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GB The Extra Pharmacopoeia (Martindale) 27th Edition, pp. 1815-1816:- "Suloctidil"
US The Theory and Practice of Industrial Pharmacy (Lachman, Liberman and Kanig) 2nd Edition; see pp. 439-464
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(54) **Suloctidil compositions**

(57) Pharmaceutical compositions, for oral administration, contain Suloctidil (1-[p-(isopropylthio)-phenyl]-2-octylamino-1-propanol) in a sustained-release form. The preferred form is a tablet containing two separate and discrete portions, one of which is a prompt-release portion while the other is slow-release. The active agent has peripheral and cerebral vaso-dilating activity and may be used to relieve circulatory insufficiency.

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FIG. 1

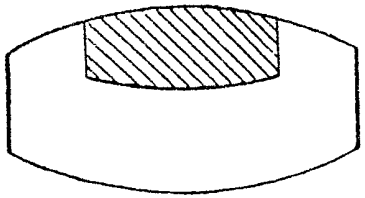


FIG. 3

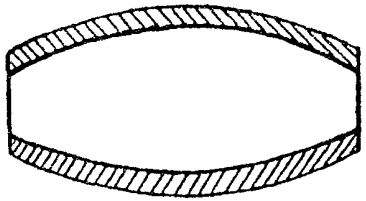


FIG. 4

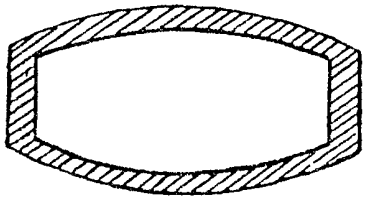
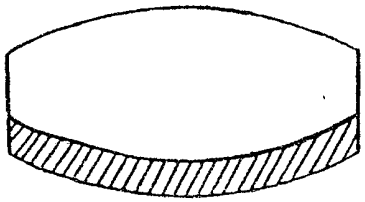


FIG. 2



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SPECIFICATION

A sustained-release product containing suloctidil

Suloctidil, i.e. 1-[p-(isopropylthio)-phenyl]-2-octylamino-1-propanol, is an activating agent of the central and peripheral arterial microcircle used in the therapy of chronic cerebral circulatory insufficiency.

It has recently been put on the market in a few countries among which Italy, where it is sold under different trademarks including Locton® (Lepetit).

Post-marketing surveillance studies confirm that this product is effective and well tolerated.

This drug however has the disadvantage that intrinsically it has a rather high disappearance rate in the body. Thus, by plotting the blood concentration of the drug versus time, the curve obtained after a single administration shows that the concentration of this drug falls to a level below the desired therapeutic range in a short period of time. This problem is now in part obviated by administering this drug several times during the day (three times a day is the number of administrations generally prescribed by physicians and suggested in the package brochure).

The object of the present invention is a sustained-release product containing Suloctidil, suitable for oral administration. The term "sustained-release product" identifies a product in which a drug is initially made available to the body in an amount either sufficient to, or not undesirably in excess of the amount needed to cause the desired pharmacological response as rapidly as is consistent with the properties of the drug determining its intrinsic availability for absorption and at the same time, provides for maintenance of the activity within the desired therapeutic range for a desirable number of hours which is greater than that obtained with the usual single dose.

The main advantage of this sustained-release product is that it will provide a slow and constant supply of drug to the organism. Further, another advantage of this product is that the daily dosages could be reduced to two, one in the morning and the other at night thus limiting the number of "missed" doses because of patient's forgetfulness. This advantage should not be disregarded since missed doses, particularly in elderly patients who generally need this drug, is a real problem. In particular the present invention provides for a tablet which contains two separate and discrete portions, a prompt-release portion and a slow-release portion. The two portions of the tablet can be compounded in many different ways to provide a dosage form that gives rapid initial Suloctidil levels and the continuous levels of Suloctidil desired.

