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CHEWABLE TABLETS OF ANTIBACTERIAL AGENTS

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U.S. Cl. 424—227 10 Claims

ABSTRACT OF THE DISCLOSURE

Pleasant tasting, chewable tablets of certain antibacterial agents such as amplicillin are prepared by the use in the formulation of both mannitol and solid polyethylene glycol, e.g. about 300 mgm. mannitol and 1.0 to 20 mgm. "Carbowax 6000" per tablet.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of our prior, copending applications Ser. Nos. 368,991 and 368,992 filed May 20, 1964 and both now abandoned.

BACKGROUND OF THE INVENTION

Field of the invention

This invention relates to therapeutic, antibacterial compositions suitable for oral administration. More particularly, this invention relates to certain chewable tablets containing ampicillin, hetacillin, a form of tetracycline, oxacillin, cloxacillin or dicloxacillin and also containing both mannitol and solid polyethylene glycol.

Description of the prior art

Chewable tablets containing mannitol are well-known, as illustrated by U.S. Patent 3,145,146 to Lieberman et al. and "Erythrocin" chewable tablets marketed by Abbott Laboratories. Tablets containing solid polyethylene glycol, but not also mannitol, have been disclosed, as by Cooper et al. in U.S. Patent 2,857,313 and by Gakenheimer in U.S. Patent 2,540,253.

SUMMARY OF THE INVENTION

Many individuals, particularly children, find it difficult to swallow tablets or capsules containing a medicament such as the antibacterial agents of the present invention, that is, α-aminobenzylpenicillin (also called ampicillin), hetacillin, a form of tetracycline, oxacillin, cloxacillin and dicloxacillin. Therefore it is desirable to provide the medicament in the form of a chewable tablet. However, because of flavor considerations, the antibacterial agent cannot simply be combined with a conventional binder to form a pleasant tasting chewable tablet.

It is an objective of this invention to provide a chewable tablet containing one of the antibacterial agents specified above which has a pleasant tasting flavor. It is a further objective of this invention to provide such a chewable tablet which is easily administered to and ingested by children. It is an additional objective of this invention to formulate such a tablet in a manner which

will prevent capping and chipping during the tabletting process.

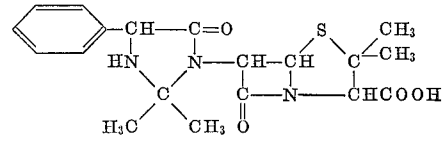
The objects of this invention are attained, briefly, by providing a chewable therapeutic tablet comprising from about 0.0625 to 0.250 gm. of an antibacterial agent selected from the group consisting of α-aminobenzylpenicillin, hetacillin, a form of tetracycline, oxacillin, cloxacillin and dicloxacillin, from about 0.300 to 0.400 mg. of mannitol and from about 0.001 to 0.020 gm. of solid polyethylene glycol which preferably has an average molecular weight in the range of 6000 to 7500.

DETAILED DESCRIPTION

As used herein the terms oxacillin, cloxacillin and dicloxacillin include the free acid forms and the nontoxic, pharmaceutically acceptable cationic salts of those penicillins. The preparation and properties thereof have been described, inter alia, in U.S. Patents 2,996,501, 3,239,507 and 3,317,389.

Ampicillin is the generic name for D-(—)-α-aminobenzylpenicillin. As used herein, the term ampicillin includes the free acid (i.e. amphoteric) form, the anionic salts with acids such as hydrochloric acid, the cationic salts with bases such as sodium hydroxide and the hydrates of that penicillin. Their preparation and properties have been described, inter alia, in U.S. Patents 2,985,648, 3,140,282, 3,144,445 and 3,157,640 and in an application of our colleagues Herbert H. Silvestri and David A. Johnson filed Oct. 29, 1962 as U.S. Ser. No. 233,943 and issued Apr. 27, 1965 as U.S. Patent 3,180,862.

Hetacillin is the generic name for 6-(2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic acid which has the structure



As used herein, the term hetacillin includes the "free acid" illustrated above and its nontoxic, pharmaceutically acceptable cationic salts of the acidic carboxylic acid group and its nontoxic, pharmaceutically acceptable acid addition anionic salts (i.e., salts of the basic nitrogen). Their preparation and properties are described in Belgian Patent 642,851 and in an application of our colleagues David A. Johnson and Charles A. Panetta filed Jan. 6, 1965, as U.S. Ser. No. 423,677 and issued Aug. 3, 1965, as U.S. Patent 3,198,804.

