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VASODILATOR COMPOSITIONS COMPRISING ALKYL NICOTINATES

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This invention relates to new esters of nicotinic acid and compositions containing the same which cause vasodilatation when applied to the skin or administered parenterally.

The object of this invention is to provide compositions, such as oil solutions, salves, creams, ointments and liniments, suitable for application to the skin of humans or animals or for intramuscular injection, which compositions produce vasodilatation in the region of application and which are not significantly irritating to tissues under medicinal conditions.

The vessels of the human body that supply blood to the tissues and organs comprise the arteries, the arterioles and the capillaries. The arterioles are little arteries, the extremely fine terminal branches of the arteries. They connect with the capillary bed, the most profusely branched part of the vascular system. The spreading network distributes thin-walled capillaries to all parts of every tissue and organ. In the most active tissues, where metabolism occurs at a rapid rate, the capillaries are close together. The diffusion of oxygen into these tissues or organs is thereby assisted. Less active tissues, such as fat, have fewer capillaries. In any tissue not all of these capillaries are open and functioning at all times.

The arteriolar walls are encircled by smooth muscle fibers. These are always in a state of partial constriction. Vasoconstriction is the term applied to further contraction of these smooth muscles, decreasing the diameter of the arterioles and reducing the blood supply to the capillary bed. Relaxation of the smooth muscles, opening the arterioles and increasing the volume of blood flowing into and through the capillaries of that region, is called vasodilatation. The latter not only permits blood to flow into the capillaries more rapidly, but also fills capillaries which prior to the dilatation contained no blood. It opens up previously empty, non-functioning capillaries, increasing the amount of blood available to all parts of the organ or tissue.

The compositions which I have discovered have the unique property of producing vasodilatation in the region to which they are applied. Either through action on the vasomotor nerves or on the circular smooth muscles themselves, relaxation of the muscles is brought about and the caliber of the arterioles is increased.

I have discovered that compositions of alkyl esters of nicotinic acid in oils or oily emulsions have this property of vasodilatation when applied

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to the epidermis of humans or animals. I have further discovered that this physiological effect results when the solutions are administered parenterally, i. e., intramuscularly.

The alkyl esters of nicotinic acid which I prefer to use are those esters in which the alkyl group has 4 to 8 carbon atoms. The nicotinic acid esters of alcohols having less than 4 carbon atoms are irritating to the dermal surfaces, causing in some cases inflammation, edema or eczema. Those having more than 8 carbon atoms produce the same undesirable effects, the decyl ester being more of an irritant than a vasodilator. Of the esters of alcohols having 4 to 8 carbon atoms, I prefer to use n-hexyl nicotinate. The hexyl ester is the most effective of the group and in therapeutic concentrations it is substantially free of undesirable side effects.

Solutions of these esters are made up in mineral, vegetable or animal oils or greases, or emulsions thereof. Especially suitable are olive, sesame or corn oils. Glycerol, ethylene glycol, propylene glycol and polyethylene glycols which latter compounds are commercially available in various degrees of polymerization and various consistencies from liquid to wax, are also suitable. These excipients may be liquids, greases, waxes or soft solids. They may also be soluble or insoluble in water.

While the alkyl nicotinates are relatively stable against oxidation, they will slowly darken upon standing for long periods exposed to light and oxygen. The solutions are much more stable, especially solutions in vegetable oils, such as corn oil, which contain natural anti-oxidants.

The concentration of the alkyl nicotinate may vary over fairly wide ranges. The preferred range is 1 to 10%. However, more dilute solutions of the esters have utility. The effect of such solutions is merely less in magnitude and duration. More concentrated solutions are also useful if it is desired to bring about vasodilation more rapidly and in a more pronounced manner.

