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ENCAPSULATED ACACIA SYRUP ADHESIVE OVERLAID N-ACETYL-p-AMINOPHENOL BEADLET CORES RETAINING THEREON DEXTROMETHORPHAN, CHLORPHENIRAMINE, AND PHENYLEPHRINE

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9 Claims

This invention relates, in general, to novel pharmaceutical compositions and to a process for the production thereof. More particularly, the invention relates to beadlets which contain at least two active medicaments and to the production and use of such beadlets.

It is common practice in the prior art to produce pharmaceutical compositions in beadlet form by dusting or sprinkling a powdery medicament on a non-toxic core material which has been pre-wetted with a non-toxic adhesive. In the past, non-pareil seeds have been conventionally used as the core material. The present invention is predicated upon the discovery that N-acetyl-p-aminophenol, a compound which has analgesic and antipyretic activity, is well suited for use as a core upon which other medicaments can be deposited. Since N-acetyl-p-aminophenol is often present as an active ingredient of cough and cold remedies, the present invention provides a unique means for supplying this ingredient, i.e., as a carrier for other compounds which are often found in such remedies. The elimination of the inert core material, and its replacement by a material which is therapeutically active, serves to minimize the size of the beadlets without decreasing the therapeutic potentcy thereof. Furthermore, since the size of the beadlets is kept at a minimum, smaller size capsules can be used for their encapsulation.

Thus, in its broadest embodiment, the present invention is concerned with the use of therapeutically active N-acetyl-p-aminophenol as a core in the production of pharmaceutical beadlets.

In a more limited embodiment, the invention is concerned with beadlets, suitable for incorporation into hard shell gelatin capsules, which beadlets contain N-acetyl-p-aminophenol in combination with other medicaments which are often found in conventional cough and cold remedies.

The present products can best be described in terms of the method of their production. Thus, in the first step of the preparative method, i.e., the production of the core material, N-acetyl-p-aminophenol crystals are moistened by mixing such crystals with an acacia syrup of the type fully described hereinafter. The acacia syrup serves as an adhesive which will bind to the N-acetyl-p-aminophenol crystals any powdery material which is sprinkled or dusted thereon. After the N-acetyl-p-aminophenol crystals have been moistened, the invention can proceed through either of two separate preparative routes. The choice of the route to be followed in any given instance will be governed by the compatibility or incompatibility of the N-acetyl-p-aminophenol and the other medicament or medicaments to be incorporated into the product. In the first such route, applicable particularly where the N-acetyl-p-aminophenol and the medicament or medicaments to be overlaid thereon are imcompatible, the moistened crystals are dusted with finely powdered tricalcium phosphate, following which the coated crystals are dried at an elevated temperature. The dry product, thus obtained, is in the form of discrete particles or beadlets. These beadlets are moistened with acacia syrup and the active medicament, or medicament mixture, is sprinkled or dusted thereon.

The acacia syrup serves to bind the medicament powder to the crystalline N-acetyl-p-aminophenol core. It will be quite obvious that, while the first preparative route is necessarily used where there is a compatibility problem, it could be employed also where medicaments which are compatible with N-acetyl-p-aminophenol are to be embodied into the product. In the second preparative route, referred to heretofore, a powdery medicament, or medicament mixture which is compatible with N-acetyl-p-aminophenol, is applied, by sprinkling or dusting, directly onto the N-acetyl-p-aminophenol crystals which were moistened with acacia syrup in the first step of the preparative method. In this latter route, which is only applicable where the medicaments used are compatible with N-acetyl-p-aminophenol, there is eliminated the steps of dusting with tricalcium phosphate, drying and re-wetting the dried N-acetyl-p-aminophenol beadlets.

Depending upon the quantity of medicament, or medicament mixture, to be incorporated into the product, it may be necessary to repeat the sprinkling or dusting operation, described heretofore, a number of times. By this it is meant that it may not be possible or expedient to apply the entire quantity of medicament to the N-acetyl-p-aminophenol core in one dusting or sprinkling operation. In such case, the beadlets, after the first dusting or sprinkling operation is completed, are moistened a second time with acacia syrup, following which a second portion of the medicament or medicament mixture is sprinkled or dusted thereon. These moistening and dusting procedures are repeated, in sequence, until the desired quantity of medicament has been added to the product. In either of the aforementioned preparative methods, after all of the medicament has been applied, the product which is still in the form of discrete particles or beadlets, is moistened once again with acacia syrup, following which the beadlets are dusted with tricalcium phosphate and dried at an elevated temperature.

