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THEOPHYLLINE-NOSCAPINE SUSTAINED RELEASE COMPOSITION FOR TREATMENT OF ASTHMA

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This invention relates to a novel therapeutic preparation for the treatment of bronchial and cardiac asthma for human and veterinary use. More particularly, the invention concerns a sustained release type pharmaceutical preparation containing predetermined dosages of theophylline, or its salts or complexes, and a nonaddictive antitussive agent .

Theophylline (1,3-dimethylxanthine) has had long and extensive use for the treatment in human patients of bronchospasm, cardiac asthma, hypertensive headache, and as a diuretic, and in the veterinary field as an asthma remedy and heart stimulant for animals. It may be administered orally, rectally, or parenterally. Theophylline has two chief disadvantages, one of which is its poor solubility. Hence it is frequently administered in the form of double salts or complexes, such as the salt with ethylenediamine (aminophylline). The other major disadvantage is that in many patients, large or even average dosages of theophylline or its derivatives may cause gastric irritation, vomiting and nausea, to the extent that it becomes necessary to discontinue its use. This vomiting may lead to rejection of active material before a sufficiently large quantity has been absorbed to accomplish the required therapy. Rectal administration may produce local irritation, and parenteral administration is often painful or possibly dangerous.

Because the diuresis resulting from the administration of theophylline is prompt and ceases when the drug is withdrawn, it is frequently necessary to administer to patients suffering from bronchial or cardiac asthma dosages of theophylline at frequent intervals, sometimes as often as once per hour when the patient is awake. At the same time it is known that immediately following oral administration of theophylline there is a tendency for the theophylline level in the blood, as measured in micrograms per ml., to rise to a maximum within the first few minutes to about an hour, thereafter remaining at a fairly high level for about 4 hours. The work of R. Calesnick, J. C. Munch, J. R. Di Palma and V. R. Altarelli, "Bioassay of Theophylline Preparations Using Human Subjects," published in British Medical Journal, July 2, 1960, vol. ii, pages 33–35, confirms that in this respect the various salts and complexes behave similarly to theophylline itself, and suggests that blood concentrations and clinical effectiveness of various well-known theophylline preparations depend on the dosage of pure theophylline present after the various agents undergo hydrolysis in the gastric juice. Hence there has been a tendency in the known therapeutic preparations of theophylline to aim at too high a blood level, thus aggravating this condition. When a plain theophylline tablet is taken, the absorption produces an excessive blood level for a limited period, followed by elimination via liver or kidneys, resulting in a drop to a blood level which is

too low for clinical effectiveness. A desirable action lasts about four hours before the blood level drops below the effective limit. Accordingly there is a need for a theophylline dosage form which will liberate a portion of the active ingredient for prompt action to last say four hours, followed by a second release for availability in maintaining proper blood level for the remainder of the period of medication.

Efforts have been made in this field of therapy to reduce the adverse effects of theophylline and its derivatives and to control blood levels by combining the drug with antacids or by the application of enteric coatings, but have proved inadequate, so that the known beneficial properties of the drug have not been utilized to their fullest extent. It is also known to combine theophylline drugs with sedatives, such as pentobarbital or phenobarbital, but these have the disadvantage of being subject to the danger of being habit forming.

In accordance with the present invention it has been found that theophylline, or its salts or complexes, may be combined with a nonaddictive antitussive agent in such manner that the adverse gastric effects of the theophylline are minimized while at the same time the diuretic effects are potentiated or enhanced. The invention contemplates the provision of combinations of theophylline and its derivatives and of the antitussive agent in various suitable dosage forms, including pellets, tablets, capsules, and the like.

In accordance with one form of the invention, there is provided a tablet or pellet which includes the entire dosage of theophylline and antitussive agent for release at one time following ingestion. This form may include a retardant coating.

In accordance with another form of the invention, there is provided a sustained release type of dosage form in which the dosage of medicaments is divided into two or more stages, the first dosage amount taking immediate effect, with access to the second or later dosage amounts being delayed for a predetermined period of time.