These compositions are absorbed remarkably rapidly through the skin, producing vasodilatation within a few minutes. There is no detectable irreversible edema at the site of application nor is there any adverse degree of irritation. There is a sensation of warmth in the area treated, due to the increased flow of blood to the region. The dilatation lasts for 2 to 4 hours. An example of this phenomenon is the application of a 10% solution of n-hexyl nicotinate in olive oil to an area of the inner forearm about 1 inch in di-

ameter. A marked vasodilatation results, spreading over the entire surface of the forearm and reaching its maximum in about 45 minutes. After about two hours the dilatation recedes back to normal. In many such experiments no untoward effects have been observed.

Tests on the ears of rabbits of 10% solutions of n-butyl nicotinate in vegetable oils give similar results. Here the vasodilatory effect may be readily observed as the vessels themselves can be seen directly. They stand out as dark red lines against the semi-transparent ear. Within several minutes of application vasodilatation occurs. There is no edema at the site of application. Tests with trypan blue are negative, an indication of lack of irritation.

A series of tests on rabbits of n-butyl and n-hexyl nicotinates in 5% solution in sesame oil indicates that daily application of the compositions for periods as long as 5 weeks produces no edema or irritation. The hair is clipped from the rabbits' backs and 0.5 cc. of solution is applied to two areas daily. Pronounced vasodilatation is produced immediately following application and persists for 2–3 hours. At the end of three weeks tests with trypan blue indicate no irritation. The animals show no ill effects. At the end of five weeks the solutions elicit the identical response from ears of the rabbits under testing as from untreated rabbits. Microscopic examination of the treated tissues of the animals shows no histopathological abnormalities.

While the compositions I describe and claim are intended primarily for topical administration, certain of them are suitable for intramuscular injection. These comprise compositions of alkyl nicotinates in bland oils, such as peanut oil or propylene glycol, which exhibit no undesirable effects upon injection and which act as depots for the alkyl nicotinates. The action of the composition is thereby prolonged.

The pronounced vasodilatation produced by these compositions and the absence of undesirable side effects such as irritation or edema, indicate that these compositions will find valuable use in the treatment of peripheral vascular diseases distinguished by reduction or elimination of the flow of blood to tissues and in those conditions where increased flow of blood to the tissues will facilitate restoration to normal. Such a malady is Raynaud's disease, which has been generally attributed to hyperactivity of the vasoconstrictor centers. The vessels affected are primarily the digital arteries and arteroles. Relaxation of the circular vasomotor muscles counteracts the spasms of contraction.

The alkyl esters of nicotinic acid may be made by any of the usual methods. The following examples illustrate preferred methods.

Example 1

550 g. of nicotinic acid are mixed with 2450 g. of pure thionyl chloride. After the initial reaction subsides, the mixture is refluxed for an hour. The excess thionyl chloride is then distilled off on a steam bath, the last traces being removed at reduced pressure. The residue is crystalline nicotinyl chloride hydrochloride. To it is added 1 liter of dry n-butyl alcohol. The reaction proceeds spontaneously, after which the mixture is refluxed for an hour. Most of the excess butanol is distilled off in vacuo and the residue cooled in ice and made alkaline with 1500 g. of 33% aqueous potassium carbonate. The oil is separated, dried and fractionated. n-Butyl nicotinate is isolated as a colorless oil of B. Pt. 127–128° C. at 11 m. m. The yield is 554 g. (69%).

Example 2

The nicotinyl chloride hydrochloride prepared in the above manner from 123 g. of nicotinic acid is dissolved by warming it for a few minutes with 158 g. of dry pyridine. To this solution 270.5 g. of n-hexyl alcohol are added in a thin stream. After completion of the addition, the mixture is refluxed for an hour. Upon chilling, pyridine hydrochloride precipitates. This is removed and the resulting solution is diluted with dry ether to 2 liters. Further pyridine hydrochloride precipitates on chilling and is removed. Removal of solvent and distillation under nitrogen give 161.5 g. of n-hexyl nicotinate (78% yield) as a straw-colored liquid of B. Pt. 106–108° C. at 0.3 m. m.

