, based on the overall formulation. In cases it may be used at 8 or 10 or 15% w/w or greater. It may be present at a concentration of up to 50% w/w, suitably up to 40 or 35 or 30 or 25% w/w, or in cases at up to 20 or 10 or 8 or 5% w/w. Its concentration may for example be from 1 to 10% w/w, or from 1 to 5% w/w or from 2 to 4% w/w, such as about 3.5% w/w. In cases its concentration may be from 2 to 40% w/w or from 10 to 30% w/w or from 15 to 25% w/w, such as about 20% w/w.

An organic solvent (b) may be present at a concentration of 10% w/w or greater, or at 15 or 20 or 25 or 30% w/w or greater. It may be present at a concentration of up to 42 or 40 or 38 or 35% w/w. Its concentration may for example be from 10 to 40% w/w or from 25 to 40% w/w or from 30 to 40% w/w, such as about 34% w/w.

A thickening agent may be present at a concentration of 0.2% w/w or greater, or of 0.5% w/w or greater. It may be present at a concentration of up to 5% w/w, suitably up to 3% w/w. Its concentration may for example be from 0.5 to 5% w/w or from 0.5 to 3% w/w, such as from 1 to 2% w/w or from 1 to 1.8% w/w or from 1.2 to 1.6% w/w.

The balance of the formulation, allowing also for the DAS, the salicylic acid or derivative and any other active agents or excipients present, may be water.

Thus according to a preferred embodiment, the DAS and salicylic acid or derivative are used in a formulation which contains:

(a) from 2 to 10% w/w (or from 2 to 5% w/w) of a polyoxyalkylene-based solubilising agent;

(b) from 20 to 40% w/w (or from 30 to 40% w/w) of an organic solvent, in particular an alcohol;

(c) from 0.5 to 5% w/w of a thickening agent; and optionally

(d) the balance water.

In an embodiment of the invention, it may be preferred for the formulation not to contain a bismuth salt. In an embodiment, it may be preferred for the formulation not to contain a copper salt. In an embodiment, it may be preferred for the formulation not to contain an antibiotic, in particular erythromycin or an erythromycin derivative such as is referred to in US-4,692,329. In an embodiment, it may be preferred for the formulation not to contain a halogenated salicylanilide, in particular a halogenated salicylanilide other than a brominated salicylanilide.

In another embodiment, it may be preferred for the formulation not to contain a peroxide, in particular an organic peroxide, more particularly a diacyl peroxide, for example benzoyl peroxide. In a further embodiment, it may be preferred for the formulation not to contain a silicone, for instance as referred to in WO-2009/009135.

The invented formulation is usable as a leave-on formulation in the treatment of acne. In the present context, a leave-on product or formulation is one which is suitable and/or adapted and/or intended to be applied to the skin and then left in contact with the skin for a subsequent period such as 60 seconds or more, or 2 or 3 or 4 or 5 or 10 minutes or more. It may be left on the skin for 30 minutes or more, or for an hour or more, or for 2 or 3 or 4 or 5 or even up to 8 or 10 or 12 or 14 hours or more, in cases for 16 or 18 or 20 hours or more . During this period, the product or formulation is not rinsed or washed off the skin, either with water or with another skin care product such as a toner. It may be left in contact with the skin indefinitely, or at least until the skin is next treated.

A leave-on product or formulation may be applied to the skin in any suitable manner, for example using the hands or via a substrate such as a sponge, pad, swab, brush, tissue, cloth, wipe, patch or film. It may be applied in the form of a spray or roll-on. It may be applied with gentle rubbing. It may for instance be applied once daily.

The formulation of the invention may be prepared *in situ*, at or immediately before its point of use, for instance its application to the skin or another surface. Thus according to a second aspect, the present invention provides a kit for preparing a topical leave-on anti-acne formulation containing 3.5% w/v or greater of a DAS, such as a formulation according to the first aspect, the kit comprising a source of a DAS and a source of

salicylic acid or a derivative thereof, together with instructions for combining the two compounds so as to make the formulation at or before the point of intended use, and/or for the co-administration of the two compounds to the skin, provided that the salicylic acid derivative is not a halogenated salicylanilide. The two compounds may each be present in a suitable respective vehicle.