A preferred tablet is in the form of a "bull's-eye", i.e. a tablet of slow-release product with the insertion of a much smaller tablet of the prompt-release formulation that appears on one surface (see Figure 1 of the accompanying drawing) wherein the dotted parts are the prompt-release formulation. This tablet might optionally be sugar-coated. However, a "layered" tablet can also be manufactured (see Figure 2 and 3 of the accompanying drawing) wherein two or three separate layers of granulation which may be made to release the drug either promptly or slowly are incorporated into one tablet or also as an inner, core, slow-release portion surrounded by an outer prompt-release dosage component, the latter optionally in the form of a coating shell (see Figure 4 of the accompanying drawing). Preferably, but of course not necessarily, the prompt-release and the slow-release granules are differently colored. The amount of Suloctidil contained in the two portion tablet as well as the final size of the tablet may vary within wide ranges consistent however with a suitable posology and obviously in an acceptable tablet size. Generally, tablets containing from about 100 to about 400 mg of Suloctidil are preferred but tablets containing from about 200 to about 350 mg of active principle are most preferred. Generally, the prompt-release portion is formulated so as to disintegrate rapidly after ingestion thus providing the initial dose of medication, while the slow-release portion is formulated so as to render the drug available for absorption at a slow and more or less constant rate. The prompt release portion of the tablet comprises from about 12 to about 25% of the total tablet weight of Suloctidil. The remaining prompt-release portion comprises from 10 to 30% of the total tablet weight of inert pharmaceutical excipients. These pharmaceutical excipients may include diluents i.e. inert substances added to increase the bulk of the tablet such as calcium phosphate, calcium sulphate, calcium carbonate, kaolin, mannitol, corn starch, silicon dioxide and like diluents; binders i.e. agents used to impart cohesive qualities to the powdered material such as starch, gelatin, sugars, natural and synthetic gums, and like agents, lubricants, i.e. ingredients added to the tablet to prevent adhesion of the tablet material to the surface of the punches during compression, such as precipitated silica, magnesium stearate, calcium stearate, stearic acid, calcium phosphate, sodium bicarbonate and the like, and disintegrating agents, i.e. substances added to facilitate disintegration of the tablet after administration, such as corn or potato starches, methylcellosolve, carboxymethelcellulose, alginic acid, polyvinylpyrrolidone, sodium laurylsulfate, polyoxyethylene derivatives of sorbitan, esters, lecithins and the like. The specific excipients employed in the prompt-release formulation containing Suloctidil as well as their respective amounts is not critical and any of the formulations containing Suloctidil now marketed can be employed. However, lubricants are generally employed in concentrations of from 0.5 to 6% of the prompt-release portion weight while, considering that a rapid disintegration is desired, disintegrators are employed in concentrations of from 10 to 50% of the prompt-release tablet weight.

The slow-release portion of the tablet comprises from about 27 to about 55% of the total tablet weight of Suloctidil and from about 8 to about 36% of the total tablet weight of inert pharmaceutical excipients. A non-ionic or anionic surface-active agent, which promotes bio-erosion of the slow-release tablet must be

included within the pharmaceutical excipients contained in the slow-release portion of the tablet. Among the preferred surface-active agents there are fatty acids of sorbitol copolymerized with ethylene oxide, such as polioxyethylene sorbitan monoleate, marketed under the trademark Tween® 80, laurylsulphates and dioctylsulfosuccinates, such as sodium lurylsulphate and sodium dioctylsulfosuccinate, and lecithins. Said surface-active agent is employed in an amount of from about 0.1% to about 2% of the slow-release portion weight and preferably from about 0.3 to about 0.8%. Furthermore, it is necessary to include in the slow-release portion of the tablet a couple of additives which control the release of the active principle. One is a water-soluble cellulose derivative, such as methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, while the other one is slow solubilizer of polymeric molecules, generally polyethylene glycol with a molecular weight higher than 1000, that favors the bio-erosion of the tablet surface. The cellulose derivative is generally employed in an amount of between 2 and 30% of the slow-release portion weight and preferably between 2 and 10%, while polyethylene glycol may be employed in an amount of between 2 and 15% of the slow-release portion weight, and preferably between 2 and 8%. Depending on the particular cellulose derivative employed, it may be necessary to add a water soluble dehydrating agent to prevent a possible swelling effect of the cellulose derivative.

Generally, in these cases a sugar is preferably used. It may be employed in an amount varying from 0% (when the cellulose derivative does not give rise to any swelling effect and therefore no dehydrating agent has to be added) and 20% of the weight of the slow-release portion. For practical reasons among the sugars which may be employed for this purpose, sucrose, lactose and galactose are preferably used. Besides the above additives, the slow-release portion of the tablet may contain diluents which are insoluble and do not swell, such as calcium sulphate, calcium phosphate, silicon dioxide, talc, kaolin, and anti-adhesive substances such as precipitated silica, calcium phosphate and the like, and some hydrophobic lubricants such as magnesium stearate, calcium stearate, stearic acid, castor oil and hydrogenated fatty acid esters.

