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Received PCT 10/12/96
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COSMETIC DELIVERY SYSTEM FOR SALICYLIC ACID AND PROCESS FOR PREPARATION OF SAME

The present invention relates to liposomal dispersions containing un-neutralized salicylic acid and a process for their preparation. More particularly, the present invention relates to a cosmetic dispersion that allows for the incorporation of large amounts of salicylic acid within the hydrophobic compartment of the liposomal bilayer, without the necessity of pre-neutralization or salt formation of the corresponding salicylate, while simultaneously permitting the pH of the external aqueous compartment to be adjusted with soluble organic bases.

Salicylic acid is an active ingredient long-known to those skilled in the formulation of cosmetic and topical products. Dandruff has been treated with ointments containing 2 percent salicylic acid. As a keratolytic agent, salicylic acid will soften and swell the epidermis. At concentrations higher than 2 percent, salicylic acid is an efficacious anti-acne agent and is bactericidal. The formation of salts of salicylic acid, such as sodium salicylate formed by the combination of salicylic acid and sodium hydroxide, greatly improves the water solubility of the free acid, but substantially modifies the biological response to salicylic acid.

Salicylic acid is nearly insoluble in water (limit of solubility approximately 0.2 percent at room temperature). When incorporated into cosmetic solutions, salicylic acid requires the addition of cosolvents such as ethanol, isopropanol or dimethylsulfoxide. These solutions exhibit low pH (approximately 2), and as a consequence may be irritating to the skin. Development of aesthetic cosmetic formulations under these constraints of pH greatly limits the range of formulation types. For example, hydrocolloid gels will not form at this extreme of pH. Many other cosmetic ingredients are rendered unstable under these conditions.

A general reference for the formulation of cosmetic compositions containing salicylic acid follows:

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Description : paged ...1... to paged ...13...
Claim(s) : paged ...14... to paged ...16...
Drawing(s) : paged ...1... to paged ...-...
Abstract : paged ...17... to paged ...-...
DATE OF RECEIPT .....

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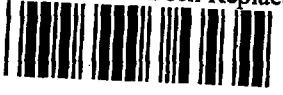
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The *Weiner and Fielder* U.S. Patent No. 5,049,392 relates to a method of producing liposomes specifically via osmotic shock; the resultant liposomes may contain NSAID's including salicylic acid.

The *Fountain* U.S Patent No. 5,133,965 relates to a wound dressing comprised of liposomes generated by a solvent-dilution method; the resultant liposomes may contain salicylic acid.

It is therefore an object of the present invention to provide a liposomal composition, particularly a topical formulation, and a process for its preparation, that permits the generation of liposomes containing salicylic acid, that allows

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the adjustment of the pH of the external aqueous compartment to pH ranges approaching neutrality, and that ensures that the greater proportion of the salicylic acid in the formulation remains as the free acid.

Other objects and features of the present invention will become apparent when considered in combination with the following summary and detailed description of certain preferred embodiments and examples of the present invention.

The foregoing and related objects are achieved by providing a cosmetic composition containing:

a) an effective amount of polar lipids known to form, either alone or in combination, liposomal bilayers;

b) an effective amount of salicylic acid;

c) an effective amount of a polar, membrane-impermeant, water-soluble organic base; and,

d) the balance up to 100 percent by weight of water based upon the total composition weight.

In addition, the composition may also contain an effective amount of any other suitable cosmetic or pharmaceutic ingredient, amoung which and specifically suited to the purpose are any of the many commercially available raw materials intended to function as antioxidants, preservatives, anti-inflammatory agents, and hydrocolloids.

The cosmetic liposomes of the invention can optionally also comprise other ingredients as are conventionally employed in cosmetic products. Examples of other ingedients include but are not limited to perfumes, colorants such as staining dyes and pigments, humectants, anti-dandruff agents, anti-acne agents, germicides, sunscreens, emollients, vitamins, sterols and other lipids.

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Particularly preferred pigments, when present, include calcium oxide, barium oxide and aluminum oxide, iron oxides, titanium dioxide, and mica.

Particularly preferred humectants include butylene glycol, glycerol, sorbitol and other polyols.

Particularly preferred antidandruff agents include selenium, selenium salts, resourcinol and coal tar.

Particularly preferred anti-acne agents include benzoyl peroxide and resourcinol.

Particularly preferred germicides include the parabens, kathon CG, phenoxyethanol and germall 115.

Particularly preferred sunscreens include octyl methoxycinnimate and butyl methoxydibenzoylmethane.

Particularly preferred emollients include cyclomethicone, dimethicone, and lanolin derivatives.

Particularly preferred hydrocolloids include hyaluronic acid, guar, carrageenan, alginic acid, polymethacrylates and their derivatives.

Particularly preferred vitamins include vitamin E, vitamin A palmitate and Vitamin C.

Particularly preferred sterols include sitosterol, stigmasterol, phytosterols and cholesterol.

Particularly preferred other lipids include ceramides, cerebroside and other sphingolipids

The preferred method of manufacture involves extrusion under conditions of extremely high pressure generated by commercially available equipment such as the Microfluidizer

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(Microfluidics Corp., Newton, Mass.). The liposomes are produced in the presence of insoluble salicylic acid and the bilayer-forming lipids devoid of any organic bases or buffers. After production, the pH of the external aqueous compartment is adjusted with a membrane-impermeant organic base.

