LONG-ACTING WAX-LIKE TALC PILLOWS OF PENICILLIN

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Fig. 1

Fig. 2

Fig. 3

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LONG-ACTING WAX-LIKE TALC PILLAGE OF PENICILLIN

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The present invention relates to a solid oral penicillin tablet adapted to provide a prolonged therapeutic blood level for a period of time of up to twelve hours.

PRIOR ART

In penicillin therapy, many attempts have been made to provide oral dosage units which can be administered in such a manner as to afford a sustained therapeutic level of the drug in the body fluids over a substantial period of time. One attempt to solve this problem has been by the addition of buffers to a penicillin tablet to inactivate a certain amount of the gastric juices to allow passage of the penicillin in active form into the intestinal tract, but it is known that such large amounts of buffer are required that a dosage unit of enormous size is obtained.

A further attempt has been to provide a tablet as shown in British specification 781,832 wherein the constituents of the tablet comprise a water-soluble medicament shellac and excipients. This tablet provides an initial high therapeutic blood level of penicillin which decreases rapidly within six to seven hours, and therefore does not provide any worthwhile sustained therapeutic blood level of penicillin.

It has therefore been found desirable to provide a solid oral penicillin tablet which is adapted for partial disintegration in the presence of the gastric juices thereby providing a substantially high initial therapeutic blood level of penicillin and for slow disintegration of the remaining portion of the tablet in the intestinal tract thereby providing a sustained therapeutic blood level of penicillin for a period of time much longer than has been obtained in the prior art preparations.

APPLICANTS' DEVELOPMENT

In accordance with the present invention, there is now provided a solid oral penicillin tablet which is adapted to provide a continuous therapeutic blood level of penicillin for a period of about ten to twelve hours. As can be appreciated by those skilled in the art, the novel penicillin tablet of the present invention reduces the frequency of administration and provides a better utilization of the total amount of penicillin administered.

The penicillin tablet of the present invention is made up essentially of a matrix core containing a substantial amount of penicillin which is surrounded by an enteric layer over which is deposited a further amount of penicillin.

More specifically, the central core is adapted for slow disintegration in the intestinal tract thereby providing a sustained blood level of penicillin and comprises a water-soluble penicillin salt, a hydrophobic agent, a hydrophilic agent, a hydrophilic fibrous material, and a water-insoluble binder. Surrounding this central core are a series of concentric layers which are present in the following sequence: a barrier layer (to separate the penicillin salt of the core and subsequent incompatible materials); an enteric coating; a further barrier layer; a bonding layer (to facilitate the adhesion of the penicillin); a penicillin layer containing a water-soluble penicillin salt. If a more pharmaceutically elegant tablet is desired, the following layers are added: a further barrier layer; a smoothing layer; and finally a finishing layer which provides an attractive appearance.

The central compressed core is obtained by the compression on a tablet-making machine of an intimate mixture of a water-soluble penicillin salt, a hydrophobic agent, a hydrophilic agent, a hydrophilic fibrous material and a water-insoluble binder. The central core is thus specially designed to produce a prolonged release of penicillin in the intestinal tract by the counter-balancing actions of the hydrophobic and hydrophilic agents which are set in motion by the presence of the hydrophilic fibrous material when the core is exposed to the action of intestinal juices.

The penicillin salts used are preferably water-soluble salts, for example, potassium, sodium, calcium and ammonium salts of penicillin G or V (phenoxymethyl penicillin acid). The amount of penicillin salt which can be incorporated into the core has been found to be about 400,000 international units, but a higher amount could be used with the limiting factor being the practical size of the finished tablet. In the outer layer, the amount of penicillin may be between 30,000 and 200,000 international units. If desired, part of the penicillin may be replaced by a sulfon drug, for example, sulfadiazine, sulfamethazine and others and mixtures thereof.

