967,610

# PATENT SPECIFICATION

NO DRAWINGS

**967,610**

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COMPLETE SPECIFICATION

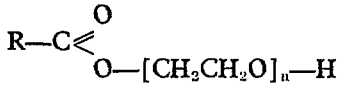
## Sustained Release Medicament Formulations

We, F. HOFFMANN-LA ROCHE & Co. Aktiengesellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

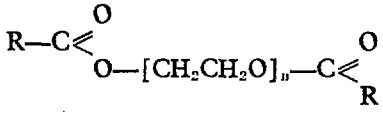
The present invention relates to sustained release medicament formulations, particularly sustained release non-vitamin tablets and capsules, and to a process for the manufacture thereof.

Sustained release formulations in solid unit dosage forms are now well known to the art. The sustained release of most of these formulations depends on one of three principles: (1) diffusion, (2) ion exchange, and (3) adsorption. However, since it is usually desirable to give a patient a large initial dose of drug and then smaller doses to sustain the drug level in the body, special techniques have had to be employed with the application of all of the above sustained release principles to give the patient a large initial dose. For example, the concentration of the drug is graded so that the greatest concentration is in the surface layers of the tablets or pellets. The technique used for making tablets and pellets of this type involves a number of disadvantages, not the least of which is the necessity for multiple steps and the frequent changing of the concentration of the drug in the coating material. Another technique frequently employed involves the use of capsules containing a mixture of normal release pellets with sustained release pellets. Among the disadvantages of this technique is the necessity of forming two different types of pellet and then intimately mixing these in the required proportion.

The tablets and pellets of the invention are composed of from 0.5 to 30 per cent (preferably 5 to 15 per cent) of a non-vitamin medicament [which term is used to include a mixture of such medicaments], from 5 to 85 per cent (preferably 30 to 60 per cent) of a carboxylic acid ester [which term is used to include a mixture of carboxylic acid esters] having a melting point of 65°C or above and from 1 to 10 per cent of a polyoxyethyleneglycol monoester or diester, which esters have the formulæ



and



respectively in which $n$ is 43 to 137 and R is the hydrocarbyl residue of a $C_{12}$ to $C_{18}$ fatty acid, or a mixture thereof. Other desirable but not strictly necessary ingredients are starch (1 to 20 per cent), lubricant (0.5 to 3 per cent) and filler (1 to 50 per cent). The foregoing percentages are percentages by weight based on the total weight of the unit dosage form; that is to say, the weight of the tablet or pellet.

The tablets and capsules of the present invention avoid the disadvantages associated with prior sustained release tablet and capsule formulations by providing uniform sustained release tablets and pellets which have the medicament uniformly dispersed therein. These tablets and pellets provide a sustained release of the medicament by erosion—an entirely different principle of release. An important advantage of tablets and pellets provided by the invention is that they inherently provide for an initial release of large quantities of medicament and a sustained release of smaller quantities of medicament over relatively long periods of time (e.g. about 4 to 12 hours) and so maintain the desired level in the blood. The

[*Price 4s. 6d.*]

high initial release of drug generally takes place over the period of an hour or less. Thus, about 20 to 50 per cent of the drug is released in this time and the remainder is released slowly. Hence, no immediate release layer is required in the tablets and no immediate release pellets are required in addition to sustained release pellets in capsules. A further advantage of the tablets of the invention is that the use of a sugar or enteric coating is not strictly necessary since the taste of the tablets is not objectionable even when somewhat bitter medicaments are employed. Of course such coatings can be employed if desired.

Suitable medicaments for inclusion in the formulations of the invention are *dextro*methorphan hydrobromide, clidinium bromide, acetylsalicylic acid, phenacetin, phenylephrine hydrochloride, phenindamine, amphetamine sulphate, ephedrine hydrochloride, chlordiazepine, chlordiazepoxide hydrochloride and mixtures thereof, but it will be appreciated that this list is by no means exhaustive.