Particularly preferred membrane lipids include the synthetic phospholipids such as dipalmitoylphosphatidylcholine, natural phospholipids such as soya lecithin or egg yolk lecithin, phosphatidylethanolamines, phosphatidylserines, cereamides, cerebrosides, and phosphatidylglycerides.

Particularly preferred organic bases include the basic amino acids such as arginine, lysine and glutamine, and triethanolamine.

An effective amount of the membrane-forming lipid phase is preferably from 0.1% to 10% by weight, more preferably from 0.5% to 5.0% by weight, and most preferably from 1.0% to 4.0% by weight, based upon the total composition weight.

An effective amount of salicylic acid is from 0.05% to 20% by weight, more preferably from 1% to 15% by weight, and most preferably 5% to 12% by weight, based upon the total composition weight.

An effective amount of organic base is from 0.05% to 25% by weight, more preferably from 1% to 20% by weight, and most preferably from 2 to 15% by weight, based upon the total composition weight.

The cosmetic composition of the invention is useful as a moisturizer, a moisturizing gel, an anti-dandruff lotion, a cleanser and a toner.

The present invention will now be described in greater detail with reference being made to the drawing and the following examples and preferred embodiments. It should, of

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course, be recognized that the drawing and the following examples and preferred embodiments of the invention are intended solely for the purpose of illustration, and are not intended as limiting the scope thereof.

FIG. 1 represents a penetration study for salicylic acid recovered from skin strips of human panalists following application of liposomes containing salicylic acid.

In a preferred embodiment, the cosmetic composition of the present invention comprises:

a) about 0.1% to 10% by weight of a membrane-forming lipid phase;

b) about 0.05% to 20% by weight of salicylic acid;

c) about 0.05% to 25% by weight of arginine or a similar water-soluble organic base;

d) about 40% to 99.8% by weight of water;

e) 0% to about 20% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

The advantages of the present invention include the fact that the cosmetic composition has the unexpected ability to sustain a neutral pH (7.0) in the external aqueous milieu, without neutralizing the salicylic acid to the corresponding salicylate. Once neutralized, the bulk dispersion can be utilized in a wide array of finished product types.

In a more preferred embodiment, the cosmetic composition of the present invention comprises:

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a) about 0.5% to 5% by weight of a membrane-forming lipid phase;

b) about 1.0% to 15% by weight of salicylic acid;

c) about 1.0% to 20% by weight of arginine or a similar water-soluble organic base;

d) about 50% to 98.5% by weight of water;

e) about 1% to 20% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

In a most preferred embodiment, the cosmetic composition of this invention comprises:

a) about 1% to 4% by weight of a membrane-forming lipid phase;

b) about 5% to 12% by weight of salicylic acid;

c) about 2% to 15% by weight of arginine or a similar water-soluble organic base;

d) about 60% to 90% by weight of water;

e) about 5% to 15% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

The ingredients used in the composition of this invention should be of a quality or purity (such as U.S.P. or N.F.)

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suitable for cosmetic use and should be compatible when used together in a particular composition. Unless indicated otherwise, the physical properties of the components of the composition of the present invention specified herein are the properties of these components before they are mixed with the composition's other ingredients.

Among the commercially available suitable membrane forming lipids are the various purified soya lecithins available from Natterman (Cologne, Germany), Lucas Meyer (Illinois), Avanti Polar Lipids (North Dakota), and Nikko Chemical (Tokyo, Japan).

Among the commercially suitable soluble organic bases are L-Arginine, L-Lysine, L-Glutamine, available from Tanabi (Woodcliff lake, New Jersey) and Triethanolamine, available from Acro Chemical Company (Farmingdale, New York).

Salicylic acid is available from Universal Preserv-A-Chem, Inc. (Brooklyn, New York).

The composition of the present invention may be prepared by the following process steps, which are carried out at room temperature (25C) under 1 atmosphere pressure of argon gas (to limit any opportunity for oxidation):

a) Use of a marine or propellar-type mixer to disperse the membrane-forming lipid in the total quantity of water available to the formulation. In this first embodiment, the mixing occurred at 500 to 1500 rpm and lasted for 1 hour. The remaining water-insoluble phases are then added to the wetted lipids, along with the salicylic acid and any germicides or preservatives. Any additional cosmetic excipients or active ingredients are then added to the batch. In this second embodiment, the mixing was continued at 500 to 1500 rpm for 1 hour with caution to avoid vortex and entrainment of air.

b) In order to facilitate hydration of the batch prior to high-shear processing, the batch was then homogenized with

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a rotot/stator-type homogenizer running at 3,000 rpm for 30 minutes.

c) At this stage the batch was subjected to high-shear processing, specifically microfluidization. In this process, the liquid is extruded through two 100 micron pores. The jetting streams collide within an interaction chamber, and then the liquid is extruded to ambient pressure. The combination of shear and prssure change completes the dispersion of the insoluble phases and produces liposomes as verified by freeze-fracture electron microscopy.

d) The pH of the batch at this stage is acidic (pH approximately 2.0) due to the limited solubility of salicylic acid in water (approximately 0.2%). A batch titration was then performed with arginine to acheive a final pH of 6.5 to 7.5. the amount of arginine required is determined by the total availability of titratable groups. However, less than 1% salicylic acid is neutralized by this process.

e) Finally, any necessary additional cosmetic ingredients meant to occupy solution volumes outside the liposomes may be added. Such materials might include thickeners or other rheologic agents, emollients, humectants and germicides.