As a suitable hydrophobic agent, there may be mentioned those selected from alkaline earth metal stearates or palmitates, for example, aluminum, calcium and magnesium stearates or palmitates and solid hydrogenated vegetable fats, for example, hydrogenated castor oil and hydrogenated cotton seed oil. Preferably a hydrophobic agent is used in an amount of 0.5 to 5.0 percent by weight.

As a hydrophilic agent there is selected one which has swelling properties. As an example of suitable hydrophilic agents having swelling properties, there may be mentioned carboxymethyl cellulose and salts thereof, alginic acid and salts thereof and water-soluble carrageeanates, guar gum, gum tragacanth, methyl cellulose, hydroxyethyl cellulose and sodium potassium or ammonium cellulose sulphate. The hydrophilic agent is used in an amount of 0.5 to 5.0 percent by weight.

With reference to the hydrophilic fibrous material that may be used, there may be mentioned purified cellulose having an average particle size of from 30 to 50 microns, which is available commercially under the trademark "Sokkafloc" manufactured by the Brown Company, Berlin, New Hampshire, U.S.A. Also suitable would be ground citrus pulp having a particle size smaller than 1,000 microns. This fibrous material is used in an amount of from 2 to 10 percent by weight.

In the preparation of the tablet of the present invention the following procedure is preferably used. The penicillin salt and a portion of the hydrophilic agent and hydrophilic fibrous material are blended together, then
wetted with a non-aqueous solution of a water-insoluble binder, for example, ethyl cellulose, polyvinyl acetate, polyvinyl chloride, cellulose acetate or celite and formed into granules by standard methods used in the art. The granules are dried to a moisture content of not higher than 0.5 percent by weight, blended with the hydrophilic agent and the balance of the hydrophobic agent and the hydrophobic fibrous material, and then compressed in a low humidity atmosphere to form the compressed core of the tablet of the present invention.

This penicillin core is then transferred to a standard coating pan for further treatment using methods known in the art. First, there is applied a barrier layer which separates the penicillin salt in the core from any incompatible material which will be used in subsequent coatings. This barrier layer is essentially a water-soluble, solid, wax-like polymeric material which is compatible with penicillin and to which is preferably added an inert filler. As examples of such a suitable water-soluble wax-like polymeric material there may be mentioned polyethylene glycols having a molecular weight of from 1500 to 6000, and the corresponding mixed polymers of ethylene and propylene glycols. The barrier layer is applied from a dispersion in a solvent in which the penicillin salts are insoluble, for example, carbon tetrachloride.

The tablets are then coated with the enteric coating which will protect the core from attack in the stomach but permit disintegration in the intestinal tract. As an enteric coating material there may be used any of those well known in the art, for example, cellulose acetate phthalate, medicail shellac, or polyvinyl acetate phthalate having an acetyl content of from 4 to 15% and a phthalal content of from 40 to 70%.

Since the enteric coating is incompatible with the penicillin salt to be subsequently applied, a further barrier layer is applied over the enteric coating. This layer serves also as a grossing coat to round out the edges of the tablets. This second barrier layer which is added a grossing agent comprises a water-soluble, solid, wax-like polymeric material, similar to the one used in the first barrier layer and a film-forming material, for example, polyvinyl pyrrolidone and an inert grossing agent, for example, talc. This second barrier and grossing layer is applied from an alcoholic dispersion. Alternatively, the second barrier and grossing layer can be replaced by a barrier layer made up essentially of sugar grossing applied from an aqueous medium.

Next there is applied a bonding layer consisting of a mixture of a solid wax-like polymeric material and a film-forming polymer, for example, polyvinyl pyrrolidone, which is applied in an alcoholic solvent. Or, alternatively, the bonding layer can consist of a mixture of sucrose and a film-forming material, for example, polyvinyl pyrrolidone applied from an aqueous alcoholic solution. The bonding layer has adhesive properties to provide a base for subsequent layers.

