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TOPICAL ANTITUSSIVE PREPARATIONS

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This invention relates, in general, to the preparations having antitussive activity. More particularly, it relates to antitussive-containing compositions which are suitable for topical use.

Compounds having antitussive activity are well-known in the art. It has been the practice in the past to administer these compounds either as oral medication or intravenously by injection. This is, in part, attributable to the fact that the absorption of drugs, in general, through the unbroken skin has been considered to be an exceedingly inefficient means of administering same. Topical preparations having antitussive activity are not now, and have not heretofore been, available.

It is the object of this invention to provide novel antitussive preparations.

It is a more particular object of this invention to provide compositions which function effectively as antitussive agents, when applied topically.

Other objects of the invention will be obvious and will, in part, appear hereinafter.

Thus, in its most comprehensive embodiment, the present invention involves novel topical preparations containing orally active antitussive agents. In its more restrictive embodiments, the invention involves the formulation of orally active antitussive agents into effective topical preparations and the use of such preparations as a means for alleviating coughing. Unexpectedly, it has been found that antitussive agents, which are effective when administered in oral dosage form, are effective as topical preparations when they are embodied in suitable vehicle or carrier. In the present specification and claims, the expression "orally active" will be employed to denote the class of antitussive agents suitable for use in the practice of the present invention.

Thus, in carrying out our invention, one may use any compound which is known to be effective, or which, by any standard test procedure, is determined to be effective, as an antitussive agent when administered in oral dosage form. For example, antitussive agents, such as codeine, dihydrocodeinone, α -dimethylaminoethyl-o-chlorobenzhydrol, 1- α -2-methyl-8-methoxy-6,7-methylenedioxy-1-(6,7-dimethoxy-3-phthalidyl)-1,2,3,4-tetrahydroisoquinoline, and medicinally acceptable acid addition salts thereof, such as the hydrochloride, hydrobromide, sulfate, etc., salts are known orally active antitussive agents and compounds of this nature are suitable for use in the practice of this invention. However, particularly outstanding results have been obtained when d-3-methoxy-N-methylmorphinan, or a medicinally acceptable salt thereof, is employed as the antitussive component of our products. Accordingly, d-3-methoxy-N-methylmorphinan, or a medicinally acceptable salt thereof, is used in preparing the preferred products of the invention. Salts of d-3-methoxy-N-methylmorphinan which are well suited for use include the hydrochloride, hydrobromide, salicylate, stearate, oleate and benzoate salts.

A preferred procedure for determining whether a particular compound possesses oral antitussive activity, and, hence, whether it is suitable for use in the practice of the invention disclosed herein, is the procedure entitled "A Method for the Evaluation of Antitussive Agents in the Unanesthetized Dog" described in the Journal of

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Pharmacology and Experimental Therapeutics, volume 108, No. 2, June 1953, pages 217 to 223, inclusive.

In the practice of this invention, one may use any carrier, or combination of carriers, which is known to be useful in the formulation of topical pharmaceutical preparations. As employed in the present specification and claims, the term "carrier" includes materials, either lipophilic or hydrophilic in nature, which are solid, semi-solid or ointment-like in consistency at normal room temperatures, as well as those which are liquid. The term also embodies emulsions which include the carrier as a substituent. Carriers having lipophilic properties are employed in the preferred embodiment of the invention. Such carriers are characterized in that they are not miscible with water and in that they do not absorb water. Thus, for example, one may use a lipophilic ointment base, such as petrolatum or lard in preparing our novel products. Lipophilic carriers which are liquid in nature, such as mineral oils, vegetable oils, for example, olive oil, coconut oil, and fatty acid esters, for example, isopropyl myristate, isopropyl palmitate, etc., can also be employed. Oil-in-water emulsions of such lipophilic carriers will also be found to be well suited for use. In addition, any hydrophilic carrier which is known to be useful in the formulation of topical pharmaceutical preparations can be used in the practice of the present invention. Such carriers are characterized in that they are miscible with, or dispersible in, water or in that they absorb water. Such carriers may contain water as an internal or external phase. Carriers of this type include lanolin, hydrophilic petrolatum, lanolin absorption bases, polyethylene glycols, and acacia and tragacanth bases, as well as emulsions which contain same.