The above procedure is generic to all of the specific types of compositions, and may be modified as necessary to achieve the preparataion of a specific final product. Different ingredients may require modification in the order of addition of materials, depending on whether the intentionis to locate the ingredient internal or external to the liposome, whether the ingredient is water-soluble, or whether the ingredient behaves as an acid or base.

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EXAMPLES

Example 1 (Salicylic Acid Liposome)

Phase	Ingredient	Parts by Weight
1	Lecithin	1.0
1	Water	83.0
2	Salicylic Acid	10.0
2	Phenonip	1.0
2	Vitamin E Acetate	1.0
3	Arginine	4.0

The ingredients in Phase 1 were mixed by a propeller rotating at 500 to 1,500 rpm for one hour. The ingredients of Phase 2 were added, and mixing continued for an additional one hour. The batch was then subjected to high-shear extrusion at 12,000 psi of pressure through a 100 micron pore. Dynamic laser light scattering revealed a particle diameter of 200 nanometers. Carboxyfluoroscein labeling indicated intact liposomes. Freeze-fracture transmission electron microscopy substantiated the presence of vesicles. After microfluidization, the arginine was added, and the pH increased from 2.0 to 6.7.

FIG. 1 contrasts the penetration of salicylic acid into the epidermis of the volar forearm of human panelists. The degree of penetration was determined by HPLC analysis of solubilized Scotch Tape strips. A control comprised of a sodium sterate emulsion containing 10 percent salicylic acid was prepared. Both the experimental liposome and the control emulsion were diluted 1 to 10 in a gel of polymethacrylate and applied at equivalent sites. The figure reveals that the penetration of salicylic acid was facilitated by liposomal inclusion. The level of liposomal salicylic acid was found to be, and continued to be, safe, non-irritating, moisturizing product.

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Example 2 (Moisturizing Liposome)

Phase	Ingredient	Parts by Weight
1	Lecithin	2.0
1	Sitosterol	0.5
1	Water	84.5
1	Trehalose	1.0
1	NaPCA	1.0
2	Salicylic Acid	5.0
2	Phenonip	1.0
2	Vitamin E Linoleate	1.0
2	Vitamin A Palmitate	1.0
3	Arginine	3.0

The product was processed utilizing a procedure analogous to that described above for Example 1. The sample was diluted 1 to 4 in a 0.5 percent polymethacrylate gel and applied to the skin. After two hours, the final product was found to be, and continued to be, safe, non-irritating, moisturizing product.

Example 3 (Anti-Acne Liposome)

Phase	Ingredient	Parts by Weight
1	Lecithin	2.0
1	Cholesterol	0.3
1	Glycine	1.0
1	Resourcinol	0.1
1	Water	86.6
2	Salicylic Acid	5.0
2	Chlorphenesin	2.5
3	Arginine	2.5

The product was processed utilizing a procedure analogous to that described above for Example 1. The sample was diluted 1 to 4 in a 0.5 percent polymethacrylate gel. After dilution, the product was innoculated with 1×10^7 cfu per gram of *p.acne*. At 48 hours, no bacteria could be detected. The final product was applied to the skin beneath the eye of an adult human male. After two hours, no indication of irritation was

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present, and the product continued to be a safe and non-irritating anti-acne formulation.

Example 4 (Moisturing Liposome Gel)

Phase	Ingredient	Parts by Weight
(a) Preproduct		
1	Lecithin	2.0
1	NaPCA	1.0
1	Glycine	1.0
1	Trehalose	1.0
1	Water	86.6
2	Salicylic Acid	2.0
2	Chlorphenesin	2.5
3	Arginine	0.5
(b) Final Product		
4	Butylene glycol	3.1
4	Carbomer 941	0.3

The product was processed utilizing a procedure analogous to that described above for Example 1. The sample was found to have a viscosity of 28,000 centipoise. The final product was topically applied to the skin of the forearm of adult human male. After two hours, no indication of irritation was present, and the product continued to be a safe and non-irritating moisturizer.

Thus, while the aforementioned embodiments of the present invention have been shown and described, it will be obvious that many changes and modifications may be made thereunto without departing from the spirit and scope of the invention as defined in the appended claims.

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CLAIMS

1. A cosmetic composition comprising:

a) An effective amount of a membrane-forming lipid phase known to form, either alone or incombination, liposomes;

b) An effective amount of salicylic acid which becomes localized within the lipidic, hydrophobic environement of the liposomal bilayers;

c) An effective amount of a membrane-impermeant, water-soluble organic base; and,

d) the balance up to 100% by weight of water.