Then there is applied a penicillin layer made up essentially of a penicillin salt which is applied from a non-aqueous suspension which may contain an alkaline buffer and an inert filler, for example, talc. After the penicillin layer, there is applied in a non-aqueous medium, a barrier layer as above, a grossing layer as above and finally a finishing layer which is essentially a film coating made up of an ethereal, wax-like polymeric material, for example, polyethylene glycols, a film forming polymer, for example, polyvinyl acetate, polyvinyl acetate phthalate, having a phthalal content of from 40 to 70 percent and an acetyl content of from 4 to 15 percent, a finely divided silica, talc and may include colouring and flavouring agents.

The present invention will be more fully illustrated by referring to the accompanying drawings in which:

FIGURE 1 is an enlarged side elevation of the improved tablet of the present invention,

FIGURE 2 is a view similar to FIGURE 1 but partially sectioned to show the various layers and coatings surrounding the compressed core of a preferred tablet of the present invention, and

FIGURE 3 is a graph showing the penicillin blood levels obtained with a single tablet of the present invention.

Referring to FIGURES 1 and 2 of the drawings, the tablet 10 comprises a central compressed penicillin core 12 which is adapted for sustained release of the penicillin in the intestinal tract. A water dispersible barrier coat 14 surrounds the core 12 to prevent the solvents used in applying the enteric coating 16 from leaching the penicillin present in the core 12. The barrier coat 14 also serves to separate the penicillin present in the core 12 from any subsequent coatings with which it may be incompatible. Following the barrier coat 14, is an enteric coating 16 which protects the penicillin core 12 from attack by gastric secretions.

Following the enteric coating 16, is a further barrier and grossing coat 18. This second barrier coating is present to separate the enteric coating 16 from the penicillin layer 22 and also serves as a grossing coat to round out the tablet. Next is a bonding coat 20 to provide adhesion for the penicillin layer 22, which is present to provide initial blood levels on ingestion of the tablet. Over the penicillin layer 22 is a further barrier coat 24 then a smoothing layer 26 and finally a finishing coat 28 which provides a smooth outer surface of pleasing appearance.

**EXAMPLE I**

**Core tablets**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium penicillin G (1600 u./m.gm.)</td>
<td>423.0</td>
</tr>
<tr>
<td>Calcium carbonate (light pt.)</td>
<td>33.75</td>
</tr>
<tr>
<td>Purified fibrous cellulose (30-50 microns)</td>
<td>82.50</td>
</tr>
<tr>
<td>Sodium carboxymethylcellulose (high viscosity)</td>
<td>6.00</td>
</tr>
</tbody>
</table>

The above powders are blended together and then mixed with 240 ml. of a 10 percent ethyl cellulose solution in denatured ethyl alcohol. This mixture is granulated by methods known in the art and to the dried granules a blend of the following powders is added.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified fibrous cellulose (30-50 microns)</td>
<td>10.5</td>
</tr>
<tr>
<td>Sodium carboxymethylcellulose (high viscosity)</td>
<td>6.00</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>12.0</td>
</tr>
</tbody>
</table>

This mixture is compressed to form 1500 cores, each weighing approximately 0.4 gm. and containing 400,000 international units of penicillin. These cores are then placed in a conventional coating pan and coated in eight different steps.

**COATING STEP #1 (BARRIER LAYER)**

The tablets are coated with 200 ml. of a mixture containing:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene glycol (M.W. 6000)</td>
<td>45.0</td>
</tr>
<tr>
<td>Isopropyl myristate ml.</td>
<td>2.8</td>
</tr>
<tr>
<td>Talc</td>
<td>73.0</td>
</tr>
<tr>
<td>Amorphous silica (3-5 microns)</td>
<td>4.4</td>
</tr>
<tr>
<td>Carbon tetrachloride, q.t. to 200 ml.</td>
<td>6.00</td>
</tr>
</tbody>
</table>

This mixture is applied in 20 applications of 10 ml. and serves to completely seal in the penicillin of the core tablet.

