

- 1 -

NEW ALKALOID DERIVATIVES, THEIR USE AND
PHARMACEUTICAL FORMULATIONS CONTAINING THEM

The present invention relates to new alkaloid derivatives, to processes for their production and to novel pharmaceutical compositions and dosage forms containing them. More specifically, the present invention relates to the therapeutic use of new salts of indole alkaloids that are effective in the treatment of syndromes affecting the elderly, particularly conditions that are related to changes in cerebral metabolism and reduced blood flow.

Many naturally occurring alkaloids, synthetic alkaloid analogues and derivatives of naturally occurring alkaloids and alkaloid analogues have extensive use in pharmacology for treatment of numerous pathological conditions and also for inducing desired physiological states in healthy patients. Examples include the alkaloids used in the cardiovascular field, in obstetrics and in neurology.

In general alkaloids are nitrogenous bases that occur in plants, particularly those of the families *Papaveraceae*, *Apocynaceae*, *Papilionaceae*, *Ranunculaceae* and *Solanaceae*. Most alkaloids are characterised by the presence of one or more nitrogen atoms located in a heterocyclic ring system. General discussions of alkaloids are to be found in standard text books and particular reference is to be made, for example, to the Chapter entitled "Alkaloids" in Organic Chemistry, 3rd Edition, Fieser, L.F. and Fieser, M., Reinhold Publishing Corporation, 1956 and the Chapter entitled "Alkaloids and other Amino-Acid Derivatives" in The Biosynthesis of Natural Products, Bu'Lock, J.D., McGraw-Hill Publishing Company Limited, 1965 and in particular to "The Alkaloids Chemistry and Physiology, R.H.F. Marske and H.L. Holmes (Eds.), Academic Press Inc., Publishers.

Naturally occurring alkaloids generally have substituent groups which are susceptible to modification and derivatisation and synthetic alkaloids and derivatives of naturally occurring alkaloids may be prepared by, for example, subjecting a naturally occurring alkaloid to one or more of the following chemical modifications:

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- (i) esterification,
- (ii) hydrolysis of an ester group,
- (iii) salification,
- (iv) conversion of a primary, secondary, or tertiary amino group respectively to a secondary, tertiary or quaternary amino group
- (iv) epimerisation,
- (vii) conversion of a salt to a free base,
- (ix) etherification of a hydroxy group,
- (x) conversion of an etherified hydroxy group to a free hydroxy group.

Ester derivatives produced by procedure (i) may have one or more -OH groups converted to ester groups by reaction with a C₁-10 carboxylic acid or they may have -COOH groups converted to -COOR groups where R is C₁-6 alkyl. Similarly in procedure (iv) an H-N= group may be converted to an RN= group where R is as defined above and in procedure (x) an OH group may be converted to an -OR group where R is as defined above.

The term "synthetic alkaloid analogues and derivatives of naturally occurring alkaloids" as used herein is intended to include naturally occurring alkaloids which have been subjected to one or more of the above modification steps (i) to (x).

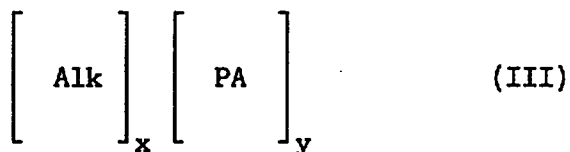
Typical alkaloids in widespread use include vincamine and apovincamine and their derivatives, raubasine, apocuanzine, nicergoline and hydergin.

A disadvantage of available alkaloids and alkaloid derivatives is that they generally are highly hydrophilic and consequently are not readily converted into dosage forms which are adapted to partition into the lipid phase. Also available dosage forms are not readily adapted for transcutaneous administration nor for formulation into convenient sustained release forms.

We have now developed a novel class of alkaloid derivatives which avoid these disadvantages.

Thus according to the present invention there are provided salts of phosphatidic acids and pharmacologically active, naturally occurring or synthetic alkaloids, or alkaloid derivatives.

The salts of the invention may be represented by the formula



wherein

Alk represents a cation derived from said pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative,

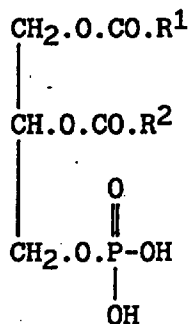
PA represents an anion derived from a phosphatidic acid or a anions derived from a mixture of different phosphatidic acids, and

x:y is from 2:1 to 1:2.

