REPEAT ACTION PHARMACEUTICAL COMPOSITIONS IN THE FORM OF DISCRETE BEADLETS


No Drawing. Filed Aug. 9, 1965, Ser. No. 478,437
18 Claims. (Cl. 167—82)

ABSTRACT OF THE DISCLOSURE

Pharmaceutical compositions, in the form of beadlets suitable for filling into hard shell pharmaceutical capsules, are described. In one embodiment, the beadlets are characterized in that the medicament therein is released in two separate and distinct doses. In part, this is accomplished by means of an enteric coating containing zein and an abiotic acid type resin. In another embodiment beadlets are described in which the active medicament is released in a more or less continuous fashion over a predetermined period of time.

The embodiment of such beadlets into pharmaceutical grade hard shell capsules is also described.

This invention relates, in general, to novel pharmaceutical compositions. More particularly, the invention relates to compositions, in the form of small discrete beadlets, which beadlets contain an active drug component and are capable of being embodied, in large numbers, into conventional, pharmaceutical hard shell capsules.

It is recognized in the art that, in certain instances, an active drug is advantageously embodied in a formulation which permits or causes the drug to be liberated in some desired regulated pattern of release. For example, it is often useful to administer certain drugs in the form of a repeat action composition, whereby a predetermined quantity of the drug is liberated shortly after the composition is administered to the patient, with a second predetermined quantity being released at some subsequent time. On the other hand, it has been proven useful, in the case of certain drugs, to formulate same into compositions which have sustained release characteristics. The active medicament is released from such a dosage form in a more or less continuous manner over a predetermined period of time.

In a comprehensive embodiment, the present invention provides pharmaceutical compositions in the form of beadlets, which beadlets are characterized in that the medicament therein is released in two separate and distinct doses, i.e., repeat action beadlets.

In another comprehensive embodiment, the invention provides pharmaceutical compositions in the form of beadlets, which beadlets are characterized in that the medicament therein is released in a more or less continuous fashion over a predetermined period of time, i.e., sustained release beadlets.

In a more restricted embodiment, the invention provides capsules which contain a multiplicity of the medicament-containing repeat action beadlets.

In another restricted embodiment, the invention provides capsules which contain a multiplicity of the medicament-containing sustained release beadlets.

In a still more restricted embodiment, the invention provides capsules which contain (1) a multiplicity of repeat action beadlets having embodied therein an active drug component and (2) a multiplicity of sustained release beadlets having embodied therein an active drug component other than that embodied in the aforesaid repeat action beadlets.

In general, the present invention is applicable to (1) any drug which is advantageously administered in the form of a repeat action composition and (2) to any drug which is advantageously administered in the form of a sustained release composition. Included among the drugs which are administered beneficially in repeat action dosage form are the well known 7-chloro - 2 - methylamino-5-phenyl-3H,1,4-benzodiazepine-4-oxide, and its medicinally acceptable acid addition salts; 7-chloro - 1-methyl-5-phenyl - 3H,1,4-benzodiazepin-2(1H)one, and its medicinally acceptable acid addition salts; 1-methyl-3-benzoyloxy-quinuclidinium halides; etc. Such drugs, as well as others, can be employed in the practice of this invention. Included among the drugs which are administered beneficially in sustained release form are the known dextroamphetamine, and its medicinally acceptable acid addition salts; the aforementioned 1-methyl-3-benzoyloxy-quinuclidinium halide; etc. Such drugs, and others, can be employed as the active drug component of the sustained release beadlets of this invention. For convenience, however, the invention will be described herein with particular reference to repeat action beadlets which contain 7-chloro - 2 - methylamino-5-phenyl-3H,1,4-benzodiazepine-4-oxide, and its medicinally acceptable acid addition salts, (hereinafter referred to collectively as chlor Diazepoxide) as the active ingredient and with particular reference to the use of dextroamphetamine sulfate in formulating beadlets having sustained release characteristics. Moreover, while the invention will be described herein with particular reference to a dosage form, i.e., capsules, which contain (1) chlor Diazepoxide-containing repeat action beadlets (2) dextroamphetamine-sulfate-containing sustained release beadlets, it will be fully understood that the invention is operable, in like manner, to provide capsules having embodied therein beadlets which contain either of these drugs as the only active medicament.