According to one embodiment, the formulation or kit of the invention may contain both (i) a DAS and (ii) salicylic acid or a derivative thereof, each encapsulated (for instance microencapsulated) in a separate delivery vehicle; this might for instance allow their release, and hence their contact with one another, only at the intended site of administration.

According to a third aspect of the invention, there is provided a formulation according to the first aspect, for use in the treatment of acne. The formulation is for topical application to the skin, typically human skin, as a leave-on formulation. The formulation may be prepared *in situ*, at or immediately before the point of administration: this aspect of the invention thus pertains to any use of (i) a DAS and (ii) salicylic acid or a derivative thereof in the topical treatment of acne, the two compounds being administered either simultaneously or sequentially and subsequently left in contact with the skin.

A fourth aspect of the invention provides the use of (i) a DAS and (ii) salicylic acid or a derivative thereof, in the manufacture of a formulation for the treatment of acne, wherein the formulation is a topical leave-on formulation, provided that the salicylic acid derivative is not a halogenated salicylanilide. The DAS will typically be used as an antibacterial agent, and/or as an anti-acne agent, in the manufacture of the formulation. The salicylic acid or derivative will typically be used as an anti-acne agent, for example a keratolytic agent, in the manufacture of the formulation.

A fifth aspect provides the use of a formulation according to the first aspect as an anti-acne or in particular as a skin care agent, for non-therapeutic purposes. The formulation may for example be used for cosmetic purposes such as to improve the appearance, feel or smell of the skin. It may be used as a toiletry.

A sixth aspect provides a method of treatment of a patient who is suffering from or at risk of suffering from acne, the method involving administering to the patient a therapeutically effective amount of a formulation according to the first aspect. The formulation should be applied topically to the patient's skin, and left in contact with the skin after its application. It is suitably administered to a patient who is suffering from acne.

In the context of the present invention, treatment of a condition encompasses both therapeutic and prophylactic treatment, of either an infectious or a non-infectious condition, in either a human or animal but in particular a human. It may involve complete or partial eradication of the condition, removal or amelioration of associated symptoms, arresting subsequent development of the condition, and/or prevention of, or reduction of risk of, subsequent occurrence of the condition. It will typically involve use of the invented formulation as an anti-acne agent. It may involve use of the formulation, at least partially, as an antibacterial agent (in particular against one or more propionibacteria, such as *P. acnes* and/or in some instances *P. granulosum*).

Acne is a multifactorial disease of the pilosebaceous follicles of the face and upper trunk, characterised by a variety of inflamed and non-inflamed lesions such as papules, pustules, nodules and open and closed comedones. Its treatment can therefore encompass the treatment (which embraces prevention or reduction) of any of these symptoms, and references to use as an anti-acne agent may be construed accordingly. In particular, the treatment of acne encompasses the treatment (including prevention) of lesions and/or scarring associated with acne. It also encompasses the inhibition of propionibacterial activity which could cause or be otherwise associated with acne or its symptoms.

In an embodiment, the invented formulation is used to treat non-inflamed lesions. In an embodiment, it is used to treat inflamed lesions.

In general, the present invention will be used for the treatment of symptoms which are directly due to acne rather than for instance infections which may arise as a consequence of treating acne with other actives such as antibiotics, and/or secondary

infections caused by opportunistic pathogens, which can arise in skin already affected by acne.

In the treatment of acne according to the invention, the formulation may be applied to the patient's skin for example once every 24 hours, or twice every 24 hours for instance in the mornings and evenings. It may also of course be applied at frequencies lower than these. It should be left in contact with the skin following its application, as described above: typically it may be left on the skin until the next dose of the formulation is applied. This can allow the DAS and the salicylic acid or derivative to continue acting against acne for a period of time after each application.