Preferably the ratio x:y is from 1.2:1 to 1:1.2, most preferably from 1.1:1 to 1:1.1.

In the novel salts of the invention, the pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative is an indole alkaloid, especially one of the classes referred to above.

The term "phosphatidic acid" as used herein, can represent a compound having the formula.



wherein R₁ and R₂, which may be the same or different, each represents a C₁₀₋₂₄ alkyl group, a C₁₀₋₂₄ alkenyl group, or a C₁₀₋₂₄ alkadienyl group. Said groups may be represented by the formulae C_nH₂₊₁, C_nH₂₋₁ or C_nH₂₋₃

Preferably, n is from 15 to 24, most preferably 15 or 17.

In more specific terms, the present invention relates to new salts of basic indole alkaloids with natural or synthetic phosphatidic acids that exhibit increased bioavailability when administered by mouth, rectally, transcutaneously or epicutaneously. For reasons explained below, the transcutaneous and transepidermal routes are the administration routes of choice for the new substances according to the invention.

An especially useful class of alkaloid salts according to the invention are ones prepared from alkaloids that act predominantly on the peripheral blood flow, such as vincamine, ethyl apovincamate and its analogues, raubasine, nicergoline and ergot alkaloids that improve the cerebral metabolism or increase cerebral blood flow.

According to a further aspect of the invention there are provided pharmaceutical compositions comprising a salt according to the invention, preferably one of the preferred salts referred to above, and a pharmaceutically acceptable excipient.

The salts according to the invention are especially well adapted for formulation into sustained release pharmaceutical dosage forms capable of releasing their pharmacologically active substance (i.e. the pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative) over a period of time and in particular to release the pharmaceutically active substance transcutaneously.

For this purpose, the sustained release forms are preferably in the form of a cutaneous patch, plaster or bandage.

The novel salts provided according to the invention are highly lipophilic and exhibit excellent bioavailability when administered orally, transcutaneously or transepidermally. The new salts are particularly valuable, when incorporated in plasters or appropriate gels or suitable pharmaceutical forms, in the treatment of peripheral circulatory disturbances of the brain and other parts of the body where increased blood flow improves organ function. The products are also suitable for use in the dermatological and cosmetic fields for the treatment of both surface and deep microcirculatory disturbances.

The salts of the invention may be prepared by a process comprising salification of (a) a pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative and (b) one or more phosphatidic acids, each of said reactants (a) and (b) being in free form or in the form of a salt-forming derivative.

The salification is preferably carried out in a solution for both reactants.

The solvent is preferably selected from halogenated hydrocarbons, ketones, ethers and mixtures thereof.

Suitable phosphatidic acids for use as salifying agents are natural or synthetic phosphatidic acids. In general these possess acyl chains (which may be the same or different and saturated or unsaturated) linked via an ester bond to the oxygen atoms of glycerol. Included are natural phosphatidic acids comprising compounds having different fatty acids present in the ratio corresponding to the natural ratio in the compounds from the plant or animal tissue from which they originate.

The salification is normally carried out in non-protic solvents, generally starting from alkaloids in the form of the free base or salified with weak acids and from free phosphatidic acid(s). Alternatively, the salification may be carried out using a trans-salification procedure (or double decomposition reaction) in which a salt of an alkaloid with an anion X^- is reacted with a salt of a phosphatidic acid with a cation Y^+ , wherein the salt $Y^+.X^-$ is essentially insoluble in the reaction medium. An example is the reaction of a hydrochloride of an alkaloid with a sodium or potassium salt of phosphatidic acid(s).

The salts of the pharmacologically active, naturally occurring or synthetic alkaloids, or alkaloid derivatives thus obtained are highly soluble in non-protic solvents, from which they can be isolated by concentration and if necessary evaporation to dryness or by insolubilisation in non-solvents such as hexane or petroleum ether.

The salts may normally be obtained by reacting the reagents in molar proportions (1M:1M). Salification is generally complete when complete solubility of the reagents in the chosen solvent is achieved.

When treated with water, the novel salts of the invention can adopt a micellar form and distribute themselves quantitatively in non-miscible lipophilic organic solvents. The salts of the invention are believed to acquire their lipophilic character from the ability of the acyl chains to wrap themselves around the most polar central nucleus i.e. the region of the molecule constituted by the pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative, with the result that they can form a liposomal microdispersion in aqueous media.