The carboxylic acid esters employed in the formulations of the invention are those carboxylic acid esters having a melting point of 65°C or above, preferably in the range of 65°C to 80°C. These carboxylic acid esters include the following: (a) substantially saturated waxes, that is to say substantially saturated solid mixtures of fatty acid esters of high monohydric aliphatic and/or phytosterol alcohols (e.g. carnauba wax and beeswax), (b) substantially saturated fats; that is to say, a substantially saturated mixed glyceryl ester of high fatty acids such as stearic acid and palmitic acid, or mixtures of such glyceryl esters, (c) glyceryl tristearate or glyceryl tripalmitate, (d) substantially saturated diglycerides of high fatty acids (e.g. castorwax) or mixtures of saturated monoglycerides, diglycerides and triglycerides of higher fatty acids (e.g. of stearic acid). Mixtures of any of these can of course be employed. The preferred carboxylic acid ester is castorwax.

The polyoxyethylene-glycol monoesters and diesters of fatty acids used in the practice of the invention must, as mentioned earlier, be esters of $C_{12}$ to $C_{18}$ fatty acids such as stearic acid, oleic acid and lauric acid. Polyoxyethylene-glycol distearate having a molecular weight of *ca* 6000 is preferred. Other esters which can be employed include polyoxyethylene - glycol - (4000) distearate, polyoxyethylene - glycol - (6000) dioleate, polyoxyethylene - glycol - (6000) dilaurate, polyoxyethylene - glycol - (4000) dilaurate and the corresponding monoesters.

The lubricants which may be optionally included in the formulations of the invention are alkaline-earth-metal stearates (e.g. magnesium stearate, calcium stearate), talc. etc.

Starch is optionally included and is particularly useful in tablets since it serves to disintegrate the tablets into many pellets, each of which then erodes. The starches which can be employed include corn starch and potato starch (corn starch being preferred).

Excipients which may be included in the formulations are, *inter alia*, lactose, mannitol and sucrose (lactose being preferred). The quantity of excipient has an effect on the rate of release of the medicament. In general, the greater the quantity of excipient employed the greater the release of medicament during the first hour.

The process for the manufacture of the sustained release medicament formulations according to the invention comprises intimately mixing together in the required percentages the medicament, the polyoxyethylene-glycol ester and the carboxylic acid ester components and, if desired, starch and/or excipients and forming the mixture into tablets or pellets with the aid of a lubricant if desired. A preferred embodiment comprises melting the polyoxyethylene-glycol ester and carboxylic acid ester components together at a temperature of from 85°C to 120°C and then suspending the medicament, starch and excipient therein by mixing (e.g. stirring). The molten mass is then chilled by any suitable technique such as pan-chilling, drum-chilling or spray-chilling. When the molten mass is solidified by drum-chilling or pan-chilling the resultant solid waxy mass is comminuted through a suitable mill (such as a Model U FITZPATRICK comminuting machine) to form pellets; for example, pellets of from 16 to 40 mesh. The lubricant is then added and the pellets compressed into tablets in conventional tableting compression machines if desired.

Alternatively, the lubricant can be added directly to the molten mass. Spray-chilling is especially suitable since it eliminates the need for further milling. If hard-shell capsules rather than tablets are desired, the pellets are simply inserted into the hard-shell capsules by techniques standard in the encapsulating art. Other variations in the process can be employed, such as adding the excipient and/or the starch after cooling of the molten mass but prior to tableting or simply mixing all the ingredients together in the dry state and then compressing the mixture into tablets.

The following Examples are illustrative of the formulations of the invention and the way in which they may be manufactured.

EXAMPLE 1

Formulation

| Ingredients | Composition mg/tablet |
|---|---|
| Polyoxyethylene-glycol-(6000) distearate | 5.0 |
| Castorwax | 45.0 |
| Lactose | 22.5 |
| Clidinium bromide [1-methyl-3-benziloyloxy-quinuclidinium bromide] | 7.5 |
| Magnesium stearate | 1.0 |

*Process*

The polyoxyethylene-glycol distearate and the castorwax are melted together at 90°C. The lactose and clidinium bromide (both in powder form) are suspended therein with stirring. The molten mass is then pan-chilled and the resulting solid mass milled through a FITZPATRICK hammer mill. Fine particles below 40 mesh and granules above 16 mesh are removed by screening. The magnesium stearate is added to the remainder which is then barrel-rolled and compressed in the form of tablets.

The tablets of the foregoing composition which are manufactured in the foregoing manner give a release rate of 33% in the first hour, 60% by the third hour and 88% by the seventh hour when tested by the half-change method. This method consists in subjecting the tablets to gastric juices for one hour, then to a 1:1 mixture of gastric and intestinal juices for one hour, then to a 1:4 mixture of gastric and intestinal juices for one hour and so on.