**COATING STEP #2 (ENTERIC LAYER)**

The tablets are then coated, with 54 ml. of a 15% w/v solution of polyvinyl acetate phthalate in denatured alcohol.

This solution is applied in six applications of 9 ml. using talc as a dusting powder to prevent the tablets sticking together after each application. This layer provides acid resistant properties to protect the tablet from attack by gastric secretions, during passage through the stomach.
2,991,226

**5 COATING STEP #3 (BARRIER AND GROSSING LAYER)**

The tablets are coated with 300 ml of a mixture containing:

- **Talc** — 110.0 gm
- **Polyethylene glycol (M.W. 6000)** — 67.5 gm
- **Isopropyl myristate** — 4.2 ml
- **Amorphous silica (3-5 microns)** — 6.6 gm
- **Polyvinyl pyrrolidone** — 5.4 gm
- **Denatured alcohol, q.s. to 300 ml**

The mixture is applied in 30 portions of 10 ml each. This layer provides a barrier between the enteric layer and subsequent layers and also rounds out the edges of the tablets.

**COATING STEP #4 (BONDING LAYER)**

The tablets are then coated with 50 ml of the solution containing:

- **Polyvinyl pyrrolidone** — 7.5 gm
- **Polyethylene glycol (M.W. 4000)** — 7.5 gm
- **Denatured alcohol, q.s. to 50 ml**

This solution is applied in 5 applications of 10 ml using talc as a dusting powder to prevent the tablets sticking together after each application. This layer has adhesive properties due to its high content of polyvinyl pyrrolidone.

**COATING STEP #5 (PENICILLIN LAYER)**

The tablets are then coated with a mixture containing:

- **Potassium penicillin G** — 112.5 gm
- **Magnesium stearate** — 7.5 gm
- **Talc** — 15.0 gm
- **Calcium carbonate** — 12.0 gm
- **Isopropyl myristate** — 7.5 ml
- **Methylparahydroxybenzoate** — 135 ml
- **Denatured alcohol, q.s. to 90 ml**

This mixture is applied in 12 ml portions with thorough drying between each application. The total amount applied is sufficient to provide 100,000 units of penicillin per tablet.

If a pharmaceutically elegant tablet is desired, the following layers are subsequently applied.

**COATING STEP #6 (BARRIER LAYER)**

The tablets are then coated with 100 ml of the same mixture used in step #4.

**COATING STEP #7 (GROSSING LAYER)**

The tablets are coated with 300 ml of the same mixture used in step #3. Thirty applications of 10 ml are used. This provides further smoothing of the surface of the tablets.

**COATING STEP #8 (FINISHING LAYER)**

The tablets are coated with 200 ml of a mixture containing:

- **Polyethylene glycol (M.W. 6000)** — 48.3 gm
- **Stearic acid** — 0.08 gm
- **Isopropyl myristate** — 3.0 ml
- **Polyvinyl acetate phthalate** — 3.9 gm
- **Amorphous silica (3-5 microns)** — 4.8 gm
- **Talc** — 20.0 gm
- **Saccharin insoluble** — 0.06 gm
- **D, and C, Yellow #11** — 0.5 gm
- **Denatured alcohol, q.s. to 200 ml**

This mixture is applied in twenty-five 8 ml applications and provides a smooth, hard finish of attractive appearance and pleasant taste.

The completed tablet contains 400,000 units of penicillin in the core and 100,000 units in the coating.