It has surprisingly been found that when the novel salts of the invention are administered in the form of gelled aqueous microdispersions (lipogels), or incorporated in controlled release plasters applied to various parts of the body, they have considerable therapeutic advantages over the traditional dosage forms of alkaloids. It has been shown that in these dosage forms the new salts according to the invention have a different level of bioavailability, with attendant positive effects on their activity.

It has also been found (and this constitutes one of the most important aspects of the invention) that when the lipophilic salts of the above alkaloids are applied in controlled-release formulations at the base of the neck adjacent to the bifurcation of the branches of the internal carotid and common carotid arteries, or below the ear adjacent to the deep carotid artery or the anterior auricular and posterior occipital arteries, they can maintain active levels of the drug in the brain for prolonged periods. This is a necessary requirement in the treatment of chronic diseases such as metabolic disturbances caused by changes in the microcirculation, which are common in the elderly. Application of the compounds of the invention in this way is particularly applicable to salts according to the invention wherein the alkaloid is nicergoline or adrenergic ethyl apovincamate.

Salts of the alkaloids with phosphatidic acids in liposomal or pseudoliposomal form have been found, in accordance with the invention, to interact rapidly with the cell structures and diffuse rapidly through the tissues where they can easily gain access to the lumen of the arteries, through which they can travel to the site of action.

These new salts can be applied to the above sites in dosages of between 5 and 50 mg given as one or more doses per day depending on the individual receptor response.

It is clear that if consistent results are to be obtained in chronic degenerative diseases there must be a constant supply of the drug to the target organ in quantities sufficient to produce the required effect. This may be achieved using salts according to the invention.

Controlled-release transcutaneous pharmaceutical forms have proved suitable for the administration of the new salts according to the invention since they enable the drug to be directed to the target organ with minimal involvement of the peripheral organs.

Controlled-release plasters have proved to be particularly effective for this purpose since between 5 and 50 mg of salts of the various alkaloids can be incorporated in the reservoir. Liposomal forms of the same salt applied in the form of lipogels, with or without the presence of conventional phospholipids, have also proved effective. The plaster form has also proved extremely practical for long-term use, as is necessary in this case. However, the salts according to the invention can also be incorporated and administered in other conventional forms such as tablets, oily solutions, suppositories, etc.

The salts according to the invention can be applied in the form of aqueous microdispersions or lipogels or in conventional gels and emulsions to large areas of the body such as the upper and lower limbs to treat superficial and deep microcirculatory disturbances.

The salts according to the invention can be applied topically to treat Raynaud's disease, scleroderma, acrocyanosis and other forms of atherosclerosis of the limbs (heavy legs, intermittent claudication, etc.). In diseases of this type the products act by increasing the capillary blood flow in the tissues by acting on the myocytes in the capillary arterioles and prearterioles.

The products also have cosmetic applications in conditions where the superficial microcirculation is impaired by atherosclerosis due to aging and in the treatment of cellulitis.

The new salts according to the invention produce better results than the basic alkaloids (i.e. the pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative used to form the salts) under these conditions because they are better distributed in the surface tissue and remain present at the site of action for longer periods of time.

The examples given below serve to illustrate the invention without in any way limiting its scope.

Example I: Preparation of ethyl apovincamate dipalmitoyl glycerylphosphatidate

3.50 g ethyl apovincamate base are dissolved in 15 ml methylene chloride with stirring and 6.48 g dipalmitoyl glyceryl phosphatidic acid added at ambient temperature.

When the reagents have dissolved completely, the solution in methylene chloride is evaporated to dryness under vacuum at a temperature not exceeding 40°C until the solvent has been completely eliminated. The residue is dispersed in n-hexane at 5°C and filtered. This yields 9.95 g of a white solid with the following characteristics:

m.p. 50°C ca

$[\alpha]_D = +50.13^\circ (c=0.5 \text{ in } \text{CHCl}_3)$

$^{31}\text{P-NMR}$ 2.65ppm

Example II: Preparation of the salt of ethyl apovincamate with
hydrogenated soya phosphatidic acid

3.50 g ethyl apovincamate base are dissolved in 15 ml methylene chloride with stirring and 7 g hydrogenated soya phosphatidic acid (natural ratio of fatty acids) with a mean molecular weight determined by acid-base titration of 698 are added. When the reagents have dissolved completely, the solution in methylene chloride is evaporated to dryness under vacuum at a temperature not exceeding 40°C until the solvent has been completely eliminated. The residue is dispersed in n-hexane at 5°C and filtered. This yields 10.5 g of a white solid with the following characteristics:

m.p. 52.8°C

$[\alpha]_D = 27.8^\circ$ (Conc = 1% CHCl₃).