2) A cosmetic composition comprising:

a) about 0.1% to 10% by weight of a membrane-forming lipid phase;

b) about 0.05% to 20% by weight of salicylic acid;

c) about 0.05% to 25% by weight of arginine or a similar water-soluble organic base;

d) about 40% to 99.8% by weight of water;

e) 0% to about 20% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

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3) A cosmetic composition comprising:

a) about 1% to 4% by weight of a membrane-forming lipid phase;

b) about 5% to 12% by weight of salicylic acid;

c) about 2% to 15% by weight of arginine or a similar water-soluble organic base;

d) about 60% to 90% by weight of water;

e) about 5% to 15% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

4) A process for the preparation of a cosmetic composition containing:

(i) membrane-forming lipids dispersed in the form of liposomes;

(ii) salicylic acid preferrentially localized within the liposome bilayer membranes;

(iii) an organic base, impermeant to membranes, preferntially localized in the aqueous compartment outside the liposome;

(iv) water; and,

(v) other suitable cosmetic ingedients,

comprising the steps of:

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a) dispersing by mixing the membrane-forming lipids, and any soluble component intented to be encapsulated within the internal aqueous compartment of the liposome, in the aqueous phase of the composition;

b) adding the salicylic acid to the crude dispersion without neutralization;

c) adding any other lipid-soluble components;

d) processing the crude, hydrated dispersion under conditions of high shear adequate to manufacture liposomes;

e) adding any other components intended to be localized in the aqueous compartment outside the liposome; and,

f) neutralizing the aqueous environment external to the liposome by the addition of wtaer-soluble, membrane-impermeant base.

5) The process according to Claim 4, wherein a preproduct is first prepared, and then subsequently the final product is produced.

6) The process according to Claim 4, wherein the final product is produced without the preparation of a preproduct.

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ABSTRACT

COSMETIC DELIVERY SYSTEM FOR SALICYLIC ACID AND PROCESS FOR PREPARATION OF SAME

A cosmetic composition which includes:

a) membrane lipids dispersed in the form of liposomes;

b) un-neutralized salicylic acid localized within the membrane lipid bilayer of the liposome;

c) other cosmetic ingredients located in either the membrane compartment, or in either of the external or internal aqueous compartments or some combination thereof;

d) an organic, water-soluble membrane-impermeant base; and,

e) water.

This composition enables the inclusion of salicylic acid as the free acid in products of neutral pH.

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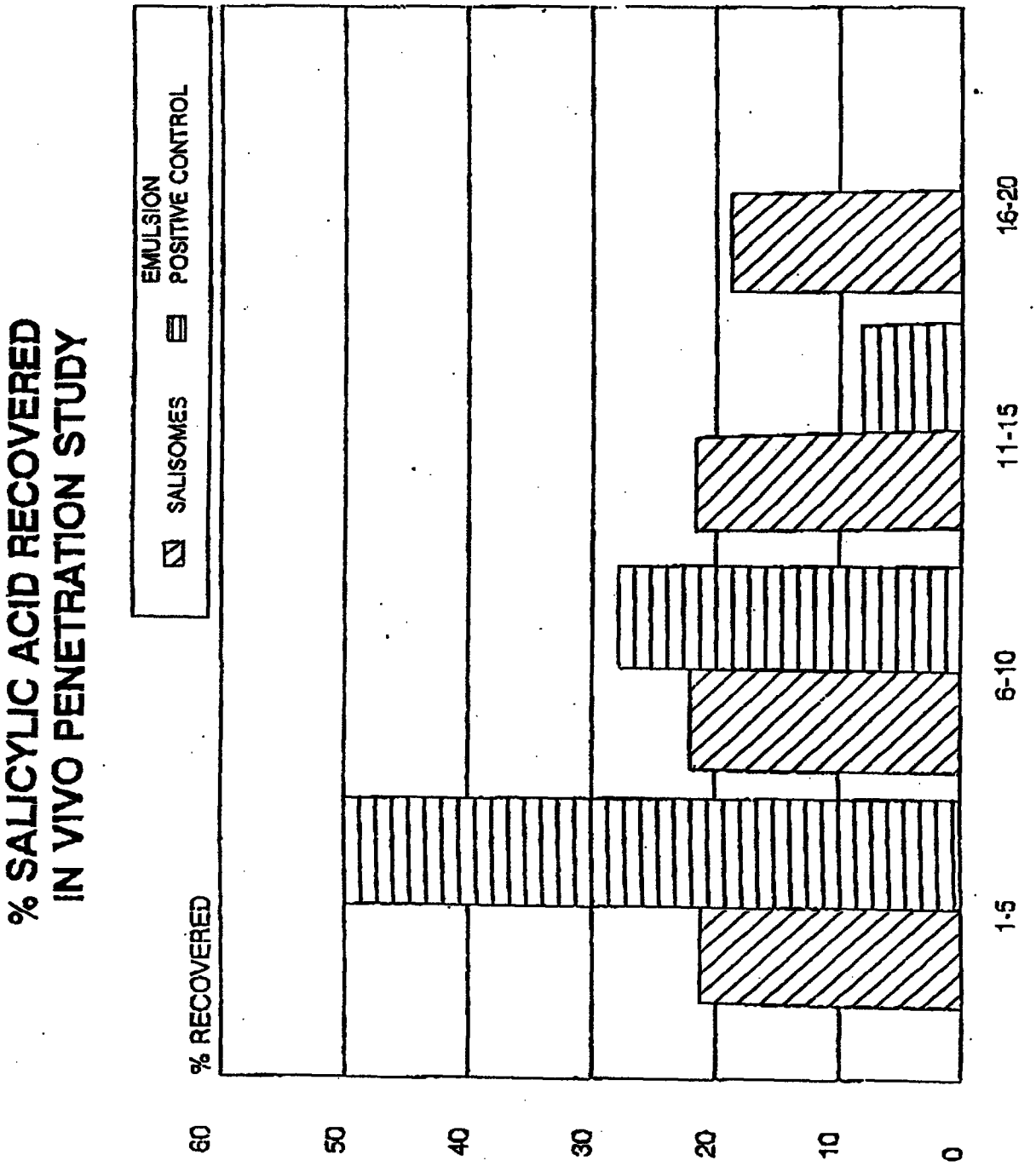

