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SUSTAINED RELEASE PHARMACEUTICAL PREPARATIONS

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This invention relates in general to certain new and useful improvements in pharmaceutical preparations and, more particularly, to medicated granules which release the medication into the human system gradually over a sustained period of time and methods of making the same. This application is a continuation-in-part of my copending application Serial No. 461,354, filed October 11, 1954, now Pat. No. 2,736,682, which is, in turn, a continuation of an earlier application Serial No. 195,369, filed November 13, 1950, now abandoned.

It has been accepted practice in the compounding of pharmaceutical tablets to provide certain types of tablets with what has been commonly referred to as an enteric coating. The enteric coating is one which will resist the action of the gastric juices in the stomach and will not dissolve therein or be otherwise affected thereby so that the drug which is incorporated in the tablet will pass through the stomach and into the intestine. The so-called enteric coating is of such a nature that it will be dissolved very readily in the intestinal fluids so that the drug which has been enclosed in the enteric coating will become effective in the intestinal tract rather than in the stomach. Such tablets, however, are merely "delayed action" tablets. In other words, by selecting an enteric coating of the proper type and by using an appropriate amount, it is possible to delay the effective entry of the drug into the patient's system for a number of hours. The so-called "enteric coated" tablet is also used when it is desirable to introduce the medicament into the patient's intestinal tract without discharging any of the medicament into the stomach. These procedures are useful in certain applications, but the patient sooner or later receives the entire dosage in a single shot, so to speak.

Recently, efforts have been made to provide delayed dosage by surrounding an enteric coated core with a second layer or group of layers of medicament and then, largely for appearance, covering the resulting tablet, ellipsoid or sphere with a soluble sugar coating. The theory is that the sugar coating and outer layers dissolve in the stomach and almost immediately release the initial dosage which lasts the patient for several hours. Meanwhile, the enteric coated core will have reached the intestinal tract and will dissolve therein very rapidly, releasing the second dosage. Even if this theory were borne out in practice, the net result would merely be a spaced interval "two shot" medication which is very little different in therapeutic effect from the simple business of giving the patient two smaller tablets at the same intervals. As a matter of fact, however, the existing methods of forming enteric coatings are not particularly accurate and the enteric coatings now in use are not always completely reliable. The research of Maney and Kuever (J. Am. Pharm. Soc. 30, 1941, p. 276), and of Abbott and Seeport (Pharm. J. 151, 1943, p. 52), suggests that various known enteric materials yield varying results and some such coatings seem to resist disintegration for periods up to five or six hours. Actual tests

with various types of enteric coatings using the in vitro method of Maney and Kuever have shown that most available enteric coatings dissolved to an appreciable extent in the gastric juices of the stomach or at least are attacked by such gastric juices to such an extent as to lose physical or structural strength, a factor which has been hitherto overlooked. In the stomach, peristalic action is severe enough to disrupt the physically weakened enteric coating and the drum or medicament enters the system with a surge, as has been discovered by blood level studies. The important point, however, is that enteric coatings, however efficient or inefficient they may be, merely withhold the medicament for some "time-delay" period and then release it to the patient's system in the same "surge dose" as though the period of time delay had not occurred. In other words, the patient ultimately gets the surge.

However, recent pharmacological investigations have shown that with many drugs the patient responds far better to sustained minute-incremental dosage, that is to say, very minute quantities administered at very short intervals continuously over sustained periods of time. This can be referred to, for want of a better term, as the "trickle system." Such procedures have been recognized for quite some time with respect to liquid medications such as the trickle treatment with penicillin for syphilis. The use of conventional enteric coated tablets, however, for the reason heretofore set out will not achieve even an approxiation of sustained minute-incremental dosage.

It is the primary object of the present invention, therefore, to provide a pharmaceutical preparation having a unique and novel composition and structure, which, as a result of a drug or medicament, can be administered in a persistent sustained incremental dosage.

It is also an object of the present invention to provide a pharmaceutical preparation which is capable of maintaining a desired level of medication within the patient's system over prolonged periods of time.

It is a further object of the present invention to provide a pharmaceutical preparation which has a unique and novel composition and structure, which is simple and precise in its action and which is economical to produce.

It is also an object of the present invention to provide methods of making pharmaceutical preparations of the type stated.

With the above and other objects in view, my invention resides in the novel features of form, construction, arrangement, and combination of parts presently described and pointed out in the claims.

Broadly speaking, the present invention resides in the discovery that a pharmaceutical preparation adapted for sustained minute-incremental dosage can be made by intimately mixing various enteric water insoluble excipients, such as shellac, with powdered drugs to form a somewhat pasty mass which is then spread on drying trays and dried to produce a rough granular material. This granular material is crushed and remixed with the excipient to form a pasty mass which is then spread on trays and dried again to form a rough granular material. This procedure of crushing, mixing with excipient, and tray-drying is repeated a number of times and finally the end product is screened to produce a granular material having granules of substantially uniform size. It has been found that, in such granules, the excipient and the medicament are intimately mixed or dispersed throughout the mass of each granule in the form of very minute particles. Visual examination of the granules under high-magnification shows that the surface thereof is not covered with a continuous film of the dried excipient or a continuous film of the medicament, but,

rather, is dotted with minute particles of the dried excipient and minute particles of the medicament in a sort of heterogeneous arrangement. Furthermore, this general physical structure exists throughout the granule. By both in vitro tests and blood level studies, it has been established that these granules, when in the human stomach and intestinal tract are neither soluble or insoluble in the strictest sense of these terms, but, instead, the medicament leaches out steadily in minute increments or doses, that is to say, as a sustained "trickle."