³¹P-NMR 2.65, 4.06ppm

Example III: Preparation of the salt of nicergoline with
hydrogenated soya phosphatidic acid

4.84 g ethyl apovincamate base are dissolved in 50 ml methylene chloride with stirring and 7 g hydrogenated soya phosphatidic acid (natural ratio of fatty acids) with a mean molecular weight determined by acid-base titration of 698 are added. When the reagents have dissolved completely, the solution in methylene chloride is evaporated to dryness under vacuum at a temperature not exceeding 40°C until the solvent has been completely eliminated. The residue is dispersed in n-hexane at 5°C and filtered.

This yields 11.7 g of a white solid with the following characteristics:

m.p. 150-190°C (dec.)

$[\alpha]_D = +12.16^\circ$ (c=0.5 in CHCl₃)

Example IV: Preparation of the salt of vincamine with hydrogenated soya phosphatidic acid

3.54 g vincamine base are dissolved in 15 ml methylene chloride with stirring and 7 g hydrogenated soya phosphatidic acid (natural ratio of fatty acids) with a mean molecular weight determined by acid-base titration of 698 are added. When the reagents have dissolved completely, the solution in methylene chloride is evaporated to dryness under vacuum at temperature not exceeding 40°C until the solvent has been completely eliminated. The residue is dispersed in n-hexane at 5°C and filtered. This yields 10.5 g of a white solid with the following characteristics:

$$[\alpha]_D = -4.9^\circ (c=0.5 \text{ in } \text{CHCl}_3)$$

$$^{31}\text{P-NMR } 2.56, 4.21\text{ppm}$$

Example V: Preparation of nicergoline dipalmitoyl-glyceryl phosphatidate

4.84 g of nicergoline base are dissolved in 50 ml methylene chloride with stirring and 6.48 g dipalmitoyl glyceryl phosphatidic acid are added at ambient temperature. When the reagents have dissolved completely, the solution in methylene chloride is evaporated to dryness under vacuum at a temperature not exceeding 40°C until the solvent has been completely eliminated. The residue is dispersed in n-hexane at 5°C and filtered. This yields 11.1 g of a white solid with the following characteristics:

$$[\alpha]_D = +10.14^\circ (c=0.5 \text{ in } \text{CHCl}_3)$$

Example VI: Preparation of the salt of raubasine with hydrogenated soya phosphatidic acid

3.52 g raubasine base are suspended in 100 ml methylene chloride with stirring and 7 g hydrogenated soya phosphatidic acid (natural ratio of fatty acids) with a mean molecular weight determined by acid-base titration of 698 are added. When the reagents have dissolved completely, the solution in methylene chloride is evaporated to dryness under vacuum at a temperature not exceeding 40°C until the solvent has been completely eliminated. The residue is dispersed in n-hexane at 5°C and filtered. This yields 10.3 g of a white solid with the following characteristics:

$[\alpha]_D^{25} = 26.5^\circ (c=0.5 \text{ in } \text{CHCl}_3)$

$^{31}\text{P-NMR}$ 1.22, 2.38ppm

Example VII: Preparation of plasters for transdermal absorption containing the nicergoline salt of hydrogenated soya phosphatidic acid

The nicergoline salt of hydrogenated soya phosphatidic acid is incorporated in an adhesive mass that controls the release of the drug and has the following composition:

nicergoline salt of phosphatidic acid	50 mg
lactose	398 mg
saturated triglycerides	22 mg
polyisobutene	220 mg
hydrogenated colophony	195 mg
polyalkadiene	195 mg

The transdermal plaster is made up of three layers, namely a backing sheet, an adhesive film containing the active principle built up by forming several coatings, and a cover sheet. The drug is released over a period of 24 h to ensure continuous administration.