In accordance with still another aspect of the invention, there is provided a tablet or capsule in which there are included numerous individual pellets of medicament, the sum total of the medicaments in the pellets furnishing the required dosage, the distribution of the individual pellets being such that a given fraction of the pellets will release their medicament during the first hour following ingestion, the remainder of the pellets being divided into other fractions, which may be multiples in number of the first fraction, the pellets in each fraction being adapted to release their medicaments at successively longer time intervals, so that there results a continuous sustainment of the medicament dosage within the system of the patient, until the entire dosage has been utilized. This reduces the necessity for frequent medication, and permits the release and/or maintenance of desirable dosage levels in both human and animal patients.

The active ingredient for treatment of bronchial and cardiac asthma in the novel compositions of the invention is theophylline, or a salt or complex compound or derivative thereof. Among such salts and derivatives there may be used theophylline-ethylenediamine (aminophylline), theocin soluble (theophylline-sodium acetate), oxtriphylline (choline theophyllinate), theophylline-choline, and 7-hydroxyethyl-theophylline.

The nonaddictive antitussive may be any substance having cough suppressing properties, but which does not produce addiction or obstipation, such as, for example, nonhabit-forming derivatives of opium alkaloids, or any other well known antitussives which are nonhabit-forming, as thyme extract, dextromethorphan hydrobromide, and the like. However, the preferred compound of this class for the purposes of the present invention is noscapine, an alkaloid of the opium group which is reported to possess a greater antitussive effect than codeine, but with little or no side effects.

Noscapine, it should be explained, is the approved name selected by the British Pharmacopoeia Commission for narcotine ($C_{22}H_{23}NO_7$) or methoxyhydrastine (1-alpha-2 - methyl - 8 - methoxy - 6,7 - methylenedioxy - 1 -(6,7-dimethoxy-3-phthalidyl), 1,2,3,4-tetra, hydroisoquinoline, being recorded in File No. 6753 in the Trademark Search Room of the United States Patent Office. This drug will be hereinafter designated simply noscapine.

In addition there may be incorporated into the therapeutic tablets of this invention, if desired, any suitable analgesic or antipyretic agents, such as for example, aspirin or N-acetyl-p-aminophenol.

The dosage of theophylline or its derivatives per administration will vary, in the case of human patients, between about 200 mg. and about 400 mg. per administration. In the case of animals, the amount may range from about 100 mg. to 400 mg., depending upon the body weight of the animal.

The proportion of antitussive agent is not critical, and may range, for example, from about 10 mg. to about 60 mg. for each 200 mg. of theophylline, with satisfactory results.

Thus, in the case of human patients, the preferred dosage, and the one which will be used for purposes of illustration in the accompanying examples, is 200 mg. of theophylline together with 30 mg. of noscapine as the antitussive agent.

In the simplest form of the invention, a tablet is prepared in accordance with conventional procedures, such tablet consisting essentially of theophylline or a derivative thereof, and an antitussive agent, such as noscapine, in the approximate proportion of 30 mg. noscapine to each 200 mg. of theophylline, these active ingredients being compressed to form a tablet. If desired a retardant coating or an enteric coating may be applied to the outside of the tablet. A tablet of this type provides for a single release of all the medicament following ingestion.

In accordance with preferred embodiments of the invention, the theophylline or its salts or derivatives, singly or in combination with the nonaddictive antitussive agent, is incorporated into a sustained release type pellet, tablet or capsule as described in copending application Serial No. 63,736, filed October 20, 1960, now U.S. Patent No. 3,080,294, by one of the present applicants, in two or more dosages, which may be released successively over a predetermined interval of time.

A sustained release type of pharmaceutical preparation of the kind adapted to the purposes of this invention comprises basically an inner pellet either composed of medicament or of inactive material having a surrounding layer of medicament thereon, and at least one retardant coating thereon comprising a mixture of not less than about 95% by weight of said coating of a glyceride, and minor amounts of at least one fatty alcohol and of beeswax, the amount of the coating being between about 5% and about 10% by weight of the pellet to provide approximately one hour of sustainment. If desired, there can be provided an outer layer of an enteric coating to encase the entire pellet. In a pellet of this type the sustained action depends upon a percentage increase in weight of the carrier to be coated and not upon a multiplicity of coatings. This permits the liberation of predetermined amounts of medicament from coated granules which have been prepared either with a single medicament comprising or surrounding the central core or pellet, or with additional layers of coated medicament, with successive release of the medicaments after a time lapse, and with no lessening of their activity in the system of the patient.