The term "a form of tetracycline" as used herein includes tetracycline in any of its forms such as the amphoteric compound, hydrates, acid addition salts, alkali metal salts, alkaline earth metal salts, other metal salts, salts with ammonia or amines, chelates, double salts and complexes. The preferred forms of tetracycline are amphoteric tetracycline, tetracycline hydrochloride and the tetracycline sodium hexametaphosphate complex described in U.S. Patent No. 2,791,609. Other salts which

are effective include metal salts such as sodium, potassium, calcium, aluminum, magnesium, zirconium and the like and normal organic and inorganic acid addition salts such as the bromide, sulfate, nitrate, orthophosphate, acetate, tartrate, citrate and the like. Use may also be made in the present invention of other physiologically active tetracycline products such as rapidly hydrolyzed esters, chelates and complexes.

The chewable tablets of this invention may be formed according to the following technique. The antibacterial agent and mannital (and, if desired, glycine and sodium cyclamate) are mixed together in a blender. If desired, sodium saccharin and flavor concentrates are blended separately, added to the main mixture and the composition is blended for 10 minutes. The mixture is micropulverized and one-third of the magnesium stearate and one-half of the solid polyethylene glycol, e.g. "Carbowax 6000" are added to the pulverized mixture. The mixture is blended 15 minutes and compacted by slugging. The compacted material is milled and screened to separate the 20 to 40 mesh granules. The fines and granules larger than 20 mesh are collected and compacted by slugging, milled and again screened to remove the 20 to 40 mesh granules. This process is repeated until the total amount of fines is less than 15%. Additional magnesium stearate (one-third of the total amount) and the remaining solid polyethylene glycol should be added to the second slugging process to prevent binding. The remaining magnesium stearate is added to the granules and the mixture is blended for 15 minutes. It is then tabletted.

In a preferred embodiment of the present invention, use is made of oxacillin, cloxacillin, dicloxacillin or a form of tetracycline which has previously been coated as by spray-drying with a mixture of ethyl cellulose and spermaceti wax as illustrated by the following procedure (which does not form part of the present invention) for preparing coated sodium dicloxacillin:

Formula:	Amounts for 1000 grams
Sodium dicloxacillin, micronized ___grams__	250.0
Ethyl cellulose (viscosity 100 cps.) __do____	250.0
Spermaceti wax _____do____	500.0
Methylene chloride _____liters__	15.0

MANUFACTURING INSTRUCTIONS

(1) Dissolve the spermaceti wax in approximately 8 liters of methylene chloride. The operation is carried out in a 20 liter glass container with the aid of a mixer (e.g. a Lightning mixer). No heat is required.

(2) To the clear solution obtained in step #1, add the ethyl cellulose in small portions while maintaining agitation. Stir until a clear and relatively viscous solution is obtained.

(3) Strain the solution obtained in Step #2 through three layers of cheesecloth if necessary to remove any particulate contaminants.

(4) The sodium dicloxacillin is then added in small portions while maintaining agitation. A milky white suspension will result.

(5) The remainder of the methylene chloride (7 liters) is then added while agitation is maintained and complete dispersion of the sodium dicloxacillin is effected. The dispersion must be free from small lumps or agglomerates.

(6) The Nirco-Niro Laboratory Model Spray Drier is readied as follows for the following conditions:

NOTE.—Assemble completely before starting except for the atomizer.

(a) Turn on the electric heater to setting #6.

(b) Shut off the outlet air control. This will have the effect of building heat in the drier. When the inlet air gauge reads around 130° C. open the outlet air valve to position #5 (from the "close" position).

(c) When equilibrium is reached:

The inlet air gauge will read—115°–120° C.
The outlet air gauge will read—50°–55° C.

(d) Install the turbine atomizer in its proper position over a Teflon gasket and feed compressed air until the atomizer gauge reads 6 kg./cm.^{2}. At this point maximum compressed air pressure is in use (90–100 lbs.) and the turbine is turning at a rate of 40,000 r.p.m. Allow 5 minutes for equilibrium in the chamber before liquid feeding is commenced.