Such a treatment may be used continuously for a week or longer, or for 2 or 3 or 4 or 5 or 6 or 8 weeks or longer; in cases it may be used for 3 or 4 or 5 or even 6 months or longer. It may be used for up to 12 or 10 or 8 weeks. In cases it may be used for up to 6 months, or for up to 9 or 12 months or in some cases for even longer.

It has surprisingly been found that even when using relatively high concentrations of the two active agents within the invented formulation, it can be left in contact with the skin for prolonged periods, and moreover it can be applied on a daily basis over a treatment period of several weeks, without giving rise to undue skin irritation. As described above, formulations containing higher levels of anionic surfactants such as DASs have traditionally been restricted to use as wash-off products, and would not previously have been expected to be applied to, and left on, the skin once a day for several weeks without giving rise to cumulative irritation.

In accordance with the invention, the DAS may be used as an antibacterially active agent and/or as an anti-acne agent (ie as an agent which is active against acne (which includes against a symptom and/or a cause of acne) and/or against one or more micro-organisms associated with acne). Suitably it is not used purely or even primarily as a stabiliser for another substance such as an active ingredient, or as a surface active agent (surfactant), or as a wetting or solubilising or dispersing or emulsifying agent, or as a processing aid. The salicylic acid or derivative will typically be used as an anti-acne agent, for example as a keratolytic agent.

Antibacterial activity may be growth inhibitory activity or more preferably biocidal (ie lethal to the relevant organism). It may comprise activity against sessile and/or planktonic bacteria. In the context of this invention, activity against a particular species of micro-organism may be taken to mean activity against at least one, preferably two or more, strains of that species.

A formulation according to the present invention may be active as an antibacterial agent. It may be active as a bactericide. In an embodiment of the invention, the formulation is active against one or more bacteria associated with acne, such as *P. acnes* and in some instances *P. granulosum*. Antibacterial activity may be measured in conventional manner.

In accordance with the invention, the DAS and the salicylic acid or derivative are preferably contained in a vehicle which is acceptable for cosmetic use. The vehicle may be pharmaceutically acceptable. Ideally the two actives are contained in a formulation which is suitable for topical application to human or animal, in particular human, skin. A formulation which is "suitable for" topical application may also be adapted for topical application.

A suitable vehicle for a topical formulation will typically be a fluid, which term includes a cream, paste, gel, lotion, foam, ointment, varnish or other viscous or semi-viscous fluid. In an embodiment of the invention, the vehicle is a gel, for example an aqueous gel. Either or both of the DAS and the salicylic acid or derivative may be present in the form of a solution or suspension, the term "suspension" including emulsions, micellar systems and other multi-phase dispersions.

A formulation according to the invention may thus take the form of a solution, suspension, lotion, cream, ointment, varnish, foam, paste or gel, or any other physical form known for topical administration. It may comprise a formulation which is, or may be, applied to a carrier such as a sponge, pad, swab, brush, tissue, cloth, wipe, skin patch, dressing (or other material designed for application to a tissue surface) to facilitate its topical administration. It may be intended for pharmaceutical (which includes veterinary but is preferably human) use, and/or for cosmetic or other non-

medical care purposes (for example, for general hygiene or skin cleansing or for improving the appearance, feel or smell of the skin).

In an embodiment, it may be preferred for the formulation not to be coated onto, or otherwise contained in or on, a solid substrate, in particular a crepe substrate of the type described in WO-01/08657.

The vehicle in which the DAS and the salicylic acid are contained may be any vehicle or mixture of vehicles which is suitable for topical application in a leave-on product; the type chosen will depend on the intended mode and site of application. In the context of formulations for topical application to the skin, examples may for instance be found in Williams' *Transdermal and Topical Drug Delivery* (Pharmaceutical Press, 2003) and other similar reference books. See also Date, AA et al, *Skin Pharmacol Physio.*, 2006, 19(1): 2-16 for a review of topical drug delivery strategies, and also *Skin Delivery Systems*, 2006, John J Wille, Ed, Blackwell Publishing; *Textbook of Cosmetic Dermatology*, 2004, 3rd edition, Robert Baran, Howard I Maibach, Taylor & Francis; *Skin Care Beyond the Basics*, 2001, Mark Lees, Milady; and *Handbook of Cosmetic Science and Technology*, 2005, Mark Paye, AO Barel, Howard I Maibach, Taylor & Francis Ltd (USA).

