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SUSTAINED RELEASE ENCAPSULATION

Mitchell Stanley Blicharz, Blauvelt, and Gerald James Jackson, Bardonia, N.Y., assignors to American Cyanamid Company, Stamford, Conn., a corporation of Maine

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This invention relates to an improved sustained release medicament composition and a method of producing it.

Many medicaments are required to be in sustained release form to make it possible to take fewer doses during a day and to space out the release of the medicament. Sometimes the medicament is to be released gradually in the stomach, and in other cases part or all of the medicament may be released not in the stomach but in the intestines by using so-called enteric coatings. In the past, sustained release medicaments have usually been made by coating granular or finely divided medicament with a coating which dissolves slowly. The individual particles are then compressed into a tablet or filled into a capsule or otherwise incorporated in the final dosage form. Typical of such agents with which the medicament particles are coated are solutions of waxy compounds, such as glyceryl monostearate, in an ordinary coating pan. It has been quite possible to produce sustained release compositions in the manner described above, but they have certain drawbacks. First of all, it is necessary to granulate accurately to predetermined and uniform size or size range, and secondly, in the case of a number of products, the amount of additional waxy material is quite large, which adds to the cost of the medicament composition.

Another method which has been proposed is to suspend or dissolve medicament in molten material, such as waxy material, allow to solidify by cooling in sheets or cakes, and then milling to form granules. It has also been proposed to follow this procedure and then to initially coat the granules with other sustained release coatings. This method suffers from the same drawbacks as the first method described above, for it is practically impossible to duplicate granulations of exactly the same particle size distribution and if the granules are additionally coated with fairly waxy material, the amount required in the coating is quite large. As in the first method, the result is not uniform and the cost is increased.

According to the present invention it is found that if the medicament is melted, if stable at its melting temperature, or suspended in a molten material, such as waxy material, and molded into suitable dosage forms, either in permanent molds or in molds which themselves can be digested, reliable and uniform sustained release is obtained. The sustained release is quite uniform and is in no way dependent on particle or granule size, as was the case in the earlier methods described above. Additional control over sustained release times can be obtained by varying the proportion of waxy material and hence the size of the molded or cast dosage forms. In each case a particular size of molded dosage form can be maintained perfectly uniform, which was not practical with coated granules or granules obtained by milling cakes or sheets of suspended medicaments. In general, with similar compositions of medicaments the larger the size of molded or cast dosage units, the longer the disintegration time in the gastro-intestinal tract and hence the greater the degree of sustained release. The upper limit of course is set by the size of molded or cast dosage unit which can be comfortably swallowed. This depends both on unit size and on shape. For example, spheres or short cylinders with rounded ends can be swallowed in larger sizes

than some other shapes which are not so well streamlined. Of course the present invention permits maintaining a constant shape and even in one of its modifications choosing the exact shape desired. It is, of course, possible to have dosage units put up in two or more different sizes so that a portion are released more rapidly than the larger sizes. However, this refinement is rarely needed, and presents the problem that the user has to select numbers of units to obtain this desired additional effect. Also, as will be described below, it is possible to obtain a rapid release of a portion of the medicament and a sustained release of further portion in a single dosage unit, which presents advantages of uniform production and more simple use.

Surprisingly, a sustained release effect is obtained even if the medicament or one of the medicaments is melted and cast in suitable molds. However, often the presence of additional waxy material is desirable, but in such case a very much smaller amount can be used than was formerly needed when medicament particles were granulated to produce the usual sustained release granules as described above. When a sustained release is prolonged by the addition of waxy materials, which are sometimes referred to as adjuvants, it is an advantage of the invention that it is in no sense critical what particular adjuvant is used or what particular combination or adjuvants are used. Typical illustrative materials are fatty acid esters, saturated fatty acids, low melting solid alcohols, mono- and polyethers of saturated fatty alcohols, saturated solid aliphatic ketones, and pharmacologically acceptable stearols. Specific members are stearic acid, stearyl alcohol, myristic acid, and myristic alcohol, glyceryl monostearate, glyceryl tristearate, glyceryl distearate, acetylated glycerides, carnauba wax, hydrogenated tallow, hydrogenated lard, soybean oil, and similar hydrogenated glycerides, beeswax, cetyl alcohol, and the like. These typical adjuvants may be used alone or in mixture with each other or also in admixture with water soluble waxes, such as polyethylene glycols.

It has been pointed out above that it is not necessary that all of the components of the composition be heated to their individual melting points. It is sufficient if one or more are stable when melted, and the other components can be present in the form of finely divided solids suspended in the molten constituent. Obviously, of course, the medicaments must not be injured by the melting temperature of the component or components which are melted prior to casting or molding. Apart from this requirement, the present invention is applicable to any solid medicament and is not intended to be limited to particular medicaments which will be described in typical examples.

It is an advantage of the present invention that the size of the molded or cast dosage units is not sharply critical. Obviously, of course, the size must not be so minute that the surface to volume ratio is so high that rapid digestion or solution takes place, because of course this defeats the purpose of sustained release. Also, it is obvious that the upper limit on size is determined by the dosage unit or by the size which is readily swallowed by a man or animal for whom the product is intended. As a typical practical lower limit, cast dosage units of 5 mm. in cross section are useful.