Example VII: Preparation of a lipogel containing the salt of ethyl apovincamate with hydrogenated soya phosphatidic acid

The formulation used to prepare 100 kg lipogel comprises the following reagents:

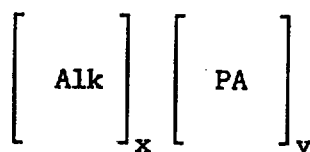
ethyl apovincamate salt of		
phosphatidic acid	1	kg
cholesterol	0.5	kg
alcohol	8	kg
butyl hydroxytoluene	0.01	kg
imidazolylnidylurea	0.30	kg
dehydroacetic acid and salts (Prevan)	0.20	kg
sodium edetate	0.15	kg
hydroxypropylmethyl cellulose	2.00	kg
water	87.84	kg



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CLAIMS

1. A salt of a pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative and a phosphatidic acid.
2. A salt according to Claim 1 having the formula



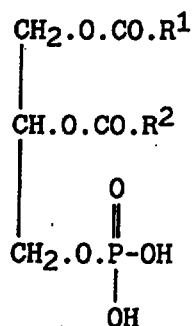
wherein

Alk represents a cation derived from said pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative,

PA represents an anion derived from a phosphatidic acid or anions derived from a mixture of different phosphatidic acids, and

x:y is from 2:1 to 1:2.

3. A salt according to Claim 2 wherein x:y is from 1.2:1 to 1:1.2, preferably from 1.1:1 to 1:1.1.
4. A salt according to Claim 2 or Claim 3 wherein the pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative is an indole alkaloid.
5. A salt according to any of Claims 2 to 4 where PA is a phosphatidic acid having the formula



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- 14 -

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wherein R_1 and R_2 , which may be the same or different each represents a C_{10-24} alkyl group, a C_{10-24} alkenyl group, or a C_{10-24} alkadienyl group.

6. A salt according to Claim 5, wherein n is from 15 to 24.
7. A salt according to Claim 6 wherein n is 15 or 17.
8. A salt according to any of Claims 1 to 7 wherein Alk is a cation derived from an indole alkaloid.
9. A salt according to any of Claims 1 to 8 wherein Alk is a cation derived from an alkaloid selected from vincamine, apovincamine, raubasine, apocuanzine, nicergoline and hydergin and their derivatives in particular ethyl apovincamate.
10. A salt according to Claim 9 wherein the alkaloid is nicergoline or ethyl apovincamate.
12. A method for producing a salt as claimed in any preceding claim which comprises reacting a pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative with a phosphatidic acid, said reaction being carried out in a solution for both reactants.
13. A method according to Claim 12 wherein the solvent is selected from halogenated hydrocarbons, ketones, ethers and mixtures thereof.
14. A pharmaceutical composition comprising a salt according to any of Claims 1 to 10 and a pharmaceutically acceptable excipient.

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15. A sustained release pharmaceutical dosage form capable of releasing a pharmacologically active substance over a period of time, characterised in that the pharmaceutically active substance is a salt as claimed in any of Claims 1 to 10.

16. A sustained release pharmaceutical dosage form as claimed in Claim 15, adapted to release the pharmaceutically active substance trans-cutaneously.

17. A sustained release pharmaceutical dosage form according to Claim 16 in the form of a cutaneous patch, plaster or bandage.

18. The use of a salt of a pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative acceptable derivative thereof, and a phosphatidic acid in the manufacture of a pharmaceutical composition.

19. The use according to Claim 18 wherein said pharmaceutical composition is for the treatment of Raynaud's disease, scleroderma, acrocyanosis and other forms of atherosclerosis of the limbs (heavy legs, intermittent claudication, etc.).

20. A cosmetic method which comprises applying to the skin surface a cosmetic composition comprising a salt as claimed in any of Claims 1 to 10 and a cosmetically acceptable carrier, especially to improve skin appearance in conditions wherein the superficial microcirculation is impaired by atherosclerosis due to aging, and in the treatment of cellulitis.

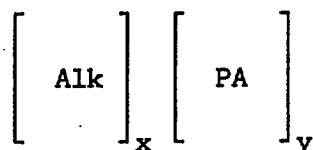
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NEW ALKALOID DERIVATIVES, THEIR USE AND
PHARMACEUTICAL FORMULATIONS CONTAINING THEM

Salts of a pharmacologically active, naturally occurring or synthetic alkaloids, or alkaloid derivatives and a phosphatidic acid are provided, which preferably have the formula



wherein

Alk represents a cation derived from said pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative,

PA represents a phosphatidic acid or a mixture of different phosphatidic acids, and

x:y is from 2:1 to 1:2.

