Description

The present invention relates to pharmaceutical formulations, for topical use, which contain pseudomonic acid or a salt or ester thereof.

Pseudomonic acid, its salts and esters, are known antibiotic agents and are described in GB—A—1,395,907. These agents are useful in treating skin, ear and eye disorders by topical administration. Various topical formulations of pseudomonic acid have been produced but have not been sufficiently stable for commercial exploitation. It has now been surprisingly found that, in the presence of polyethylene glycol, or a derivative thereof, pseudomonic acid has improved stability.

Accordingly, the present invention provides a topical formulation comprising pseudomonic acid, or a salt or ester thereof and at least 1% by weight of a poly substituted or unsubstituted alkylene-glycol or a derivative thereof.

As used herein the term 'poly-substituted or unsubstituted alkylene-glycol' refers to polymers having the following repeating unit

$$—(CH_2)_nO—$$

wherein n is an integer, preferably 2 or 3 and to such polymers wherein one or more methylene groups of each repeating unit is substituted. Suitable substituents include alkoxy groups such as methoxy as in polymethoxypropylene glycol. Such polymers are known by a variety of names, for instance, when n=2, as polyethylene glycol, polyoxyethylene, polyoxyethylene glycol and macrogol and, when n=3, as polypropylene glycol, polyoxypropylene and polyoxypropylene glycol. All these are useful in the invention as are derivatives of these polymers.

Suitable derivatives include ethers and esters of the poly-substituted or unsubstituted alkylene-glycols, such as the macrogol ethers and esters, for instance cetomacrogol, glycofurol, the 'Tweens'* and block copolymers including poly-substituted or unsubstituted alkylene-glycols such as Poloxamers which are block copolymers of polyethylene glycol and polypropylene glycol for instance the 'Pluronics'*, and cross-linked polyethylene glycol.

*'Tween'® and 'Pluronic'® are trade names for the above types of polymer.

The poly-substituted or unsubstituted alkylene-glycols and derivatives thereof may be used singly or various grades and types may be used in combination to achieve the desired physical properties of the formulation.

Preferably the formulation comprises polyethylene glycol or a derivative thereof.

Suitably the formulation comprises from 0.01 to 50% by weight of pseudomonic acid or a salt or ester thereof, preferably 0.1 to 25%, more preferably 0.5 to 10% and most preferably about 2% by weight of pseudomonic acid or a salt or ester thereof. Such formulations comprising only pseudomonic acid or a salt or ester thereof and a poly-substituted or unsubstituted alkylene-glycol or derivative thereof will, of course, contain up to 99.99% of the poly-substituted or unsubstituted alkylene-glycol or derivative thereof.

The formulation may comprise additional therapeutic agents such as antibacterial, antifungal, antiviral and antiinflammatory agents, for instance chlortetracycline, miconazole, idoxuridine and phenazone, provided that these are compatible with the pseudomonic acid or salt or ester thereof. Pseudomonic acid and its salts and esters tend to undergo a rearrangement reaction in the presence of acid and accordingly acidic agents are unlikely to be compatible with pseudomonic acid and its salts and esters.

In a particular aspect the invention provides a formulation as described above wherein pseudomonic acid, or a salt or ester thereof, is the sole therapeutic agent.

In another aspect the invention provides a topical formulation comprising pseudomonic acid or a salt or ester thereof and at least 1% by weight of polyethylene glycol or a derivative thereof.

Polyethylene glycols (PEG's) and derivatives thereof are commercially available in a variety of chain lengths and with a variety of consistencies, for instance:—

Polyethylene glycols

Liquids	Semisolids	Hard solids
PEG 200	PEG 1000	PEG 4000*
PEG 300	PEG 1540	PEG 6000
PEG 400		

* PEG 4000 is the B.P. nomenclature for PEG with mean molecular weight of 3350. This material is also known as PEG 3350 in U.S.P. nomenclature.

Polyethylene glycol derivatives

Derivative	Chemical composition	Consistency
Glycofurol	Tetrahydrofurfuryl alcohol polyethylene glycol ether	Liquid
Tween 60	Polyoxyethylene sorbitan monostearate	Semi-solid
Tween 80	Polyoxyethylene sorbitan monooleate	Liquid

These may be used singly or admixed in suitable proportions to achieve the desired consistency of formulation.

The formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from 1% up to 98% of the formulation. More usually they will form up to about 80% of the formulation.

Suitable salts of pseudomonic acid include alkali metal salts, especially sodium pseudomonate.

Suitable esters of pseudomonic acid include lower alkyl esters, especially methyl or ethyl pseudomonate.

Preferably the therapeutic agent is pseudomonic acid.

Particularly suitable formulations according to the present invention comprise at least 1% by weight of PEG or a mixture of PEG's, from 0 to 25% by weight of a PEG derivative or mixture of PEG derivatives and from 0.5 to 10% by weight of pseudomonic acid or a salt or ester thereof.