In vitro disintegration tests show that in artificial gastric juice (pH 1.5) the shell coatings are rapidly removed so that the shell penicillin is available within 15 minutes. The core tablet under these conditions is resistant to pene-

**6 OF GREATER IMPORTANCE IN ILLUSTRATION OF THIS INVENTION ARE THE BLOOD LEVELS OF PENICILLIN OBTAINED WHEN TABLETS WERE ADMINISTERED TO HUMAN SUBJECTS AS SHOWN IN THE FOLLOWING TABLE.**

**Penicillin blood levels in units of serum following a single oral dose of 500,000 units of potassium penicillin G in the form of a specially coated tablet are shown in Table II.**

**Table II**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Hours After Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>0.10</td>
</tr>
<tr>
<td>C</td>
<td>0.220</td>
</tr>
<tr>
<td>D</td>
<td>0.280</td>
</tr>
<tr>
<td>E</td>
<td>0.090</td>
</tr>
<tr>
<td>F</td>
<td>0.240</td>
</tr>
<tr>
<td>G</td>
<td>0.210</td>
</tr>
<tr>
<td>H</td>
<td>0.330</td>
</tr>
<tr>
<td>I</td>
<td>0.160</td>
</tr>
<tr>
<td>J</td>
<td>0.210</td>
</tr>
<tr>
<td>Average</td>
<td>0.210</td>
</tr>
</tbody>
</table>

The above table shown in the attached graph clearly illustrates that penicillin is rapidly absorbed from the shell layers to provide a blood level about 7 times the minimum therapeutic level (0.03 unit/ml) within one hour. The averages of the results of Table II are shown in Figure 3 of the accompanying drawings as curve A, whereas curve B shows the minimum therapeutic blood level of penicillin. The effect of this initial dose persists over the next three hours and then it is reinforced and maintained at an effective value for at least ten hours by the penicillin from the core tablet.

**EXAMPLE II**

**Core tablets**

<table>
<thead>
<tr>
<th>Core tablets</th>
<th>Gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium penicillin G</td>
<td>21,250</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>1,800</td>
</tr>
<tr>
<td>Purified fibrous cellulose (30-30 microns)</td>
<td>4,400</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose (high viscosity type)</td>
<td>320</td>
</tr>
</tbody>
</table>

The above powders are blended together in a suitable mixer and then treated with 11,000 ml of a 10% solution of ethyl cellulose in denatured alcohol to form granules by standard methods used in the art. The granules are dried to reduce the moisture content to less than 0.5% and are then blended with the following mixture:

<table>
<thead>
<tr>
<th>Core tablets</th>
<th>Gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified fibrous cellulose (30-30 microns)</td>
<td>640</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose (high viscosity type)</td>
<td>320</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>360</td>
</tr>
</tbody>
</table>
The resultant blend is then compressed to form about 80,000 tablets each containing approximately 400,000 units of penicillin.

The tablets are then transferred to a conventional coating pan for further processing. Coating layers are applied in eight different steps as follows:

**COATING STEP #1 (BARRIER LAYER)**

The tablets are coated with 8000 ml. of a mixture containing:

- Polyethylene glycol (M.W. 6000) \( \text{gm.} \) 2000
- Isopropyl myristate \( \text{ml.} \) 200
- Amorphous silica (3-5 microns) \( \text{gm.} \) 3150
- Talc \( \text{gm.} \) 200
- Carbon tetrachloride, q.s. to 8000 ml.

This mixture is applied in 12 portions in the customary manner to form a water-dispersible layer which seals in the penicillin of the core tablets.

**COATING STEP #2 (ENTERIC LAYER)**

The tablets are next coated with 2100 ml. of a 20% solution of polyvinyl acetate phthalate in denatured alcohol. This solution is applied in six portions and the tablets are dusted with 800 gm. of talc after each portion, to prevent them sticking to each other.

This layer confers acid resistant properties to the tablets, which will protect them from attack by gastric secretions, during passage through the stomach.

**COATING STEP #3 (BARRIER AND GROSSING LAYER)**

The tablets are coated with 900 ml. of a 15% aqueous solution of gelatin and then with 10,000 ml. of a mixture containing:

- Calcium carbonate \( \text{gm.} \) 2900
- Corn starch \( \text{gm.} \) 1100
- Sucrose \( \text{gm.} \) 8000
- Distilled water to make 10,000 ml.

