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Shear

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[54] **SUSTAINED RELEASE MEDICANT**

[75] Inventor: **Jeff L. Shear**, Creve Coeur, Mo.

[73] Assignee: **KV Pharmaceutical Company**, St. Louis, Mo.

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[51] **Int. Cl.²** **A61K 9/22**

[58] **Field of Search** 424/19–22, 424/34, 35; 117/47, 100, 104; 264/118, 129, 131, 148

[56] **References Cited**

UNITED STATES PATENTS

2,811,483	10/1957	Aterno et al.	424/35 X
2,895,880	7/1959	Rosenthal	424/359 X
3,115,441	12/1963	Hermelin	424/22
3,247,064	4/1966	Maekawa et al.	424/35 X
3,361,631	1/1968	Weinstein	424/35
3,480,468	11/1969	Carletti et al.	117/84
3,524,756	8/1970	Signorino et al.	117/72
3,555,144	1/1971	Pazar et al.	424/2
3,646,192	2/1972	Magid	424/35
3,728,445	4/1973	Bardani	424/22
3,758,679	9/1973	Seidler	424/19

Primary Examiner—Shep K. Rose

Attorney, Agent, or Firm—Sidney B. Ring; Hyman F. Glass

[57] **ABSTRACT**

This invention relates to a sustained release pharmaceutical preparation of a medicant prepared by

1. Compacting a wet pharmaceutical preparation;
2. Drying and granulating the compacted preparations of (1);
3. Sealing the granules of (2);
4. Coating (3) with an enteric-soluble coating.

The medicant employed in the pharmaceutical preparation is preferably blended with an inert material.

16 Claims, No Drawings

SUSTAINED RELEASE MEDICANT

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.

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 medicant into the patient's intestinal tract without discharging any of the medicant 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.

However, 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." As a result, there have been devised various methods of preparing sustained release pharmaceutical preparations which allow the medication to effect a "sustained trickle" by releasing minute-incremental dosages, which are continuously released over sustained periods of time.

One of these methods is described in U.S. Pat. No. 2,809,916 which describes a 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 granulated material, again breaking up the rough granular material by light crushing, whereby to reduce it again to granular particles, as second mixing, drying and crushing operations constituting a second cycle, said process consisting of not less than three 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.

I have now discovered an improved method of preparing sustained release pharmaceutical preparations which are prepared by a process comprising:

1. compacting a wet pharmaceutical preparation;
2. drying and granulating the compacted preparation of (1);
3. sealing the granules of (2);
4. coating (3) with an enteric-soluble coating,

The preferred method comprises:

1. blending the medicant with desired inert materials to form a uniform blend of active medicant and inert materials;
2. wetting (1) with sufficient liquid material so as to act as a binder on compacting;
3. compacting (2) such as by extrusion to form a spaghetti-like material which is dried, broken and screened to the desired particle size;
4. spraying the particles of (3) with a liquid such as a solution, for example aqueous sugar, dusting with a powder such as talc and allowing them to dry so as to seal the granules to prevent the enteric coating from penetrating to active ingredients;
5. coating the granules of (4) with a solution of excipients such as an alcoholic solution of shellac, and preferably dusting with stearic acid or stearic acid salts and allowing to dry to form an enteric-soluble coating.

The enteric coated sealed granules of (5) may be further coated one or more times by additional treatment with the excipient to yield the desired sustained release pharmaceutical preparation.

A wide variety of inert materials, either singly or in combination, which are pharmaceutically acceptable, can be blended with active medicant. They include: (1) inorganic materials such as salts, for example, carbonates, such as calcium carbonate, magnesium oxide, magnesium carbonate, etc.; (2) phosphates such as calcium phosphate, dicalcium phosphate, tricalcium phosphate, etc.; (3) milk sugars such as milk sugar impalpable, edible or spray dried lactose; (4) film formers; etc.; (5) starch, sugar, combinations of starch and sugar, etc.

The medicant employed in the pharmaceutical preparation is preferably blended with an inert material so that the medicant comprises at least about 5% of the weight of the combined weight of medicant-inert material, such as from about 5–95%, for example, at least 15%, but preferably at least about 25%, with an optimum of about 30–50%. Preferably the inert material comprises at least about 50% of the combined weight of medicant and inert material.

I have further discovered that where the active medicant is uniformly blended with inert materials prior to the preparation of the sustained release product one obtains a product which has more predictable sustained release properties. For example, where a product is made where the medicant is blended with an inert material as compared to the same material not blended with the inert material, one obtains a product which will consistently deliver 90 to 100% of the medication per capsule. In contrast, a product similarly prepared without blending with inert materials prior to preparation of the sustained release product may deliver medication inconsistently over a wide range, such as for example 50% of the dosage in one capsule and 160% of the dosage in another capsule, thus causing underdosages, and possible toxic effects due to overdosages.

Excipients employed herein may be aqueous or solvent based, including any suitable materials such as sugars or any of the film forming materials shown in Table I, 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 methyethyl ketone, zein in isopropanol, etc.