In the preparation of sustained release pellets in accordance with the invention, there may be employed as a central core, pellet or granule, a mixture of cane sugar and corn starch, or wheat or potato or rice starch. The mixture is finely ground and worked into approximately round granules in a rotating pan in conventional manner to produce granules or basic pellets having a mesh size between about 10 and 20 mesh. If desired, however, small pellets of the active theophylline ingredient alone or together with the noscapine, may also be formulated as the core. Thus, a given amount of material comprising the core may be coated by spraying with a saturated solution of sucrose, or with a solution of cellulose acetate-phthalate, or with a solution of a pharmaceutical glaze or of a vegetable gum, and then tumbled in a rotating pan while drying with a blast of cool air, followed by screening to 10 to 20 mesh size. Where single sustained release tablets of the theophylline-noscapine combination are to be prepared, these compounds may serve as the core.

In the preparation of sustained action tablets, the sugar-starch core pellets or the medicament pellets, prepared as described, are placed in a rotating pan and treated with a solution of an adhesive material in a volatile organic solvent, in an amount sufficient to cover the surface of each pellet. There may be employed for this purpose any of the conventionally employed adhesives or excipients, such as cellulose acetate-phthalate, polyvinyl pyrrolidone, acacia, or shellac. The volatile solvent may be any solvent which evaporates rapidly leaving no toxic residue, for example, alcohol, ether, acetone, or chloroform. When the surface of the sugar-starch pellets has become tacky owing to evaporation of the solvent, there is added the theophylline or its derivative, or the mixture of the same with the nonaddictive antitussive agent, in the form of a fine powder, sufficient to coat evenly and adhere to the pellet surfaces. This process is continued until the requisite dosage amount has been impregnated evenly on the surface of each pellet. The coating operation can be carried out in any conventional type of equipment, such as, for example, a 36-inch diameter coating pan of the rotating type operating, for example, at a speed of about 30 r.p.m. The pan is provided with means for admitting a flow of heating or cooling air.

A pellet or tablet core, prepared as described, and with no additional coating, may be prepared containing 200 mg. of theophylline or theophylline derivative and 30 mg. of noscapine for each 200 mg. of theophylline present. It will, upon oral administration, provide immediate release of the drugs in the stomach of the patient. If desired, an enteric coating, such as a solution of cellulose acetate-phthalate in chloroform, may be applied to provide a glaze protective coating which is unaffected by the stomach juices, but which will dissolve in the alkaline intestinal fluids, releasing the drugs in the intestinal tract. If the coatting solution is applied in an amount of approximately 2 pints per 50 lbs. of pellets, a coating is produced which will withstand the action of the stomach juices for approximately one hour, thus providing sufficient time for passage of the carrier into the intestinal tract.

Where it is desired to provide a sustained release type of dosage form, the dosage of medicaments is divided into two or more portions, the basic pellet or tablet core previously described containing, for example, half of the medicament. Thus, a basic pellet or tablet core is prepared containing 115 mg. theophylline and 15 mg. noscapine, either as solid ingredients, or as a coating upon a pellet of sugar and starch, as previously described. The basic pellet is then coated with sufficient weight of retardant material of the glyceride-fatty alcohol-beeswax type previously described to provide for three hours retardation,

and finally coated with the second half of the medicament.

The fat-wax retardant coating used is one which is substantially unaffected by stomach or gastric juices, and which retards the action of the intestinal fluids. It is thus enteric in character, but by reason of a slight degree of acidity it serves to neutralize the alkaline intestinal fluid and hence to delay its action on the coating. Moreover, the ingredients of the coating impart to it a melting point higher than body temperature (98° F.), thereby providing a further retarding or delaying action to the effect of the intestinal fluid. It has been found that for each application of the retardant composition to the pellet amounting to between about 5% and about 10% by weight of the pellet, and preferably averaging about 7.5% by weight of the pellet, approximately one hour of retardation in the intestinal tract is obtained.