Chlor Diazepoxide is useful, and it is used, in treating various neuroses and in elevating the mood of depressed patients. Dextroamphetamine, and its medicinally acceptable acid addition salts, are broadly used, and they are used, as anorexicogenic agents. In addition to their individual utilities, chlor Diazepoxide and dextroamphetamine are beneficially administered, in combination, in the treatment of obese patients and, particularly in the treatment of emotionally disturbed obese patients.

Thus, the present invention provides an oral dosage form, i.e., capsules, containing (1) beadlets which contain and furnish two separate and distinct doses of an active medicament, e.g., chlor Diazepoxide, and/or (2) beadlets which contain and permit an active medicament, e.g., dextroamphetamine, to be released therefrom in a continuous fashion. In the case of the chlor Diazepoxide-containing beadlets, the first dose of chlor Diazepoxide is liberated from the beadlets shortly after the capsule containing same is administered to the patient. The second dose of chlor Diazepoxide is released from the beadlets at some subsequent time, for example, about four hours after the release of the first. For convenience, the chlor Diazepoxide-containing beadlets, because of the particular pattern in which the active drug is released therefrom, will be referred to herein simply as repeat action beadlets. On the other hand, since, in the case of the dextroamphetamine-sulfate-containing beadlets, the active medicament is released more or less continuously over an extended period of time, for example, up to about eight hours, such beadlets will be referred to herein simply as sustained release beadlets.

The repeat action chlor Diazepoxide beadlets are readily prepared. In the preparative method, powdered chlor Diazepoxide, preferably in the form of the free base, is dispersed, e.g., by dusting, onto a medicinally acceptable core material. As the core material, non-pareil seeds are
preferably employed. It should be understood that, while the non-pareil seeds will be referred to herein collectively as the "core," each such non-pareil seed is a separate core. Adhesion of the chloridiazepoxide on the core is accomplished by overlaying, e.g., by spraying, the core with a specially prepared, edible acacia syrup adhesive prior to applying the chloridiazepoxide thereon. Thus, the first step of the preparative method is the spraying of the adhesive on the core and the second step involves the dusting of chloridiazepoxide onto the thus sprayed core. The syrup which is employed as the adhesive in the first step of the preparative method, i.e., the non-pareil syrup, and this syrup, and its preparation, will be described hereinafter. The chloridiazepoxide which, in the second step of the process, is dusted directly on the adhesive-treated core is the repeat action dose, i.e., the second dose which is released to the patient's system. The chloridiazepoxide-coated core is, in the third step of the preparative method, dried by appropriate means. After drying, an appropriate number of edible enteric coatings are overlayed each chloridiazepoxide-coated core to provide a composition which will be referred to hereinafter as an enteric coated beadlet. The number of enteric coats which will be applied in this step of the process is variable. Generally, the application of at least about ten separate enteric coats is desirable. It will be obvious, however, that a fewer or a greater number of such coats can be applied to afford desired modifications in the release characteristics. The enteric coating composition which is used in this step of the process is also an important feature of this invention. This coating composition, its preparation and the manner in which it is applied will be described hereinafter. When the final enteric coating is completely dry, an additional quantity of powdered chloridiazepoxide is dispersed, e.g., by dusting, on the beadlets. In this second dusting step, the acacia syrup, referred to heretofore, is used once again as the adhesive. As was the case in the first dusting operation, the beadlet is overlayed with the adhesive, preferably by spraying, following which the chloridiazepoxide powder is dusted thereon. The chloridiazepoxide, which is applied to the enteric coated beadlets in this second dusting step, is the dose which will be released first into the system of the patient when the capsule containing the beadlets is swallowed. In the final step of this preparative method, the repeat action chloridiazepoxide beadlets, which are thus obtained, are dried by appropriate means.