(e) Start liquid feed to the turbine from a 2 liter separatory funnel connected to the turbine by a short piece of Teflon tubing. Feed at a rate of 60 ml. per minute.

(f) Monitor the operation to maintain the following drying conditions throughout the entire operation:

Inlet air—115°–120° C.
Outlet air—45°–50° C.

(g) Stop the atomizer and turn the electric heater to position M (exhaust fan); allow 5 minutes in this position before lifting cover.

(h) Lift cover with the aid of the hydraulic lift and collect product from the walls. The product is not expected to stick to the wall of the chamber other than by electrostatic forces.

(i) Dry product in vacuum oven overnight at room temperature. The methylene chloride residue is less than 1%.

(j) The free flowing coated sodium dicloxacillin product is passed through a 40 mesh screen and collected.

The tablets of this invention are especially useful for pediatric use—i.e., for the administration of the specified antibacterial agents, e.g. α-aminobenzylpenicillin, to young children who are unable or refuse to swallow regular tablets. The tablets of this invention offer all of the established therapeutic benefits of other oral preparations of the specified antibacterial agents, e.g. α-aminobenzylpenicillin. Thus, they may be used for the control of infections due to the specified antibacterial agents, e.g. α-aminobenzylpenicillin, sensitive organisms such as respiratory tract, genitourinary tract, and gastrointestinal tract infections. The α-aminobenzylpenicillin, hetacillin and tetracycline tablets of this invention are effective against gram-positive as well as many gram-negative organisms; and the oxacillin, dicloxacillin and cloxacillin tablets are particularly effective against gram-positive bacteria, including especially those resistant to benzylpenicillin. The tablets are administered in the same dosages as other oral preparations of the specified antibacterial agents, e.g. α-aminobenzylpenicillin. Thus, for children the tablets may be administered to provide daily about 50 mg. α-aminobenzylpenicillin or cloxacillin or oxacillin (or 25 mg. of the tetracycline or of hetacillin or 12.5 mg. of dicloxacillin) per kg. of body weight per day given in three or four divided doses; in particularly severe infections this dosage is doubled.

The following examples illustrate preferred embodiments of this invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Example 1

Into a suitable blender there are placed α-aminobenzylpenicillin trihydrate (160 parts by weight), mannitol (350 parts by weight), glycine (100 parts by weight), and sodium cyclamate (75 parts by weight) and the mixture is blended for about 15 minutes. Sodium saccharin (7.5 parts by weight) and dry flavoring agents (1.80 parts by weight) are blended separately for 15 minutes and added to the foregoing mixture. The composition is then mixed for 10 minutes following which it is micropulverized in a mill. Magnesium stearate (4 parts by weight) and "Carbowax 6000," a polyethylene glycol having an average molecular weight of 6000 to 7500 (1 part by weight) are added to the pulverized composition and the mixture is blended for 15 minutes. The blended mixture is then compacted by slugging and the compacted material is reduced to particulate form by passing it through a mill. The mix-

ture is then screened to remove the 20 to 40 mesh granules. The fines and the granules larger than 20 mesh are compacted, milled and again screened to collect the 20 to 40 mesh granules. This process is repeated until the amount of fines is reduced to less than 15%. After the second compacting process, magnesium stearate (4 parts by weight) and "Carbowax 6000" (1 part by weight) are added to the granules, at least 85% of which are 20 to 40 mesh, and the mixture is blended 15 minutes and then formed into one-half inch flat, beveled tablets. The hardness of the tablets, as determined on a Strong-Cobb-Arner hardness tester, is between 10 to 15 kgs. Each tablet contains the following amounts of ingredients:

	Gm.
α-Aminobenzylpenicillin trihydrate (equivalent to about 0.138 gm. of α-aminobenzylpenicillin activity)	0.160
Mannitol	0.3500
Sodium cyclamate	0.0750
Sodium saccharin	0.0075
Glycine	0.1000
Magnesium stearate	0.0120
"Carbowax 6000" powder	0.0020
Dry flavoring agents	0.00177
Total tablet weight	0.70827

The resultant tablets have a pleasant taste and are easily ingested by children.