% SALICYLIC ACID RECOVERED
IN VIVO PENETRATION STUDY
EMULSION
SALISOMES
POSITIVE CONTROL
% RECOVERED
60
50
40
30
20
10
0
1-5
6-10
11-15
16-20

FIG. 1

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✓ Description : paged 1. to paged 13.
✓ Claim(s) : paged 14 to paged 16.
✓ Drawing(s) : paged 1/1 to paged —.
✓ Abstract : paged 17. to paged —.

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The present invention relates to liposomal dispersions containing un-neutralized salicylic acid and a process for their preparation. More particularly, the present invention relates to a cosmetic dispersion that allows for the incorporation of large amounts of salicylic acid within the hydrophobic compartment of the liposomal bilayer, without the necessity of pre-neutralization or salt formation of the corresponding salicylate, while simultaneously permitting the pH of the external aqueous compartment to be adjusted with soluble organic bases.

Salicylic acid is an active ingredient long-known to those skilled in the formulation of cosmetic and topical products. Dandruff has been treated with ointments containing 2 percent salicylic acid. As a keratolytic agent, salicylic acid will soften and swell the epidermis. At concentrations higher than 2 percent, salicylic acid is an efficacious anti-acne agent and is bactericidal. The formation of salts of salicylic acid, such as sodium salicylate formed by the combination of salicylic acid and sodium hydroxide, greatly improves the water solubility of the free acid, but substantially modifies the biological response to salicylic acid.

Salicylic acid is nearly insoluble in water (limit of solubility approximately 0.2 percent at room temperature). When incorporated into cosmetic solutions, salicylic acid requires the addition of cosolvents such as ethanol, isopropanol or dimethylsulfoxide. These solutions exhibit low pH (approximately 2), and as a consequence may be irritating to the skin. Development of aesthetic cosmetic formulations under these constraints of pH greatly limits the range of formulation types. For example, hydrocolloid gels will not form at this extreme of pH. Many other cosmetic ingredients are rendered unstable under these conditions.

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the adjustment of the pH of the external aqueous compartment to pH ranges approaching neutrality, and that ensures that the greater proportion of the salicylic acid in the formulation remains as the free acid.

Other objects and features of the present invention will become apparent when considered in combination with the following summary and detailed description of certain preferred embodiments and examples of the present invention.

The foregoing and related objects are achieved by providing a cosmetic composition containing:

a) an effective amount of polar lipids known to form, either alone or in combination, liposomal bilayers;

b) an effective amount of salicylic acid;

c) an effective amount of a polar, membrane-impermeant, water-soluble organic base; and,

d) the balance up to 100 percent by weight of water based upon the total composition weight.

In addition, the composition may also contain an effective amount of any other suitable cosmetic or pharmaceutic ingredient, amoung which and specifically suited to the purpose are any of the many commercially available raw materials intended to function as antioxidants, preservatives, anti-inflammatory agents, and hydrocolloids.

The cosmetic liposomes of the invention can optionally also comprise other ingredients as are conventionally employed in cosmetic products. Examples of other ingedients include but are not limited to perfumes, colorants such as staining dyes and pigments, humectants, anti-dandruff agents, anti-acne agents, germicides, sunscreens, emollients, vitamins, sterols and other lipids.

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Particularly preferred pigments, when present, include calcium oxide, barium oxide and aluminum oxide, iron oxides, titanium dioxide, and mica.

Particularly preferred humectants include butylene glycol, glycerol, sorbitol and other polyols.

Particularly preferred antidandruff agents include selenium, selenium salts, resourcinol and coal tar.

Particularly preferred anti-acne agents include benzoyl peroxide and resourcinol.

Particularly preferred germicides include the parabens, kathon CG, phenoxyethanol and germall 115.

Particularly preferred sunscreens include octyl methoxycinnimate and butyl methoxydibenzoylmethane.

Particularly preferred emollients include cyclomethicone, dimethicone, and lanolin derivatives.

Particularly preferred hydrocolloids include hyaluronic acid, guar, carrageenan, alginic acid, polymethacrylates and their derivatives.

Particularly preferred vitamins include vitamin E, vitamin A palmitate and Vitamin C.

Particularly preferred sterols include sitosterol, stigmasterol, phytosterols and cholesterol.

Particularly preferred other lipids include ceramides, cerebroside and other sphingolipids

The preferred method of manufacture involves extrusion under conditions of extremely high pressure generated by commercially available equipment such as the Microfluidizer

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(Microfluidics Corp., Newton, Mass.). The liposomes are produced in the presence of insoluble salicylic acid and the bilayer-forming lipids devoid of any organic bases or buffers. After production, the pH of the external aqueous compartment is adjusted with a membrane-impermeant organic base.

Particularly preferred membrane lipids include the synthetic phospholipids such as dipalmitoylphosphatidylcholine, natural phospholipids such as soya lecithin or egg yolk lecithin, phosphatidylethanolamines, phosphatidylserines, cereamides, cerebrosides, and phosphatidylglycerides.