A leave-on formulation does not necessarily need to contain water. It does however generally need to contain lower concentrations – compared to a wash-off formulation – of potentially irritating substances, contact sensitisers and other substances (dyes, for example) that cannot be left in contact with the skin. Ideally a leave-on formulation is free of contact sensitisers. Whereas a wash-off skin cleanser will contain detergents or surfactants (typically more than one, and often including anionic surfactants) and foam boosters, a leave-on formulation is less likely to contain such components. For example, a leave-on formulation will typically contain less than 25% w/v of surfactants (in particular anionic surfactants) other than the DAS, ideally less than 20% w/v or less than 15 or 10 or 8% w/v. A leave-on formulation may contain a sunscreen and/or other skin protectants such as antioxidants or moisturisers. It may contain a gentle exfoliant such as an alpha-hydroxy acid or microbeads.

Either or both of the DAS and the salicylic acid or derivative may be carried in or on a delivery vehicle which is suitable for targeting or controlling its release at the intended site of administration, for instance to target a desired site and/or time of delivery. Such a vehicle may for instance target the active substance(s) to the skin or follicles. It may delay or otherwise control release of the substance(s) over a particular time period. Either or both of the substances may be microencapsulated: suitable encapsulating entities include liposomes, niosomes, aspasomes, cubosomes, microsponges, microemulsions, hydrogels and solid lipid nanoparticles. Particularly suitable liposomes, for topical application to the skin, are those made from stratum corneum lipids, eg ceramides, fatty acids or cholesterol.

The formulation may contain excipients and other additives known for use in pharmaceutical or cosmetic formulations. Examples of suitable additives include emollients, moisturisers, perfumes, antioxidants, preservatives, stabilisers, gelling agents and other thickeners, sunscreens, colouring agents and surfactants; others may be found in Williams' *Transdermal and Topical Drug Delivery* (see above). For the treatment of acne, however, it may be preferred for the formulation not to contain an emollient. For a leave-on formulation, it may be preferred for surfactants other than the DAS to be included at low levels, if at all, or to be mild surfactants such as cocamidopropyl betaine, sodium or ammonium cocoyl isethionate, sodium carboxymethyl coco polypropylamine, disodium cocoamphodiacetate, cocamine oxide, PEG-3 cocamide, disodium cocamphodiacetate, sodium lauroyl lactylate or decyl glucoside.

The formulation may further contain additional active agents such as antimicrobial (in particular antibacterial) or anti-acne agents. For example, it may contain one or more agents selected from anti-acne agents, anti-inflammatories, anti-irritants, anti-proliferatives, antibiotics, anti-androgens, sebostatic agents, anti-pruritics, immunomodulators, agents which promote wound healing and mixtures thereof.

An additional antimicrobial agent may be selected from biocides, disinfectants, antiseptics, antibiotics, bacteriophages, enzymes, anti-adhesins, immunoglobulins, antimicrobially active antioxidants and mixtures thereof; it may be active as a bactericide, in particular against propionibacteria. It may however be preferred for the

DAS and the salicylic acid or derivative to be the only active agents in the formulation, or at least to be the only antimicrobially or antibacterially active agents and/or the only anti-acne active agents.

A formulation according to the invention may be incorporated into, and hence applied in the form of, another product such as a cosmetic (eg a foundation or blusher), a hair care product such as a shampoo, skin care preparation (for example a skin cleanser, toner or moisturiser or a face mask), a pharmaceutical (which includes veterinary) preparation, a cosmeceutical preparation, or a toiletry product (for instance a bath or shower additive or a soap). An aspect of the present invention can provide such a product. Moreover the invention can embrace the use of (i) a DAS and (ii) salicylic acid or a derivative thereof, in the manufacture of such a product for use in the topical treatment of acne.