The topical antitussive preparations of this invention are prepared simply by adding the antitussive agent to, and intimately mixing it with, the carrier. The conditions under which the components of the product are admixed will be determined, to a great extent, by the physical characteristics of the carrier in use. For example, where the carrier employed is solid, semi-solid, or ointment-like in consistency at ordinary room temperatures, the production of our novel preparations will be facilitated by liquefying the carrier, by heating same, prior to adding the antitussive agent thereto. In such an instance, the antitussive agent is added to, and distributed throughout, the liquefied base, following which the mixture is allowed to cool to room temperature. At room temperature, the product will be obtained in the form of a topical preparation and the consistency of such product will be comparable to that of the carrier used. Where, however, the carrier in use is a more or less free-flowing liquid at ordinary room temperatures, satisfactory products can be obtained by adding the antitussive agent to, and mixing it with, the liquid carrier at room temperature. If desired, distribution of the antitussive agent throughout the liquid carrier can be facilitated by heating the carrier prior to adding the antitussive agent thereto. Ordinarily, however, it will not be necessary to heat a carrier which is already liquid at room temperature. In any instance where heating is used, care should be taken to employ temperatures which are below that at which the antitussive agent decomposes.

The ratio of the antitussive agent to carrier used in producing the novel topical preparations of this invention can be varied within rather wide limits. In general, however, in formulating our products from about 0.01 times to about 20.0 times the normal oral dosage unit of the orally active antitussive agent will be used for each gram of carrier employed. The preferred products of the invention are prepared using from about 0.2 times to

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bout 10.0 times the normal oral dosage unit of the anti-tussive agent for each gram of carrier employed.

The normal oral dosage units of the antitussive agents used in the practice of the present invention are reported in the literature. For example, the normal oral dosage unit of 1- α -2-methyl-8-methoxy-6,7-methylenedioxy-1,6,7-dimethoxy-3-phthalidyl)-1,2,3,4-tetrahydroisoquinoline is within the range of from about 15 mg. to about 0 mg. The normal oral dosage unit of d-3-methoxy-N-methylmorphinan, as the hydrobromide salt, is within the range of from about 10 mg. to 20 mg. and that of dihydrocodeinone, as the bitartrate or hydrochloride salt, is within the range of from about 5.0 mg. to 15.0 mg. Where the normal oral dosage unit of a compound is reported in the literature in terms of the normal oral dosage unit of a particular salt, or of particular salts thereof, one may readily calculate the normal dosage unit of the base compound, or the normal dosage unit of another salt thereof, which is equivalent to normal dosage unit of the reported compound. In the alternative, one may readily determine, by standard test procedures, as, for example, by the method described in the Journal of Pharmacology and Experimental Therapeutics, volume 108, No. 2, June 1953, pages 217 to 223, inclusive, the dosage range within which a particular antitussive agent is effective.

It should be fully understood that, while the present invention includes topical preparations consisting of a single antitussive agent and a single carrier, it is not necessarily restricted to such preparations. If desired, a mixture of orally active antitussive agents can be used in formulating the products and/or a combination of carrier materials can be employed. In addition, many of the conventional ingredients of topical preparations, for example, eucalyptol, thymol, menthol, etc., may be incorporated into the product.

The manner in which our preparations are employed will be readily apparent from the foregoing description, as well as from the examples which follow. Ordinarily, from about 1.0 gram to about 5.0 grams of our novel topical preparations will be applied, in a thin layer, to the subject to be treated. Obviously, the product can be used in either greater or lesser quantities, if so desired.

For a fuller understanding of the nature and objects of his invention, reference may be had to the following examples which are given merely as further illustrations of the invention and are not to be construed in a limiting sense. All parts given in the examples are parts by weight, unless otherwise indicated.

Example 1

In this example, 62.5 parts of petrolatum were heated moderately until liquefied. Thereafter, 0.888 part of d-3-methoxy-N-methylmorphinan was added thereto and intimately mixed therewith. When the d-3-methoxy-N-methylmorphinan was distributed throughout, the mixture was allowed to cool to room temperature. At room temperature, the preparation, thus obtained, was in the form of an ointment.