As indicated heretofore, the repeat action beadlets, described in the preceding paragraph, provide two separate and distinct doses of chloridiazepoxide. The first dose is released shortly after the capsule containing the beadlets is administered orally to the patient. The second dose is released at some predetermined point of time subsequent to the release of the first dose. The duration of time intervening the release of the first and second doses is determined, for the most part, by the amount of enteric coating, i.e., the number of enteric coats, applied to the chloridiazepoxide-coated core. As indicated heretofore, it is preferable to apply at least about ten separate coats. It has been found that when ten coats of the enteric coating are applied, the time which elapses between the release of the first dose and second dose is about four hours. By applying a fewer number of enteric coatings, the interval between the release of the first dose and the second dose will be decreased. By applying a greater number of enteric coatings, the time intervening the release of the two doses will be increased. By preliminary experiment, one can determine the precise number of coatings to be applied to provide the interval desired between the release of the two doses.

The sustained release beadlets which contain dextro-amphetamine sulfate are also readily prepared. In the preparative method, dextroamphetamine sulfate, in the form of a powder, is dusted onto a medicinally acceptable core material, such as, non-pareil seeds. As was the case heretofore, the non-pareil seeds will be referred to collectively as the "core," with the understanding that each seed is a separate core. Adhesion of the powdered dextro-amphetamine sulfate to the core is accomplished by spraying the core with the aforementioned edible acacia syrup adhesive, prior to dusting the powdered dextroamphetamine sulfate thereon. Each dextroamphetamine sulfate-coated core is then coated with a permeable film, using, as the film-forming composition, an edible composition comprising shellac, polyethylene glycol and an anhydrous lower aliphatic alcohol. The number of coats of the aliphatic oil-containing coating composition applied in this step of the process is variable. However, the application of at least about ten separate coats is preferred. When the coating operation has been completed, it is advantageous, but not absolutely necessary, to allow the film-coated beadlets to age for a period of about four days, at a temperature of from about 60 °C. to 65 °C. It appears that aging at an elevated temperature allows the shellac-polyethylene glycol film to reach a desired equilibrium. After aging, a representative sampling of the beadlets are tested by conventional in vitro procedures to determine the release rates. A half-life release method is used for this determination. A typical release pattern is about 5% release of the medicament after thirty minutes, about 15% release after two hours, about 63% release after four hours and about 71% release after six hours. If the release rate is faster than desired, additional film coating compositions which will retard solution are applied as needed. When the desired release rate is achieved, the beadlets are sprayed again with the acacia adhesive, following which, by dusting, they are overlayed with an additional quantity of dextroamphetamine sulfate. The overlayed portion of the medicament is liberated shortly after the capsule containing the pellets is administered to the patient.

The acacia syrup which is used as the adhesive in the practice of this invention comprises powdered gum acacia, sucrose and distilled water. The quantities of powdered gum acacia and sucrose which are used in preparing the adhesive composition are variable. In the preferred practice of the invention, however, there will be used a syrup containing from about 5% to 15% by weight of powdered gum acacia, 35% to about 45% by weight of sucrose and from about 40% to about 60% by weight of distilled water. A preferred adhesive composition contains about 9.5% to 10.0% by weight of gum acacia, from about 38% to about 38.5% by weight of sucrose and from about 51.5% to about 52.5% by weight of distilled water. The adhesive is prepared simply by adding the gum acacia and sucrose to water and stirring thereon. This can be accomplished at room temperature, or at a temperature which is elevated somewhat above room temperature.

The enteric coating which is used in preparing the repeat action chloridiazepoxide beadlets of this invention is a composition produced by mixing the following named ingredients, in the quantities hereinafter indicated:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abietic acid-type rosin</td>
<td>25 to 30</td>
</tr>
<tr>
<td>Zein</td>
<td>10 to 20</td>
</tr>
<tr>
<td>Wetting agent</td>
<td>0.05 to 0.5</td>
</tr>
<tr>
<td>Anhydrous lower aliphatic alcohol</td>
<td>46 to 60</td>
</tr>
<tr>
<td>Plasticizer</td>
<td>1 to 10</td>
</tr>
</tbody>
</table>

As the anhydrous lower aliphatic alcohol component, there can be used, for example, methyl alcohol, ethyl alcohol or any such alcohol in which the lacquer is soluble. A preferred enteric coating contains about 825.0 parts by weight of an abietic acid-type rosin sold commercially as Nello Rosin; 432.0 parts by weight of zein; 36.0 parts by weight of white neutral soap as the wetting agent; 171.0 parts by weight of white oleic acid as the plasticizer; and about 1500.0 parts by weight of ethyl
alcohol. In lieu of white neutral soap, there can be used as the wetting agent, for example, Pluronic F-68, dioctyl sodium sulfosuccinate, sodium lauryl sulfate, a poloxymethylene sorbitan fatty acid ester, such as, poloxethylene sorbitan monooleate, etc. In lieu of oleic acid, castor oil, dioctyl phthalate, triacetin, etc. can be used as the plasticizer.