From the foregoing description, it will be apparent that this invention has general applicability in the production of beadlets which contain two or more active medicaments, one of which is N-acetyl-p-aminophenol. However, the invention has particular applicability in the production of beadlets, suitable for filling into capsules, which contain as the active ingredients, dextromethorphan or a medicinally acceptable salt thereof; a medicinally acceptable salt of phenylephrine; and a medicinally acceptable salt of chlorpheniramine. As used herein, the expression "medicinally acceptable salt" connotes a salt of the corresponding free base with a medicinally acceptable acid. The expression "medicinally acceptable acid" includes inorganic acids, such as, hydrochloric acid, phosphoric acid, nitric acid, etc. and organic acids, such as, acetic acid, benzoic acid, citric acid, malic acid, maleic acid, tartaric acid, salicylic acid, etc. In its most preferred embodiment, the present invention provides beadlets which comprise N-acetyl-p-aminophenol and dextromethorphan hydrobromide as the active ingredients; beadlets which contain N-acetyl-p-aminophenol, chlorpheniramine maleate and phenylephrine hydrochloride as the active ingredients; and capsules which contain a mixture of those beadlets in quantities adjusted to provide desired dosages of the various pharmaceutically active ingredients. It will be appreciated that, in certain instances, the quantity of medicament-containing beadlets which may be required to provide desired dosages of the active ingredients may not be sufficient to achieve complete capsule fill. Where this occurs, inert, non-toxic material of approximately the same particle size, for example, non-pareil seeds, can be added to the capsules to fill same. Additionally, where a quantity of N-acetyl-p-aminophenol is required in the final product which is greater than

the quantity provided by its use as the core material for the beadlets, N-acetyl-p-aminophenol, in the form of crystals having a size approximating that of the coated beadlets, can be incorporated, as is, into the capsules.

In carrying out the present invention, N-acetyl-p-aminophenol crystals are first charged into some suitable vessel. A conventional tablet coating pan has been found to be especially well suited for use. Thereafter, a relatively small amount of acacia syrup is charged into the vessel and thoroughly mixed with the N-acetyl-p-aminophenol crystals. The quantity of acacia syrup which is used in the practice of this invention is variable. In general, however, the acacia syrup is employed in an amount which is sufficient only to moisten the N-acetyl-p-aminophenol crystals. Under ordinary circumstances, this will be accomplished by using a quantity of acacia syrup which is equivalent to about 0.5% to about 2.0% of the weight of the N-acetyl-p-aminophenol crystals to be moistened. In the second step of the preparative method, the moistened N-acetyl-p-aminophenol crystals are either dusted or sprinkled with a medicament, or with a medicament mixture, or, in the alternative, the moistened crystals are, in sequence, dusted with tricalcium phosphate, dried, moistened with acacia syrup and ultimately dusted with a medicament, or a medicament mixture. The quantity of tricalcium phosphate which is used in the last mentioned embodiment of the invention is variable. Preferably, however, the amount of tricalcium phosphate used will be equivalent to from about 2.0% to about 5.0% of the dry weight of the N-acetyl-p-aminophenol crystals present. In either of the foregoing embodiments, after the addition of the active medicament or medicament mixture to the product is completed, the product, which is in the form of particles or beadlets, is moistened with acacia syrup, dusted with tricalcium phosphate and dried at an elevated temperature. The beadlets thus obtained are suitable for filling into conventional pharmaceutical capsules.

