The present invention relates to new and novel pharmaceutical preparations which are useful to produce a vasodilating effect and the method for producing the said vasodilatation. In particular, it comprehends pharmaceutical preparations comprising a pharmaceutically acceptable carrier and the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide, and bis-(beta-hydroxyethyl) anil amine, the acid addition salts and the method of causing vasodilatation.

This application is a continuation-in-part of applicant's co-pending application, Serial No. 335,646, filed August 24, 1959, now United States Patent No. 3,092,634.

An object of this invention is the provision of new and improved therapeutic agents which may be used to relax blood vessels, thereby causing a vasodilatation, with consequent lowering of the systemic blood pressure as well as improving the circulation of blood through the tissues which these vessels supply. While the immediate effect of a reduction of the blood supply to an area may be evidenced through hypotension, this state, if allowed to persist, will result in gangrene and loss of a limb. Should this reduced blood supply occur in a vital area, such as the blood supply of the heart muscle or the blood supply of the brain, the immediate effects may be total incapacitation and very often death.

The method of treatment of such circulatory disturbances involves the institution of appropriate vasodilating measures, either by pharmacologic means or through surgery. Because of the general widespread nature of occlusive arterial disease, the surgical approach is of limited value and has been found useful in relatively few types of these pathologic entities. In addition, the indication for surgery to a patient with an already deteriorating vascular system further detracts from this manner of therapy. Conservative medical management remains the method of choice for approaching problems of diminished blood circulation resulting from occlusive vascular disease. Vasodilating drugs have been widely employed for this purpose although with varying success. Among the drugs utilized for vasodilation are included nicotinic acid; its derivatives, and the inorganic and organic nitrates. Both of these classes of compounds have many specific advantages, as well as limitations (in the scope of their application to vascular medicine). Thus, it is found that the action of nicotinic acid is fleeting and, since short transient vasodilatation is of little value in the overall management of these disease entities, continued administration of nicotinic acid therapy becomes a necessity. This is both impractical and uneconomical for the patient. Another limitation of the use of nicotinic acid is its predominant action on the vessels of the skin, resulting in both a feeling of discomfort and an onset of a disturbing reddening of the skin which has been noted as "flushing." Severe headaches is also common for the patient who takes nitrates in larger doses, and this limits the amount of the drug which may be administered, consequently may prevent a patient from receiving the optimal therapeutic dosage.

The nicotinic acid salt of the bis-nitric acid ester of diethanolamine although having the same empirical formula (C₂H₅O₂N₂) as the "amide" monohydrate exhibits different chemical and pharmacologic properties. The major and significant difference between the two resides in the manner and site of action of these drugs.

The salt, which is a polar compound, is dissociated at the pH of physiologic fluid so that rapid tissue availability of the nicotinic acid moiety results, when the compound reaches the physiologic pH range of the blood stream. This earlier availability of nicotinic acid permits the vasodilatation of the vessels of the skin to precede that of the deeper vessels which results from the nitric acid ester of diethanolamine portion of the molecule. Thus, the more fleeting vasodilatation of the nicotinic acid is supported and sustained by the onset of secondary action of the nitrates. This synergism of physiologic effects is extremely important since it permits a more effective and direct approach to the problem of obtaining an increased blood supply to surface areas and consequently is important to the treatment of cold induced vaso-constictor disorders of the skin, such as Raynaud's disease, acrocyanosis, chilblains and the like. Since the nicotinic amide is much more resistant to cleavage through the polar bond of the salt, the "amide" compound begins its principal actions through the nitrate moiety on the deeper vessels. In the course of its metabolic degradation, however, the pharmacologic activity is transferred to the nitric acid portion and the vessels of the skin. Thus, virtually opposite pathways of pharmacologic activity are obtained through the administration of these separate compounds, although a similar end-result of an increased blood supply to the tissues is obtained. It is just these differences in the mechanism of therapeutic action that bestow special significance to each of these compounds in therapy. Each compound has an important and valuable place in supplying a special pharmacologic effect for a particular patient requirement.

When it is desired to utilize for therapy the bis-nitric acid ester of nicotinic acid-bis-(beta-hydroxyethyl)-amide, or its acid salts, or the salt, the method of choice is a direct administration of the salt, nicotinic acid, as a tablet or a capsule, the concentration of active material per unit dose is adjusted so that it contains from 3 to 50 mg. of active material and is administered according to the patient's needs.