In addition to compositions of alkyl nicotinates in oils such as olive, almond, corn, sesame and peanut, and in fats and waxes such as lanolin, petrolatum, the various commercially available more or less highly polymerized polyethylene glycols of from liquid to waxy consistency, cocoa butter, beeswax and solutions, emulsions, and mixtures thereof, the following additional examples illustrate other compositions adapted for topical administration.

Example 3

Ointment.—5 parts of n-hexyl nicotinate are thoroughly mixed with 95 parts of simple white ointment U. S. P. (composed of 90 parts of petrolatum, 5 parts of lanolin and 5 parts of white wax).

Example 4

Water-soluble salve.—10 parts of n-octyl nicotinate are thoroughly mixed into a fused, homogeneous mixture of 15 parts of glycerol monostearate, 15 parts of cetyl alcohol, 35 parts of glycerol and 35 parts of diethylene glycol. 10–30 parts of water are stirred into the warm composition and the stirred mass is allowed to cool. The resulting composition is water-dispersible and removable by washing. The consistency of the product is adjusted by controlling the amount of water added.

Example 5

Liniment.—5 parts of isoamyl nicotinate, 25 parts of methyl salicylate and 70 parts of olive oil are thoroughly admixed.

Example 6

Liniment cream.—15 parts of ethylene diglycol stearate are heated with 9 parts of n-butyl nicotinate to 70° C. and stirred until homogeneous. 15 parts of warm oil of wintergreen are added to the warm solution and thoroughly mixed therewith. The warm mixture is then poured slowly into 61 parts of water heated to 70° C., with rapid agitation. Cooling results in a soft cream.

The foregoing examples are intended to illustrate various compositions which are suitable for application and are not intended to limit either the spirit or the scope of the invention. It is clear that in these examples, any other alkyl nicotinate, in which the alkyl group contains 4 to 8 carbon atoms, may be substituted for the particular ester specified.

I claim:

1. A peripheral vasodilator composition adapt-

ed for topical application comprising an alkyl ester of nicotinic acid in which the alkyl group contains 4 to 8 carbon atoms in a vehicle adapted to therapeutic application and having incorporated therein a bland, high-boiling, adherent excipient serving to limit the volatility of said alkyl nicotinate and assist in distributing it over the body surface.

2. A peripheral vasodilator composition adapted for topical application comprising n-hexyl nicotinate in a vehicle adapted to therapeutic application and having incorporated therein a bland, high-boiling, adherent excipient serving to limit the volatility of said alkyl nicotinate and assist in distributing it over the body surface.

3. A peripheral vasodilator composition adapted for topical application comprising an alkyl ester of nicotinic acid in which the alkyl group contains 4 to 8 carbon atoms in a vehicle adapted to therapeutic application and having incorporated therein a bland, high-boiling, adherent excipient serving to limit the volatility of said alkyl nicotinate and assist in distributing it over the body surface in which the alkyl nicotinate constitutes about 1–10% of the total ingredients.

4. A peripheral vasodilator composition adapted for topical application comprising n-hexyl nicotinate in a vehicle adapted to therapeutic application and having incorporated therein a bland, high-boiling, adherent excipient serving to limit the volatility of said alkyl nicotinate and assist in distributing it over the body surface in which the n-hexyl nicotinate constitutes about 1–10% of the total ingredients.

5. A peripheral vasodilator composition adapted for topical application comprising an alkyl ester of nicotinic acid in which the alkyl group contains 4 to 8 carbon atoms and a vegetable oil.

6. A peripheral vasodilator composition adapted for topical application comprising n-hexyl nicotinate and a vegetable oil.

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REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
1,611,978	Wolffenstein	Dec. 28, 1926

OTHER REFERENCES

Chem. Abstracts, vol. 36, pages 7239–40.

Chem. Abstracts, vol. 31, page 6657.

Berichte, vol. 277, page 1787.

Bean and Spies—A Study of the Effects of Nicotinic Acid and Related Pyridine and Pyrazine Compounds on the Temperature of the Skin of Human Beings, published in the American Heart Journal, vol. 20, 1940, pages 62–75.