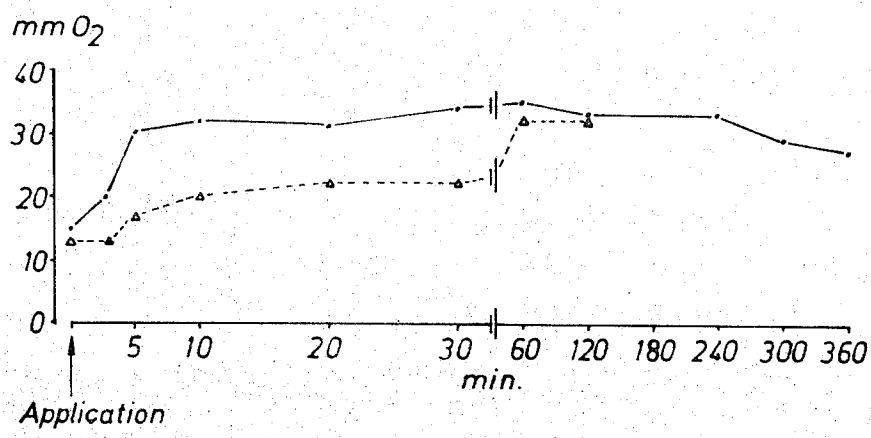
Jan. 8, 1974 F. BOSSERT ET AL 3,784,684

CORONARY DILATOR IN A PHARMACEUTICAL DOSAGE UNIT FORM

Filed Aug. 21, 1972



——— 1 mg/kg perlingually (capsule accoding to the invention)

------- 1 mg/kg per os (tragacanth)

Mean values from 5 tests each.

United States Patent Office 3,784,684 Patented Jan. 8, 1974

3,784,684

CORONARY DILATOR IN A PHARMACEUTICAL DOSAGE UNIT FORM

Friedrich Bossert, Wuppertal-Elberfeld, Wulf Vater, Opladen, Kurt Bauer, Opladen-Lutzenkirchen, and Karl-Heinz Adams, Cologne, Germany, assignors to Bayer Aktiengesellschaft, Leverkusen, Germany

Filed Aug. 21, 1972, Ser. No. 282,476
Claims priority, application Germany, Aug. 24, 1971, P 21 42 316.5; Feb. 29, 1972, P 22 09 526.7
Int. Cl. A61j 3/07
U.S. Cl. 424—37 16 Claims

ABSTRACT OF THE DISCLOSURE

An instant oral-release capsule is produced having a shell of gelatine which contains a mixture of

(a) 1 part by weight of 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine;
(b) 6 to 50 parts by weight of at least one polyalkylene glycol of 2 or 3 carbon atoms in the alkylene moiety and a mean molecular weight of 200 to 4000; and
(c) 0 to 10 parts by weight of at least one alcohol of 2 to 8 carbon atoms and 1, 2 or 3 hydroxy groups.

The present invention relates to a new dosage unit form for a known coronary dilator, 4-(2'-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine, and a method for its production. See U.S. Pats. 3,485,847; 3,644,627; and Canadian Pats. 868,909; 868,910; 868,911.

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 with 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 overdosage.

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'-nitrophenyyl)-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/dehydroascorbic 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); however, (after one to one-and-a-half hours) the decomposition product can be already detected.

If the active ingredient is made up in tablets or dragées (British Pat. No. 1,173,862) 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 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 preparation which contain stabilized 1,4-dihydropyridines and are so made that they are also absorbed when administered perlingually therefore represent a therapeutic advance in the art.

The present invention provides an instant oral-release capsule having a shell of gelatine preferably incorporating an opacifier and a dye, said shell containing a mixture of:

(a) one part by weight of 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine;
(b) 6 to 50 parts by weight of at least one polyalkylene glycol having 2 or 3 carbon atoms in the alkylene moiety and a mean molecular weight of 200 to 4000; and
(c) 0 to 10 parts by weight of at least one alcohol containing 2 to 8 carbon atoms and having 1, 2 or 3 hydroxy groups.

In a particularly preferred capsule of the present 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.

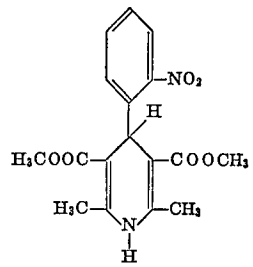
A particularly preferred proportion of the at least one polyalkylene glycol in the mixture is 15 to 35 parts by weight.

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 the 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 generally contain a specific measured amount of the pharmaceutical composition which is enough for a single dose.

The use of capsules according to the present invention containing 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 dosage, 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 a known compound, 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy - 1,4 - dihydropyridine which has been administered in a variety of conventional pharmaceutical formulations including common gelatine capsules and with conventional carriers including polyalkylene glycols. (See U.S. Pats. Nos. 3,485,847; 3,644,627; Canadian Pats. Nos. 868,909; 868,910; 868,911; and British patent specification No. 1,173,862). This compound has 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.

Lower alcohols having 2 to 8 carbon atoms and 1 to 3 hydroxy 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: flavoring agents (aromas), essential oils, preferably peppermint oil, fennel oil, anise oil, caraway oil, lemon oil or eucalyptus oil), and sweetening agents (e.g. saccharin, sodium saccharin (soluble saccharin) and glycyrrhizinic acid ammonium salt).

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

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

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" (Color 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" (Color Index No. 15 985) and, if desired, preservatives (e.g. p-aminobenzoic acid, sorbic acid, and benzyl alcohol) are homogeneously worked into the composition.

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.

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.

The graph illustrates the action of the active ingredient according to the invention upon administration in various ways to dogs which have been anaesthetized and catheterized 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 (micronized substance in tragacanth). The mean values are given for 5 tests each.