Finally, if desired, either or both the formulations may contain some coloring agent as known in the art. If a tablet as in Figure 4 of the drawing is desired wherein the prompt-release layer, which coats the slow-release inner core, is in the form of a sugar-coating, it may be prepared by the usual techniques alternating sugar syrup layers to dusting with mixtures of the active principle and one or more inert excipients such as silicon dioxide, talc, calcium carbonate, kaolin, etc. The tablets according to the present invention are prepared by techniques well known in the industrial pharmacy field. In particular, the prompt-release and the slow-release formulations are prepared and granulated separately.

Although the two compositions can be processed according to both the wet-granulation and the dry-granulation methods, the wet-granulation is highly preferred in both cases. As for the slow-release formulation, Suloctidil is preferably mixed first with a tablet binder solution such as a gelatin solution, glycerogelatin or starch paste and other similar binders.

Then, all the other desired excipients are added and mixed carefully. When the formulation process is complete, the composition is granulated by passing it through a screen of suitable size. The granules thus obtained, are dried until they have the desired residual moisture content. This granulated material may then be further comminuted to a smaller particle size suitable for compression, and suitable excipients can be added thereto to avoid the granules sticking to the punches or dies during the compression. This step can be carried out either by dusting or dry mixing with adsorbents such as precipitated silica, bi- or tribasic calcium phosphate, talc, etc. Finally, the granulated material is suitably lubricated and optionally added with disintegrating agents.

Also for the slow-release formulation, the different excipients are gradually added to the active principle. If the formulation is overwetted so as to give a collapsed mass, the water excess is eliminated before the granulation step by the addition of a highly absorptive inert diluent such as silicon dioxide. The granulation can then be carried out either by passing the blend through a suitable screen or through a plate containing holes of suitable size. Also in this case, after drying the granules thus obtained, it may be necessary to reduce their particle size to improve the compression. One or more anti-adhesive agents and lubricants are then added and mixed well to give the end granules. These granules, like those of the prompt-release formulation, are employed to feed a compacting press and give the two-portion tablets shown in the accompanying drawing, according to the conventional techniques known in this art.

The following non-limitative examples further illustrate the invention.

EXAMPLE 1

Preparation of the prompt-release granules

The following composition is used for preparing the granules which form the prompt-release portion of 25,000 tablets:

Ingredient	*Grams*
Suloctidil	2500
Calcium phosphate	50
Aerosil® V 200	125
Gelatin	75
Glycerin	25
Mannitol	125
Corn starch	1747.5
Precipitated silica	100
Magnesium stearate	125
FDC Red 3 (E 127)	2.5

1) A solution of the gelatin and the glycerin in distilled water (450 g) is added to the Suloctidil while stirring.

2) The Aerosil® V 200, the mannitol, and some corn starch (1672.5 g) are then added to the obtained mixture, and the whole blend is then mixed until a homogeneous mass is obtained.

3) A starch paste is prepared by mixing the remaining corn starch with the coloring agent and distilled water (675 g). The mixture is heated on a water-bath until a red starch paste is obtained.

4) The starch paste is then added to the mixture prepared according to item 2) above and the whole is stirred until a homogeneous mass is obtained.

5) This mass is sifted through an oscillating granulator equipped with a screen with openings of about 3-3.5 mm. The granules are then dried at 40°C for a few hours.

6) The granules thus obtained are then forced through a screen with openings less than 1.5 mm.

7) The obtained granules are mixed with the tribasic calcium phosphate, magnesium stearate and precipitated silica.

EXAMPLE 2

Preparation of the slow-release granules

The following composition is used for preparing the granules which form the slow-release portion of 25,000 tablets:

Ingredients	*Grams*
Suloctidile	5000
Tribasic calcium phosphate	250
Tween® 80	30
Polyethylene glycol 6000	265.75
Sucrose	412.5
Methocel® A 15	300
Aerosil® V 200	300
Precipitated silica	550
Magnesium stearate	166.75

1) The Methocel® A 15 is added to a solution of the Tween® 80, the sucrose, the polyethylene glycol 6000 and distilled water (1675 g) heated on a water-bath and the obtained mixture is cooled while stirring.

2) The mixture prepared according to 1) is added to a mixture of Suloctidil and the calcium phosphate while stirring until a collapsed mass is obtained. The Aerosil® V 200 is then added thereto.