While this invention is not intended to be limited thereby, the following are examples of pharmaceutical preparations which can be made in accordance with the present invention:

Example I

3 lbs. of dicalcium phosphate and 1 lb. d-amphetamine sulfate is mixed in the dry. To this mixture, wax-free shellac (3 lb. cut—U. S. P. grade) is slowly added with agitation and in sufficient amount to produce a pasty mass which is spread out on cloth drying trays and air dried for 7–10 hours. The resulting product, when removed from the drying trays, forms a free flowing granular mass in which the granules have an average size of wheat grains. These granules are then crushed to about the size of coarse sugar and again mixed with enough shellac (of the type above) until a pasty mass results. This mass is again placed on cloth drying trays and dried, thereby again forming a granular mass as before. The above procedure is repeated for a total of eleven times, using a total of about ½ gallon of shellac (dry solids content 46%). The first four mixing-drying steps are repeated over a time cycle which involves about 7 to 10 hour drying periods and all subsequent mixing-drying steps include about 20 to 22 hour drying periods. These time periods can be speeded up by placing the drying trays in a hot room. The hot room should be maintained at about 100° to 120° F. with a relative humidity not in excess of 30% and the material dried until the granules are hard and frangible, that is to say, will form fine-grained particles upon crushing. Final yield is approximately 5.6 lbs. of granules of heterogeneous and irregular shapes.

Upon assay, the granules are precisely uniform in constituency. In other words, any given weight of granules will be found to contain the same dosage of amphetamine. Of course, each batch should be assayed and the actual amphetamine content by weight or percentage determined. It has been found that by following a standardized manufacturing procedure, successive batches of granules have closely similar assays well within admissible limits of pharmaceutical accuracy. However, this is not overly important since the granules thus formed are measured into capsules or tableted by conventional procedure for administration to the patient and any variations in drug content, as shown by the assay of the specific batch, can be taken into account in making up the capsule or tablet.

Example II

A dry mixture of 3 oz. d-amphetamine sulfate, 12 oz. secobarbital and 3 lbs. dicalcium phosphate is taken up with shellac as per Example I employing approximately 1 gallon shellac in eleven successive mixing-drying steps. Yield approximately 5½ lbs. of granules.

Example III

A dry mixture of 7 oz. pentobarbituric acid, 7 oz. phenobarbital and 2 oz. d-amphetamine sulfate, 3 lbs. calcium carbonate is taken up in shellac as per Example I employing nine successive mixing-drying steps.

Example IV

A dry mixture of 2 oz. scopolamine aminoxide hydrobromide, and 5 lbs. dicalcium phosphate were taken up in shellac as per Example I employing eleven successive mixing-drying steps.

Example V

A dry mixture of 2 lbs. mephobarbital, 2½ oz. homatropine methylbromide, 1 oz. atropine methyl nitrate, ½ oz. hyoscine hydrobromide, and 6 lbs. kaolin were taken up in shellac as per Example I employing eleven successive mixing-drying steps.

Example VI

A dry mixture of 4 lbs. mannitol hexanitrate 7% (with 13 parts lactose) was taken up in shellac as per Example I employing eleven successive mixing-drying steps.

Example VII

A dry mixture of 3 lbs. pyralimine maleate and 1 lb. vitamin C were taken up in 60 oz. (liquid) of shellac as per Example I employing fifteen successive mixing-drying steps to produce 5.5 lbs. of finished granules. 275 mgs. of such granules were filled into a No. 3 capsule, giving a dosage of 150 mgs. pyralimine maleate and 50 mgs. of vitamin C.

The above described procedure has been employed in making granules with a wide variety of drugs or medicinals, such as, for instance, scopolamine methylbromide, pentaerythritol tetranitrate, sodium nitrite, hexamethonium chloride, veratrum viride, reserpine, stilbesterol, methyl testosterone, phenobarbitol, pyralimine, digitoxin, caffeine, and antibiotics, such as penicillin, and the like. In each instance, the quantity of the drug is calculated by usual arithmetic methods well known in pharmaceutical manufacturing. It should also be noted that, instead of dicalcium phosphate, other suitable inert carriers, such as calcium carbonate, tri-calcium phosphate, magnesium oxide, magnesium carbonate, kaolin, starch, or lactose, may be used. Where the drug or medicament has sufficient bulk, it is even possible to eliminate the use of an inert carrier, as shown by Example VII.