Thus, by applying three coatings of retardant composition in succession, each representing 7.5% by weight of the pellets, a delay of four hours is attained. Accordingly there can be prepared a pellet made up of a basic pellet comprising or coated with theophylline and noscapine, followed by three coatings of retardant, then a second coating of the medicaments, and finally an outer coating of an enteric nature, such as cellulose acetate-phthalate. The drug coatings represent a total of 200 mg. theophylline and 30 mg. noscapine, divided into two equal parts. The pellet permits one hour time to release the first half of the medication and to reach the retardant coating, and the remainder of the medication is released after 3 hours.

In a modification of this aspect of the invention, tablets may be prepared in which half the dosage is distributed among a large number of small basic pellets carrying the retardant coating, and the remainder of the dosage is incorporated in a tablet mix forming a binder, the whole being compressed to form the final tablet. The binder may be acacia, calcium carbonate, or any other conventional tabletting substance.

The preferred coating composition, which is only slowly affected by the intestinal fluids, comprises a mixture of not less than about 95% by weight of a glyceride and minor amounts of at least one fatty alcohol and of beeswax. The glyceride will generally range between 95% and 99% by weight of the mixture, the fatty alcohol weight between about 0.1% and 0.3%, and the beeswax weight between about 0.01% and 0.05%. The ingredients are dissolved in a suitable organic volatile solvent and maintained at a temperature sufficient to keep the ingredients in solution. The glyceride may be any suitable glyceryl ester of a fatty acid or a hydrogenated aliphatic acid, such as, for example, glyceryl monostearate, glyceryl distearate, or glyceryl ester of hydrogenated castor oil, but glyceryl monostearate is preferred. The fatty alcohol is any suitable long-chain alcohol, such as cetyl, myristyl, or stearyl alcohol. The beeswax is a purified grade, such as white bleached beeswax.

For a rapidly absorbed medicament such as theophylline and its derivatives, a preferred coating composition in accordance with the invention comprises:

Ingredient:	Weight per carrier, mg.
Glyceryl monostearate	45–55
Cetyl alcohol	0.25–0.75
Myristyl alcohol	0.25–0.75
Bleached white beeswax	0.005–0.24

These ingredients are dissolved in chloroform and the solution is kept at 65–67° C. to maintain the ingredients in solution.

In accordance with still another aspect of this invention, sustained release tablets are prepared in which the dosage is so arranged that there is obtained a continuous sustainment of the medication, predetermined fractions of the total dosage being successively released at selected time intervals, until the entire dosage has found its way into the system of the patient. This is accomplished by subdividing the individual fractions over a series of basic pellets. One series of the pellets provides release during a period of one hour, for example, by action of the gastric juices. A second series of pellets provides release during a second hour, a third series during a third hour, and a fourth series during a fourth hour, and so on. Thus by including as many such series as are desired, a combination of pellets can be made which will provide a continuous feed of the medicaments into the system, whether it be in the stomach or in the intestinal tract. For release in the intestinal tract use is made of the retardant fat-wax coating previously described. Usually release over a period of four hours will accomplish the purpose of a given dosage of theophylline or its derivatives.

By preparing, for example, four series of pellets, each series containing approximately the same concentration of theophylline per pellet, but with each series representing a different release time, then mixing the four series of pellets thoroughly and as uniformly as possible, and then incorporating an amount of the mixed pellets representing a dosage of 200 mg. theophylline and 30 mg. noscapine into a binder to form a tablet, there is obtained, in accordance with the invention, a sustained release therapeutic preparation containing the total dosage, which will be released to the extent of about ¼ in the stomach, and the remainder during a period of three hours in the intestinal tract, in three successive portions at intervals of about one hour. This permits maintaining a substantially uniform blood level of the drug, and eliminates the need for hourly administrations as was the practice heretofore. The pellet series can also be mixed and put up to provide total dosages as described, in the form of capsules or similar containers.

The following examples serve to illustrate the invention, but the invention is not to be regarded as limited thereto.

Example 1

200 mg. theophylline and 30 mg. of noscapine are mixed with 230 mg. of acacia and compressed to form a tablet.