The therapeutic use of the salts of the invention in the treatment of syndromes affecting the elderly, particularly conditions that are related to changes in cerebral metabolism and reduced blood flow are described, as well as cosmetic methods.

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- 13 -

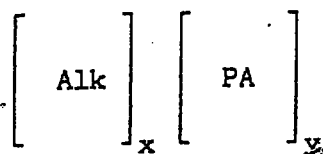
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- ☐ Description : paged to paged
☒ Claim(s) : paged ..8. to paged ..5..
☐ Drawing(s) : paged to paged
☐ Abstract : paged to paged

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CLAIMS:

1. A salt of a pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative and a phosphatidic acid, said salt having the formula



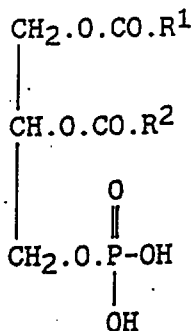
wherein

Alk represents a cation derived from said pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative,

PA represents an anion derived from a phosphatidic acid or anions derived from a mixture of different phosphatidic acids, and

x:y is from 2:1 to 1:2.

2. A salt according to Claim 1 wherein x:y is from 1.2:1 to 1:1.2, preferably from 1.1:1 to 1:1.1.
3. A salt according to Claim 1 or Claim 2 wherein the pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative is an indole alkaloid.
4. A salt according to any of Claims 1 to 3 where PA is a phosphatidic acid having the formula



wherein R¹ and R², which may be the same or different each represents a C₁₀₋₂₄ alkyl group, a C₁₀₋₂₄ alkenyl group, or a C₁₀₋₂₄ alkadienyl group.

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5. A salt according to Claim 4, wherein R^1 and R^2 , which may be the same or different each represents a C_{15-24} alkyl group, a C_{15-24} alkenyl group, or a C_{15-24} alkadienyl group.
6. A salt according to Claim 5 wherein R^1 and R^2 , which may be the same or different each represents a $C_{15 \text{ or } 17}$ alkyl group, a $C_{15 \text{ or } 17}$ alkenyl group, or a $C_{15 \text{ or } 17}$ alkadienyl group.
7. A salt according to any of Claims 1 to 6 wherein Alk is a cation derived from an indole alkaloid.
8. A salt according to any of Claims 1 to 7 wherein Alk is a cation derived from an alkaloid selected from vincamine, apovincamine, raubasine, apocuanzine, nicergoline and hydergin and their derivatives in particular ethyl apovincamate.
9. A salt according to Claim 8 wherein the alkaloid is nicergoline or ethyl apovincamate.
10. A method for producing a salt as claimed in any preceding claim which comprises reacting a pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative with a phosphatidic acid, said reaction being carried out in a solution for both reactants.
11. A method according to Claim 10 wherein the solvent is selected from halogenated hydrocarbons, ketones, ethers and mixtures thereof.
12. A pharmaceutical composition comprising a salt according to any of Claims 1 to 9 and a pharmaceutically acceptable excipient.
13. A sustained release pharmaceutical dosage form capable of releasing a pharmacologically active substance over a period of time, characterised in that the pharmaceutically active substance is a salt as claimed in any of Claims 1 to 9.

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- 15 -

14. A sustained release pharmaceutical dosage form as claimed in Claim 13, adapted to release the pharmaceutically active substance trans-cutaneously.
15. A sustained release pharmaceutical dosage form according to Claim 14 in the form of a cutaneous patch, plaster or bandage.
16. The use of a salt of a pharmacologically active, naturally occurring or synthetic alkaloid, or alkaloid derivative acceptable derivative thereof, and a phosphatidic acid as claimed in any of Claims 1 to 9 in the manufacture of a pharmaceutical composition.
17. The use according to Claim 16 wherein said pharmaceutical composition is for the treatment of Raynaud's disease, scleroderma, acrocyanosis and other forms of atherosclerosis of the limbs (heavy legs, intermittent claudication, etc.).
18. A cosmetic method which comprises applying to the skin surface a cosmetic composition comprising a salt as claimed in any of claims 1 to 9 and a cosmetically acceptable carrier, especially to improve skin appearance in conditions wherein the superficial microcirculation is impaired by atherosclerosis due to aging, and in the treatment of cellulitis.

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