The acacia syrup which is used as the adhesive in the several steps of the described process is a slightly viscous liquid produced by mixing from about 10% to about 20% by weight of acacia, from about 45% to about 60% by weight of sugar and from about 30% to about 35% by weight of water. The syrup which is used in the preferred embodiment of the invention contains from about 12% to about 13% by weight of acacia, from about 50% to 52% by weight of sugar and from about 36% to about 37% by weight of water. The tricalcium phosphate which is used can be of various particle sizes. However, a very finely powdered tricalcium phosphate is preferably employed. Finally, while the particle size of the N-acetyl-p-aminophenol crystals is not particularly critical, the crystals should be sufficiently large in size to serve as the core material but, at the same time, they should not be so large that, when coated, they cannot be conveniently filled into conventional pharmaceutical capsules. In the preferred embodiment of the invention, N-acetyl-p-aminophenol crystals of 20 mesh size are used.

As indicated heretofore, in its preferred embodiment, the present invention provides capsules filled both with beadlets comprising a crystalline N-acetyl-p-aminophenol core overlayed with dextromethorphan hydrobromide and with beadlets comprising a crystalline N-acetyl-p-aminophenol core overlayed with chlorpheniramine maleate and phenylephrine hydrochloride. The number of such beadlets used in the filling of the capsules will vary, depending upon the quantity of active ingredients provided by each beadlet and the dosage of each such ingredient with which it is desired to be furnished by the individual capsules. The primary objective of the invention is to provide capsules containing a safe and therapeutically effective dose of each drug. In general, such capsules will contain, in total, from about 80 mg. to about 140 mg. of N-acetyl-p-aminophenol, from about 10 mg. to about 20 mg. of dextromethorphan, from about 0.25 mg to about 3.0 mg. of chlorpheniramine maleate and from about 1.0 mg. to about 10.0 mg. of phenylephrine hydrochloride. In accordance with the present invention, this can be accomplished by incorporating into the capsules (1) beadlets containing from about 55 mg. to about 80 mg. of N-acetyl-p-aminophenol and from about 10 mg. to 20 mg. of dextromethorphan hydrobromide together with (2) beadlets containing from about 25 mg. to about 60 mg. of N-acetyl-p-aminophenol, from about 0.25 mg. to about 3.0 mg. of chlorpheniramine maleate and from about 1.0 mg. to about 10 mg. of phenylephrine hydrochloride. In the alternative, the objectives of the invention can be achieved by incorporating into individual capsules (1) a sufficient number of beadlets to provide from about 55 mg to 65 mg. of N-acetyl-p-aminophenol and 10 mg. to 20 mg. of dextromethorphan hydrobromide, (2) a sufficient number of beadlets to provide from about 30 mg. to about 45 mg. of N-acetyl-p-aminophenol, from about 0.25 mg. to about 3.0 mg. of chlorpheniramine maleate and from about 1.0 mg. to about 10 mg. of phenylephrine hydrochloride, (3) N-acetyl-p-aminophenol crystals to increase the content thereof to within the range of from about 115 mg. to 140 mg. and (4) granular inert filler material, e.g., non-pareil seeds sufficient to achieve complete capsule fill.

Although in the preceding paragraph the invention is described with reference to the dosages of dextromethorphan in the form of its hydrobromide salt, it will be understood that the free base or some other acid addition salt of the free base can be used. In such instances, the amount of dextromethorphan free base or salt provided per capsule will be equivalent to the amount of free base furnished by the designated dosages of the hydrobromide salt. Similarly, it is to be understood that, where a salt other than the maleate salt of chlorpheniramine is employed, or where a salt other than the hydrochloride salt of phenylephrine is used, the quantity of such salt provided per capsule will be adjusted to furnish a quantity of free base equivalent to that furnished by the maleate salt of chlorpheniramine or by the hydrochloride salt of phenylephrine.

For a fuller understanding of the nature and objects of this invention, reference may be had to the following examples which are given as an illustration of the invention and are not to be construed in a limiting sense.

EXAMPLE 1

(a) Production of coated N-acetyl-p-aminophenol crystals

Into a coating pan, there was charged 37.0 grams of N-acetyl-p-aminophenol crystals. Thereafter, these crystal were wetted with 0.5 cc. of an acacia syrup prepared by mixing 12.0 grams of acacia syrup, 50.0 grams of sugar, 36.0 grams of water. When the crystals were moist, 1.75 gram of finely powdered tricalcium phosphate was added thereto and mixed therewith. Subsequently, the crystals were dried using a blast of warm air.