The topical preparation, produced as described in the preceding paragraph, was evaluated for its antitussive activity by a procedure entitled "A Method for the Evaluation of Antitussive Agents in the Unanesthetized Dog" described in the Journal of Pharmacology and Experimental Therapeutics, volume 108, No. 2, June 1953, pages 217 to 223, inclusive. This test method involves the inducement of a cough by electrical stimulation of the trachea through previously implanted copper electrodes into the tracheal submucosa. The antitussive activity of the product is, according to this test method, evaluated on the basis of percent inhibition of the incidence of the induced cough. Healthy mongrel dogs weighing about 5.6 kg. and 8.9 kg. were used in evaluating the topical preparation of this example, as well as in

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evaluating the topical preparations of the examples which follow hereinafter. The product was applied to the test animals topically, the chest thereof being clipped and shaved and the ointment being applied directly to the skin.

In evaluating the topical preparation of this example, there was applied topically, in a uniform manner to the clipped and shaved chest of each of two dogs, a 20.0 gram dose of this preparation. It was found that 30, 45, 60, and 90 minutes after application, the incidence of induced cough was inhibited 10%, 33%, 47% and 40%, respectively.

These results demonstrate that the topical preparation, so tested, is effective as an antitussive agent when applied topically.

Example 2

In this example, 100.0 parts of Vicks Vaporub were heated moderately until liquefied and 0.142 part of d-3-methoxy-N-methylmorphinan was added thereto and mixed therewith. Vicks Vaporub is a lipophilic petrolatum ointment base containing essential oils. It is a proprietary product of Vick Chemical Company, Division of Richardson-Merrill Inc., Wilmington, Delaware. When the d-3-methoxy-N-methylmorphinan was distributed throughout the vehicle, the mixture was allowed to cool to room temperature. At room temperature, the preparation, thus obtained, was in the form of an ointment.

The topical preparation, the formulation of which is described in the preceding paragraph, was evaluated for its antitussive activity by the test method described in Example 1. There was applied, in a uniform manner, to the clipped and shaved chests of each of two dogs, a 20.0 gram dose of the preparation. It was observed that 30, 45, 60, 75, 90 and 105 minutes after application, the incidence of induced cough was inhibited 20%, 67%, 63%, 53%, 33% and 27%, respectively.

These results indicate that the topical preparation of this example functions very effectively as a topical antitussive preparation.

Example 3

In this example, 100.0 parts of petrolatum were heated moderately until liquefied and 0.2 part of the benzoate salt of d-3-methoxy-N-methylmorphinan was added thereto and intimately mixed therewith. When the d-3-methoxy-N-methylmorphinan benzoate was distributed throughout the petrolatum, the mixture was cooled to room temperature. At room temperature, the preparation, thus obtained, was in the form of an ointment.

The topical preparation, produced as disclosed in the preceding paragraph, was evaluated for its antitussive activity by the method described in Example 1. A 20.0 gram dose was applied, in a uniform manner, to the clipped and shaved chests of each of two dogs. It was found that 45, 60, 90, 120 and 150 minutes after application, the incidence of induced cough was inhibited 40%, 40%, 37%, 37% and 27%, respectively.

These results indicate that the topical preparation of this example has highly effective antitussive activity.

The benzoate salt used in preparing the topical preparation of this invention is prepared simply by admixing d-3-methoxy-N-methylmorphinan and benzoic acid in a suitable solvent, that is, in a solvent in which both are soluble, and isolating the reaction product. It should be understood, however, that neither the salt nor the preparation thereof constitutes a part of the present invention.

Example 4

In this example, 70.0 parts of petrolatum were heated moderately until liquefied and 0.1547 part of the salicylic acid salt of d-3-methoxy-N-methylmorphinan was added thereto and mixed therewith. When the d-3-methoxy-N-methylmorphinan salicylate was distributed throughout

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the liquefied petrolatum, the mixture was allowed to cool to room temperature. At room temperature, the preparation, thus obtained, was in the form of an ointment.

The topical preparation, produced as described in the preceding paragraph, was evaluated for its antitussive activity by the test method described in Example 1. A 20.0 gram dose of the preparation was applied, in a uniform manner, to the clipped and shaved chests of each of two dogs. It was found that 30, 40, 45, 60 and 90 minutes after application, the incidence of induced cough was inhibited 17%, 47%, 50% and 37%, respectively.

These results demonstrate that the topical preparation of this example functions effectively as an antitussive agent.

