

[54] **CONTROLLED RELEASE
MEDICAMENT**

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[57] **ABSTRACT**

The invention relates to novel extended-release medicament preparations, particularly in tablet form, and to a method of preparing same. The preparations of the invention are based on the desired medicament, an excipient such as a sugar, a defined class of binder and a "barrier" salt such as magnesium stearate.

12 Claims, No Drawings

CONTROLLED RELEASE MEDICAMENT

BACKGROUND OF THE INVENTION

It is often desirable and sometimes even necessary that a particular medicament be released in the gastrointestinal tract over a prolonged period of time. Ordinary tablets and capsules release the contained medicament substantially completely upon disintegration and at one time the usual method of providing an approximation of extended-release of the medicament was to administer to the patient a number of tablets or capsules at intervals of perhaps 3 or 4 hours.

Recently a large number of different types of delayed-release or extended release tablets or capsules have been developed but these mostly suffer from various disadvantages including complexity of manufacture and/or inadequate performance. In particular one commonly available type of capsule contains a number of different type of granules, each type containing the medicament but designed to dissolve after different periods of time in the gastrointestinal tract. These granules are typically coated with an enteric coating but do not achieve anything like a linear release of the medicament but rather release dosages of the medicament at timed intervals. Apart from the difficulty of manufacture of such capsules, there is the additional difficulty of making sure that each capsule contains the same proportions of each type of timed-release granule. Moreover for certain purposes, even that type of medicament gives an inadequate performance owing to the impossibility of achieving a continuous and preferably substantially linear release of medicament.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide shaped, orally-administrable medicinal preparations, particularly tablets, with extended-release characteristics.

It is a further object to provide tablets which upon oral administration release their medicament over a period up to about 12 hours after administration.

Yet another object of the invention is to provide tablets which release their medicament continuously over a period of some hours.

A still further object of the invention is to provide tablets which release their medicament approximately linearly with time during their passage through the gastrointestinal tract.

According to the present invention there is provided a shaped, orally administrable medicinal preparation having extended-release characteristics in the gastrointestinal tract, which comprises a solidly-compacted, substantially void-free body of medicament-solid excipient-binder granules, said binder being a pharmaceutically acceptable cellulose derivative dicarboxylic-acid ester, said body including also a calcium or magnesium salt of a higher fatty acid in an amount sufficient to provide same with a 1 to 12 hour release pattern.

The present invention also provides a method for preparing a shaped, orally administrable medicinal preparation having extended-release characteristics in the gastrointestinal tract which comprises preparing a mixture of a medicament with a solid excipient, said mixture having a particle size of -100 mesh, granulating said mixture with a pharmaceutically acceptable

cellulose derivative dicarboxylic acid ester binder, and compressing the dried granules under high pressure to form an essentially void-free shaped preparation, said preparation including also a calcium or magnesium salt of a higher fatty acid in an amount sufficient to provide same with a 1 to 12 hour release pattern.

DESCRIPTION OF PREFERRED EMBODIMENTS

The medicament which may be included in the medicinal preparations of this invention may be any medicament which can be administered in tablets, capsules, or the like. Thus, for example, the medicament may be a tranquilizer, a diuretic, a sedative, an antibiotic, a vitamin, an analgesic, or the like. However, the invention is of particular value for the administration of various steroid drugs, which commonly, if administered by means of an ordinary tablet or capsule, give rise to what is known as "steroid shock." This undesirable effect of the normal mode of administration of steroids can be largely or completely overcome by administering the steroid by means of an extended-release tablet which enables the steroid to be released in the gastrointestinal tract over a period of some hours. This extended release of medicaments, and particularly of steroids, has the additional advantage that the peak blood levels of the medicament are maintained lower, and consequently less of the medicament is metabolized to non-effective derivatives. This in turn enables considerably lower overall dosages of the medicament to be employed.

