

PATENT SPECIFICATION

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(54) CAPSULES COMPRISING A CORONARY-DILATING COMPOUND

(71) We, BAYER AKTIENGESSELLSCHAFT, body corporate organised under the laws of Germany, of 509 Leverkusen-Bayerwerk, Germany, 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 a new dosage unit form for a known coronary-active 1,4-dihydropyridine and a method for its production.

Disturbances of the coronary blood-flow resembling an attack and manifesting themselves clinically in the form of a so-called angina pectoris attack are a vitally important indication and demand immediate treatment with a drug.

As the time of occurrence of such attacks is not foreseeable, the patient suffering from angina pectoris must carry drugs on him so that he can treat himself in the event of an attack. These drugs and their forms of preparation must meet a whole series of requirements as follows to permit rapid and reliable treatment by the patient himself.

1. The forms of preparation of these drugs must be such that they can be reliably and readily taken by the patient in spite of his limited ability to act during an attack.

2. As substances which act therapeutically in angina pectoris are as a rule highly-active drugs which require exact dosage, their form of preparation must be so adapted that an adequate dosage is infallibly ensured.

3. An attack of angina pectoris is usually accompanied by intolerable pain and feelings of extreme anxiety. Physiologically, the impaired blood-flow through the heart during an attack can result in permanent damage to the cardiac muscle which in an extreme case can lead to death. Drugs which are employed in the

therapy of angina pectoris must therefore become fully effective in the shortest possible time (within a few minutes).

The requirements mentioned in 1 to 3 cannot be met by injectable solutions, which can only be administered parenterally, or by solutions that can only be given orally, in the form of drops. It is difficult for an untrained person to administer a parenteral injection to himself under ordinary conditions, and impossible during an attack of angina pectoris. The doses of the solutions for oral administration, which must be taken in the form of drops, cannot be determined with sufficient accuracy by the patient whose capability to react is greatly restricted. There is also a danger of over-dosage.

It is already known that 1,4-dihydropyridine derivatives act as coronary dilators and can be used in the treatment of the above disease. Substances which belong to this group of compounds do not dissolve readily and are extremely light-sensitive.

If the substances in dissolved form are exposed to daylight, irreversible decomposition rapidly occurs. For example, 4-(2'-nitrophenyl) - 2,6 - dimethyl - 3,5 - diacetyl - 1,4-dihydropyridine decomposes to 2,6 - dimethyl - 3,5 - diacetyl - 4 - (2' - nitrosophenyl) - pyridine, which can be detected after only a few minutes in the UV spectrophotometer. Depending on the intensity of the daylight, the substance decomposes quantitatively over a period of 10 to 20 minutes.

So labile is the redox system of 1,4-dihydropyridines, that the addition of reducing agents, oxidizing agents, or redox systems (e.g. Fe II / Fe III, ascorbic acid / dehydro-ascorbic acid) cannot check rapid decomposition. Storage of the substance and its solution in thick dark-brown bottles delays decomposition (when the bottle is exposed to daylight); how-

[Price

ever (after one to one and half hours) the decomposition product can be already detected.

If the active ingredient is made up in tablets or dragees (British Patent No. 1173862) it does not act rapidly enough because of too slow absorption, so that the high therapeutic potential of these active compounds cannot be fully exploited. There is therefore an urgent need to provide the 1,4-dihydropyridines in such a form that they are sufficiently stabilized for practical use and that their pronounced coronary dilating action can also be fully exploited in practice.

It is also known that perlingually administered drugs are rapidly absorbed and that they therefore have a rapid onset of action (e.g. nitroglycerol) (Sollman, T., "A Manual of Pharmacology", W. B. Saunders Co., Philadelphia, Pa., 1957, p 631).

Forms of presentation which contain stabilised 1,4-dihydropyridine and are so made that they are also absorbed when administered perlingually therefore represent a therapeutic advance.

This invention now provides an instant oral-release capsule having a shell of gelatine preferably incorporating an opacifier and a dye, the said shell enclosing a mixture of:—

- (1) one part by weight, being a therapeutic dose, of 4 - (2' - nitrophenyl) - 2,6 - dimethyl - 3,5 - dicarbomethoxy - 1,4 - dihydropyridine;
- (2) 6 to 85 parts by weight of at least one polyalkyleneglycol having 2 or 3 carbon atoms in the alkylene radicals and a mean molecular weight of 200 to 4000; and
- (3) 0.5 to 10 parts by weight of at least one alcohol containing 2 to 8 carbon atoms and having 1, 2 or 3 hydroxyl groups.