Example 2

In a blender there are mixed for 15 minutes tetracycline hexametaphosphate, mannitol, sodium saccharin, dry flavor, sodium cyclamate and glycine. There is then added a mixture of flavors and dissolved in methylene chloride. This entire mixture is blended for another 15 minutes and is then micropulverized in a mill. The micropulverized mixture is placed in a blender and sufficient methylene chloride is added to form a uniform moist granulation. The wet granulation is passed through a granulating machine and dried overnight at room temperature. The dried granulation is pulverized in a mill and magnesium stearate is added. The mixture is blended for 15 minutes and compacted by slugging. The compacted material is then passed through a mill to reduce the particle size. The granular material is screened to separate the 20–40 mesh granules. The fines and the granules larger than 20 mesh are compacted and again reduced in size and screened to collect the 20–40 mesh granules. This process is repeated until the fines are less than 15% of the total composition. The 20–40 mesh granules and remaining fines are placed in a blender and magnesium stearate and "Carbowax 6000" (a polyethylene glycol having an average molecular weight of 6000 to 7500) are added. The mixture is blended for 15 minutes and put through a tabletting machine. The resultant tablets have a hardness as determined on a Strong-Cobb-Arner hardness tester, of 8 to 10 kgs. Each tablet contains the following amounts of ingredients:

	Gm.
Tetracycline hexametaphosphate (this is equivalent to 0.131 gm. of tetracycline hydrochloride activity)	0.1750
Mannitol	0.3500
Sodium cyclamate	0.07500
Sodium saccharin	0.00750
Glycine	0.100
Magnesium stearate	0.0140
"Carbowax 6000"	0.0030
Flavors	0.00187
Total tablet weight	0.72637

The resultant tablets have a pleasant taste and are easily ingested by children.

Example 3

In the manner of Example 1, chewable hetacillin tablets are prepared containing in each tablet the following amounts of ingredients:

	Gm.
Hetacillin	0.1380
Mannitol N.F.	0.3500
Sodium cyclamate N.F.	0.0750
Saccharin sodium N.F.	0.0075
Aminoacetic acid N.F.	0.1000
Methylparaben U.S.P.	0.001275
Propylparaben U.S.P.	0.000142
Flavoring agents	0.0018
"Carbowax 6000," micropulverized	0.0100
Gelatin U.S.P.	0.0010
Red-colored granulation	0.0133
Magnesium stearate U.S.P.	0.0120
Total tablet weight	0.710017

Example 4

In the manner of Example 1, four lots of chewable tablets are produced in which the *a*-aminobenzylpenicillin is replaced, on a per tablet basis, with 125 mgm. sodium oxacillin, 125 mgm. sodium cloxacillin and 62.5 and 125 mgm. sodium dicloxacillin, respectively, which has been previously coated as described above.

The examples above illustrate the use of a single antibacterial agent in the tablets of the present invention but the invention is not limited thereto. Thus the glycine in the formulations given above can be replaced by a therapeutic dosage of a second antibacterial agent to provide, for example, an antibacterial composition comprising a mixture of about one to two parts by weight of hetacillin or ampicillin with one part by weight of dicloxacillin.

When desired for specific purposes and rendered pharmaceutically compatible, there may be admixed with the antibacterial agents specified above various other additional medicaments, such as antihistamines, sulfa drugs (e.g. sulfadiazine, sulfabenzamide, sulfacetamide, sulfanilamide, sulfapyridine, sulfathiazole, sulfapyrazine, sulfaguanidine, sulfathalidine, sulfasuxidine, sulfisoxazole, sulfamylon, phthalysulfacetamide, N'-3,4-dimethylbenzoylsulfanilamide, benzylsulfanilamide and N'-2-(2-quinoxalyl)sulfanilamide), lipotropic agents (particularly methionine, choline, inositol and beta-sitosterol and mixtures thereof), stimulants of the central nervous system (e.g. caffeine, amphetamines), local anesthetics, analgesics (e.g. aspirin, salicylamide, sodium gentisate, p-acetylaminophenol, phenacetin, codeine), laxatives (e.g. phenolphthalein), sedatives (e.g. barbiturates, bromides), salts of penicillin (e.g. potassium penicillin G, procaine penicillin G, 1-ephenamine penicillin G, dibenzylamine penicillin G, other salts disclosed by U.S. Patent 2,627,491; these combinations are particularly useful to enable variation of the pattern of blood levels obtained), phenoxymethylpenicillin and salts thereof, other antibiotic agents (e.g. streptomycin, dihydrostreptomycin, bacitracin, polymixin, tyrothricin, erythromycin, Aueromycin, Terramycin, oleandomycin, chloramphenicol, magnamycin, novobiocin, cycloserine; in some cases such combinations attack a wider range of organisms or show synergistic efficacy or provide decreased toxicity with equal efficacy), vitamins (e.g. vitamins A, A_1, B_1, B_2, B_6, B_{12} and members of that family, folic acid and members of that family, vitamins C, D_2, D_3 and E), hormones (e.g. cortisone, hydrocortisone 9α-fluorocortisone, 9α-fluorohydrocortisone, prednisone and prednisolone), anabolic agents (e.g. 11, 17-dihydroxy-9α-fluoro-17-α-methyl - 4 - androsten - 3-one; 17α-ethyl-19-nortestosterone) and antifungal agents (e.g. mycostatin).