According to a seventh aspect of the present invention, there is provided a dialkyl sulphosuccinate (DAS) for use in the topical treatment of acne, wherein the DAS is applied in a leave-on formulation containing 3.5% w/v or greater of the DAS. An eighth aspect provides the use of a DAS in the manufacture of a topical formulation for the treatment of acne, wherein the formulation is a leave-on formulation containing 3.5% w/v or greater of the DAS. The DAS will typically be used as an antibacterial agent, and/or as an anti-acne agent, in the manufacture of the formulation. A ninth aspect provides the use of a DAS as a leave-on topical anti-acne or skin care agent, for non-therapeutic purposes, for example for cosmetic purposes such as to improve the appearance, feel or smell of the skin, wherein the DAS is applied at a concentration of 3.5% w/v or greater. A tenth aspect provides a method of treatment of a patient who is suffering from or at risk of suffering from acne, the method involving topically applying to the patient's skin a formulation containing 3.5% w/v or greater of a DAS, and leaving the formulation in contact with the skin after its application. The formulation is suitably administered to a patient who is suffering from acne, for example using a dosage regime of the type described above.

According to an eleventh aspect, the invention provides a topical skin care formulation containing 3.5% w/v or greater of a DAS, which formulation is suitable and/or adapted

and/or intended for use as a leave-on product. The formulation may be an antibacterial or anti-acne formulation. It may be for use in or as a cosmetic.

Preferred features of the seventh to the eleventh aspects of the invention – for example as to the nature and concentration of the DAS and any additional substances formulated with it – may be as described above in connection with the first to the sixth aspects. In particular, the DAS may be formulated in a gel containing a polyoxyalkylene-based solubilising agent, an organic solvent (in particular an alcohol), and optionally a thickening agent and/or water. It may be formulated with salicylic acid or a derivative thereof, and/or with an antioxidant such as AO 2246 or AO 425.

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", mean "including but not limited to", and do not exclude other moieties, additives, components, integers or steps. Moreover the singular encompasses the plural unless the context otherwise requires: in particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

Preferred features of each aspect of the invention may be as described in connection with any of the other aspects. Other features of the invention will become apparent from the following examples. Generally speaking the invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims and drawings). Thus features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. Moreover unless stated otherwise, any feature disclosed herein may be replaced by an alternative feature serving the same or a similar purpose.

The present invention will now be further described with reference to the following non-limiting examples.

Example 1 – anti-acne activity

A trial was carried out on human subjects to assess the activity, in skin prone to acne, of formulations according to the invention. The test formulations were:

A a formulation containing 5% w/v dioctyl sodium sulphosuccinate (docusate sodium; DOSS) and 2% w/v salicylic acid in an aqueous gel.

B a formulation containing 5% w/v DOSS, 2% w/v salicylic acid and 1.75% w/v Antioxidant 2246 (AO 2246), in the same aqueous gel as formulation A.

C as a negative control, an alcohol-free, active-free aqueous gel (see below).

D as a positive control, a commercially available anti-acne product (Garnier™ "Pure A Intensive Treatment Night Gel", purchased in the EU). On assay, this was found to contain 2% w/v salicylic acid.

The aqueous gel used as the base for formulations A and B was a micro-emulsion containing ethanol, propylene glycol, diethylhexyl sodium sulphosuccinate, propylene glycol laurate, PEG-8 caprylic/capric glycerides, hydroxypropylcellulose, sodium hydroxide and the balance water.

The gel used as the negative control contained propylene glycol, carbomer, tromethamine, methylparaben, propylparaben and the balance water. The ingredients of the commercially available positive control were listed as "aqua, alcohol denat., glycerin, BIS-PEG-18 methyl ether dimethyl silane, acrylates/C10-30 alkyl acrylate crosspolymer, triethanolamine, camphor, Centella Asiatica / Centella Asiatica extract, Cucumis Sativus/Cucumber Fruit extract, Hamamelis Virginiana / Witch Hazel extract, salicylic acid, zinc PCA, hexylene glycol, PEG-60 hydrogenated castor oil, pentylene glycol, propylene glycol, fragrance, benzyl salicylate, hexyl cinnamal, limonene, linalool".