In a particularly preferred capsule of the invention, the shell incorporates a dye that absorbs light of wavelength 250—460 nm and an opacifier, and the mixture contains 1 to 10, preferably 5 to 8 parts by weight of the at least one alcohol.

A particularly preferred proportion of the at least one polyalkylene glycol in the mixture is 15 to 35 parts by weight.

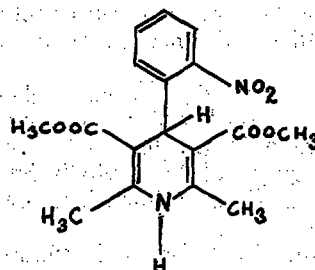
The invention also provides a process for the production of the capsules of the invention, comprising mixing the ingredients (1) to (3) and any other ingredients, and enclosing the resultant mixture in a gelatine capsule.

The expression "instant oral-release capsule" means a capsule, having a shell, generally of gelatine, containing a fluid pharmaceutical composition which can be released from the shell by biting and breaking the latter, the subject bites this capsule thereby releasing its contents into his mouth from where the medicament is immediately absorbed into his system. Each capsule will contain a specific measured amount of the pharmaceutical composition which is enough for a single thera-

peutic dose, allowing for the fact that, depending on the patient's condition and the severity of his attack he may need to take a single capsule or a plurality of capsules on any one occasion.

The use of capsules according to the invention of the 4 - (2' - nitrophenyl) - 2,6 - dimethyl - 3,5 - dicarbomethoxy - 1,4 - dihydropyridine has the following advantages: the capsule can be taken immediately by the patient himself in the event of a heart attack and takes effect within a few minutes. There can be no doubt about the dose received by the patient, as it is fixed by the amount of active ingredient contained in the instant oral-release capsule. Administration is extremely simple: it is carried out perlingually, which dispenses with the necessity for example of first counting out a certain number of drops containing the active ingredient. Such procedure is impossible in the present case anyway, because the active ingredient is too light-sensitive.

The active ingredient used in the capsules of the invention is the known compound 4 - (2' - nitrophenyl) - 2,6 - dimethyl - 3,5 - dicarbomethoxy - 1,4 - dihydropyridine (see British Patent Specification No. 1 173 862) of the formula



Polyalkylene glycols having a mean molecular weight of 200 to 4000 suitable for use according to the invention are also known. Polyethylene and/or polypropylene glycol having a mean molecular weight of 300 to 600 [e.g. polyglycols (Hoechst), Lutrol 9 (BASF), Polydiols (Hüls), Carbowaxes (Union Carbide)] are preferably used. [The words "Lutrol" and "Carbowax" are Registered Trade Marks].

Lower alcohols having 2 to 8 carbon atoms and 1 to 3 hydroxyl groups suitable for use in accordance with the invention are also known. Glycerol, propylene glycol, butylene glycol or benzyl alcohol are preferably used.

The mixture contained in the capsule may also contain one or more further ingredients apart from those specifically mentioned above. In particular the following auxiliary agents may be employed: flavouring agents (aromas), essential oils preferably peppermint oil, fennel oil, anise oil, caraway oil, lemon oil or eucalyptus oil, and sweetening agents (e.g. saccha-

rin, sodium saccharin, (soluble saccharin), and glycyrrhizinic acid ammonium salt).

5 The dye incorporated into the gelatine shell of the capsule preferably absorbs light in the wavelength range, 250—460 nm, more preferably 280—420 nm. A preferred dye is the foodstuff dye "Gelborange-S" (Sunset yellow) (Colour Index No. 15 985). The dye should of course have no toxic effect when used according to the invention.

10 A preferred opacifier for incorporation into the gelatine shell is titanium dioxide.

15 The gelatine shell used in accordance with the invention preferably consists, in its ready-to-use state, of 54 to 80% of gelatine, 10 to 36% of glycerol or sorbitol and 7 to 15% of water and 0.5 to 5% of an opacifier such as titanium dioxide, an iron oxide (such as yellow iron oxide, red iron oxide or brown iron oxide) or calcium carbonate, and the dye "Gelborange-S". (Colour Index No. 15.985). The gelatine composition for the capsule shell can conveniently be prepared by mixing 40 to 66% of pure gelatine with 8 to 36% of glycerol (or sorbitol) and 22 to 34% of water and by allowing the mixture to swell for some time. Thereafter, this composition is melted at 60°C until free of bubbles and the opacifier and the dye "Gelborange-S" (Colour Index No. 15.985) and if desired preservatives (e.g. p-aminobenzoic acid, sorbic acid, and benzyl alcohol) are homogeneously worked into the composition.