Particularly preferred organic bases include the basic amino acids such as arginine, lysine and glutamine, and triethanolamine.

An effective amount of the membrane-forming lipid phase is preferably from 0.1% to 10% by weight, more preferably from 0.5% to 5.0% by weight, and most preferably from 1.0% to 4.0% by weight, based upon the total composition weight.

An effective amount of salicylic acid is from 0.05% to 20% by weight, more preferably from 1% to 15% by weight, and most preferably 5% to 12% by weight, based upon the total composition weight.

An effective amount of organic base is from 0.05% to 25% by weight, more preferably from 1% to 20% by weight, and most preferably from 2 to 15% by weight, based upon the total composition weight.

The cosmetic composition of the invention is useful as a moisturizer, a moisturizing gel, an anti-dandruff lotion, a cleanser and a toner.

The present invention will now be described in greater detail with reference being made to the drawing and the following examples and preferred embodiments. It should, of

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course, be recognized that the drawing and the following examples and preferred embodiments of the invention are intended solely for the purpose of illustration, and are not intended as limiting the scope thereof.

FIG. 1 represents a penetration study for salicylic acid recovered from skin strips of human panalists following application of liposomes containing salicylic acid.

In a preferred embodiment, the cosmetic composition of the present invention comprises:

a) about 0.1% to 10% by weight of a membrane-forming lipid phase;

b) about 0.05% to 20% by weight of salicylic acid;

c) about 0.05% to 25% by weight of arginine or a similar water-soluble organic base;

d) about 40% to 99.8% by weight of water;

e) 0% to about 20% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

The advantages of the present invention include the fact that the cosmetic composition has the unexpected ability to sustain a neutral pH (7.0) in the external aqueous milieu, without neutralizing the salicylic acid to the corresponding salicylate. Once neutralized, the bulk dispersion can be utilized in a wide array of finished product types.

In a more preferred embodiment, the cosmetic composition of the present invention comprises:

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a) about 0.5% to 5% by weight of a membrane-forming lipid phase;

b) about 1.0% to 15% by weight of salicylic acid;

c) about 1.0% to 20% by weight of arginine or a similar water-soluble organic base;

d) about 50% to 98.5% by weight of water;

e) about 1% to 20% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

In a most preferred embodiment, the cosmetic composition of this invention comprises:

a) about 1% to 4% by weight of a membrane-forming lipid phase;

b) about 5% to 12% by weight of salicylic acid;

c) about 2% to 15% by weight of arginine or a similar water-soluble organic base;

d) about 60% to 90% by weight of water;

e) about 5% to 15% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

The ingredients used in the composition of this invention should be of a quality or purity (such as U.S.P. or N.F.)

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suitable for cosmetic use and should be compatible when used together in a particular composition. Unless indicated otherwise, the physical properties of the components of the composition of the present invention specified herein are the properties of these components before they are mixed with the composition's other ingredients.

Among the commercially available suitable membrane forming lipids are the various purified soya lecithins available from Natterman (Cologne, Germany), Lucas Meyer (Illinois), Avanti Polar Lipids (North Dakota), and Nikko Chemical (Tokyo, Japan).

Among the commercially suitable soluble organic bases are L-Arginine, L-Lysine, L-Glutamine, available from Tanabi (Woodcliff lake, New Jersey) and Triethanolamine, available from Acro Chemical Company (Farmingdale, New York).

Salicylic acid is available from Universal Preserv-A-Chem, Inc. (Brooklyn, New York).

The composition of the present invention may be prepared by the following process steps, which are carried out at room temperature (25C) under 1 atmosphere pressure of argon gas (to limit any opportunity for oxidation):

a) Use of a marine or propellar-type mixer to disperse the membrane-forming lipid in the total quantity of water available to the formulation. In this first embodiment, the mixing occurred at 500 to 1500 rpm and lasted for 1 hour. The remaining water-insoluble phases are then added to the wetted lipids, along with the salicylic acid and any germicides or preservatives. Any additional cosmetic excipients or active ingredients are then added to the batch. In this second embodiment, the mixing was continued at 500 to 1500 rpm for 1 hour with caution to avoid vortex and entrainment of air.

b) In order to facilitate hydration of the batch prior to high-shear processing, the batch was then homogenized with

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a rotot/stator-type homogenizer running at 3,000 rpm for 30 minutes.

c) At this stage the batch was subjected to high-shear processing, specifically microfluidization. In this process, the liquid is extruded through two 100 micron pores. The jetting streams collide within an interaction chamber, and then the liquid is extruded to ambient pressure. The combination of shear and prssure change completes the dispersion of the insoluble phases and produces liposomes as verified by freeze-fracture electron microscopy.

d) The pH of the batch at this stage is acidic (pH approximately 2.0) due to the limited solubility of salicylic acid in water (approximately 0.2%). A batch titration was then performed with arginine to acheive a final pH of 6.5 to 7.5. the amount of arginine required is determined by the total availability of titratable groups. However, less than 1% salicylic acid is neutralized by this process.

e) Finally, any necessary additional cosmetic ingredients meant to occupy solution volumes outside the liposomes may be added. Such materials might include thickeners or other rheologic agents, emollients, humectants and germicides.