The desired lacquer composition is prepared readily by adding the resin, a wetting agent and plasticizer to the anhydrous alcohol and stirring until a homogenous solution. This can be accomplished at room temperature or at a temperature which is elevated somewhat above room temperature. Prior to its use as the entraining coating, however, the lacquer composition, described heretofore, is diluted further with from 80% to about 10% of its weight of an anhydrous lower aliphatic alcohol.

The permeable film-forming composition which is used in producing the sustained release dextroamphetamine beads of this invention comprises shellac, a polyleylene glycol wetting agent, for example, polyleylene glycol 4000, polyleylene glycol 6000, polyleylene glycol 20,000, and a lower molecular weight aliphatic alcohol, such as, methyl alcohol, ethyl alcohol, etc. The composition is prepared simply by mixing the various ingredients at a temperature which is elevated somewhat above room temperature. The quantities of the three ingredients comprising these products can be varied within relatively wide ranges. However, in the preferred embodiment of the invention there is used a composition containing from about 45% to about 55% by weight of shellac, from about 40% to about 50% by weight of polyleylene glycol 6000 and from about 10% to about 20% by weight of ethyl alcohol.

As indicated heretofore, the number of coats of the enteric coating composition which are applied to the chlordiazepoxide-coated beads is variable. In the preferred practice of the invention four distinct and separate coats are first applied, with the pellets being dried and then coated with talc and sucrose between each coat. Thereafter, six additional coats of the enteric coating are applied, with the pellets being dried and dusted with talc between each coat. The number of shells-polyleylene glycol coats which are applied in the production of the sustained release dextroamphetamine beads is similarly variable. In the preferred practice of the invention, about ten separate and distinct coats are applied with the beads being dusted with talc and dried between each coat.

The manner in which the several enteric coats are applied to the chlordiazepoxide coated core and the manner in which the shellac coats are applied to the dextroamphetamine-coated core will be obvious to persons skilled in the art. In general, conventional coating techniques and equipment are used. Briefly, however, the coating processes involve the placing of an appropriate number of medicament-coated cores in the standard coating pan, followed by the addition thereto of a sufficient quantity of the coating composition to completely wet the cores. The pan is rotated until all of the coating composition has been taken up by the cores. In the case of the coating for the dextroamphetamine seeds, it is preferred to keep the coating composition warm to prevent the precipitation of the polyethylene glycol 6000 therefrom. When the first coating operation is completed, the beads are dried. Thereafter, the remaining coats are applied in a similar manner.

The repeat action chlordiazepoxide beadlet and the sustained release dextroamphetamine beadlets, are in the practice of this invention, filled into suitable hard shell capsules. Untreated non-pareil seeds are used as inert fillers to obtain a proper capsule fill. The number of chlordiazepoxide-containing beadlets and the number of dextroamphetamine sulfate-containing beadlets to be incorporated into a single capsule is variable. In any instance, the number of beadlets filled into any one capsule will be determined by the levels of active medicament which it is desired to have in the final product. The number of beadlets needed to achieve such level of medication will be dependent upon the amount of medicament present in the individual pellets. The primary objective is to provide capsules containing a safe, but yet effective, dose of the drugs. Generally, however, a sufficient number of each type beadlet will be added to the capsule to provide a unit dosage containing from about 10 mg. to about 25 mg. of chlordiazepoxide base and 10 mg. to 25 mg. of dextroamphetamine sulfate.