3) The obtained mass is sifted through an oscillating granulator equipped with a screen with openings of about 6.0-6.5 mm. The obtained granules are dried at 40°C for a few hours, then forced through a screen with openings of less than 1.5 mm and dried again for a few additional hours.

4) The granules obtained under 3) above are mixed with the precipitated silica and the magnesium stearate.

EXAMPLE 3

Preparation of a bull's-eye tablet

1) The granules prepared according to item 7) of example 1 are compressed with a Ronchi AM 13/8 rotary tablet machine with punches of 8.5 mm. The obtained tablets - pink in color - are 4 ± 0.1 mm thick and weigh about 195 mg.

2) Each tablet prepared according to 1) above is placed in the middle of a 11.5 mm punch of a Kilian Prescoter rotary tablet machine fed with the granules obtained according to item 4) of example 2. The two-portion tablets thus obtained, wherein the small pink tablet prepared according to 1) above appears on one surface of the final tablet, weigh about 486 mg.

Alternatively, the bull's-eye tablet may be prepared also by placing the small prompt-release tablet on a layer of slow-release granulation and then compressing.

Each tablet thus obtained has the following composition (the weights are in milligrams):

Prompt-release portion	
– Total weight of the prompt-release portion	195
– Suloctidil	100
– Inert pharmaceutical excipients	95
Slow-release portion	
– Total weight of the slow-release portion	291
– Suloctidil	200
– Surface-active agent	1.2
– Agents controlling the release of the active principle	22.6
– Inert pharmaceutical excipients	67.2
Total weight of the tablet	486

The thus obtained tablets were tested for the dissolution rate of the active principle by means of the Diffutest[R] apparatus. With this apparatus which consists of a thermostatic chamber adjusted to 37°C with a wheel bearing some clamps fixed to rotate at 30 rpm, the tablet undergoes a series of chemical and mechanical conditions that simulate physiological conditions and since they are preset, the results of the test are reproducible (Chiaromonte D. et al. - Il Farmaco - Ed. Pratica - XXV/4, 257; 1970).

In practice, a carefully weighed tablet (equivalent therefore to a suitable amount of active principle) is placed in a special bottle and a fixed amount of simulated gastric juice is added thereto. The bottle is inserted in the proper bottle holder in the thermostatic chamber and it is turned at 30 rpm for a fixed period of time. Afterwhich, the suspension is poured in a separate container and the amount of active principle released is measured by conventional analytical techniques. A fixed amount of simulated intestinal juice is added to the tablet remaining in the bottle and again rotated for a fixed time. In all, the tablet undergoes the following cycle of treatment:

I) 1 h in artificial gastric juice pH 1.5
II) 1 h in artificial gastric juice pH 4.5
III) 2 h in artificial gastric juice pH 6.9
IV) 2 h in artificial gastric juice pH 6.9
V) 2 h in artificial gastric juice pH 7.2

After each rotation period, the amount of active principle released in the suspension is measured. The amount of active principle released is referred to one gram and the percent release is then calculated by means of the following equation:

$$\% \text{ release} = \frac{K \times 100}{Z}$$

wherein

K = milligrams of active principle released by the tablet in each rotation period

Z = milligrams of active principle per tablet

EXAMPLE 4

Determination of the percentage of Suloctidil released after the different rotation periods

A) *Preparation of the simulated gastric juice*

1N HCl (118 ml) and distilled water (700 ml) are placed in a 1000 beaker; 1N NaOH (84 ml) is then added with stirring. The pH is checked, since it must be 1.5 ± 0.05. Then distilled water is added to make 1000 ml.

B) *Preparation of simulated intestinal juice*

Potassium monophosphate (3.42 g) is poured in a 100 ml volumetric flask, and distilled water is added to volume. Three 25 ml portions of this solution are transferred into three separate 1000 ml beakers. In each beaker 1N NaOH (38 ml) and distilled water (about 700 ml) are added with stirring. The pH is adjusted to 4.5 in the first beaker, to 6.9 in the second one and to 7.2 in the third one by the addition of 1N HCl. Each solution is transferred into a 1000 ml volumetric flask and distilled water is added to volume.

C) *Assay procedure*

Suitable amounts of simulated gastric juice and simulated intestinal juice are prepared and heated to 37°C. A sustained-release SUloctidil tablet of example 3 is carefully weighed and placed in a 120 ml rotating bottle. Simulated gastric juice (75 ml) is added and the rotating bottle is inserted in the suitable clamp of the thermostatic cell, previously adjusted to 37 ± 0.5°C, and rotated at 30 rpm. The five step cycle described above is run.