Analyses expressed herein as mcg./ml. or mcg./mgm. refer according to the usual custom to micrograms of tetracycline hydrochloride equivalents. Thus, pure tetra-

cycline hydrochloride has a potency of 1000 mcg./mgm. and pure tetracycline base of 1080 mcg./mgm., etc.

In the present invention and particularly in the examples, hetacillin free acid is taken as the standard with an activity of 1000 mcg./mgm. and when other salts are used, the weight taken is that which gives an equivalent amount of activity, i.e., 1096 mgms. of potassium hetacillin are equivalent in activity to 1000 mgms. of hetacillin free acid. The relationship is stoichiometric.

In the case of ampicillin in the standard with an activity of 1000 mcg./mgm. is anhydrous ampicillin and thus ampicillin trihydrate has a potency of 865 mcg./mgm.

In the case of dicloxacillin, the standard is the free acid with an activity of 1000 mcg./mgm. and thus the sodium salt is 920 mcg./mgm.

In the actual formulations use is often made as is customary in this field of an overfill, e.g., of ten percent, of each active ingredient as compared to labelled potency.

While in the foregoing specification various embodiments of this invention have been set forth in specific detail and elaborated for the purpose of illustration, it will be apparent to those skilled in the art that this invention is susceptible to other embodiments and that many of the details can be varied widely without departing from the basic concept and the spirit and scope of the invention.

We claim:

1. A chewable therapeutic tablet comprising from about 0.0625 to 0.250 gm. of an antibacterial agent selected from the group consisting of α-aminobenzylpenicillin, hetacillin, a form of tetracycline, oxacillin, cloxacillin and dicloxacillin, from about 0.300 to 0.400 gm. of mannitol and from about 0.001 to 0.020 gm. of solid polyethylene glycol.

2. A tablet according to claim 1 in which the antibacterial agent is α-aminobenzylpenicillin.

3. A tablet according to claim 1 in which the antibacterial agent is hetacillin.

4. A tablet according to claim 1 in which the antibacterial agent is a form of tetracycline.

5. A tablet according to claim 1 in which the antibacterial agent is oxacillin, cloxacillin or dicloxacillin.

6. A chewable therapeutic tablet comprising from about 0.0625 to 0.250 gm. of an antibacterial agent selected from the group consisting of α-aminobenzylpenicillin, hetacillin, a form of tetracycline, oxacillin, cloxacillin and dicloracillan, from about 0.300 to 0.400 gm. of mannitol and from about 0.001 to 0.020 of solid polyethylene glycol having an average molecular weight in the range of 6000 to 7500.

7. A tablet according to claim 6 in which the antibacterial agent is α-aminobenzylpenicillin.

8. A tablet according to claim 6 in which the antibacterial agent is hetacillin.

9. A tablet according to claim 6 in which the antibacterial agent is a form of tetracycline.

10. A tablet according to claim 6 in which the antibacterial agent is oxacillin, cloxacillin or dicloxacillin.

References Cited

UNITED STATES PATENTS

3,145,146 8/1964 Liebeman et al. -- 424—14 XR

LEWIS GOTTS, Primary Examiner

S. H. ROSE, Assistant Examiner

U.S. Cl. X.R.

260—358; 424—271, 361