There are various ways in which the compositions of the present invention can be prepared after one or more constituents of the composition have been melted. If the composition is to be administered in hard shelled gelatin capsules, the capsules may be used themselves as the molds, always of course provided that the melted constituent melts at a low enough temperature so that the gelatin is not excessively softened or melted. It is also possible, and in many cases advantageous, to use metal or other molds to produce the cast product.

Sometimes it is desirable to have a dosage unit which will release a portion of the medicament quite rapidly and the balance more slowly. It is an advantage that the present invention can be used to achieve this effect very simply by having a portion of the medicament in the cast or molded unit associated with a material which dissolves rapidly in the gastric juice, such as for example water soluble or dispersible waxes. The present invention, therefore, includes not only dosage units which are all of the sustained release type but also those which release a portion of their medicament more rapidly.

When waxy adjuvants are used, an example of the saving is the reduction of the amount of adjuvant required to as little as 2%, a very large saving, which of course is reflected in a reduced cost.

The invention will be described in greater detail in conjunction with the following specific examples, in which the parts are by weight unless otherwise specified.

Example 1

Meprobamate was melted and then poured into hard shell gelatin capsules. No. 2 hard shell capsules were used and each contained 408 mg. of meprobamate. Release time was tested in this as in other examples unless differently specified by using artificial simulated gastric juice for the first two hours followed by simulated intestinal juice. The results are as follows:

Time, hrs.	Percent released
½	12.8
2	56.3
4	84.6
5.5	97.5

This example is not necessarily the ideal formulation. It shows, however, that even without added adjuvants a substantial degree of sustained release is obtained.

Example 2

Molten meprobamate at a temperature of 100°–105° C. was mixed with glyceryl monostearate in two different proportions and filled into No. 2 hard shell capsules, the weights varying between 400 and 410 mg. The release results are as follows:

	1% Glyceryl Monostearate, percent	2% Glyceryl Monostearate, percent
½ hr.	15.2	11.9
2 hrs.	51.7	38.4
4½ hrs.	88.0	70.2
7 hrs.	96.1	81.3

It will be noted that with 1% adjuvant the release times were not greatly different from meprobamate castings without any adjuvants but a marked increase in release time resulted with 2% of adjuvant.

Example 3

A mixture of molten meprobamate and various proportions of glyceryl monostearate (temperatures 105° to 110° C.), were mixed with powdered d-amphetamine sulfate and filled into gelatin capsules, producing doses from 400 to 416 mg. of meprobamate and 15–16 mg. of d-amphetamine. The release results are as follows:

	2% Glyceryl Monostearate, percent Released		4% Glyceryl Monostearate	
	d-Amphetamine	Meprobamate	(15 mg.) d-Amphetamine, percent	Meprobamate (400 mg.) percent
½ hr.	19.8	12.0	18.5	10.3
2 hrs.	37.6	32.6	40.4	37.8
4½ hrs.	82.1	81.0	74.6	72.3
7 hrs.	91.1	89.8	85.8	84.2

It will be noted that the release time of the highly soluble amphetamine salt was well controlled by the meprobamate.

Example 4

A combined initial and sustained release medicament was prepared by pouring a portion of molten meprobamate into capsules and another portion of a mixture of meprobamate with soluble wax, polyethylene glycol. The mixture with the soluble material gives a rapid initial release and the solidified meprobamate is released more slowly, as is brought out in Example 1.

Example 5

A molten mixture, (55°–58° C.), of glyceryl monostearate and polyethylene glycol with an average molecular weight of about 4000 was prepared. Finely divided solid d-amphetamine sulfate was suspended in the mixture of waxes and cast in molds. Products were obtained which showed sustained release, the release weight being varied by varying the relative proportions of glyceryl monostearate and polyethylene glycol.

Example 6

Glyceryl monostearate was melted at the temperature given in Example 5 and polyethylene glycol and propyl thiouracil were dissolved in the melt. This was then poured into molds, and produced sustained release capsules.

Example 7

40 grams of glyceryl monostearate was heated to 65° C. and when completely melted, 8.4 grams of Pathilon ethochloride powder stirred in. The mixture was heated and stirred until the Pathilon was completely dissolved, the temperature rising to 80° C., and was then poured into No. 1 hard shell gelatin capsules and allowed to harden. There were 79 mg. of Pathilon per capsule and sustained release first in artificial gastric juices and then in artificial intestinal fluid was tested. The results were as follows:

Release rate, hr.:

½	6.2%	Artificial gastric fluid.
2	16.9%	
4½	52.4%	Artificial intestinal fluid.
7	75.3%	

We claim:

1. A cast pharmaceutical hard shell gelatin capsule product having a cross section of at least 5 mm. but below a size at which swallowing is difficult and filled with a sustained release pharmaceutical composition containing up to about 2% of an adjuvant selected from the group consisting of stearic acid, stearyl alcohol, myristic acid, myristic alcohol, glyceryl monostearate, glyceryl tristearate, glyceryl distearate, acetylated glycerides, carnauba wax, hydrogenated tallow, hydrogenated lard, soybean oil, beeswax, cetyl alcohol, polyethylene glycol having an average molecular weight of about 4,000, and mixtures thereof, together with a medicament not damaged by heating to the melting point of said adjuvant.

2. A product according to claim 1 in which the cast product contains meprobamate which has been melted and hardened.

3. A product according to claim 1 in which a d-amphetamine powder is dispersed in the meprobamate after melting and before it has been hardened.

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LEWIS GOTTS, *Primary Examiner.*

S. K. ROSE, *Assistant Examiner.*