(b) Production of medicament mixture

Into a mixer, there was charged 2.0 grams of tricalcium phosphate and 0.2 gram of FD&C Yellow #5 Lake. These ingredients were admixed until uniform. Thereafter, 1.10 grams of chlorpheniramine maleate was added and mixed with the powder until a uniform mixture was obtained. Subsequently, 5.5 grams of phenylephrine hydrochloride was added to and mixed with the powdery product following which the entire mixture was ground through a Fitz Mill to allow a 60 mesh powder.

(c) Production of medicament-containing beadlets

37.0 grams of the dry coated crystals, produced as described in section (a) of this example, were placed in a suitable mixing vessel. Thereafter, 0.4 cc. of an acacia syrup, produced by mixing 12.0 grams of acacia, 50.0 grams of sugar, 36.0 grams of water, was added to, and mixed with, the dry crystals. Subsequently, the medica-

ment powder, produced as described in section (b) of this example, was sprinkled on the moistened crystals. The medicament powder was applied as four separate coats with 0.4 cc. of acacia syrup being sprinkled on the crystals between each coat. The total amount of medicament powder applied was about 2.21 grams.

After the completion of the application of the active medicament material had been completed, the product was wetted once again with 0.4 cc. of acacia syrup following which 1.75 grams of tricalcium phosphate was sprinkled thereon. The beadlets were then dried at a temperature from about 40° C. to about 45° C.

The 51.33 grams of the beadlets, thus obtained were admixed with 24.6 grams of N-acetyl-p-aminophenol and the mixture diluted to 185 grams using 20 mesh blue non-pareil seeds. This mixture was filled into the No. 3 hard shell capsules, each to an average fill weight of 185 mg. Each capsule contained approximately 5.50 mg. of phenylephrine hydrochloride, 1.10 mg. chlorpheniramine maleate and 61.6 mg. of N-acetyl-p-aminophenol.

EXAMPLE 2

(a) Production of dextromethorphan-coated N-acetyl-p-aminophenol crystals

Into a suitable coating pan, there was charged 62.0 grams of N-acetyl-p-aminophenol crystals. These crystals were moistened by mixing same with 0.6 cc. of a syrup prepared from 12.0 grams of acacia, 50.0 grams of sugar, 36.0 grams of water. Thereafter, a mixture comprising 16.50 grams of dextromethorphan hydrobromide and 0.10 gram of FD & C Red #3 Lake was prepared and 2.34 grams of the mixture were sprinkled onto the wetted crystals. The coating pan was allowed to rotate using warm air to continuously dry the product. The product was then wetted once again using 0.6 cc. of the aforementioned acacia syrup and 2.36 grams of the colored dextromethorphan mixture was sprinkled thereon. This operation was repeated five times with an additional 2.36 grams of the dextromethorphan mixture being incorporated into the product each time, each dusting being followed by a moistening of the product with 0.6 cc. of the acacia syrup. When all of the dextromethorphan product had been incorporated into the product, the product was wetted once again with acacia syrup and 1.75 gram finely powered tricalcium phosphate was sprinkled thereon. The beadlets thus obtained were dried overnight at temperatures from 40° C. to 45° C.

Subsequently, 84.19 grams of the beadlets produced as described in the preceding paragraph were mixed with 24.6 grams of N-acetyl-p-aminophenol and the mixture was diluted with a blue 20 mesh non-pareil seeds to a total weight of 185 grams. The mixture was filled into #3 hard shell capsules to an average fill weight of 185 mg. Each capsule contained about 86.6 mg. of N-acetyl-p-aminophenol and about 16.5 mg. of dextromethorphan hydrobromide.

EXAMPLE 3

In this example, a product containing dextromethorphan hydrobromide, chlorpheniramine maleate, phenylephrine hydrochloride and N-acetyl-p-aminophenol was prepared. In producing this product, there was used beadlets produced as described in Example 1 and beadlets produced as described in Example 2.