The excipient to be used in the medicinal preparations of the invention may be any suitable solid excipient normally employed in medicinal tablets provided of course that it can be obtained as a very fine powder or milled to produce such a fine powder. Typical excipients are lactose, sucrose, dextrose, dextrose monohydrate, starch, and the like, the sugars being particularly suitable because of their solubility in water. The particle size of the excipient should be below 100 mesh and preferably below 200 mesh (the mesh size in question refer to either U.S. standard or British standard mesh since they are practically identical, corresponding to a particle size of less than about 150 microns for 100 mesh and less than about 75 microns for 200 mesh; there is a slightly greater difference between the U.S. and British meshes in the lower sieve sizes i.e., larger particle sizes). Conveniently the excipient is mixed with the active medicament and thereafter milled to the required particle size e.g., by the use of a pharmaceutical hammer mill or other pulverizer fitted with a screen of the required mesh size.

The binder employed in the preparations of this invention is, as stated above, a pharmaceutically acceptable cellulose derivative dicarboxylic acid ester. Such esters have free carboxylic acid groups, and hence are pH sensitive. Cellulose esters derived from both a fatty acid, particularly a lower fatty acid, and a dicarboxylic acid, are particularly suitable and of these materials the ester which is currently considered the most suitable and which moreover is a recognized pharmaceutical ingredient in most countries, is cellulose acetate phthalate. Although a solvent may not be necessary if the ingredients are sufficiently fine and the tableting pressures are sufficiently high, in the presently preferred embodiment of the process of the invention the ester is

employed dissolved in a suitable volatile organic solvent such as acetone, alcohols or chlorinated hydrocarbon, and this solution is used for the granulation process. Such a granulation procedure is known in the art as wet-granulation or moist-granulation. The finely powdered mixture of medicament and excipient is moistened with the binder solution in a mixer, and the moistened material usually in the form of a dough is pressed through one or more screens to produce granules having a size between about one-half to 3 millimeters in diameter. The prepared granules are thereafter dried by evaporation of the solvent. Where the nature of the materials permits, evaporation of the solvents may be hastened by the application of moderate heat in a draft or under reduced pressure. The dried granules may then be screened again to a particle size suitable for the size of tablet or shaped preparation to be made, (hereinafter for the sake of convenience, jointly referred to as tablets). The granulation procedure is carried out according to well known procedures, while care is taken to avoid introducing too much of the binder which would tend to produce coated granules. Normally, satisfactory granulation can be achieved by using a 5 to 30 percent concentration of the binder in the organic solvent and in the case of cellulose acetate phthalate a 10 to 20 percent and particularly a 15 percent solution in acetone is particularly preferred. However, the mixing operation at the start of the granulation procedure may be accompanied by some evaporation of the solvent and accordingly there is some degree of latitude in both the amount of solution employed for the granulation and the concentration of binder therein. When dry-mixing is used, i.e., without solvent, it may be advisable for some medications to carry out the process step-wise by high pressure slugging of a part of the mixture, after which these slugs are broken and screened in a suitable comminuting mill before they are returned to the mixer for incorporation with the remainder of the mixture. Usually the amount of binder required is from about 5 to 15 percent based on the weight of the active ingredient and excipient. The amount of binder employed has some effect on the properties of the final preparation and greater amounts of binder will generally result in preparations having a longer release period.

In a modification of the invention the above described class of binder is partially replaced e.g., up to the extent of about 10 percent by weight with a pH insensitive pharmaceutically acceptable binder such as ethyl cellulose. The preparations prepared according to this embodiment of the invention show a slower release and moreover a tendency for a slower rate of release initially in the intestinal fluids.

The last of the essential ingredients of the preparations of the invention is a calcium or magnesium salt of a higher fatty acid such as for instance calcium or magnesium palmitate, stearate or oleate. Of these materials, magnesium stearate is at present preferred. Such materials have been employed as mold lubricants for tableting operations but primarily serve a different purpose in the preparations of this invention. These materials are metallic soaps of an essentially water insoluble character, and in accordance with the invention they appear to act as a barrier to delay penetration of

fluids into the center of the tablet. The amount of calcium or magnesium soap employed in accordance with the invention may be greater than is normally used for mold release purposes e.g., up to about 10 percent by weight of the medicament plus excipient, although commonly less than 5 percent and typically $\frac{1}{2}$ to 2 percent will be sufficient. The use of the calcium or magnesium soap as a barrier to the penetration of fluids to the center of the tablet delays disintegration of the tablet and ensures that release of the medicament occur essentially only at the exposed surface of the tablet.