For the sake of completeness, the preparation of the salicylic acid salt of d-3-methoxy-N-methylmorphinan, used in this example, is hereinafter described, although it should be understood that neither the compound itself, nor the process for its production, comprises part of this invention. A mixture of 24 grams of d-3-methoxy-N-methylmorphinan and 13 grams of salicylic acid in 50 cc. of acetone was first prepared. The solution was filtered and the filter was rinsed with 25 cc. of acetone. The clear solution was stirred at room temperature and 180 cc. of water was added thereto. The clear mixture was then seeded with crystals of d-3-methoxy-N-methylmorphinan salicylate and stirring was continued for a period of about 6 hours. During this period of time, the salicylate salt commenced to crystallize. At the end of the six hour mixing period, an additional 100 cc. of water was added slowly to a mixture from a dropping funnel. The mixture was thereafter stirred for an additional 2 hours with cooling by means of an ice-water bath. The salicylate salt crystallized from solution and it was obtained by filtration, subsequently washed with 50 cc. of cold water and dried at room temperature in a vacuum desiccator. There was obtained a yield of 32 grams of pure colorless d-3-methoxy-N-methylmorphinan salicylate, representing a yield of about 88.3% of theory. The compound melted at a temperature of 98–100° C. uncorrected and it analyzed as follows:

$C_{25}H_{31}NO_4$.—Calculated: 73.32% C; 7.63% H. Found: 73.44% C; 7.90% H.

Example 5

In this example, 100.0 parts of petrolatum were heated moderately until liquefied. Thereafter, 0.146 part of d-3-methoxy-N-methylmorphinan and 0.153 part of oleic acid were added thereto. The mixture was stirred continuously to form, in situ, the oleic acid salt of d-3-methoxy-N-methylmorphinan and to distribute said salt throughout the carrier. The mixture was allowed to cool and, at room temperature, the preparation, thus obtained, was ointment-like in consistency.

The topical preparation, produced as described in the preceding paragraph, was evaluated for its antitussive activity by the test method described in Example 1. It was found that 30, 60, 120, 150 and 180 minutes after the application of a 20.0 gram dose to the clipped and shaved chests of each of two dogs the incidence of induced cough was inhibited 13%, 53%, 47%, 33% and 23%, respectively.

These results demonstrate the effectiveness of the preparation of this example as a topical antitussive agent.

Example 6

In this example, a mixture of 61.0 parts of polyethylene glycol 4000, 34.0 parts of polyethylene glycol 400 and 5.0 parts of distilled water was first prepared. Thereafter, 0.142 part of d-3-methoxy-N-methylmorphinan was added thereto and distributed throughout. At room temperature, a preparation was obtained which was ointment-like in consistency.

The topical preparation, produced as described in the preceding paragraph, was evaluated for its antitussive

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activity by the test method described in Example 1. It was found that the preparation functioned effectively when applied topically.

Example 7

In this example, 100.0 parts of white petrolatum were heated moderately above room temperature until liquid in consistency. Thereafter, 0.4 part of 1- α -2-methyl-8-methoxy-6,7-methylenedioxy-1-(6,7-dimethoxy-3-phthalidyl)-1,2,3,4-tetrahydroisoquinoline was added thereto. The mixture was stirred until the antitussive agent was distributed throughout the liquefied carrier. The mixture was thereafter allowed to cool to room temperature at which temperature the topical preparation, thus obtained, was paste-like in consistency.

The topical preparation, produced as disclosed in the preceding paragraph, was evaluated as a topical antitussive agent by the test method described in Example 1; and it was found to be effective.

Example 8

In this example, 100 parts of white petrolatum were heated moderately until liquefied. Thereafter, 0.20 part of codeine was added thereto and intimately mixed therewith. When the codeine was homogeneously distributed throughout the liquefied carrier, the mixture was allowed to cool to room temperature, and at such temperature, it assumed the form of an ointment.

The topical antitussive preparation, thus obtained, was evaluated by the test method described in Example 1 and found to be effective.

Example 9

In this example, 100 parts of white petrolatum were heated moderately until liquefied. Thereafter, 0.02 part of dihydrocodeinone was added thereto and intimately mixed therewith. Mixing was continued until the dihydrocodeinone was homogeneously distributed throughout the liquefied petrolatum. The product was then allowed to cool to room temperature at which temperature it assumed an ointment-like consistency.

The preparation, thus obtained, was evaluated for use as a topical antitussive agent by the method described in Example 1. It was found to be effective.

Example 10

In this example, 710 mg. of α -(dimethylaminoethyl)-o-chlorobenzhydrol were mixed, at a temperature of about 60° C., with a sufficient quantity of petrolatum to make 100 grams. Mixing was continued while the mixture was allowed to cool to room temperature. At room temperature, the preparation was ointment-like in consistency.