Table I

Materials Employed as Film Formers		
Natural Films	Semi-Synthetic Films	completely Synthetic Films
Tree Exudates and Extracts:	Cellulose Derivatives:	Vinyl Polymers:
Arabic	Carboxymethylcellulose	Polyvinylpyrrolidone
Tragacanth	Methylcellulose	Polyvinylalcohol
Karaya	Hydroxypropyl-methylcellulose	Carboxylvinyl Polymer
Larch	Hydroxypropylcellulose	Acrylic Polymers:
Ghatti	Hydroxyethylcellulose	Polyacrylic Acid
		Polyacrylamide
Seed or Root:	Ethylhydroxy-ethylcellulose	Ethylene Oxide Polymers
Locust Bean	Starch Derivatives:	
Guar	Carboxymethylstarch	
Psyllium Seed	Hydroxyethylstarch	
Quince Seed	Hydroxypropylstarch	
Seaweed Extracts:	Microbial Fermentation Gums:	
Agar	Dextran	
Algin	Polysaccharide	
Carrageenan	B-1459 (Kelzan)	
Furcellaran	Others:	
Others:	Low Methoxyl Pectin	
Pectin	Propylene Glycol	
Gelatin and Other Proteins	Alginate	
Starch	Triethanolamine Alginate	
	Carboxymethyl Locust Bean Gum	
	Carboxymethyl Guar Gum	

Stearic acid, calcium stearate, talc and combinations thereof can also be employed.

The following examples are presented for purposes of illustration and not of limitation.

EXAMPLE 1

1. Blending of Medicant: A medicant (Phenformin HCl) 1 part is uniformly blended with 2 parts of an inert material (starch 25%/sugar 75%).

2. Wetting: This medicant-inert material blend is wetted down with water.

3. Compacting, Drying, Sizing: The wetted medicant-inert material is then extruded through an orifice having a diameter of 1/16 inch to yield a spaghetti-like material which is then dried, broken up and screened to the desired particle size (about 16–24 mesh).

4. Sealing: These sized, dried, extruded, medicant-inert material particles are then sprayed with an aqueous solution of sugar (89% active) at a ratio of 9 parts of aqueous solution of sugar to 100 parts of particles; and then dusted with a powder (talc) at 10 parts of talc per 100 parts of particles; and then allowed to dry. This seals the particles.

5. Enteric Coating: These sealed particles are then spray coated with an alcoholic solution of shellac (36% shellac) at a ratio of 14 parts of alcoholic shellac to 100 parts of sealed particles and then dusted with a powder (stearic acid) at a ratio of 25 parts of stearic acid to 100 parts of sealed particles and then allowed to dry.

EXAMPLE 2

The process of Example 1 was repeated except that the product of Example 1 was coated with calcium stearate/talc enteric coatings instead of one coating and by repeating the (5) Enteric coating step 3 times.

EXAMPLE 3

The process of Example 1 was repeated except that the inert material was not blended with medicant, all other steps being the same.

EXAMPLE 4

The product of Example 1 which contained the inert material in (1) Blending was compared with the product of Example 3 without inert material.

The release of medicant per interval was tested by the following procedures:

1. National Formulary revolving bottle test procedure (NF-XIII);
2. Modified revolving bottle test procedure;
3. Wiley test procedure.

These tests demonstrated that the product of Example 1 containing the inert material consistently released 90–100% of the theoretical medication per unit dosage whereas the product of Example 3 would vary widely, sometimes yielding 50% and other times yielding as high as 160% of theoretical medication per unit dosage. Such control minimizes the possible side effects of over dosages and insures treatment with the desired dosage.

Although Phenformin HCl is employed in the above examples to illustrate a medicant which can be employed in this invention, other medicants can be employed, for example, the following: nitroglycerin, phenylpropanolamine HCl, phenylephrine HCl, chlorpheniramine maleate, caffeine, D-amphetamin SO_4, amobarbital, pyrilamine maleate, pentaerythritol tetranitrate, isosorbide dinitrate, propantheline bromide, phenobarbital, methapyrilene HCl, theophylline HCl, etc.

Other medicants which can be employed herein will be obvious to those skilled in the art.

I claim:

1. A process of preparing a sustained release pharmaceutical preparation of a medicant which comprises (1) blending a medicant with desired inert materials; (2) wetting the blend with sufficient liquid material so as to act as a binder on compacting; (3) compacting the wetted blend by extruding to form a spaghetti-like material; (4) drying, breaking and screening the extruded material to the desired particle size; (5) spraying the particles with a solution of a film-forming material; (6) dusting the sprayed particles with a powder and drying to form a seal on the particles; and (7) coating the sealed particles with a solution of an excipient so as to form an enteric-soluble coating on the sealed particle.

2. The process of claim 1 wherein the medicant comprises 5–95% of the medicant-inert material blend.

3. The process of claim 1 where the medicant comprises 30–50% of the medicant-inert material blend.

4. The process of claim 1 where the inert material is a mixture of 25% starch and 75% sugar and there is 1 part medicant to 2 parts inert material.

5. The process of claim 1 where medicant-inert material blend is wetted with water.

6. The process of claim 1 where the wetted blend is extruded through an orifice having a diameter of 1/16 of an inch to form the spaghetti-like material.

7. The process of claim 1 where the dried and broken extruded material is screened to about a 16–24 mesh size.

8. The process of claim 1 where the screened particles are sprayed with an 89% aqueous solution of sugar, as the film-forming material, in a ratio of 9 parts aqueous solution to 100 parts of particles.

9. The process of claim 1 where the sprayed particles are dusted with powdered talc in a ratio of 10 parts talc per 100 parts of particles.

10. The process of claim 1 where the sealed particles are ccated with 14 parts of a 36% alcoholic solution of shellac to 100 parts of particles and then dusted with 25 parts stearic acid per 100 parts sealed particles.

11. The process of claim 1 where the sealed particles are coated with a calcium stearate/talc enteric coating.

12. The process of claim 1 where the enteric coating step is repeated three times.

13. The process of claim 10 where the enteric coating step is repeated three times.

14. The process of claim 12 where the enteric coating step is repeated three times.

15. The product obtained by the process of claim 1.

16. The product obtained by the process of claim 10.

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