The calcium or magnesium soaps may be added to the other ingredients either prior to or subsequent to granulation, or some of the metallic soap may be added prior to the granulating procedure and the remainder mixed with dried granules prior to compression.

The dried granules of medicament plus excipient plus binder, either containing or admixed with the calcium or magnesium soap are then formed into a substantially void-free tablet under high pressure. Normal tableting procedures employ pressures considerably lower than those utilized in accordance with the process of this invention, and are typically around one-half the pressures needed in accordance with this invention in order to achieve a void-free tablet. Tableting pressure depends primarily on the thickness of tablet it is desired to produce and for instance for a 13/64 inch thick tablet, a tableting pressure which will give a hardness of at least about 5 to 6 kilograms on a hardness tester of U.S.P. specification must be employed to produce the necessary consolidation of the ingredients and achieve a substantially void-free tablet. Failure to use a sufficiently high pressure would result in either premature disintegration of the tablet or penetration of fluids into interstices with resulting deleterious effects on the release pattern of the medication. Typical die loads for tablets of the above size are 15 to 20 tons.

It is an advantage of the present invention that tablets may be made in a straight-forward manner while achieving extended-release characteristics of a predetermined period. In the preferred embodiments of the invention the release pattern approaches linearity, with release of the medicament starting in the gastric fluids when the active ingredient is appreciably water-soluble and continuing as the tablet passes into the intestinal fluids. The structure of the tablet provides a relatively larger surface for the release of medicament in the acidic gastric fluid, under which conditions the pH sensitive binder is less soluble, and as the tablet proceeds through a gastrointestinal tract into a more alkaline environment with a concomitant increase in the solubility of the binder, disintegration proceeds at the surface of the tablet so reducing the total surface area of the tablet exposed to the fluids.

When the active ingredient is practically water-insoluble very little is released in the stomach fluid whereas release occurs in the intestinal fluid. Otherwise the dissolution behaviour is the same.

The invention is illustrated by the following examples. In these examples the screen sizes mentioned are U.S. standard mesh and the abbreviation CAP stands for cellulose acetate phthalate.

Example 1

To prepare 1,000 extended-release tablets each containing 15 mg. of ethisterone (17 β -hydroxypregn-4-en-20-yn-3-one):

100 g. of lactose USP is admixed with 15 g. of ethisterone and the mixture pulverized by the use of a pharmaceutical hammer mill fitted with a 100 mesh screen. The finely powdered mixture of medicament and excipient is placed in a mixer and granulated by the addition of a solution of 15 g. of CAP in 50 cc. of acetone USP. The granules are dried at 100° F for a period of about 8 hours and finally screened through a number 16 mesh screen. The granules so produced are thoroughly admixed with 1 g. of magnesium stearate and formed into tablets weighing 131 mg. by the use of a 9/32 inch punch at 20 ton load to form tablets of 13/64 inch in thickness.

When gently agitated first for one hour in simulated gastric fluid and thereafter for one hour in simulated intestinal fluid, these tablets showed a release of 45 percent of the medicament at the end of the first hour and a release of all the remaining medicament at the end of the second hour.

EXAMPLE 2

To prepare 1,000 extended-release tablets each containing 98.9 mg. of sodium amobarbital (sodium 5-ethyl-5-(3-methylbutyl)barbituric acid):

300 g. sucrose is admixed with 98.9 g. sodium amobarbital and powdered to pass a 100 mesh screen as described in Example 1. The finely powdered mixture is granulated with a solution of 50 g. CAP in 250 cc. acetone, and the granules dried as described previously. The dried granules are screened through number 15 mesh screen and thoroughly mixed with 2 g. magnesium stearate and 2 g. talc. This admixture is then formed into tablets of 453 mg. by the use of a 13/32 inch punch at 20 ton load to form tablets of 7/32 inch in thickness.