The topical preparation, produced as described in the preceding paragraph, was evaluated for its antitussive activity by the test method described in Example 1. It was found to be effective.

The α -(dimethylaminoethyl)-o-chlorobenzhydrol employed in this example was obtained in the following manner: a solution of α -(dimethylaminoethyl)-o-chlorobenzhydrol hydrochloride was treated with ammonium hydroxide to pH 10. The solution was extracted with chloroform and the chloroform layer was washed with water and subsequently evaporated to dryness. The residue was α -(dimethylaminoethyl)-o-chlorobenzhydrol. The foregoing description of the production of α -(dimethylaminoethyl)-o-chlorobenzhydrol is given for the sake of completeness. Neither the compound, nor the method for its production, constitute a part of the present invention.

We claim:

1. A process for reducing the incidence of coughs which comprises applying topically, to a subject requiring antitussive therapy, a preparation comprising a mixture of (1) an orally active antitussive agent selected from the group consisting of codeine, dihydrocodeinone, 1- α -2-

methyl-8-methoxy-6,7 - methylenedioxy-1-(6,7-dimethoxy-3-phthalidyl)-1,2,3,4-tetrahydroisoquinoline, α -(dimethylaminoethyl)-o-chlorobenzhydrol, d-3-methoxy-N-methylmorphinan and medicinally acceptable acid addition salts thereof and (2) a lipophilic carrier.

2. A process for reducing the incidence of coughs which comprises applying topically, to a subject requiring antitussive therapy, a preparation comprising a mixture of (1) an orally active antitussive agent selected from the group consisting of codeine, dihydrocodeinone, 1- α -2-methyl-8-methoxy - 6,7 - methylenedioxy - 1 - (6,7-dimethoxy - 3 - phthalidyl) - 1,2,3,4-tetrahydroisoquinoline, α - dimethylaminoethyl - o - chlorobenzhydrol, d - 3 - methoxy - N - methylmorphinan and medicinally acceptable acid addition salts thereof and (2) a hydrophilic carrier.

3. A topical antitussive preparation, in ointment form, comprising a lipophilic ointment base and an antitussive agent selected from the group consisting of codeine, dihydrocodeinone, 1- α -2-methyl-8-methoxy-6,7 - methylenedioxy-1-(6,7-dimethoxy-3-phthalidyl) - 1,2,3,4-tetrahydroisoquinoline, α - (dimethylaminoethyl)-o-chlorobenzhydrol, d-3-methoxy-N-methylmorphinan and medicinally acceptable acid addition salts thereof.

4. The product of claim 3 wherein the antitussive agent is codeine.

5. The product of claim 3 wherein the antitussive agent is dihydrocodeinone.

6. The product of claim 3 wherein the antitussive agent is 1- α -2-methyl-8-methoxy,6,7 - methylenedioxy - 1 - (6,7-dimethoxy-3-phthalidyl)-1,2,3,4-tetrahydroisoquinoline.

7. The product of claim 3 wherein the antitussive agent is α -(dimethylaminoethyl)-o-chlorobenzhydrol.

8. The product of claim 3 wherein the antitussive agent is d-3-methoxy-N-methylmorphinan.

9. The product of claim 3 wherein the antitussive agent is a medicinally acceptable salt of d-3-methoxy-N-methylmorphinan.

10. The product of claim 9 wherein the hybromide salt of d-3-methoxy-N-methylmorphinan is employed.

11. The product of claim 9 wherein the benzoate salt of d-3-methoxy-N-methylmorphinan is employed.

12. The product of claim 9 wherein the salicylate salt of d-3-methoxy-N-methylmorphinan is employed.

13. The product of claim 9 wherein the oleate salt of d-3-methoxy-N-methylmorphinan is employed.

14. A topical antitussive preparation, in ointment form, comprising a hydrophilic ointment base and an antitussive agent selected from the group consisting of codeine, dihydrocodeinone, 1- α -2-methyl-8-methoxy-6,7-methylenedioxy - 1 - (6,7 - dimethoxy-3-phthalidyl)-1,2,3,4-tetrahydroisoquinoline, α -(dimethylaminoethyl)-o-chlorobenzhydrol, d-3-methoxy-N-methylmorphinan and medicinally acceptable salts thereof.

15. The product of claim 14 wherein d-3-methoxy-N-methylmorphinan is employed.

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