Preferably the pseudomonic acid or salt or ester thereof represents 1 to 5% of the formulation, most preferably about 2% of the formulation.

Formulations of the invention may be produced by conventional pharmaceutical techniques. Thus ointments and creams are conveniently prepared by melting and mixing together the solid or semi-solid PEG's or PEG analogues or derivatives, and stirring in the therapeutic agent and any other ingredients. The product is then slowly cooled and filled into containers such as collapsible metal or plastic tubes.

Liquid preparations, such as ear and eye drops, are produced by dissolving the therapeutic agent in the liquid PEG's or PEG analogues or derivatives and the other ingredients are then added. The resulting solution or suspension is distributed into glass or plastic bottles or in single dose packs such as soft gelatin capsules which are then heat sealed.

If necessary the formulation may be milled at any suitable stage of the process.

A suitable sterilisation procedure may be included in the above processes if necessary. Alternatively raw materials are obtained in sterile conditions and the formulations are produced aseptically.

The invention will now be illustrated by the following Examples:

Example 1

Liquid formulation

Pseudomonic acid is dissolved in PEG 400 and the formulation adjusted, by addition of further PEG 400, to contain 2% by weight of pseudomonic acid.

Example 2

Ointment formulation

	% w/w
PEG 400	59
PEG 4000	39
Pseudomonic acid	2

The formulation is produced by melting the mixture of PEG's and stirring in the pseudomonic acid.

Example 3
Lotion formulation

	% w/w
PEG 400	74
Ethanol	24
Pseudomonic acid	2

Example 4
Drop formulation

	% w/w
PEG 400	74
Glycofurol	24
Pseudomonic acid	2

Example 5

	% w/w
Cetomacrogol emulsifying ointment	65
Polyethylene glycol 200	33
Pseudomonic acid	2

Stability test

The stability of the formulations in Examples 1 and 2 was compared with that of pseudomonic acid alone by storing samples at either 30 or 37°C for 12 months. The amount of therapeutic agent remaining at 2 months and at the end of this period was assayed and is given in the Table:

Formulation	% remaining after			
	2 months		12 months	
	30°C	37°C	30°C	37°C
Pseudomonic acid	78	Dec*	Dec	Dec
Example 1	98	97	91	87
Example 2	100	90	92	89

* Dec—melted with decomposition.

Claims

1. A topical formulation comprising pseudomonic acid or a salt or ester thereof and at least 1% by weight of a poly-substituted or unsubstituted alkylene-glycol or a derivative thereof.
2. A formulation as claimed in Claim 1 comprising pseudomonic acid, an alkali metal salt or a C_{1-4} alkyl ester thereof.
3. A formulation as claimed in Claim 1 or Claim 2 comprising pseudomonic acid or a salt or ester thereof as sole therapeutic agent.
4. A formulation as claimed in any one of Claims 1 to 3 comprising from 0.01 to 50% by weight of pseudomonic acid or a salt or ester thereof.
5. A formulation as claimed in any one of Claims 1 to 4 comprising polyethylene glycol or a derivative thereof.
6. A formulation as claimed in Claim 5 comprising at least 1% by weight of polyethylene glycol or a mixture of polyethylene glycols and from 0 to 25% by weight of a polyethylene glycol derivative or a mixture of polyethylene glycol derivatives.
7. A formulation as claimed in any one of Claims 1 to 6 comprising polyethylene glycol 400.

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2. A formulation as claimed in Claim 1 comprising pseudomonic acid, an alkali metal salt or a C_{1-4} alkyl ester thereof.
3. A formulation as claimed in Claim 1 or Claim 2 comprising pseudomonic acid or a salt or ester thereof as sole therapeutic agent.
4. A formulation as claimed in any one of Claims 1 to 3 comprising from 0.01 to 50% by weight of pseudomonic acid or a salt or ester thereof.
5. A formulation as claimed in any one of Claims 1 to 4 comprising polyethylene glycol or a derivative thereof.
6. A formulation as claimed in Claim 5 comprising at least 1% by weight of polyethylene glycol or a mixture of polyethylene glycols and from 0 to 25% by weight of a polyethylene glycol derivative or a mixture of polyethylene glycol derivatives.
7. A formulation as claimed in any one of Claims 1 to 6 comprising polyethylene glycol 400.

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8. A formulation as claimed in Claim 7 additionally comprising polyethylene glycol 4000, glycofurol or cetomacrogol.

9. A formulation as claimed in any one of Claims 1 to 8 additionally comprising an anti-inflammatory agent.

10. A process for producing a formulation as defined in any one of Claims 1 to 9 which process comprises admixing pseudomonic acid or a salt or ester thereof and liquid or molten poly-substituted or unsubstituted alkylene-glycol.