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

**EXAMPLE**

(a) **Production of dextroamphetamine sulfate beadlets**—12,750 parts of #26 mesh, non-pareil seeds were charged into a 28" baffled rotary coating pan. Subsequently, there was sprayed on these seeds, 1500 cc. of a syrup containing the following named ingredients in the quantities hereinafter indicated:

- **Parts**
  - Powdered acacia .............................................. 317.8
  - Sucrose .......................................................... 1254.6
  - Distilled water ............................................ 1708.0

After spraying with the syrup, the non-pareil seeds were dusted with 2244.0 parts of dextroamphetamine sulfate. The beadlets were then dried overnight at a temperature of 43° C.

Thereafter, a coating solution was prepared by mixing 1320 parts of shellac, 132 parts of polyleylene glycol 6000 and sufficient ethyl alcohol to make 6000 parts by volume. This solution was applied to the coated non-pareil seeds, described in the preceding paragraph, in ten separate coats, there being used in each coating operation, 600 cc. of the coating solution. Between coats, the beadlets were dusted with 700 parts by weight of talc. Between each coat, the beadlets were dried with warm air for a period of about 20 to 30 minutes. After ten coats of the shellac solution had been applied thereto, the beadlets were aged for a period of about four days at a temperature of from about 60° C. to 65° C. When the aging step was completed, the beadlets were tested, in vitro, by a half change method to determine the release rate of dextroamphetamine sulfate. Thereafter, the beadlets were overlayed with the immediate release portion of chlordiazepoxide sulfate. This was accomplished by spraying the beadlets with 800 cc. of acacia syrup and, subsequently, dusting the sprayed pellets with 395 parts of dextroamphetamine sulfate.

(b) **Production of chlordiazepoxide beadlets**—13,350 parts of #26 mesh non-pareil seeds were charged into a 28" baffled rotating coating pan. These seeds were sprayed with a syrup comprising 118 parts of powdered gum acacia, 464.0 parts of sucrose and sufficient distilled water to make 800 cc. The sprayed seeds were then dusted with 1782.0 parts of chlordiazepoxide. After the chlordiazepoxide had been dusted onto the seeds, the seeds were dried overnight at a temperature of 43° C. Thereafter, the beadlets, thus obtained, were coated with an enteric coating. The coating which was used contained the following named ingredients in the quantities hereinafter indicated:

- **Parts**
  - Nello Rosin ...................................................... 825
  - Zein .......................................................... 432
  - White neutral soap ........................................ 36
  - Anhydrous ethyl alcohol ................................... 1500
  - White oleic acid .......................................... 171

Prior to its use in the coating operation, 1500 cc. of the aforementioned coating solution was first diluted with 1500 cc. of anhydrous ethyl alcohol. Thereafter, four separate coats, each utilizing 600 cc. of the coating solution,
were applied. Between each coat, the beadlets were dusted with a mixture of 180 parts of sucrose and 820 parts of tale. Thereafter, six additional separate coats of the lacquer solution, each coat utilizing 600 cc. of the coating solution, were applied to the beadlets. Between each of these coats, the beadlets were dusted with about 1500 parts of tale. The beadlets were then dried overnight at a temperature of about 43°C.

In the final step of the process, the enteric coated chlordiazepoxide beadlets were sprayed with 650 cc. of the acacia-sucrose syrup described heretofore and the sprayed beadlets were then dusted with 1580 parts of chlordiazepoxide.

(c) Formulation of an oral dosage form containing repeat action chlordiazepoxide beadlets and sustained release dextroamphetamine sulfate beadlets.—The sustained release dextroamphetamine beadlets and the repeat action chlordiazepoxide beadlets, produced as described in Sections (a) and (b), respectively, of this example, were embodied into hard shell capsules. More specifically, into a No. 1 size capsule, there was added 550 chlordiazepoxide-containing beadlets, 422 dextroamphetamine sulfate-containing beadlets and 70 neutral non-pareil seeds to provide a unit dosage containing 15 mg. of chlordiazepoxide and 15 mg. of dextroamphetamine sulfate. It was established that the chlordiazepoxide was released from the beadlets in two separate and distinct 7.5 mg. doses, the first dose being released immediately, the second being released approximately four hours after the first. In the case of the dextroamphetamine sulfate-containing beadlets, the dextroamphetamine was released according to the following pattern: 30 minutes, 37%; 2 hours, 44%; 4 hours, 68%; and 7 hours, 83%.