30 The mixture constituting the filling of the capsule according to the invention is conveniently prepared by dissolving 4 - (2' - nitrophenyl) - 2,6 - dimethyl - 3,5 - dicarbomethoxy - 1,4 - dihydropyridine in the alcohol and polyalkylene glycol with slight heating and

stirring. The filling into the gelatine capsules can be carried out according to known methods for example with SCHERER, LEINER, NORTON or ACCOGEL machines. After filling, the capsules are generally dried and are then ready to use.

40 The accompanying drawing is a graph showing the very rapid onset of action with perlingual absorption, in particular in comparison with oral administration of the active ingredient of the invention in tragacanth.

45 The graph illustrates the action of the active ingredient according to the invention upon administration in various ways to dogs which have been anaesthetised and catheterised in the coronary sinus. The rise in oxygen pressure in the blood of the coronary veins after perlingual administration of 1 mg/kg of the active ingredient according to the invention in the form of a mixture of glycerol, polyethylene glycol and water was recorded in comparison with the application into the stomach of 1 mg/kg of the active ingredient (micronised substance in tragacanth). The mean values are given for 5 tests each.

60 The curve clearly shows the immediate onset of action following perlingual administration. After five minutes the maximal value is almost reached, whereas after administration into the stomach the oxygen pressure only attains the same value after 60 minutes. Administration of the active ingredient in solid formulation, such as tablets, dragees or the like reveals even less favourable values.

70 The process of the photochemical decomposition of the active ingredient in an ethanol solution when exposed to the light of the wavelength of 360 nm can be seen from the Table.

TABLE

Progress of the photolysis of 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine in ethanol at a wavelength of 360 nm.

Time (sec.)	Extinction	Concentration of the initial product	Concentration of the decomposition product	Conversion %
0	0.220	4.62×10^{-5}	0.10^{-5}	0
10	0.199	4.11×10^{-5}	0.51^{-5}	11.0
25	0.173	3.48×10^{-5}	1.14^{-5}	25.7
40	0.151	2.95×10^{-5}	1.67^{-5}	36.1
55	0.132	2.49×10^{-5}	2.13^{-5}	46.1
70	0.113	2.03×10^{-5}	2.59^{-5}	56.1
85	0.098	1.67×10^{-5}	2.95^{-5}	63.9
100	0.086	1.38×10^{-5}	3.24^{-5}	70.1
130	0.069	0.97×10^{-5}	3.65^{-5}	79.0

Examples (capsule filling):

- | | | |
|----|---------------------|----------|
| 1) | Active ingredient | 3 parts |
| 5 | Propylene glycol | 15 parts |
| | Polyoxyethylene 300 | 82 parts |
| 2) | Active ingredient | 5 parts |
| | Butyleneglycol | 3 parts |
| | Lutrol 9® | 92 parts |
| 3) | Active ingredient | 3 parts |
| 10 | Glycerol | 5 parts |
| | Water | 5 parts |
| | Peppermint oil | 2 parts |
| | Polyglycol 400 | 85 parts |
| 4) | Active ingredient | 2 parts |
| 15 | Benzyl alcohol | 3 parts |
| | Lemon oil | 1 part |
| | Polydiol 200® | 94 parts |

It is decidedly surprising that solutions of the above-identified coronary-active 1,4-dihydropyridine, which even when contained in brown bottles or ampoules substantially decompose upon exposure to daylight in a very short time to pharmacologically inactive compounds, are stable for several months in the preferred capsule according to the invention whose shell contains titanium dioxide and the foodstuff dye "Gelborange-S" (Colour Index No. 15.985).