11. A formulation as defined in any one of Claims 1 to 9 for use in treating the human or animal body.

Patentansprüche

1. Eine Rezeptur für topische Anwendung, enthaltend Pseudomonsäure oder ein Salz oder einen Ester derselben und mindestens 1 Gewichtsprozent eines substituierten oder nicht-substituierten Polyalkylenglykols oder eines Derivates davon.

2. Rezeptur wie in Anspruch 1 beansprucht, enthaltend Pseudomonsäure, ein Alaklimetallsalz oder einen C_{1-4}-Alkylester derselben.

3. Eine Rezeptur wie in Anspruch 1 oder 2 beansprücht, welche Pseudomonsäure oder ein Salz oder einen Ester derselben als einzigen therapeutischen Wirkstoff enthält.

4. Eine Rezeptur wie in irgendeinem der Ansprüche 1 bis 3 beansprucht, enthaltend 0,01 bis 50 Gewichtsprozent an Pseudomonsäure oder eines Salzes oder Esters davon.

5. Eine Rezeptur wie in irgendeinem der Ansprüche 1 bis 4 beansprucht, enthaltend Polyäthylenglykol oder ein Derivat davon.

6. Ein Rezepteur wie in Anspruch 5 beansprucht, welche mindestens 1 Gewichtsprozent Polyäthylenglykol oder einer Mischung aus Polyäthylenglykolen und 0 bis 25 Gewichtsprozent eines Derivates von Polyäthylenglykol oder einer Mischung von Derivaten von Polyäthylenglykol enthält.

7. Eine Rezeptur wie in irgendeinem der Ansprüche 1 bis 6 beansprucht, enthaltend Polyäthylenglykol 400.

8. Eine Rezeptur wie in Anspruch 7 beansprucht, welche zusätzlich Polyäthylenglykol 4000, Glykofurfural (Glycofurol) oder Cetomacrogol (Polyäthylenglykol- bzw. Polyoxyäthylenglykolmonocetyläther) enthält.

9. Eine Rezeptur wie in irgendeinem der Ansprüche 1 bis 8 beansprucht, welche zusätzlich einen entzündungshemmenden Wirkstoff enthält.

10. Ein Verfahren zur Herstellung einer Rezeptur wie in irgendeinem der Ansprüche 1 bis 9 definiert, welches Verfahren das Vermischen von Pseudomonsäure oder eines Salzes oder eines Esters derselben und eines flüssigen oder aufgeschmolzenen substituierten oder unsubstituierten Polyalkylenglykols umfaßt.

11. Eine Rezeptur wie in irgendeinem der Ansprüche 1 bis 9 definiert, zur Anwendung bei der behandlung des Meschlichen oder Tierischen Koerpers.

Revendications

1. Formulation à usage local, caractérisée en ce qu'elle comprend de l'acide pseudomonique ou un sel ou un ester de celui-ci et au moins 1% en poids d'un alcoylène-glycol polysubstitué ou non-substitué ou d'un dérivé de celui-ci.

2. Formulation suivant la revendication 1, caractérisée en ce qu'elle comprend de l'acide pseudomonique, un sel de métal alcalin ou un ester alcoylique en C_{1-4} de celui-ci.

3. Formulation suivant la revendication 1 ou la revendication 2, caractérisée en ce qu'elle comprend de l'acide pseudomonique ou un sel ou un ester de celui-ci en tant qu'unique agent thérapeutique.

4. Formulation suivant l'une quelconque des revendications 1 à 3, caractérisée en ce qu'elle comprend de 0,01 à 50% en poids d'acide pseudomonique ou d'un sel ou d'un ester de celui-ci.

5. Formulation suivant l'une quelconque des revendications 1 à 4, caractérisée en ce qu'elle comprend un polyéthylène-glycol ou un dérivé de celui-ci.

6. Formulation suivant la revendication 5, caractérisée en ce qu'elle comprend au moins 1% en poids de polyéthylène-glycol ou d'un mélange de polyéthylène-glycols et de 0 à 25% en poids d'un dérivé de polyéthylène-glycol ou d'un mélange de dérivés de polyéthylène-glycol.

7. Formulation suivant l'une quelconque des revendications 1 à 6, caractérisée en ce qu'elle comprend du polyéthylène-glycol 400.

8. Formulation suivant la revendication 7, caractérisée en ce qu'elle comprend de plus de polyéthylène-glycol 400, du glycofurol ou du cétomacrogol.

9. Formulation suivant l'une quelconque des revendications 1 à 8, caractérisée en ce qu'elle comprend de plus un agent anti-inflammatoire.

10. Procédé pour produire une formulation suivant l'une quelconque des revendications 1 à 9, caractérisé en ce qu'on mélange de l'acide pseudomonique ou un sel ou un ester de celui-ci et un alcoylène-glycol polysubstitué ou non-substitué liquide ou fondu.

11. Formulation suivant l'une quelconque des revendications 1 à 9, caractérisée en ce qu'elle est utile dans le traitement du corps humain ou animal.

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