The detailed compositions of Formulations A to C are shown in Table 1 below.

Table 1

Ingredient (% v/v or w/v)	Formulation A	Formulation B	Negative Control
Water	36.45	34.7	87.97
Ethanol	34	34	NA
Propylene glycol	14	14	9.99
Diethylhexyl sodium sulphosuccinate	5	5	NA
Propylene glycol laurate	3.5	3.5	NA
PEG 80 caprylic/capric glycerides	3.5	3.5	NA
Salicylic acid	2	2	NA
Hydroxypropyl cellulose	1.3	1.30	NA
Sodium hydroxide	0.25	0.25	NA
Methylene di-t-butyl-cresol (AO 2246)	NA	1.75	NA
Carbomer	NA	NA	1.0
Tromethamine	NA	NA	0.88
Methylparaben	NA	NA	0.18
Propylparaben	NA	NA	0.02

The trial was a two-centre randomised, blinded controlled parallel group study in 70 male or female subjects aged 16 to 35 years. Two groups, each of 23 subjects, were treated with one of the two test formulations A and B, whilst two groups of 12 subjects each were treated with either the negative control (formulation C) or the positive control (formulation D). Treatments (1 g of the relevant formulation) were applied topically by hand to the entire face by the participants at home, once daily over an eight week study period. Once applied, the formulations were left on the skin rather than being rinsed off. No concomitant anti-acne medications were permitted and previous treatment was stopped at least four weeks before the baseline visit.

Treatments were randomly assigned to the subjects using a computer-generated code. Treatment application was double-blind for the placebo and test treatments and observer-blind for the positive control (different tube, overlabelled). Lesion counts were performed at baseline and on study days 15, 29 and 57. Adverse events such as skin irritation were documented by spontaneous reporting.

A sample size of 20 had 80% power to detect a difference in mean lesion count of 9.91 assuming that the standard deviation was 15.0 using a one sample Student's t-test with a 0.05 two-sided significance level. An adjustment due to multiple comparisons was not planned. All comparisons were versus baseline (intragroup not intergroup).

The results, in terms of the percentage reduction in lesion counts from the "baseline" at day 1, are summarised in Tables 2 to 5 below.

Table 2 – inflamed spots

TREATMENT	Percent reduction from baseline		
	Day 15	Day 29	Day 57
Formulation A	-5.8	11.9	31.3****
Formulation B	4.8	18.5*	31.6****
Formulation C	17.1*	16.5*	29.9**
Formulation D	12.4*	-1.0	20.8

*P = 0.01 – 0.05, **P = 0.001 – 0.01, ***P = 0.0001 – 0.001, ****P<0.0001 derived from mean counts.

Table 3 – non-inflamed spots

TREATMENT	Percent reduction from baseline		
	Day 15	Day 29	Day 57
Formulation A	17.1*	32.5***	35.3****
Formulation B	16.5*	26.5**	33.9****
Formulation C	0.5	12.3	9.8
Formulation D	-1.2	11.5	-8.7

Table 4 – total number of spots

TREATMENT	Percent reduction from baseline		
	Day 15	Day 29	Day 57
Formulation A	6.7	23.1***	33.5****
Formulation B	10.7*	22.6**	32.8****
Formulation C	8.6	14.4	19.6*
Formulation D	6.3	4.6	7.5

Table 5 – categorical analyses

TREATMENT	Percent of participants with ≥33% reduction from baseline at week 8		
	Inflamed spots	Non-inflamed spots	Total number of spots
Formulation A	47.6	42.9	47.6
Formulation B	50.0	50.0	50.0
Formulation C	25.0	8.3	25.0
Formulation D	33.3	20.0	16.7

Of the adverse events reported during the treatment period, all were assessed to be mild and most to be unlikely to be linked to the test formulations. Four of the subjects assigned to formulation A discontinued treatment; in only one case was this due to local irritation associated with product application and in another to facial erythema and a distal skin reaction which was considered as possibly related to the test product. No subjects using formulation B or either control formulation reported any side effects considered to be product related.

The trial results can be summarised as follows.

- Both treatments according to the invention, using Formulations A and B, produced significant reductions in inflamed spots, non-inflamed spots and total lesions.

- Greatest activity was observed against non-inflamed lesions (otherwise known as open and closed comedones, or blackheads and whiteheads respectively). This activity was detectable by day 15. Most inflamed spots arise from comedones (sometimes microcomedones which are not visible or palpable).

- The treatments using Formulations A and B also performed better than the positive control, a marketed product containing the same concentration of salicylic acid.

- The formulations of the invention – in particular formulation B – were well tolerated, despite their relatively high concentrations of the anionic surfactant DOSS and the keratolytic salicylic acid. They therefore appeared to be suitable for application as leave-on products.

Without wishing to be bound by these theories, it is possible that the DAS acts, via its detergent action, to reduce the number of pre-existing comedones and/or to prevent the formation of new comedones. In other words, it may loosen the "mortar" (interstitial lipids) in which the "bricks" (the corneocytes) are set. The DAS appears to retain at least some of its detergent activity after its initial application, and so can continue to have an effect on acne lesions whilst it remains in contact with the skin. Surprisingly, however, that contact does not appear to cause the skin irritation that might have been expected.

It is also possible that the DAS, via its known detergent and penetration enhancing effects, may facilitate the follicular penetration of salicylic acid. Again these effects appear to continue after the formulation is first applied to the skin, thus boosting the anti-acne effects of the salicylic acid and providing prolonged activity against acne lesions when the formulation is left in contact with the skin.

At the same time, the DAS and the salicylic acid appear to interact in a way that causes the combination to be less of an irritant than might have been expected from the properties of its individual components. It is particularly surprising that this effect can be observed even after eight weeks of treatment, by which time any cumulative irritancy caused by the two actives would have been expected to manifest itself and to have been reported by the subjects and/or their medical advisors. This effect is likely to be of value in formulating "mild" skin care preparations which can be left in contact with the skin for a prolonged anti-acne effect.

Example 2 – topical anti-acne formulations

The results from Example 1 show not only that the combination of a DAS with salicylic acid can be effective against acne, but also that the combination can be safely applied to the skin in the form of a leave-on acne treatment product. This can be of use

in preparing topical anti-acne formulations and products – such as cosmetics or toiletries – containing the combination.

A topical formulation for use in treating acne may for example be prepared by formulating a DAS such as dioctyl sodium sulphosuccinate, or a pharmaceutically acceptable derivative thereof, with salicylic acid or a pharmaceutically acceptable derivative thereof, in a suitable fluid vehicle, optionally together with conventional additives. Such vehicles and additives may be for instance as found in Williams' *Transdermal and Topical Drug Delivery* (see above) and other similar reference books, and/or in Rolland A *et al*, "Site-specific drug delivery to pilosebaceous structures using polymeric microspheres", *Pharm Res* 1993; 10: 1738-44; Mordon S *et al*, "Site-specific methylene blue delivery to pilosebaceous structures using highly porous nylon microspheres: an experimental evaluation", *Lasers Surg Med* 2003; 33: 119-25; and Alvarez-Roman R *et al*, "Skin penetration and distribution of polymeric nanoparticles", *J Controlled Release* 2004; 99: 53-62. They may be as used in the Example 1 formulations or as described in connection with the first aspect of the invention.

Such formulations may be prepared and administered using known techniques. They may for example take the form of creams, lotions, foams, ointments or gels. They may be applied to the skin using the fingers or via a suitable substrate such as a sponge or pad, and suitably rubbed into the skin surface so as to remain there for a prolonged period afterwards. The concentrations of the DAS and the salicylic acid or derivative may be in the ranges described above, dependent on the chosen active substances and the intended use of the formulation.

Claims

1. An anti-acne formulation containing (i) 3.5% w/v or greater of a dialkyl sulphosuccinate (DAS) and (ii) salicylic acid or a derivative thereof, wherein the formulation is suitable for application as a topical leave-on formulation, and provided that the salicylic acid derivative is not a halogenated salicylanilide.

2. A formulation according to claim 1, wherein the DAS is in the form of a salt in which the sulphonic acid group is present as the sulphonate $-S(O)_2-O^-$.

3. A formulation according to claim 1 or claim 2, wherein the DAS is in the form of a metal salt.

4. A formulation according to claim 3, wherein the metal salt is a sodium salt.

5. A formulation according to any one of the preceding claims, wherein the DAS is a C_8 to C_{18} dialkyl sulphosuccinate.

6. A formulation according to claim 5, wherein the DAS is a dioctyl sulphosuccinate.

7. A formulation according to any one of the preceding claims, wherein the salicylic acid derivative is a salicylate.

8. A formulation according to claim 9, wherein the salicylate is a metal salicylate.

9. A formulation according to any one of claims 1 to 6, wherein the salicylic acid is present in the form of the free acid.

10. A formulation according to any one of the preceding claims, wherein the concentration of the DAS is 4% w/v or greater.

11. A formulation according to any one of the preceding claims, wherein the concentration of the salicylic acid or derivative is 0.5% w/v or greater.

12. A formulation according to claim 11, wherein the concentration of the salicylic acid or derivative is 1% w/v or greater.

13. A formulation according to any one of the preceding claims, which additionally contains (a) a polyoxyalkylene-based solubilising agent, and (b) an organic solvent, in particular an alcohol.

14. A formulation according to any one of the preceding claims, which additionally contains a thickening agent.

15. A formulation according to any one of the preceding claims, which additionally contains an antioxidant.

16. A formulation according to any one of the preceding claims, which is in the form of a cream, paste, gel, lotion, foam, ointment, varnish or other viscous or semi-viscous fluid.

17. An anti-acne formulation which is substantially as herein described.

18. A kit for preparing an anti-acne formulation containing 3.5% w/v or greater of a DAS, the kit comprising a source of a DAS and a source of salicylic acid or a derivative thereof, together with instructions for combining the two compounds so as to make the formulation at or before the point of intended use, and/or for the co-administration of the two compounds to the skin, provided that the salicylic acid derivative is not a halogenated salicylanilide.

19. A formulation according to any one of claim 1 to 17, for use in the treatment of acne, wherein the formulation is applied topically as a leave-on formulation.

20. A formulation according to any one of claims 1 to 17, for use according to claim 19, wherein the formulation is applied to the skin and then left on the skin for a subsequent period of an hour or more.

21. A formulation according to any one of claims 1 to 17, for use according to claim 20, wherein the formulation is applied to the skin once daily, and left on the skin between applications.

22. A formulation according to any one of claims 1 to 17, for use according to any one of claims 19 to 21, wherein the treatment is continued for a period of at least 4 weeks.

23. Use of (i) a DAS and (ii) salicylic acid or a derivative thereof, in the manufacture of a topical leave-on formulation for the treatment of acne, wherein the formulation contains 3.5% w/v or greater of the DAS, and provided that the salicylic acid derivative is not a halogenated salicylanilide.

24. Use of a formulation according to any one of claims 1 to 17 as an anti-acne or skin care agent, for non-therapeutic purposes.

25. A method of treatment of a patient who is suffering from or at risk of suffering from acne, the method involving administering to the patient a therapeutically effective amount of a formulation according to any one of claims 1 to 17, wherein the formulation is applied topically to the patient's skin and is left in contact with the skin after its application.

26. A dialkyl sulphosuccinate (DAS) for use in the topical treatment of acne, wherein the DAS is applied in a leave-on formulation containing 3.5% w/v or greater of the DAS.

27. Use of a DAS in the manufacture of a topical formulation for the treatment of acne, wherein the formulation is a leave-on formulation containing 3.5% w/v or greater of the DAS.

28. Use of a DAS as a leave-on topical anti-acne or skin care agent, for non-therapeutic purposes, wherein the DAS is applied at a concentration of 3.5% w/v or greater.

29. A method of treatment of a patient who is suffering from or at risk of suffering from acne, the method involving topically applying to the patient's skin a formulation containing 3.5% w/v or greater of a DAS, and leaving the formulation in contact with the skin after its application.