Example 2

100 gm. of theophylline and 15 gm. of noscapine are thoroughly mixed and compressed to form a tablet core on a standard tabletting machine. The core is treated with a retardant fat-wax solution having the following composition:

Glyceryl monostearate	gm.	900
Cetyl alcohol	gm.	25
Myristyl alcohol	gm.	25
Bleached white beeswax	gm.	10
Chloroform	gallons	1

in three successive coatings to achieve a total weight increase of 22.5%, and a three hour period of sustainment. The tablet core is then treated with an adhesive solution having the composition:

Cellulose acetate-phthalate	lb.	1.0
Acetone	gallons	1.0

to provide a tacky surface. An additional 100 gm. of theophylline and 15 gm. of noscapine are applied to the surface by tumbling in a coating pan, and then the tablets are finished and dried. If desired a final coating of cellulose acetate-phthalate may be applied. The resulting tablet provides a four hour period of sustainment.

Example 3

The preparation of continuous sustained action tablets or capsules in accordance with the invention is carried out as follows. As a starting material there are used basic pellets consisting of 20% sugar and 80% cornstarch by weight, having a mesh size between about 60 and 80 mesh, which are thoroughly dried. To prepare 100,000 sustained action tablets or capsules each containing

a dosage of 200 mg. theophylline and 30 mg. noscapine, a mixture of 200 gm. of theophylline and 30 gm. of noscapine is prepared. 230 gm. of basic pellets are placed in a slowly revolving coating pan to which there are added as needed portions of a 5 gallon batch of cellulose acetate-phthalate coating solution prepared as described in Example 2. When the pellets become tacky, the medicament mixture is dusted into the revolving pan and the mass is additionally stirred manually or mechanically until all the medicaments are coated on the surface of the basic pellets. The interior of the pan can be coated with a suitable lubricant such as a silicone oil, to prevent adhesion of the pellets. When the coating is completed and the solvent has evaporated, the pellets comprise 560 gms. of medicaments and pellet materials plus the weight of solids picked up in the coating step, with approximately equal cocentrations of medicament per pellet, uniformly distributed. The basic pellets then comprise a matrix of cellulose acetate-phthalate in which the drugs are distributed, extending over the surface of the inner portion of sugar-starch, with some portions of the drugs extending beyond the matrix surface. A light finishing coat of cellulose acetate-phthalate may be applied if desired. The pellets as thus prepared are capable of releasing the medicaments during a perod of one hour or less in the stomach.

One-fourth of the total weight of the foregoing coated pellets is set aside.

The remaining three-fourths of the pellets must be coated so as to (*a*) by-pass the stomach, and (*b*) release medicament at successive intervals of approximately one hour each. The three-fourths of the pellets is coated with cellulose acetate-phthalate as described to make certain that there is no medicament exposed, as revealed by microscopic examination, and to provide a second hour of sustainment, and to insure that they all reach the intestinal area unchanged.

One-third of the foregoing portion of pellets by weight are coated with 7.5% by weight of a fat-wax retardant coating by applying the retardant fat-wax solution described in Example 2. This portion will not dissolve in the intestinal fluid for an additional hour, i.e., having three hours of sustainment. One-half of the thus fat-wax coated pellets is removed and set aside. The other half is further treated to provide an additional 7.5% of its weight of the fat-wax retardant coating as before. This results in four different final pellet products. The third and fourth portions are subjected to several coatings of cellulose acetate-phthalate applied as before to assure unchanged passage through the stomach. The respective batches of pellets are now combined and thoroughly blended. They may be put up in gelatine or other capsules in amounts representing a total dosage of 200 mg. theophylline and 30 mg. noscapine per capsule.

If the pellets are to be prepared in tablet form, there is added to the pellet blend sufficient binder, such as acacia, together with lubricants or other inert materials, so that the total weight of the tablet batch will be such that the 100,000 tablets will each contain the required dosage of 200 mg. theophylline and 30 mg. noscapine.

Example 4

Sustained release tablets or capsules of the same type as in Example 3 are prepared by employing as the basic pellet a mixture of 200 gm. theophylline and 30 gm. noscapine to form small pellets of 60–80 mesh size or slightly larger, which are then divided into portions and coated with retardant as described in Example 3, and then made up into tablets.