EXAMPLE 2

Formulation

| Ingredients | Composition mg/tablet |
|---|---|
| Acetylsalicylic acid | 250.0 |
| Acetophenetidine | 120.0 |
| Phenylephrine | 7.5 |
| Phenindamine | 11.25 |
| Castorwax | 80.0 |
| Polyoxyethylene-glycol-(6000) distearate | 20.0 |
| Shellac | 20.4 |
| Stearic acid | 5.0 |
| Talc | 15.0 |
| Calcium stearate | 5.0 |

*Process*

The waxes and powders are mixed and granulated with a 10% alcoholic shellac solution and the resulting mixture dried at 40°C and milled. The lubricants are then added and the mixture is compressed into tablets.

EXAMPLE 3

Formulation

| Ingredients | Composition mg/tablet |
|---|---|
| *Dextro*methorphan hydrobromide | 15.0 |
| Polyoxyethylene-glycol-(6000) distearate | 7.0 |
| Castorwax | 28.0 |
| Lactose | 19.3 |
| Magnesium stearate | 0.7 |

*Process*

The castorwax and polyoxyethylene-glycol-(6000) distearate are melted together at 95°C and the powdered lactose and *dextro*methorphan hydrobromide suspended therein with stirring. The resulting melt is spray-chilled giving approximately 20-mesh spheres. Magnesium stearate is then added and blended and the resulting mixture compressed into tablets of 70 mg weight.

The tablets of the foregoing composition which are manufactured in the foregoing manner give a 40% release of *dextro*methorphan hydrobromide the first hour, 65% by the end of the third hour and 92% by the end of the seventh hour.

EXAMPLE 4

Formulation

| Ingredients | Composition mg/tablet |
|---|---|
| Chlordiazepine [7-Chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2)] | 10.0 |
| Lactose | 9.1 |
| Corn Starch | 6.5 |
| Magnesium stearate | 0.7 |
| Polyoxyethylene-glycol-(6000) distearate | 11.7 |
| Castorwax | 28.2 |

*Process*

Tablets are made from the foregoing ingredients according to the process described in Example 1.

The tablets of the foregoing composition release 39.9% of the medicament during the first hour, 61.3% by the end of the third hour and 70.4% by the end of the seventh hour.

EXAMPLE 5

Formulation

| Ingredients | Composition mg/tablet |
|---|---|
| 1-[(4¹-chloro-phenyl)-ethyl]-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro-*iso*quinoline | 30.0 |
| Castorwax | 36.0 |
| Polyoxyethylene-glycol-(6000) distearate | 4.0 |
| Magnesium stearate | 0.35 |

*Process*

Tablets are made from the foregoing ingredients according to the process described in Example 1.

The tablets of the foregoing composition release 30% of the *iso*quinoline compound during the first hour and 42% by the end of the sixth hour.

EXAMPLE 6

Formulation

| Ingredients | Composition mg/tablet |
|---|---|
| *Dextro*methorphan hydrobromide | 15.0 |
| Castorwax | 21.0 |
| Polyoxyethylene-glycol-(4000) distearate | 14.0 |
| Magnesium stearate | 0.7 |
| Lactose | 19.3 |

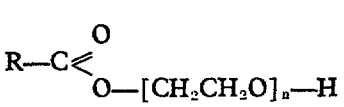
*Process*

The process is carried out as in Example 1.

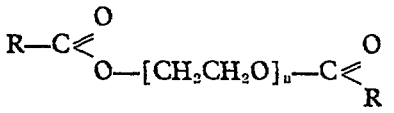
The tablets of the foregoing composition show a release rate of 48% of *dextro*methorphan hydrobromide during the first hour, 94% by the end of the third hour and 100% by the end of the seventh hour.

WHAT WE CLAIM IS:—

1) A sustained release medicament formulation, in tablet or pellet form, which comprises from 0.5 to 30 per cent of a non-vitamin medicament, from 5 to 85 per cent of a carboxylic acid ester having a melting point of 65°C or above and from 1 to 10 per cent of a polyoxyethylene-glycol monoester or diester, which esters have the formulæ



and



respectively in which $n$ is 43 to 137 and R is the hydrocarbyl residue of a $C_{12}$ to $C_{18}$ fatty acid, or a mixture thereof; the percentages being based on the total weight of the formulation.