Thus, in the single dosage form, i.e., in each capsule, there was provided chlordiazepoxide in repeat action form and dextroamphetamine sulfate in sustained release form.

(d) Formulation of an oral dosage form containing either repeat action chlordiazepoxide beadlets or sustained release dextroamphetamine sulfate beadlets:

(1) Chlordiazepoxide-containing beadlets, produced as described in Section (a) of this example were charged into No. 1 size capsules, 550 of such beadlets being employed for each capsule. A sufficient number of neutral non-pareil seeds were added to each capsule to obtain proper capsule fill. Each capsule contained 15 mg. of chlordiazepoxide, 7.5 mg. of which was released almost immediately upon administration to the patient and the remaining 7.5 mg. being released approximately four hours thereafter.

(2) Dextroamphetamine sulfate-containing beadlets, produced as described in Section (b) of this example, were charged into No. 1 size capsules, 422 of such beadlets being employed for each capsule. A sufficient number of neutral non-pareil seeds were added to each capsule to obtain proper capsule fill. Each capsule contained 15 mg. of dextroamphetamine sulfate which was released approximately as follows: 30 minutes, 37%; 2 hours, 44%; 4 hours, 68%; and 7 hours, 83%.

What is claimed is:

1. A repeat action pharmaceutical composition, in the form of discrete beadlets, each beadlet comprising (1) a medicinally acceptable core material, (2) an adhesive gum acacia composition overlaying said core material, (3) an active medicament dispersed upon said adhesive gum acacia composition overlaying said core material and retained therein by said adhesive gum acacia composition, (4) an enteric coating of an enteric acid type resin and zein overlaying the medicament-coated core, (5) an adhesive gum acacia composition overlaying said enteric coating and (6) an active medicament dispersed upon said adhesive gum acacia composition overlaying said core material, from about 35% to about 45% by weight of sucrose and from about 40% to about 60% by weight of distilled water, and the enteric coating (4) being applied in the form of a solution comprising from about 25% to about 35% by weight of an enteric acid type resin, from about 10% to about 20% by weight of zein, from about 0.05% to about 0.5% by weight of a wetting agent, from about 40% to about 60% by weight of an hydrous lower aliphatic alcohol and from about 1.0% to about 10% by weight of a plasticizer, said solution being diluted further with from about 80% to 110% by weight of an hydrous lower aliphatic alcohol also present.

2. The composition of claim 1 wherein the active medicament (3) and (6) is a member selected from the group consisting of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide and a medicinally acceptable acid addition salt thereof.

3. The composition of claim 1 wherein the active medicament (3) and (6) is 1-methyl-3-benzoyloxy quinuclidinium halide.

4. A repeat action pharmaceutical composition, in the form of discrete beadlets, each beadlet comprising (1) a non-pareil seed overlayed with (2) an adhesive gum acacia composition, (3) an active medicament dispersed upon the adhesive-overlayed non-pareil seed, (4) an enteric coating of an enteric acid type resin and zein overlaying the medicament-coated non-pareil seeds, (5) an adhesive gum acacia composition overlaying said enteric coating and (6) an active medicament dispersed upon the enteric coated core and retained therein by said adhesi-
3,365,365

hesive composition, (4) a permeable film of shellac and polyethylene glycol 4,000 to 20,000 overlying the medicament-coated core, (5) an adhesive gum acacia composition overlaying said permeable film and (6) an active medicament dispersed upon the film-coated core material and retained thereon by said adhesive composition, the adhesive component (2) and (5) being the same in each instance and having been applied in the form of a syrup comprising from about 5% to about 15% by weight of gum acacia, from about 35% to about 45% by weight of sucrose and from about 40% to about 60% by weight of distilled water, the permeable film (4) having been applied in the form of a solution comprising from about 45% to about 55% by weight of 40% to 50% solids shellac, from about 4.5% to about 5.5% by weight of a polyethylene glycol 4,000 to 20,000 and from about 40% to about 50% by weight of a lower molecular weight aliphatic alcohol.

12. A composition of claim 11 in which the active medicament is a member selected from the group consisting of dextroamphetamine and a medicinally acceptable acid addition salt thereof.