This mixture is applied in 20 portions and serves to isolate the enteric layer from subsequent coatings and also rounds out the edges of the tablets.

**COATING STEP #4 (BONDING LAYER)**

The tablets are coated with 2500 ml. of a solution containing:

- Polyvinyl pyroldiolone \( \text{gm.} \) 600
- Sucrose \( \text{gm.} \) 800
- Distilled water \( \text{ml.} \) 800
- Denatured alcohol \( \text{ml.} \) 800

This solution is applied in 5 portions and the tablets are dusted with 400 gm. of talc after each application. This layer provides a surface with adhesive properties.

**COATING STEP #5 (PENCILLIN LAYER)**

The tablets are then coated with a mixture containing:

- Potassium penicillin G \( \text{gm.} \) 7250
- Magnesium stearate \( \text{gm.} \) 480
- Talc \( \text{gm.} \) 960
- Calcium carbonate \( \text{gm.} \) 770
- Titanium dioxide \( \text{gm.} \) 200
- Isopropyl myristate \( \text{gm.} \) 480
- Methylene chloride \( \text{ml.} \) 8600
- Denatured alcohol \( \text{ml.} \) 5800

This mixture is applied in 25 portions. The total amount applied is sufficient to provide at least 100,000 units of penicillin per tablet.

**COATING STEP #6 (BARRIER LAYER)**

The tablets are coated with 8000 ml. of the same mixture used in step #1 to seal in the penicillin of the previous layer.

**COATING STEP #7 (SMOOTHING LAYER)**

The tablets are coated with 6000 ml. of a mixture containing:

- Polyethylene glycol (M.W. 6000) \( \text{gm.} \) 1440
- Polyvinyl pyroldiolone \( \text{gm.} \) 108
- Amorphous silica (3-5 microns) \( \text{gm.} \) 144
- Talc \( \text{gm.} \) 2160
- Isopropyl myristate \( \text{ml.} \) 144
- Denatured alcohol \( \text{ml.} \) 2100
- Carbon tetrachloride, q.s. to 6000 ml.

This mixture is applied in 12 portions and provides further smoothing of the tablet surface.

**COATING STEP #8 (FINISHING LAYER)**

The tablets are coated with 7500 ml. of a mixture containing:

- Polyethylene glycol (M.W. 6000) \( \text{gm.} \) 1800
- Talc \( \text{gm.} \) 750
- Amorphous silica (3-5 microns) \( \text{gm.} \) 180
- Polyvinyl acetate phthalate \( \text{gm.} \) 146
- Isopropyl myristate \( \text{ml.} \) 110
- D. and C. Yellow #11 \( \text{gm.} \) 30
- Saccharin \( \text{gm.} \) 1.5
- Artificial pineapple flavour \( \text{ml.} \) 2.25
- Denatured alcohol, q.s. to 7500 ml.

This mixture is applied in 30 portions and then the tablets are heated to 50° C. while rolling in the coating pan. This provides a smooth hard finish of attractive appearance and pleasant taste.

It should be noted that between coating steps the tablets are thoroughly dried in a low humidity atmosphere to completely remove the solvent used in each step. The completed tablets made by this process contain about 400,000 units of penicillin in the core and 100,000 units in the coating.

An in vitro disintegration test on these tablets using the U.S.P. apparatus, showed that in artificial gastric juice (pH 1.5) the outer shell coatings were rapidly removed so that the shell penicillin was available within 15 minutes. The core tablet under these conditions was resistant to penetration due to the enteric layer.

A test on the enteric coated core tablets using an apparatus designed to measure release rates of penicillin, showed the following results with artificial intestinal juice (pH 7.5).