2) A formulation as claimed in claim 1, which contains starch and/or excipients and, if required, lubricants.

3) A formulation as claimed in claim 2, which contains from 1 to 20 per cent starch and/or from 1 to 50 per cent excipient and, if required, from 0.5 to 3 per cent lubricant—the percentages being based on the total weight of the formulation.

4) A formulation as claimed in any one of the preceding claims, wherein the polyoxyethylene-glycol ester is polyoxyethylene-glycol-(6000) distearate.

EXAMPLE 5

Formulation

| Ingredients | Composition mg/tablet |
|---|---|
| 1-[(4¹-chloro-phenyl)-ethyl]-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro-*iso*quinoline | 30.0 |
| Castorwax | 36.0 |
| Polyoxyethylene-glycol-(6000) distearate | 4.0 |
| Magnesium stearate | 0.35 |

*Process*

Tablets are made from the foregoing ingredients according to the process described in Example 1.

The tablets of the foregoing composition release 30% of the *iso*quinoline compound during the first hour and 42% by the end of the sixth hour.

EXAMPLE 6

Formulation

| Ingredients | Composition mg/tablet |
|---|---|
| *Dextro*methorphan hydrobromide | 15.0 |
| Castorwax | 21.0 |
| Polyoxyethylene-glycol-(4000) distearate | 14.0 |
| Magnesium stearate | 0.7 |
| Lactose | 19.3 |

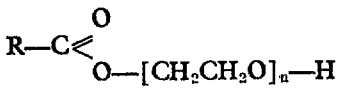
*Process*

The process is carried out as in Example 1.

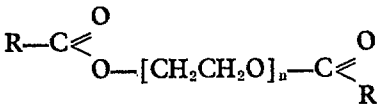
The tablets of the foregoing composition show a release rate of 48% of *dextro*methorphan hydrobromide during the first hour, 94% by the end of the third hour and 100% by the end of the seventh hour.

WHAT WE CLAIM IS:—

1) A sustained release medicament formulation, in tablet or pellet form, which comprises from 0.5 to 30 per cent of a non-vitamin medicament, from 5 to 85 per cent of a carboxylic acid ester having a melting point of 65°C or above and from 1 to 10 per cent of a polyoxyethylene-glycol monoester or diester, which esters have the formulæ



and



respectively in which $n$ is 43 to 137 and R is the hydrocarbyl residue of a $C_{12}$ to $C_{18}$ fatty acid, or a mixture thereof; the percentages being based on the total weight of the formulation.

2) A formulation as claimed in claim 1, which contains starch and/or excipients and, if required, lubricants.

3) A formulation as claimed in claim 2, which contains from 1 to 20 per cent starch and/or from 1 to 50 per cent excipient and, if required, from 0.5 to 3 per cent lubricant—the percentages being based on the total weight of the formulation.

4) A formulation as claimed in any one of the preceding claims, wherein the polyoxyethylene-glycol ester is polyoxyethylene-glycol-(6000) distearate.

* C L M S *

5) A formulation as claimed in any one of the preceding claims, wherein the carboxylic acid ester is castorwax.

6) A process for the manufacture of the sustained release medicament formulations claimed in claim 1, which process comprises intimately mixing together from 0.5 to 30 per cent of a non-vitamin medicament, from 5 to 85 per cent of a carboxylic acid ester having a melting point of 65°C or above and from 1 to 10 per cent of a polyoxyethylene-glycol monoester or diester as formulated in claim 1 or a mixture thereof and, if desired, starch and/or excipients and forming the mixture into tablets or pellets with the aid of a lubricant if desired—the percentages being based on the total weight of the formulation.

7) A process in accordance with claim 6, wherein the carboxylic acid ester and the polyoxyethylene-glycol ester are melted together at a temperature of 85°C to 120°C, the medicament, starch and/or excipient are then suspended in the mixture and the molten mass is chilled to form a solid mass, the latter comminuted to form pellets and, where required, these are compressed to form tablets.

8) A process in accordance with claim 7, wherein the chilling and comminuting steps are carried out in a single step by spray-chilling.

9) A process for the manufacture of sustained release medicament formulations, substantially as described with reference to the Examples.

10) Sustained release medicament formulations, when manufactured by the process claimed in any one of claims 6 to 9 inclusive.

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