13. The composition of claim 11 in which the active medicament is a 1-methyl-3-benzylxyloxy-quinuclidinium halide.

14. Capsules, for oral administration, containing (a) a multiplicity of the beadlets of claim 11 and (b) inert filler materials.

15. A pharmaceutical composition, in oral dosage form, said composition comprising capsules containing (a) a multiplicity of repeat action medicament-containing beadlets, each of such beadlets comprising (1) a medicinally acceptable core material, (2) an adhesive gum acacia composition overlaying said core material, (3) an active medicament dispersed upon said adhesive-treated core material and retained thereon by said adhesive composition, (4) an enteric coating of an abietic acid type resin and zein overlaying the medicament-coated core, (5) an adhesive gum acacia composition overlaying said enteric coating and (6) an active medicament dispersed upon the enteric coated core and retained thereon by said adhesive composition, (b) a multiplicity of sustained release medicament-containing beadlets, each of such beadlets comprising (7) a medicinally acceptable core material, (8) an adhesive gum acacia composition overlaying said core material, (9) an active medicament dispersed upon said adhesive treated core material and retained thereon by said adhesive composition, (10) a permeable film of shellac and polyethylene glycol 4,000 to 20,000 overlying the medicament-coated core, (11) an adhesive gum acacia composition overlaying said permeable film and (12) an active medicament dispersed upon the film coated core material and retained thereon by said adhesive composition, the adhesive compositions (2), (5), (8) and (11) being the same in all instances and having been applied in the form of a syrup comprising from about 5% to about 15% by weight of gum acacia, from about 35% to about 45% by weight of sucrose and from about 40% to about 60% by weight of distilled water, said enteric coating (4) having been applied in the form of a solution comprising from about 25% to about 35% by weight of an abietic acid type resin, from about 10% to about 20% by weight of zein, from about 0.05% to about 0.5% by weight of a wetting agent, from about 40% to about 60% by weight of an anhydrous lower aliphatic alcohol and from about 1.0% to about 10.0% by weight of a plasticizer said solution having been diluted further with from about 80% to about 110% by weight of an anhydrous lower aliphatic alcohol; and said permeable film (10) having been applied in the form of a solution comprising from about 45% to about 55% by weight of 40% to 50% solids shellac, from about 4.5% to about 5.5% by weight of a polyethylene glycol 4,000 to 20,000 and from about 40% to about 50% by weight of a lower molecular weight aliphatic alcohol.

16. The composition of claim 15 wherein the active medicament (3) and (6) is a member selected from the group consisting of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide and a medicinally acceptable acid addition salt thereof and wherein the active medicament (9) and (12) is a member selected from the group consisting of dextroamphetamine and a medicinally acceptable acid addition salt thereof.

17. The composition of claim 15 wherein the enteric coating (4) is applied in the form of a solution comprising from about 25% to about 35% by weight of an abietic acid type resin, from about 10% to about 20% by weight of zein, from about 0.05% to about 0.5% by weight of a neutral soap, from about 40% to about 60% by weight of ethyl alcohol and from about 10% to about 15% by weight of oleic acid and wherein the permeable film (10) is applied in the form of a solution comprising from about 45% to about 55% by weight of 40% to 50% solids shellac, from about 4.5% to about 5.5% by weight of a polyethylene glycol and from about 40% to about 50% by weight of ethyl alcohol.

18. The composition of claim 17 wherein the active medicament (3) and (6) is a member selected from the group consisting of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide and a medicinally acceptable acid addition salt thereof and wherein the active medicament (9) and (12) is a member selected from the group consisting of dextroamphetamine and a medicinally acceptable acid addition salt thereof.

References Cited

UNITED STATES PATENTS

3,043,747 7/1962 Long --------------------- 167--82

FOREIGN PATENTS

109,438 1/1940 Australia.

LEWIS GOTTS, Primary Examiner.
S. K. ROSE, Assistant Examiner.
UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION


John Allen Butler et al.

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

Column 4, line 60, "Percent" should read -- Percent by
Weight --.

Signed and sealed this 3rd day of March 1970.

(SEAL)
Attest:
Edward M. Fletcher, Jr.
Attesting Officer

WILLIAM E. SCHUYLER, JR.
Commissioner of Patents