Example 5

A tablet is prepared comprising a binder containing numerous pellets imbedded therein, the pellets being of the type in which one-half of the medicament dosage is contained in a basic pellet, and the second half applied over a three-hour retardant coating. A mixture of 100 gm. of theophylline and 15 gm. noscapine is formed into small pellets as described in Example 4. A three-hour period of sustainment is provided for these pellets by applying thereto successive coatings of 7.5% by weight each of the fat-wax retardant coating mixture set forth in Example 2. The pellets are coated with a solution of cellulose acetate-phthalate as described in Example 2 until tacky and there is applied to the pellets a mixture of 100 gm. theophylline and 15 gm. noscapine. Then additional cellulose acetate-phthalate is applied in only sufficient amounts to solidify the pellet, but not to completely encase it. The finished pellets are blended to form capsules containing the dosage of 200 mg. theophylline and 30 mg. noscapine per capsule, or are formed into tablets containing the same dosage per tablet as previously described. On ingestion the tablet disintegrates, the outer layer of medicament is exposed and taken up in the stomach, the retardant layer provides three hours of sustainment, and then the remainder of the medicament is exposed.

We claim:

1. A therapeutic tablet for oral administrtion for the treatment of bronchial and cardiac asthma comprising from about 100 mg. to about 400 mg. of a compound selected from the group consisting of theophylline, and its therapeutically active derivatives, and from about 10 mg. to about 60 mg. for each 200 mg. of theophylline, of noscapine, and a binding agent.

2. A therapeutic tablet for oral administration for the treatment of bronchial and cardiac asthma comprising about 200 parts by weight of a compound selected from the group consisting of theophylline, and its therapeutically active derivatives, and about 30 parts by weight of noscapine.

3. A sustained release type pharmaceutical pellet for the treatment of bronchial and cardiac asthma comprising an inner core coated with a member of the group consisting of sucrose, cellulose acetate-phthalate, pharmaceutical glazes and vegetable gums and having at least one surrounding layer thereon of a medicament comprising from about 100 mg. to about 400 mg. of a compound selected from the group consisting of theophylline, and its therapeutically active derivatives, and from about 10 mg. to about 60 mg. for each 200 mg. of theophylline, of noscapine, a coating upon each medicament layer comprising a mixture of not less than about 95% by weight of said coating of a glyceride of a long chain aliphatic carboxylic acid, and minor amounts of at least one long chain fatty alcohol and of beeswax, the weight of each coating being between about 5% and about 10% by weight of that portion of said pellet coated thereby, each such coating providing approximately an hourly increment of sustainment.

4. A sustained release type pharmaceutical vehicle for the treatment of bronchial and cardiac asthma providing a total medicament dosage of from about 100 mg. to about 400 mg. of a compound selected from the group consisting of theophylline and its therapeutically active derivatives and from about 10 mg. to about 60 mg. of noscapine for each 200 mg. of theophylline, said vehicle being adapted to release approximately one-half of said total dosage within approximately one hour and the remainder within approximately three more hours following ingestion, said vehicle including a mixture of pellets each comprising an inner core coated with a member of the group consisting of sucrose, cellulose acetate-phthalate, pharmaceutical glazes and vegetable gums and having at least one surrounding layer thereon of said medicament, a coating upon each medicament layer comprising a mixture of not less than about 95% by weight of said coating of a glyceride of a long chain aliphatic carboxylic acid, and minor amounts of at least one long chain fatty alcohol and of beeswax, the weight of each coating being between about 5% and about 10% by

weight of that portion of said pellet coated thereby, each such coating providing approximately an hourly increment of sustainment, the distribution of the individual pellets in said mixture being such that whole fractions of the total number of pellets will release their medicaments into the body during time intervals successively of one hour and multiples thereof, the sustainment period of each fraction of the pellets corresponding to one of said time intervals.

5. A sustained release type pharmaceutical tablet comprising a mixture of pellets as claimed in claim 4.

6. A sustained release type pharmaceutical capsule comprising a mixture of pellets as claimed in claim 4.

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