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Amount of penicillin in solution, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>90</td>
<td>29.5</td>
</tr>
<tr>
<td>120</td>
<td>47.3</td>
</tr>
<tr>
<td>150</td>
<td>67.8</td>
</tr>
<tr>
<td>180</td>
<td>80.2</td>
</tr>
<tr>
<td>220</td>
<td>93.5</td>
</tr>
<tr>
<td>240</td>
<td>100.0</td>
</tr>
</tbody>
</table>

This test clearly demonstrates the prolonged release of penicillin from the core tablet.

We claim:

1. A prolonged action medicinal penicillin tablet comprising a core of compressed coated granules, said granules comprised of a major amount of a water-soluble penicillin salt, a hydrophilic fibrous material, a hydrophilic agent having swelling properties and a water-insoluble binder, said granules having been coated with a mixture of dry solids comprising a hydrophilic fibrous material, a hydrophilic agent having swelling properties and a solid hydrophobic agent selected from the group consisting of alkaline earth metal salts of stearic and palmitic acids and solid hydrogenated vegetable fats, and the coated granules having then been compressed, said core being surrounded by a first barrier layer of a mixture of a major amount of talc with readily water-soluble wax-like materials se-
lected from the group consisting of polyethylene glycols having a molecular weight of from 1500 to 6000 and the corresponding mixed polymers of ethylene and propylene glycols, and an enteric coating surrounding said first barrier layer, and an outer layer of a water-soluble penicillin salt separated from said core by the barrier and enteric layers disposed between the core and the outer layer, said penicillin salt outer layer containing appreciably less penicillin than said core and being released in the stomach through the solvency action of the stomach juices to create initially a therapeutic blood level of penicillin, said barrier and enteric layers being soluble and dispersable in the intestinal fluids whereby said core is exposed to the action of the intestinal fluids and a therapeutic blood level of penicillin is maintained by the release in the intestines of the penicillin in the core over an extended period of time, the soluble penicillin salt being present in substantially the proportions of at least about 400,000 international units in the core to about 50,000 to 200,000 international units in the outer layer.

2. A tablet according to claim 1 in which the readily water-soluble wax-like material in said first barrier layer is a polyethylene glycol having a molecular weight of from 1500 to 6000.

3. A tablet according to claim 1 in which said enteric layer is surrounded by a barrier and a bonding layer, a bonding layer, a penicillin layer separated from said penicillin core by said layers, and a second barrier layer, a grossing layer and an outer finishing layer surrounding said penicillin layer.

4. A tablet according to claim 1 having a barrier and grossing layer surrounding said enteric layer and a bonding layer surrounding said last-mentioned barrier and grossing layer, the outer penicillin layer surrounding said last-mentioned bonding layer.

5. A tablet according to claim 4 wherein said bonding layer comprises a mixture of polyvinyl pyrrolidone with a readily water-soluble material selected from the group consisting of sugar, water-soluble wax-like polyethylene glycols having a molecular weight of from 1500 to 6000 and the corresponding mixed polymers of ethylene and propylene glycols.

6. A tablet according to claim 5 wherein the readily water-soluble material in said bonding layer is sugar.

7. A tablet according to claim 5 wherein the readily water-soluble material in said bonding layer is water-soluble wax-like polyethylene glycols having a molecular weight of from 1500 to 6000.

8. A tablet according to claim 1 having a second barrier layer surrounding said outer penicillin layer.

9. A tablet according to claim 8 wherein said second barrier layer comprises a mixture of talc and a readily water-soluble wax-like material selected from the group consisting of polyethylene glycols having a molecular weight of from 1500 to 6000, and the corresponding mixed polymers of ethylene and propylene glycols.

10. A tablet according to claim 9 wherein the readily water-soluble wax-like material in said second barrier layer is polyethylene glycols having a molecular weight of from 1500 to 6000.

11. A tablet according to claim 9 having a smoothing layer covering said second barrier layer and a finishing layer surrounding said smoothing layer, said finishing layer forming the exposed surface of the tablet.

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