When gently agitated for 1 1/2 hours in simulated gastric fluid followed by 6 1/2 hours in simulated intestinal fluid, these tablets showed the following release pattern;

25 percent after one-half hour
42 percent after 2 hours
55 percent after 4 1/2 hours
87 percent after 6 hours
98 percent after 7 hours
100 percent after 8 hours.

Example 3

To prepare 1,000 extended-release tablets each containing 15 mg. Dextro amphetamine sulfate:

Following the procedure of Example 1, 15 g. of Dextro amphetamine sulfate and 400 g. sucrose were powdered to pass a 100 mesh sieve and were granulated with a solution of 40 g. CAP and 5 g. ethyl cellulose in 150 cc. acetone. The granules were dried at 100° F to pass through a number 16 screen and thereafter admixed thoroughly with 1 to 2 percent of magnesium stearate. 460 mg. tablets were prepared with a 11/32 punch at 20 ton load, the tablets having a thickness of 13/64 inch.

These tablets, tested by the procedure outlined in Example 2, showed the following release pattern:

29 percent after one-half hour

55 percent after 2 hours

73 percent after 4 1/2 hours

100 percent after 7 hours.

What I claim as my invention is:

1. A method for preparing a shaped, orally administrable medicinal preparation having extended-release characteristics in the gastrointestinal tract which comprises preparing a mixture of a medicament with a solid sugar excipient, said mixture having a particle size of -100 mesh, granulating said mixture by moistening same with a 5 to 30 percent w/v solution of cellulose acetate phthalate in an amount that provides from 5 to 15 percent by weight of said cellulose acetate phthalate based on the weight of the mixture of medicament and excipient, evaporating solvent and recovering granules having a size between about 1/2 and 3 mm in diameter, and compressing the dried granules under high pressure to form an essentially void-free shaped preparation, said preparation including also a calcium or magnesium salt of a higher fatty acid in an amount of between 1/2 to 10 percent by weight based on the weight of the medicament and excipient to provide same with a 1 to 12 hour release pattern, said preparation having a hardness of at least 5 kilograms as measured on a hardness tester of U. S. Pharmacopeia specification.

2. A method as claimed in claim 1 wherein the calcium or magnesium salt is a stearate.

3. A method as claimed in claim 1 wherein the excipient is lactose and the calcium or magnesium salt is magnesium stearate.

4. A method as claimed in claim 1 wherein the excipient is sucrose and the calcium or magnesium salt is magnesium stearate.

5. A method as claimed in claim 1 wherein the mixture of medicament and sugar is granulated with a 10 to 20 percent by weight solution of the cellulose acetate phthalate in acetone, and the granules are admixed with from about 1/2 to 5 percent by weight magnesium stearate and said mixture is then pressed into substantially void-free tablets.

6. A method as claimed in claim 5 wherein the sugar is lactose.

7. A method as claimed in claim 5 wherein the sugar is sucrose.

8. A shaped orally administrable preparation having extended-release characteristics in the gastrointestinal tract comprising a solidly-compacted, substantially void-free body having a hardness of at least 5 kilograms as measured on a hardness tester of U. S. Pharmacopeia specifications, said body being formed in accordance with the process of claim 1 of compressed granules having a size between about 1/2 and 3 mm in diameter and consisting essentially of a medicament, a sugar excipient and 5 to 15 percent by weight of cellulose acetate phthalate, based on the weight of the mixture of medicament and excipient, said body including also between about 1/2 to 10 percent by weight of a calcium or magnesium salt of a higher fatty acid to provide same with a 1 to 12 hour release pattern.

9. The preparation of claim 8 in the form of a tablet.

10. The preparation of claim 9 wherein the calcium or magnesium salt is a stearate.

11. The preparation of claim 10 wherein the medicament is a steroid.

12. The preparation of claim 11 wherein the steroid is ethisterone.