It has also been found that other liquid excipients, such as a mixture of castor oil, stearic acid, and confectioner's glaze (i. e. shellac), cellulose acetate phthalate in acetone, salol in alcohol, various balsams, such as tolu in alcohol, ethyl cellulose in methyl ethyl ketone, or zein in isopropanol, can be employed in practicing the herein described invention. Similarly, by increasing the number of mixing-drying steps, it is possible to slow down the rate of entry of the drug into the patient's system and, conversely, by lowering the number of successive mixing-drying steps, it is possible to speed up the rate of entry of the drug into the patient's system. However, it has been found that a minimum of such steps is two and a practical maximum is fifteen, since additional mixing-drying steps resulting in such a slow rate of drug absorption by the patient has been found to be impractical for presently known medical purposes. Also, if desired for the sake of appearance, the granules can be placed in a coating pan and sugar coated with a plain or suitably colored sugar glaze.

It is also possible to incorporate liquid medicaments either by taking them up in an inert carrier and then granulating with shellac or other excipients as above described, or dissolving them in the liquid excipient and adding this solution to an inert carrier to create the initial granules and then carrying out the repeated regranulations using such excipient solution until all the drug bearing excipient has been incorporated. Usually, this will take five or six mixing-drying steps. Thereafter, six to nine further successive mixing-drying steps are employed using the plain (i. e. non-drug bearing) excipient.

It should be understood that changes and modifications in the form, construction, arrangement, and combination of the several parts of the pharmaceutical preparations may be made and substituted for those herein shown and described without departing from the nature and principle of my invention.

Having thus described my invention, what I claim and desire to secure by Letters Patent is:

1. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprises intimately mixing a powdered drug and shellac to produce a pasty mass, drying the mass slowly without agitation in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an addiitonal quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than 3 nor more than 15 mixing, crushing and drying cycles repeated in successive order, whereby to produce a pharmaceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract.

2. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprise intimately mixing a powdered drug and an enteric water insoluble excipient to produce a pasty mass, drying the mass slowly without agitation in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an additional quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than 3 nor more than 15 mixing, crushing and drying cycles repeated in successive order, whereby to produce a pharmaceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract.

3. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprises intimately mixing a powdered drug and a water insoluble excipient consisting of a mixture of shellac and stearic acid, whereby to produce a pasty mass, drying the mass slowly without agitation in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an additional quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than three nor more than fifteen mixing, crushing and drying cycles repeated in successive order, whereby to produce a pharmaceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract.

4. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprises intimately mixing a powdered drug and an enteric water insoluble excipient to produce a pasty mass, placing the mass on trays and drying the mass slowly without agitation in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an additional quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than three nor more than fifteen mixing, crushing and drying cycles repeated in successive order, whereby to produce a pharmaceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract.

5. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprises intimately mixing a powdered drug and an enteric water insoluble excipient to produce a pasty mass, spreading the mass in a thin layer upon trays and drying the mass slowly without agitation in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an additional quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than three nor more than fifteen mixing, crushing and drying cycles repeated in successive order, whereby to produce a pharmaceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract.

6. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprises intimately mixing a powdered drug and an enteric water insoluble excipient to produce a pasty mass, spreading the mass in a thin layer upon air pervious trays and drying the mass slowly without agitation in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an additional quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than three nor more than fifteen mixing, crushing and drying cycles repeated in successive order, whereby to produce a pharmaceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract.

7. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprises intimately mixing a powdered drug and an enteric water insoluble excipient to produce a pasty mass, spreading the mass in a thin layer upon cloth bottomed trays and drying the mass slowly without agitation in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an additional quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than three nor more than fifteen mixing, crushing and drying cycles repeated in successive order, whereby to produce a phar-

maceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract.

8. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprises intimately mixing a powdered drug and an enteric water insoluble excipient to produce a pasty mass, drying the mass slowly without agitation in a hot dry atmosphere in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an additional quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than three nor more than fifteen mixing, crushing and drying cycles repeated in successive order, whereby to produce a pharmaceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract.

9. The process for making sustained period minute-incremental dosage pharmaceutical preparations which comprises intimately mixing a powdered drug and an enteric water insoluble excipient to produce a pasty mass, drying the mass slowly without agitation in such a manner as to produce a rough granular material, breaking up the rough granular material by light crushing, whereby to

reduce it to granular particles, said mixing, drying and crushing operations constituting one cycle, and remixing the granular particles with an additional quantity of the excipient to produce a pasty mass, redrying such pasty mass slowly and without agitation in such a manner as to produce a granular material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, said second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than 3 nor more than 15 mixing, crushing and drying cycles repeated in successive order, whereby to produce a pharmaceutical material consisting of granules having slow but continuous and attenuated solubility in the gastro-intestinal tract, and coating the particles with a sugar glaze.

10. A pharmaceutical preparation made in accordance with the process of claim 1.

11. A pharmaceutical preparation made in accordance with the process of claim 2.

12. A pharmaceutical preparation made in accordance with the process of claim 3.

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