At the end of each rotating period, the suspension is transferred to a 300 ml volumetric flask. The bottle is washed with distilled water (about 10 ml) which is then added to the suspension in the volumetric flask. Absolute ethyl alcohol (about 175 ml) is then added to the suspension and the mixture is stirred vigorously for 5 minutes to dissolve the Suloctidil granules. Absolute ethyl alcohol is then added to volume, the mixture is stirred and filtered into a 300 ml Erlenmeyer flask, discarding the first 50 ml of filtered solution. The amount of Suloctidil released in these fractions is assayed spectrophotometrically at 260 nm. Simulated intestinal juice pH 4.5 (75 ml) is then added to the tablet remaining in the rotating bottle as shown in the above table and the above operations are repeated. The average release percentages at different hours obtained by the above procedure, are the following

1st hour	33%
2nd hour	44%
4th hour	67%
6th hour	86%
8th hour	96%

The disintegration time of the small prompt-release tablet of example 3 item 1), measured with the apparatus provided for by the US Pharmacopea XIX, with simulated gastric juice and keeping the temperature at 37°C, was ≤ 10 minutes.

EXAMPLE 5

Tablets with the same composition as in Example 3 and prepared substantially as described in the same example but slightly modifying the formulation process were sugar-coated with a mixture sugar syrup/water 1/2 and a slight excess of a powder composed of 20 percent ground sugar 60 percent talc and 20 percent titanium dioxide. These tablets were tested for the dissolution rate of suloctidil. Release rates determined as described in Example 4 were as follows:

1st hour	34%
2nd hour	46%
4th hour	70%
6th hour	86%
8th hour	98%

CLAIMS

1. A sustained-release product, suitable for oral administration, containing Suloctidil.
2. A sustained-release tablet containing Suloctidil.
3. A tablet according to claim 2 characterized in that it contains two separate and discrete portions one of which is a prompt-release portion while the other is slow-release.
4. A tablet according to claim 3 wherein the prompt-release portion contains from about 12 to about 25% of the total tablet weight of Suloctidil and from about 10 to about 30% of the total tablet weight of inert pharmaceutical excipients, and the slow-release portion contains from about 27 to about 55% of the total tablet weight of Suloctidil and from about 8 to about 36% of the total tablet weight of inert pharmaceutical excipients.
5. A tablet according to claim 4 wherein among the pharmaceutical excipients of the slow-release portion there is at least one anionic or non-ionic, synthetic or natural, surface-active agent to promote bio-erosion of the slow-release tablet and some release-retarding agents to control release of the active principle.
6. A tablet as in claim 5 wherein as the release-retarding agent to control release of the active principle, a combination of a water-soluble cellulose derivative and a slow solubilizer of polymeric molecules is employed.
7. A tablet as in claim 6 wherein the water-soluble cellulose derivative is selected from methyl cellulose, hydroxymethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose and the slow solubilizer of polymeric molecules is a polyethylene glycol with molecular weight higher than 1000.
8. A tablet as in claim 5 wherein the anionic or non-ionic surface-active agent is selected from the group consisting of polyoxyethylene derivatives of sorbitan esters, lauryl sulphates, dioctylsulfosuccinates and lecithins.
9. A tablet as in claim 8 wherein the surface - active agent is polyoxyethylene sorbitan monooleate.
10. A tablet as in claim 5 wherein the surface- active agent is employed in an amount of from about 0.1 to

about 2% of the slow-release portion weight.

11. A tablet as in claim 10 wherein the surface-active agent is employed in an amount of from about 0.3 to about 0.5%.

12. A tablet as in claim 6 wherein a water-soluble dehydrating agent is added to prevent a possible swelling effect.

13. A tablet as in claim 12 wherein said dehydrating agent is a sugar.

14. A tablet as in claim 13 wherein the sugar is selected from sucrose, galactose and lactose.

15. A tablet as in claim 6 wherein the water-soluble cellulose derivative is employed in an amount of from about 2 to about 30% of the slow-release portion weight and polyethylene glycol is employed in an amount of from about 2 to about 15% of the slow-release portion weight.

16. A tablet as in claim 15 wherein the water-soluble cellulose derivative and the polyethylene glycol are employed in an amount of from about 2 to about 10% and from about 2 to about 8% respectively of the slow-release portion weight.

17. A tablet as in claim 13 wherein the sugar is employed in an amount not higher than 20% of the slow-release portion weight.

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