The above procedure is generic to all of the specific types of compositions, and may be modified as necessary to achieve the preparataion of a specific final product. Different ingredients may require modification in the order of addition of materials, depending on whether the intentionis to locate the ingredient internal or external to the liposome, whether the ingredient is water-soluble, or whether the ingredient behaves as an acid or base.

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EXAMPLES

Example 1 (Salicylic Acid Liposome)

Phase	Ingredient	Parts by Weight
1	Lecithin	1.0
1	Water	83.0
2	Salicylic Acid	10.0
2	Phenonip	1.0
2	Vitamin E Acetate	1.0
3	Arginine	4.0

The ingredients in Phase 1 were mixed by a propeller rotating at 500 to 1,500 rpm for one hour. The ingredients of Phase 2 were added, and mixing continued for an additional one hour. The batch was then subjected to high-shear extrusion at 12,000 psi of pressure through a 100 micron pore. Dynamic laser light scattering revealed a particle diameter of 200 nanometers. Carboxyfluoroscein labeling indicated intact liposomes. Freeze-fracture transmission electron microscopy substantiated the presence of vesicles. After microfluidization, the arginine was added, and the pH increased from 2.0 to 6.7.

FIG. 1 contrasts the penetration of salicylic acid into the epidermis of the volar forearm of human panelists. The degree of penetration was determined by HPLC analysis of solubilized Scotch Tape strips. A control comprised of a sodium sterate emulsion containing 10 percent salicylic acid was prepared. Both the experimental liposome and the control emulsion were diluted 1 to 10 in a gel of polymethacrylate and applied at equivalent sites. The figure reveals that the penetration of salicylic acid was facilitated by liposomal inclusion. The level of liposomal salicylic acid was found to be, and continued to be, safe, non-irritating, moisturizing product.

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Example 2 (Moisturizing Liposome)

Phase	Ingredient	Parts by Weight
1	Lecithin	2.0
1	Sitosterol	0.5
1	Water	84.5
1	Trehalose	1.0
1	NaPCA	1.0
2	Salicylic Acid	5.0
2	Phenonip	1.0
2	Vitamin E Linoleate	1.0
2	Vitamin A Palmitate	1.0
3	Arginine	3.0

The product was processed utilizing a procedure analogous to that described above for Example 1. The sample was diluted 1 to 4 in a 0.5 percent polymethacrylate gel and applied to the skin. After two hours, the final product was found to be, and continued to be, safe, non-irritating, moisturizing product.

Example 3 (Anti-Acne Liposome)

Phase	Ingredient	Parts by Weight
1	Lecithin	2.0
1	Cholesterol	0.3
1	Glycine	1.0
1	Resourcinol	0.1
1	Water	86.6
2	Salicylic Acid	5.0
2	Chlorphenesin	2.5
3	Arginine	2.5

The product was processed utilizing a procedure analogous to that described above for Example 1. The sample was diluted 1 to 4 in a 0.5 percent polymethacrylate gel. After dilution, the product was innoculated with 1×10^7 cfu per gram of *p.acne*. At 48 hours, no bacteria could be detected. The final product was applied to the skin beneath the eye of an adult human male. After two hours, no indication of irritation was

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present, and the product continued to be a safe and non-irritating anti-acne formulation.

Example 4 (Moisturing Liposome Gel)

Phase	Ingredient	Parts by Weight
(a) Preproduct		
1	Lecithin	2.0
1	NaPCA	1.0
1	Glycine	1.0
1	Trehalose	1.0
1	Water	86.6
2	Salicylic Acid	2.0
2	Chlorphenesin	2.5
3	Arginine	0.5
(b) Final Product		
4	Butylene glycol	3.1
4	Carbomer 941	0.3

The product was processed utilizing a procedure analogous to that described above for Example 1. The sample was found to have a viscosity of 28,000 centipoise. The final product was topically applied to the skin of the forearm of adult human male. After two hours, no indication of irritation was present, and the product continued to be a safe and non-irritating moisturizer.

Thus, while the aforementioned embodiments of the present invention have been shown and described, it will be obvious that many changes and modifications may be made thereunto without departing from the spirit and scope of the invention as defined in the appended claims.

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CLAIMS

1. A cosmetic composition comprising:

a) An effective amount of a membrane-forming lipid phase known to form, either alone or incombination, liposomes;

b) An effective amount of salicylic acid which becomes localized within the lipidic, hydrophobic environement of the liposomal bilayers;

c) An effective amount of a membrane-impermeant, water-soluble organic base; and,

d) the balance up to 100% by weight of water.

2) A cosmetic composition comprising:

a) about 0.1% to 10% by weight of a membrane-forming lipid phase;

b) about 0.05% to 20% by weight of salicylic acid;

c) about 0.05% to 25% by weight of arginine or a similar water-soluble organic base;

d) about 40% to 99.8% by weight of water;

e) 0% to about 20% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

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3) A cosmetic composition comprising:

a) about 1% to 4% by weight of a membrane-forming lipid phase;

b) about 5% to 12% by weight of salicylic acid;

c) about 2% to 15% by weight of arginine or a similar water-soluble organic base;

d) about 60% to 90% by weight of water;

e) about 5% to 15% by weight of other suitable cosmetic ingredients, and

with all weight percentages based upon the total % composition weight.