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, dragées or the like reveals even less favorable values.

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	Decomposition product	Percent 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)

		Parts
(1)	Active ingredient	1
	Propylene glycol	15
	Polyoxyethylene 300	84
(2)	Active ingredient	5
	Butyleneglycol	3
	Lutrol 9 ®	92
(3)	Active ingredient	3
	Glycerol	5
	Water	5
	Peppermint oil	2
	Polyglycol 400	85
(4)	Active ingredient	2
	Benzyl alcohol	3
	Lemon oil	1
	Polydiol 200 ®	94

It is decidedly surprising that solutions of 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy - 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" (Color Index No. 15 985).

Furthermore, it is 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 is claimed:

1. The method of treating coronary insufficiency with the light sensitive compound 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine in a form which allows storage of said compound without photolysis prior to administration but which permits the rapid and reliable release upon need of a perlingual coronary dilating effective dosage unit amount of said compound which comprises administering into the mouth of a patient having coronary insufficiency a gelatine shell perlingual capsule having a dye that absorbs light of wave lengths from 250 to 460 nm. and an opacifier in the shell of gelatine, said shell being capable of being broken by biting, and enclosed within said shell a fluid mixture of:
   (a) 1 part by weight of said compound in a perlingual coronary dilating effective dosage unit amount;
   (b) 6 to 50 parts by weight of at least one polyalkylene glycol of 2 to 3 carbon atoms in the alkylene moiety and a mean molecular weight of 200 to 4000; and
   (c) 0 to 10 parts by weight of at least one alcohol of 2 to 8 carbon atoms and 1, 2 or 3 hydroxy groups;
and breaking said capsule in the mouth so as to release said compound for rapid perlingual absorption via the tongue and mucous membranes of the pharynx.

2. The method of claim 1 wherein said capsule is broken by biting.

3. An instant oral-release gelatine shell perlingual capsule having a dye that absorbs light of wave lengths of from 250 to 460 nm. and an opacifier in the shell of gelatine, said shell being capable of being broken by biting, and enclosed within said shell a fluid mixture of:
   (a) 1 part by weight of light sensitive 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy - 1,4-dihydropyridine in a perlingual coronary dilating effective dosage unit amount;
   (b) 6 to 50 parts by weight of at least one polyalkylene glycol of 2 or 3 carbon atoms in the alkylene moiety and a mean molecular weight of 200 to 4000; and
   (c) 0 to 10 parts by weight of at least one alcohol of 2 to 8 carbon atoms and 1, 2 or 3 hydroxy groups.

4. An instant oral-release capsule according to claim 1 which contains 15 to 35 parts by weight of said at least one polyalkylene glycol.

5. An instant oral-release capsule according to claim 1 wherein said at least one polyalkylene glycol is polyethylene glycol, polypropylene glycol or a mixture thereof.

6. An instant oral-release capsule according to claim 1 wherein said at least one alcohol is glycerol, propylene glycol, butylene glycol, benzyl alcohol or a mixture of 2 or more thereof.

7. An instant oral-release capsule according to claim 1 wherein the mean molecular weight of said at least one polyethylene glycol is 300 to 600.

8. An instant oral-release capsule as defined in claim 1 wherein 1 to 10 parts by weight of said opacifier are used.

9. An instant oral-release capsule according to claim 1 wherein 5 to 8 parts by weight of said opacifier are used.

10. An instant oral-release capsule according to claim 1 wherein the dye is Gelborange-S (Sunset Yellow, Color Index No. 15 985).

11. An instant oral-release capsule according to claim 1 wherein the opacifier is titanium dioxide, an iron oxide or calcium carbonate.

12. An instant oral-release capsule according to claim 11 wherein the iron oxide is yellow iron oxide, red iron oxide or brown iron oxide.

13. The instant oral-release capsule according to claim 1 wherein the shell of gelatine contains a mixture of
   (a) 1 part 4-(2-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine;
   (b) 84 parts polyoxyethylene 300; and
   (c) 15 parts propylene glycol.

14. The instant oral-release capsule according to claim 1 wherein the shell of gelatine contains a mixture of:
   (a) 5 parts 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine;
   (b) 92 parts Lutrol 9 ®; and
   (c) 3 parts butylene glycol.

15. The instant oral-release capsule according to claim 1 wherein the shell of gelatine contains a mixture of:
   (a) 3 parts 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine;
   (b) 85 parts Polyglycol 400;
   (c) 5 parts glycerol;
   (d) 5 parts water; and
   (e) 2 parts peppermint oil.

16. The instant oral-release capsule according to claim 1 wherein the shell of gelatine contains a mixture of:
   (a) 2 parts 4-(2'-nitrophenyl)-2-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine;
   (b) 94 parts Polydiol 200 ®;
   (c) 3 parts benzyl alcohol; and
   (d) 1 part lemon oil.

References Cited

UNITED STATES PATENTS

3,536,074	10/1970	Aufhauser	128—222
1,978,217	10/1934	Muckerjee	128—272
1,434,531	11/1922	Cyrenius	128—272
1,023,499	4/1912	Bell	128—272 X
3,485,847	12/1969	Bossert et al.	260—295.5
3,488,359	1/1970	Bossert et al.	260—295.5
3,644,627	2/1972	Bossert et al.	424—266
3,647,807	3/1972	Bossert et al.	260—295.5 R

SHEP K. ROSE, Primary Examiner

U.S. Cl. X.R.

128—272; 206—84; 424—266

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3,784,684

DATED : January 8, 1974

INVENTOR(S) : Bossert et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claims 4 through 11 and 13 through 16, line 2, change "1" to --3-- in each instance.

Claim 16, line 3, "2-dimethyl" should read --2,6-dimethyl--.

Signed and Sealed this

Twenty-eighth Day of March, 1989

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks