Convention Application for a Patent

Leo Pharmaceutical Products Ltd., a Company Limited by Shares, incorporated under the laws of Denmark,

of Industriparken 55, DK-2750 Ballerup, Denmark,

hereby apply for the grant of a Patent

for an invention entitled "Tablet"

which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered 7932902 for a patent or similar protection made in United Kingdom on 21st September, 1979.

Our address for service is: CALLINAN AND ASSOCIATES Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Dated this 19th day of September 1980.

Leo Pharmaceutical Products Ltd., a/s (Løvens Kemiske Fabrik Produktionsselskab), by its Patent Attorneys:

CALLINAN AND ASSOCIATES

To: The Commissioner
Declaration in Support of
(a) A Convention Application
(b) A Non-Convention Application

In support of the Convention Application made by
(c) LEO PHARMACEUTICAL PRODUCTS LTD. A/S
(LOVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB)
for a patent application for an invention entitled:

(d) "TABLET"

1. (a) Erling Juhl Nielsen
(b) I am authorized by LEO PHARMACEUTICAL PRODUCTS LTD. A/S
(LOVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB)
the applicant for the patent application to make this declaration on its behalf.

2. (c) The basic application as defined by Section 141 of the Act was made
in Great Britain on the 21st day of September 1979
by LEO PHARMACEUTICAL PRODUCTS LTD. A/S
(LOVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB)

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is the actual inventor of the invention and the facts upon which
the said Company is entitled to make the application are as follows:

The said Company is the assignee of the invention from the said actual inventor.

To: The Commissioner of Patents.

LEO PHARMACEUTICAL PRODUCTS LTD. A/S
(LOVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB)
Managing Director

Sign here
Double layer tablet consisting of a first layer comprising as active ingredient a pro-drug for 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]penicillanic acid, and a second layer comprising as active ingredient a pro-drug for 6-(D-α-aminophenylacetamido)penicillanic acid.

8. Tablet according to any one of claims 1-7, comprising a first layer containing pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]penicillanate hydrochloride and a second layer containing pivaloyloxymethyl 6-(D-α-aminophenylacetamido)penicillanate, said layers further containing pharmaceutically acceptable, non-toxic carriers and/or auxiliary agents, and the tablet optionally being provided with a suitable filmcoating.
Complete Specification for the invention entitled: "Tablet"

The following statement is a full description of this invention, including the best method of performing it known to me:

*Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

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The present invention relates to a particular form of pharmaceutical presentation, more specifically a double layer tablet, for use in both the human and veterinary practice.

The double layer tablet according to the present invention is intended for oral use in the treatment of infectious diseases caused by bacteria and provides a simultaneous application, to a patient in need of treatment, of a pro-drug for mecillinam (6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]penicillanic acid) and a pro-drug for ampicillin (6-(D-α-aminophenylacetamido)penicillanic acid).

From the published British patent specification No. 1,405,886 it is known that pre-formulated mixtures of certain penicillins and amidopenicillanic acid derivatives give rise to an enhanced antibacterial effect when compared with the effect of the individual compounds.

From British patents Nos. 1,215,812 and 1,293,590 it is known that pro-drugs for ampicillin and mecillinam, respectively, in the form of easily hydrolyzable esters, e.g. acyloxyalkyl esters, are particularly valuable for oral application due to the enhanced absorbability of said esters.

Among the easily hydrolyzable esters known from the above mentioned patents are the particularly suitable pivabloyloxymethyl esters of ampicillin and mecillinam, these esters having the generic names, pivampicillin and pivmecillin. 
linam, respectively. From British Patents Nos. 1,363,506 and 1,427,139 also the alkoxy carbonyloxyalkyl ester of ampicillin and mecillinam are known to be suitable esters for the said purpose.

When using the first mentioned esters, it is for stability reasons preferred to apply pivmecillinam in form of the water-soluble hydrochloride, whereas it is preferred to use pivampicillin as the sparingly soluble free base because this gives rise to lesser gastro-intestinal side-effects than the corresponding hydrochloride, confer German patent No. 2,349,971.

Following the teachings of published British patent specification No. 1,405,886 in preparing a mixture of pivampicillin and pivmecillinam hydrochloride, this would result in a product with an inferior shelf-life and a prolonged disintegration time, due to the different solubilities of the two components of the composition and interaction between them, unless specific measures are undertaken.

The lesser stability is partly due to the influence of the amino-group of pivampicillin on the pivmecillinam molecule, the latter being subjected to an aminolysis, i.e. a destruction of the molecule. This destruction is particularly notable when the composition is stored without special precautions being taken to exclude moisture. The prolonged disintegration time is caused by the simultaneous presence of insoluble pivampicillin and easily soluble pivmecillinam hydrochloride in a tablet matrix. The presence of an auxiliary agent in the form of a disintegrant, typically a starch, has no effect in a tablet containing such mixture.
However, a disintegrant is necessary to disperse the only slightly soluble pivampicillin in the stomach to avoid high local concentrations. Pivmecillinam hydrochloride is easily soluble and need no disintegrant. On the contrary, pivampicillin and a disintegrant tend in the presence of pivmecillinam hydrochloride to form a slow release preparation, presumably due to the formation of a matrix from which the pivmecillinam is only slowly liberated.

It has now been shown that it is possible to provide a double layer tablet by which the draw-backs connected with the described mixtures can be avoided. The double layer tablet according to the invention is a two-layer tablet in which the first layer contains the pro-drug for ampicillin and the second layer the pro-drug for mecillinam, the layers further containing suitable carriers and/or auxiliary agents.

The present two-layer tablets can be produced on a conventional tabletting machine for this purpose, using a first granulate containing one active ingredient together with carriers and/or auxiliary agents, and a second granulate containing the other active ingredient and the necessary carriers and/or auxiliary agents. The first granulate is dosed in the correct amount into the die and is slightly pre-compressed, the lower punch is lowered, and the second granulate is dosed into the empty space in the die, and
the tablet is finally compressed.

When providing the above granulates for producing the present double layer tablets, due consideration shall be given to the properties of the components involved.

Pivampicillin and similar pro-drugs for ampicillin are subjected to destruction of the molecule when brought into contact with organic solvents. As pivampicillin is only slightly soluble in water, an aqueous solution of a water soluble cellulose derivative, e.g. methylcellulose, may be used as granulating agent.

Pivmecillinam hydrochloride and similar pro-drugs for mecillinam are easily soluble in water, and it is thus necessary to choose an organic solvent with as little influence on the stability of the pivmecillinam molecule as possible and in which the pivmecillinam hydrochloride is only slightly soluble. Among the organic solvents used within the pharmaceutical technique, isopropanol and acetone are suitable and isopropanol is the preferred solvent because of the risks of explosion connected with the use of larger amounts of acetone.

As cellulose derivative it is preferred to use hydroxypropylocellulose because of its solubility in isopropanol.

For filmcoating the final tablets, an agent should be used which results in a strong, tenacious film. Thus, it is preferred to use hydroxypropylmethylcellulose dissolved in an aqueous solution of an alkanol, e.g. ethanol.
A double layer tablet as provided above has shown to be stable, easily disintegratable, providing a good bioavailability of the two active components. It is well suited for clinical practice.

Another embodiment of a two-layer tablet would be a tablet with a core of the first active ingredient and a coating containing the second active ingredient, but this embodiment might be less appropriate in case that the amounts used of the two active ingredients are of the same magnitude, due to difficulties in the correct centering of the core with ensuing uneven thickness of and risk for cracking of the coating during storage and handling of the final product.

The two-layer tablet according to the invention is thus the most suitable form of simultaneously administering the two active components. This pharmaceutical technique makes it possible to vary the proportions of the two active components between, e.g., 1:5 to 5:1. Preferably, the amount of active material in each layer will be between 0.050 g (50 mg) and 1.000 g, and more preferably will be between 0.100 g (100 mg) to 0.500 g (500 mg). In an especially preferred embodiment, however, a tablet in accordance with the invention will include 0.200 g (200 mg) and 0.250 g (250 mg) of active material in the first and second layers respectively.

The invention will be further illustrated by an Example which, however, shall not in any way be considered limiting the scope of the invention.
Example

Preparation of 100,000 tablets

Manufacturing formula

Pivampicillin ................. 25.00 kg
Pivmecillinam hydrochloride .... 20.00 kg
Hydroxypropylcellulose ........ 0.70 kg
Lactose .......................... 6.00 kg
Magnesium stearate ............ 0.50 kg
Methylcellulose ................. 0.30 kg
Starch, (Sta-Rx 1500\textsuperscript{R}) ....... 5.40 kg
Hydroxypropylmethylcellulose .... 1.00 kg

Manufacturing process

Pivampicillin and a part of the starch are wet granulated with an aqueous solution of methylcellulose. The "fluid bed" dried granulate is mixed with the remainder of the starch and with 1% magnesium stearate. This granulate is used as the first (lower) layer in a two-layer tablet.

Pivmecillinam hydrochloride and lactose are wet granulated with a solution of hydroxypropylcellulose in isopropanol. The "fluid-bed" dried granulate is mixed with magnesium stearate, and is used as the second (upper) layer in a two-layer tablet.
The tablets are compressed with:

- Total fill weight: 580 mg/tablet
- First layer, fill weight: 310 mg/tablet
- Second layer, fill weight: 270 mg/tablet
- Punch size: circular 12 mm diameter, convex surfaces.

The tablets are filmcoated in a "fluid bed" equipment with hydroxypropylmethylcellulose dissolved in ethanol:water, 25:75. The filmcoated tablets are dried at 35-40°C for 9 hours.

Example 2

Preparation of 100,000 tablets

Manufacturing formula

- Pivampicillin .................. 25.00 kg
- Pivmecillinam hydrochloride .... 20.00 kg
- Hydroxypropylcellulose .......... 0.50 kg
- Cellulose microcrystalline ....... 10.00 kg
- Magnesium stearate ............... 0.50 kg
- Methylcellulose .................. 0.30 kg
- Starch (Sta-Rx 1500 ) .......... 3.60 kg
- Carboxymethylstarch .............. 1.80 kg
- Hydroxypropylmethylcellulose .... 1.00 kg

Manufacturing process:

Pivampicillin and a part of the starch are wet granu-
lated with an aqueous solution of methylcellulose. The dried granulate is mixed with the remainder of the starch, the carboxymethyl starch, and with 1% magnesium stearate. This granulate is used as the first (lower) layer in a two-layer tablet.

Pivmecillinam hydrochloride is wet granulated with hydroxypropylcellulose dissolved in isopropanol. The dried granulate is mixed with the microcrystalline cellulose and magnesium stearate and is used as the second (upper) layer in a two layer tablet.

The tablets are compressed with:

Total fill weight: 617 mg/tablet
First layer, fill weight: 310 mg/tablet
Second layer, fill weight: 307 mg/tablet
Punch size: Circular, 12 mm diameter, convex surfaces.

The tablets are filmcoated in a "fluid-bed" equipment with hydroxypropylmethylcellulose dissolved in ethanol:water 25:75.

The coated tablets are dried at 35°C for 9 hours.
The starch. The starch, aminostearate. The starch, amine stearate. The starch, aminated stearate. The starch, amine stearate. The starch, aminated stearate. The starch, aminated stearate. The starch, aminated stearate.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Double layer tablet consisting of a first layer comprising as active ingredient a pro-drug for 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]penicillanic acid, and a second layer comprising as active ingredient a pro-drug for 6-(D-α-aminophenylacetamido)penicillanic acid.

2. Tablet according to claim 1, in which pro-drugs in the form of easily hydrolyzable esters are used.

3. Tablet according to claim 1, in which the active ingredient of the first layer is used in form of a salt.

4. Tablet according to claim 3, in which the active ingredient is pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]penicillanate hydrochloride.

5. Tablet according to claim 4, in which the active ingredient of the second layer is used in form of the free base.

6. Tablet according to claim 5, in which the active ingredient is pivaloyloxymethyl 6-(D-α-aminophenylacetamido)penicillanate.

7. Tablet according to claim 5 or 6, in which the second layer also comprises a disintegrant.
8. Tablet according to any one of claims 1-7, comprising a first layer containing pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]penicillanate hydrochloride and a second layer containing pivaloyloxymethyl 6-(D-α-aminophenylacetamido)penicillanate, said layers further containing pharmaceutically acceptable, non-toxic carriers and/or auxiliary agents, and the tablet optionally being provided with a suitable filmcoating.

9. Tablet according to claim 8 in which the proportions of the amounts of active material in the two layers vary between 1:5 and 5:1.

10. Tablet according to claim 8 in which the amount of active material in each layer is from 0.050 to 1.000 g, preferably from 0.1 to 0.5 g.

11. Tablet according to claim 8 containing 200 mg active material in the first layer and 250 mg active material in the second layer.

12. A pharmaceutical composition or tablet substantially with reference to any one of the Examples as hereinbefore described or disclosed.

DATED this 19th day of September, 1980.

LEO PHARMACEUTICAL PRODUCTS LTD., A/S (LOVENS KEMISKE FABRIK PRODUKTIONSAKTIFSELSKAB)
By its Patent Attorney:
CALLINAN AND ASSOCIATES