The mixture which is obtained prior to compressing of tablets may be filled into gelatin capsules, utilizing the same unit range dosage (viz. 5 to 50 mg. of active material per capsule). These capsules are administered to the patient in the same order of frequency as would be the tablets.

Solutions for injection may also be prepared by dissolving the appropriate quantities of the active material in sterile water for injection, maintaining an aseptic technique throughout. The solution may be sterilized through the process of bacteriologic filtration and filled into sterile glass ampules so that each cc. contains from 5 to 50 mg.
of active material. The solution may be administered by either intravenous or intramuscular injection, in accordance with the patient’s needs, utilizing the well-known precautions common to this method of administration.

When it is desired to take advantage of the different times of action of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide base and/or its acid addition salts, on the one hand, and the bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate on the other, the two may be combined in a tablet or any of the other dosage forms mentioned above in unit dosages so that the combined active material equals 5 to 50 mg.

Ordinarily 50 percent of each group is preferred, but if the action desired calls for more emphasis on the quicker action of one or the other, the percentage mixture may be varied.

The following examples illustrate the products of the present invention and the process for obtaining them.

**Example 1**

Tablets containing from 5 to 50 mg. of the bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate or the bis-nitric acid ester of nicotinic acid hydroxyethyl amide and its pharmacologically active salts, may be prepared by granulating the selected active ingredient with a diluent, as for example, milk sugar, sucrose or mannitol, in a ratio of at least 1 part active material to 9 parts by weight of diluent and compressing the resultant mixture. The granulating step is carried out with the aid of a granulating solution consisting of either 1 percent gelatin or 1 percent gum arabic solution. After thoroughly moistening the mass, it is passed through a No. 60 mesh screen and the resultant powder is then air dried. To this powder is then added a lubricant such as magnesium stearate, in concentration of 1 part lubricant for each 500 parts of the granulated powder, and the whole compressed into tablets of suitable size and shape. The range in concentration of active material for the tablets is from 5 to 50 mg. per unit dose, although a preferred concentration is between 10 mg. and 20 mg. of active substance per tablet.

Tablets suitable for administration by the buccal route may be prepared by admixing the active material with from equal parts to 50 parts by weight of a suitable carrier, as for example, mannitol or lactose and then adding a binder, such as gelatin or gum acacia. The mixture is moistened with 50 percent alcohol water and then compressed into tablets of suitable size and shape, so that each tablet contains from 5 to 50 mg. of active material per unit dose.

**Example 2**

Fifty parts of the bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate is mixed with 10 parts of lactose. The mixture is filled with suitable hard gelatin capsules so that each capsule contains from 5 to 30 mg. of the bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate.

By utilizing a liquid carrier, as for example, a propylene glycol, polyethylene glycol or bland vegetable oils, such as cottonseed oil or peanut oil, a liquid capsule may be obtained. A solution of the bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate in a pharmaceutically acceptable solvent is prepared at ordinary room temperature. In preparing the solution, it is desirable that the ratio of active substance to the solvent be at least one part active material and 9 parts inert solvent. Heat should be avoided. The solution is filled into soft gelatin capsules so that each capsule contains from 5 to 30 mg. of active material.

In place of bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate, there may be substituted in equal parts by weight, the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide and its acid addition salts.

**Example 3**

Should a solution be preferred as a dosage form for therapeutic administration, then both aqueous and hydroalcoholic solutions may be prepared. The preparation of an aqueous solution is accomplished by dissolving the appropriate amount of the active material (i.e., bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate, bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide and the acid addition salts) in simple syrup and adding flavoring and coloring agents, if desired. The preparation of hydroalcoholic solutions is achieved by simple solution of the active material in the desired vehicle which may consist of from 10 to 30 percent of alcohol and water. It is desirable to maintain the concentration of active material per unit dose (teaspoonful) of from 5 to 50 mg. of active material whether the aqueous syrup solutions are used or the hydroalcoholic vehicles are utilized.

**Example 4**

Solutions for injection may also be prepared by dissolving the appropriate quantity of the active material (i.e., bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate, bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide and the acid addition salts) in sterile water for injection, maintaining an aseptic technique throughout. The solution may be sterilized through the process of bacteriologic filtration and then filled into sterile glass ampules so that each contains from 5 to 50 mg. of active material. The solution may be administered by either intravenous or intramuscular injection, in accordance with the patient’s needs, utilizing the well-known precautions common to this method of administration.

**Example 5**

When it is desired to take advantage of the different times of action of the bis-nitric acid ester of bis-(beta-hydroxyethyl) amide and/or its acid addition salts, on the one hand, and the bis-nitric acid ester of bis-(hydroxyethyl) amine nicotinate, on the other, the two may be combined in a tablet or any of the other dosage forms mentioned above in unit dosages so that the combined active material equals 5 to 50 mg. Ordinarily 50 percent concentration of a compound of each group is preferred, but if the desired action calls for more emphasis on the onset of a more rapid action, then the percentages of the respective components of the mixture may be varied.

**Example 6**

When it is desired to obtain a therapeutic vasoconstricting effect, then this may be accomplished by the administration of pharmaceutical preparations comprising a pharmaceutical carrier and from 5 to 50 mg. of the bis-nitric acid ester of bis-β-(hydroxyethyl) amine nicotinate or the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide and the acid addition salts. Each unit dosage form of the pharmaceutical preparation selected contains from 5 to 50 mg. of the said active material, with a preferred concentration of from 10 mg. to 20 mg. per unit dose and is administered from 1 to 6 times daily, depending upon the individual needs of the patient. The exact dosage for a particular patient will depend upon the status of the blood vessels and the general health status of the patient. Thus, a chronically ill, geriatric patient, in a debilitated state, may require less of the drug than will the younger adult. Also the patient with concomitant heart disease may require a lesser amount of the drug than will the patient whose heart is unaffected.

The drug is administered for these purposes by any of the conventional modes of administration, such as the oral route, parenteral route and by the buccal route. A prompt physiologic effect will be observed, the onset of action beginning within 15 minutes after ingestion and
continuing over a period of from 2 to 4 hours. Repeated dosage of the drug may be administered and by proper spacing, will result in a sustained degree of vasodilation. Such vasodilation is of special value to the patient with peripheral vascular disease, as for example, thromboangiitis obliterans or gangrene of the extremities or Raynaud’s phenomenon, and also to improve the circulation in the presence of cerebrovascular disease and coronary atherosclerosis. Where a reduced blood flow is present, whether this results from a neurogenic vasospasm or from an atheromatous plaque, benefit will be obtained through the administration of the pharmaceutical preparations containing the active ingredients of the present invention.

What is claimed is:

1. A vasodilating preparation comprising from 5 to 50 mg. of a compound selected from the group consisting of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide, and the nitric ester of bis-(hydroxyethyl) amine nicotinate and the pharmacologically acceptable acid addition salts and a pharmaceutical carrier.

2. A vasodilating preparation comprising a pharmaceutical carrier and from 5 to 50 mg. of the bis-nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate.

3. A vasodilating preparation comprising a pharmaceutical carrier and from 5 to 50 mg. of bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide.

4. A vasodilating preparation comprising a pharmaceutical carrier and from 5 to 50 mg. of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide hydrochloride.

5. A vasodilating preparation comprising a pharmaceutical carrier and from 5 to 50 mg. of bis-nitric acid amide of (beta-hydroxyethyl) amide hydrobromide.

6. The method of producing vasodilation which comprises the step of the administration of a compound selected from the group consisting of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide the nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate and the pharmacologically acceptable acid addition salts, and the mixtures of the same.

7. The method of producing vasodilation which comprises the step of administration of a pharmaceutical composition comprising a pharmaceutical carrier and a compound selected from the group consisting of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide, the nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate and the pharmacologically acceptable acid addition salts, and mixtures of the same.

8. The method of producing a vasodilation which comprises the step of the administration of a pharmaceutical preparation comprising a pharmaceutical carrier and from 5 to 50 mg. of a compound selected from the group consisting of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide, the nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate and the pharmacologically acceptable acid addition salts, and mixtures of the same.

9. The method of producing a vasodilation which comprises the step of administering from 5 to 50 mg. of the nitric acid ester of bis-(beta-hydroxyethyl) amine nicotinate.

10. The method of producing a vasodilation which comprises the step of administering from 5 to 50 mg. of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide.

11. The method of producing a vasodilation which comprises the step of administering from 5 to 50 mg. of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide hydrochloride.

12. The method of producing a vasodilation which comprises the step of administering from 5 to 50 mg. of the bis-nitric acid ester of nicotinic acid (beta-hydroxyethyl) amide hydrobromide.

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