4) A process for the preparation of a cosmetic composition containing:

(i) membrane-forming lipids dispersed in the form of liposomes;

(ii) salicylic acid preferrentially localized within the liposome bilayer membranes;

(iii) an organic base, impermeant to membranes, preferntially localized in the aqueous compartment outside the liposome;

(iv) water; and,

(v) other suitable cosmetic ingedients,

comprising the steps of:

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a) dispersing by mixing the membrane-forming lipids, and any soluble component intented to be encapsulated within the internal aqueous compartment of the liposome, in the aqueous phase of the composition;

b) adding the salicylic acid to the crude dispersion without neutralization;

c) adding any other lipid-soluble components;

d) processing the crude, hydrated dispersion under conditions of high shear adequate to manufacture liposomes;

e) adding any other components intended to be localized in the aqueous compartment outside the liposome; and,

f) neutralizing the aqueous environment external to the liposome by the addition of wtaer-soluble, membrane-impermeant base.

5) The process according to Claim 4, wherein a preproduct is first prepared, and then subsequently the final product is produced.

6) The process according to Claim 4, wherein the final product is produced without the preparation of a preproduct.

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ABSTRACT

COSMETIC DELIVERY SYSTEM FOR SALICYLIC ACID AND PROCESS FOR PREPARATION OF SAME

A cosmetic composition which includes:

a) membrane lipids dispersed in the form of liposomes;

b) un-neutralized salicylic acid localized within the membrane lipid bilayer of the liposome;

c) other cosmetic ingredients located in either the membrane compartment, or in either of the external or internal aqueous compartments or some combination thereof;

d) an organic, water-soluble membrane-impermeant base; and,

e) water.

This composition enables the inclusion of salicylic acid as the free acid in products of neutral pH.

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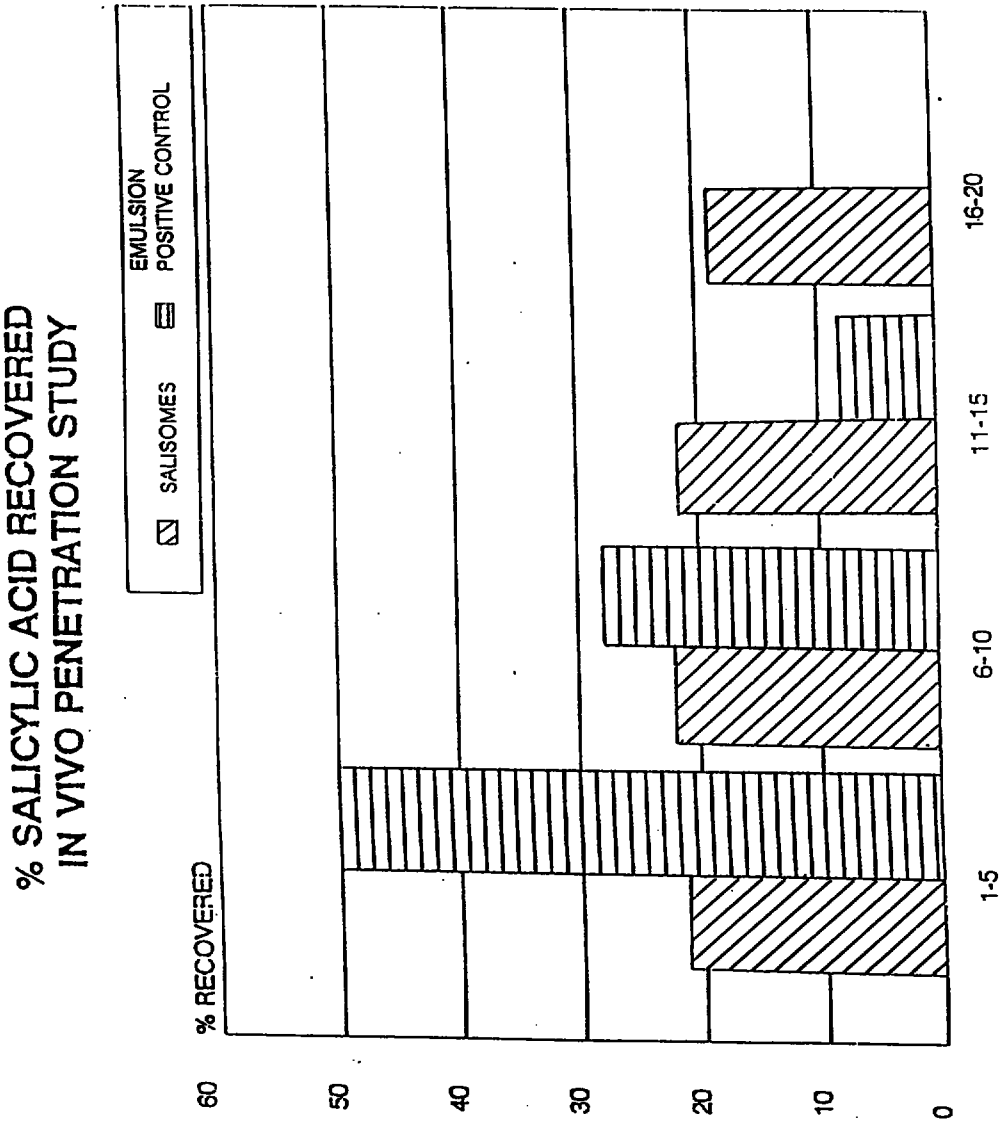


FIG. 1

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