Thus, into a blender there was charged 24.6 grams of N-acetyl-p-aminophenol crystals and 51.33 grams of the beadlets of Example 1. This mixture was mixed until uniform, following which there was added thereto and admixed therewith, 84.19 grams of the beadlets of Example 2. The mixture, thus obtained, was diluted with 24.88 grams of 20 mesh blue non-pareil seeds. The mixture was then filled into No. 3 hard gelatin capsules at an average fill weight of 185 mg. Each capsule contained 15.0 mg. of dextromethorphan hydrobromide, 1.0 mg. of chlorpheniramine maleate, 5.0 mg. of phenylephrine hydrochloride, plus an excess of about 10% of each such ingredient and 120 mg. plus an excess of about 3.0% of N-acetyl-p-aminophenol.

We claim:

1. A therapeutic composition comprising (A) hard shell gelatin capsules which are completely free of inert non-pareil seeds employed as core materials, but which can contain inert non-pareil seeds employed as fillers in a quantity sufficient to achieve complete capsule fill, and further containing (B) discrete beadlets, each such beadlet comprising (1) N-acetyl-p-aminophenol as a core material, (2) an adhesive composition overlaying said core material, (3) a medicament selected from the group consisting of dextromethorphan and a salt thereof with a medicinally acceptable acid dispersed upon the adhesive-treated core material and retained thereon by said adhesive composition, (4) an adhesive composition overlaying the medicament-coated core, and (5) tricalcium phosphate dispersed upon the adhesive-treated medicament-coated core and retained thereon by said adhesive composition, said adhesive composition (2) and (4) being a syrup comprising from about 10% to about 20% by weight of acacia, from about 45% to about 60% by weight of sugar and from about 30% to about 35% by weight of water, there being present in said capsules a sufficient number of beadlets to provide, per capsule, from about 55 mg. to about 80 mg. of N-acetyl-p-aminophenol and a quantity of said ingredient (3) to furnish a quantity of active dextromethorphan base equivalent to that furnished by about 10 mg. to about 20 mg. of dextromethorphan hydrobromide.

2. A composition of claim **1** wherein ingredient (3) is dextromethorphan hydrobromide.

3. The composition of claim **2** wherein said adhesive composition (2) and (4) is a syrup comprising from about 12% to about 13% of acacia, from about 50% to about 52% by weight of sugar and from about 36% to about 37% by weight of water.

4. A therapeutic composition comprising (A) hard shell gelatin capsules which are completely free of inert non-pareil seeds employed as core materials, but which can contain inert non-pareil seeds employed as fillers in a quantity sufficient to achieve complete capsule fill, and further containing (B) discrete beadlets, each such beadlet comprising (1) N-acetyl-p-aminophenol crystals as a core material, (2) an adhesive composition overlaying said core material, (3) tricalcium phosphate dispersed upon the adhesive treated core and retained thereon by said adhesive composition, (4) an adhesive composition overlaying the tricalcium phosphate-coated core, (5) a medicament comprising (a) a salt of chlorpheniramine with a medicinally acceptable acid and (b) a salt of phenylephrine with a medicinally acceptable acid, dispersed upon the tricalcium phosphate-coated core and retained thereon by said adhesive composition, (6) an adhesive composition overlaying the medicament mixture-coated core and (7) tricalcium phosphate dispersed upon the adhesive-treated medicament-coated core and retained thereon by said adhesive composition, said adhesive composition (2), (4) and (6) being a syrup comprising from about 10% to about 20% by weight of acacia, from about 40% to about 60% by weight of sugar and from about 30% to about 35% by weight of water, there being present in said capsules a sufficient number of beadlets to provide from about 25 mg. to about 60 mg. of N-acetyl-p-aminophenol, a quantity of a salt of chlorpheniramine to provide a quantity of chlorpheniramine base equivalent to that provided by from about 0.25 mg. to about 3.0 mg. of chlorpheniramine maleate and a quantity of a phenylephrine salt to provide an amount of phenylephrine base equivalent to that provided by from about 1.0 mg. to about 10 mg. of phenylephrine hydrochloride.

5. The composition of claim **3** wherein said medica-

ment mixture (5) comprises a mixture of chlorpheniramine maleate and phenylephrine hydrochloride.

6. The composition of claim 5 wherein said adhesive composition (2), (4) and (6) is a syrup comprising of from 12% to 13% by weight of acacia, from about 50% to 52% sugar, and from about 36% to about 37% of water.

7. A therapeutic composition comprising hard shell gelatin capsules which are completely free of inert non-pareil seeds employed as core materials, but which can contain inert non-pareil seeds employed as fillers in a quantity sufficient to achieve complete capsule fill, and further containing (A) discrete beadlets comprising N-acetyl-p-aminophenol and a medicament selected from the group consisting of dextromethorphan and a salt thereof with a medicinally acceptable acid as the active ingredients, (B) discrete beadlets comprising N-acetyl-p-aminophenol, a salt of chlorpheniramine with a medicinally acceptable acid and a salt of phenylephrine hydrochloride as the active ingredients, (C) N-acetyl-p-aminophenol crystals and (D) inert filler materials, said beadlets (A) comprising (1) N-acetyl-p-aminophenol as a core material, (2) an adhesive composition overlaying said core material, (3) a medicament selected from the group consisting of dextromethorphan and a salt thereof with a medicinally acceptable acid dispersed upon the adhesive-treated core material and retained thereon by said adhesive composition, (4) an adhesive composition overlaying said medicament-coated core and (5) tricalcium phosphate dispersed upon said adhesive-treated, medicament-coated core and retained thereon by said adhesive composition, said beadlets (B) comprising (6) N-acetyl-p-aminophenol as a core material, (7) an adhesive composition overlaying the core material, (8) tricalcium phosphate dispersed upon said adhesive-treated core and retained thereon by said adhesive composition, (9) an adhesive composition overlaying the tricalcium phosphate-coated core, (10) a medicament mixture comprising (a) a salt of chlorpheniramine with a medicinally acceptable acid and (b) a salt of phenylephrine with a medicinally acceptable acid dispersed upon the adhesive treated tricalcium phosphate-coated core and retained thereon by said adhesive composition, (11) an adhesive composition overlaying the medicament mixture-coated core, (12) tricalcium phosphate dispersed upon the adhesive-treated, medicament-coated core and retained thereon by said adhesive composition, the adhesive composition (2), (4), (6), (8) and (11) being a syrup comprising from about 10% to about 20% by weight of acacia, 40% to about 60% of sugar and 30% to about 35% of water, there being present in such capsules a sufficient number of beadlets to provide, per capsule, from about 85 mg. to 110 mg. of N-acetyl-p-aminophenol, a quantity of ingredient (3) to furnish a quantity of active dextromethorphan base equivalent to that provided by about 10 mg. to about 20 mg. of dextromethorphan hydrobromide, a quantity of a salt of chlorpheniramine to provide a quantity of chlorpheniramine base equivalent to that provided by 0.25 mg. to about 3.0 mg. of chlorpheniramine maleate, a quantity of a phenylephrine salt to provide a quantity of phenylephrine base in an amount equivalent to that provided from about 1.0 mg. to about 10 mg. of phenylephrine hydrochloride, with ingredient (C) being added to said capsules to provide each such capsule with a total content of N-acetyl-p-aminophenol within the range of from about 115 mg. to about 140 mg.

8. The composition of claim 7 wherein ingredient (3) is dextromethorphan hydrobromide and wherein medicament mixture (10) comprises (a) chlorpheniramine maleate and (b) phenylephrine hydrochloride.

9. The composition of claim 8 wherein the adhesive composition (2), (4), (6), (8) and (12) is a syrup comprising from about 12% to about 13% by weight of acacia, from about 50% to about 52% by weight of sugar and from about 36% to about 37% by weight of water.

No references cited.

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424—37, 263, 267, 330, 324

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

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It is certified that error appears in the above identified patent and that said Letters Patent are hereby corrected as shown below:

Column 1, line 36, "potentcy" should read -- potency --. Column 4, line 50, "crystal" should read -- crystals --. Column 8, line 35, "No references cited." should read

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Signed and sealed this 5th day of May 1970.

(SEAL)
Attest:

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