Furthermore it is to be described as decidedly surprising that a very rapid onset of action is achieved when using instant oral-release capsules containing a particular 1,4 - dihydropyridine, namely 4 - (2' - nitrophenyl) - 2,6-dimethyl - 3,5 - dicarbomethoxy - 1,4 - dihydropyridine. This particular 1,4 - dihydropyridine surprisingly exhibits a very special effect. In contrast to the other 1,4-dihydropyridines, it is very rapidly absorbed perlingually, that is via the tongue and mucous membrane of the pharynx. Furthermore, it is surprising that a very rapidly absorbable form, that is a liquid form, of this sparingly soluble substance has been found which can be accommodated in a gelatine instant oral-release capsule which itself shows a relatively high degree of solubility due to the nature of the material.

WHAT WE CLAIM IS:—

1. An instant oral-release capsule having a shell of gelatine enclosing a mixture of:—

- (1) one part by weight, being a therapeutic dose, of 4 - (2' - nitrophenyl) - 2,6-dimethyl - 3,5 - dicarbomethoxy - 1,4-dihydropyridine; 50
- (2) 6 to 85 parts by weight of at least one polyalkylene glycol having 2 or 3 carbon atoms in the alkylene radicals and a mean molecular weight of 200 to 4000; and 55
- (3) 0.5 to 10 parts by weight of at least



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(2) 6 to 85 parts by weight of at least one polyalkylene glycol having 2 or 3 carbon atoms in the alkylene radicals and a mean molecular weight of 200 to 4000; and

(3) 0.5 to 10 parts by weight of at least



- one alcohol having 2 to 8 carbon atoms and 1, 2 or 3 hydroxyl groups.
2. A capsule according to claim 1 in which the alcohol (3) is glycerol, propylene glycol, butylene glycol or benzyl alcohol.
3. A capsule according to claim 1 or 2 in which the said polyalkylene glycol is polyethylene glycol of molecular weight 300 to 600.
4. A capsule according to claim 1, 2 or 3 in which the said polyalkylene glycol is polypropylene glycol of molecular weight 300 to 600.
5. A capsule according to any preceding claim in which the said mixture comprises also at least one of the auxiliary agents hereinbefore specifically mentioned.
6. The capsule of any preceding claim in which the gelatine shell incorporates an opacifier.
7. A capsule according to claim 6 in which the opacifier is titanium dioxide.
8. A capsule according to claim 6 or 7 in which the gelatine shell comprises:—
- | |
|-----------------------------|
| 54—80% Gelatine |
| 10—36% Glycerol or Sorbitol |
| 7—15% Water |
| 0.5— 5% Opacifier |
9. A capsule according to any preceding claim in which the gelatine shell incorporates a dye.
10. A capsule according to claim 9 in which the gelatine shell incorporates a dye that absorbs light of wavelength 250 to 460 nm and an opacifier, and the encapsulated mixture contains 1 to 10 parts by weight of the said at least one alcohol.
11. A capsule according to claim 10 in which the encapsulated mixture contains 15 to 35 parts by weight of the at least one polyalkylene glycol.
12. A capsule according to claim 10 or 11 in which the encapsulated mixture contains 5 to 8 parts by weight of the said at least one alcohol.
13. A capsule according to claim 10, 11 or 12 in which the dye absorbs light in the wavelength range 280 to 420 nm.
14. A capsule according to claim 12 or 13 in which the dye is Gelborange-S (Sunset Yellow) (Colour Index No. 15.985).
15. A gelatine instant oral-release capsule according to claim 1 substantially as hereinbefore specifically described, or as illustrated in the Examples.
16. A gelatine instant oral-release capsule according to claim 10, substantially as hereinbefore specifically described.
17. A process for the production of a capsule according to any preceding claim comprising mixing the ingredients (1) to (3) and any other ingredients to form the mixture, and enclosing the resultant mixture in the gelatine capsule.
18. A process according to claim 17 in which the gelatine of the shell is prepared by mixing 40 to 66% of pure gelatine with 8 to 36% of glycerol or sorbitol and 22 to 34% of water, allowing the resultant mixture to swell, melting the swollen mixture at 60°C until free of bubbles, and working the opacifier (if present) and dye (if present) into the melted bubble-free mixture.
19. The process according to claim 17 or 18 in which the mixture constituting the filling of the capsule is prepared by dissolving 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine in the alcohol and polyalkylene glycol with heat and stirring.
20. A process according to claim 17 substantially as hereinbefore described or exemplified.
21. A gelatine instant oral-release capsule whenever produced by a process according to any of claims 17 to 20.

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