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2,517,513

PHARMACEUTICAL PREPARATION FOR IMPLANTATION

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Fig. 1

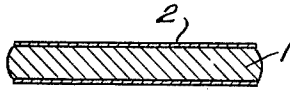


Fig. 2



Fig. 3

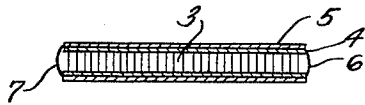


Fig. 4

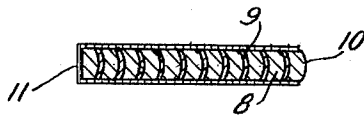
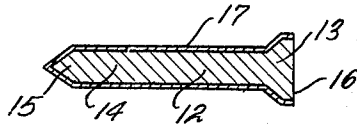


Fig. 5



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PHARMACEUTICAL PREPARATION FOR IMPLANTATION

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Section 1, Public Law 690, August 8, 1946
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5 Claims. (Cl. 128—272)

1

This invention relates to pharmaceutical preparations particularly adapted for use as depot implantates and to methods of making the same.

It is known that certain medical or pharmaceutical preparations, particularly various hormone preparations, may advantageously be introduced as a depot into the human organism in the form of so-called implantates, so that the preparations may be continuously resorbed over a period of time which may be a long time, possibly during several years, thus avoiding the practical drawbacks of frequent injections or applications through the way of digestion, and the inevitable periodical changes of the contents of the blood, respectively of the influence on the organism by such preparations, inevitably connected therewith, and finally also obtaining a substantial increase in efficiency of the preparations being used.

Such small bodies used heretofore as implantates were produced in the form of tablets in the usual manner. But it has now been found that such implantates produced in this manner do not give altogether satisfactory results because resorption of a constant value is not obtained, but the resorption varies in the course of time principally parabolically from a certain initial value to the final zero value.

This unsatisfactory result follows from the fact that, as the depot is used, the surface of such small bodies, from which the resorption takes place, decreases. While to some extent this may be counteracted by producing the small bodies with a varying composition; such procedure leads to rather complicated processes in the production of the small bodies so that little success has been obtained in this way. Such deposits of pharmaceutical preparations in the shape for example, of a solid body, as for instance a crystal or a pressed tablet, have been open to the difficulties and disadvantages set forth above.

Among the objects of the present invention is the production of implantates suitable for depot use which enable resorption of the pharmaceutical principles therein to take place at a substantially constant rate.

Another object in the production of implantates suitable for depot use which enable resorption of the pharmaceutical principles therein to take place at a predetermined rate varying in the course of time in accordance with the variation of the requirements of the organism, for instance cyclically.

Other objects include methods of producing implantates which give that result.

2

Still further objects and advantages of the present invention will appear from the more detailed description set forth below, it being understood, however, that such detailed description is given by way of illustration and explanation only, and not by way of limitation, since various changes therein may be made by those skilled in the art without departing from the scope and spirit of the present invention.

In connection with that more detailed description there is shown in the accompanying drawing, in

Figure 1 a longitudinal section through an implantate produced in accordance with the present invention; in

Figure 2 a transverse section through the implantate of Figure 1; in

Figure 3 a longitudinal section through a modified form of implantate; in

Figure 4 a longitudinal section through a further modification; and in

Figure 5 a longitudinal section through a still further modification of the present invention.

In accordance with the present invention, the difficulties and disadvantages of the prior art are eliminated by the production of implantates which may be utilized for depot purposes to give substantially uniform resorption, particularly utilizing the therapeutic or pharmaceutical preparation in the form of shaped bodies or small bodies of discrete size of suitable dimension produced so that they have the property of permitting resorption of the pharmaceutical principle contained in the body in a substantially uniform manner. One of the principal ways of producing this result is to produce the therapeutic preparation in the form of small or discrete bodies having one or more protective layers or coatings consisting of a non-resorbable, non-poisonous and mechanically harmless material covering such portions of the surface of the small bodies that the remaining free surface, from which resorption may take place, will remain constant or practically constant during the whole process of resorption or the greater part thereof.

By this means practical difficulties are eliminated since it is no longer necessary to employ preparations of varying composition and respective varying resorbability. On the contrary, in accordance with the present invention, homogeneous masses of the preparations, as for example, standard preparations, may be employed and despite the simplicity of this invention, it has been found that results are obtained far superior to those obtained with small bodies produced

according to prior art methods. Tests with small bodies produced according to the present invention show a practically constant resorption from the day on which the implantate is placed, to the day on which it is completely consumed, even in the case of implantates having a duration of several years. The implantate, therefore, may be said to constitute in the true sense of the word, an artificial gland producing constant secretion.

Another important advantage of the present invention is that it is possible to select the volume of the small bodies and their resorption surfaces quite independently of each other. In prior art methods, there are rather narrow limits for the relation that may be obtained between the resorption surface and the volume of the small bodies, when the latter are to have a practicably usable shape, and this is a disadvantage because the resorption surface defines the resorption rate, while the volume of the small bodies defines the time during which the implantate is active and it is impracticable to fix these characteristics independently of one another. So that in the prior art methods there is no way available other than to vary the geometrical shape of the small bodies, which as pointed out above for practical reasons is possible only within certain limits, and to vary the resorbability of the preparations which also is of course possible only within certain limits where the preparations must retain the desired therapeutical effect. In accordance with the present invention, however, it is possible by coating particular parts or portions of the surface to obtain any desired relation between the resorption surface and the volume of the preparation.

The shape of the small bodies produced in accordance with the present invention may be varied in many ways but it is most desirable to shape the medical preparations to the form of cylindrical, small bodies, and to coat these on their circumferential surface with the protective layer or layers referred to. If it is desired to decrease the resorption, the small bodies may also be coated with a protective layer at one of their end surfaces. The shape, for example, may be the usual tablet shape with the tablets coated with a protective layer on their circumferential surface but if desired a more oblong shape may be used as an elongated cylindrical body, the small bodies thus having a shape such as that of small sticks. The circumferential form of the cylindrical small bodies is of no consequence, i. e., it may be circular, curved, polygonal, etc.; and it is also immaterial whether the end surfaces are disposed at right angles or inclined to the longitudinal axis of the body or need the end surfaces necessarily be plane, but they may be shaped to any geometrical surface desired. While the cylindrical form is preferred, the bodies may also be conical. In this case also a nearly constant resorption surface may be obtained, the one end surface increasing approximately as much as the other end surface decreases. Again in the case of the conical bodies, the circumferential form is immaterial and the disposition of the end surface to the axis of the cone is also immaterial. If, in the case of a conical body, one end surface is covered and the other end surface is free the rate of absorption will either increase (i. e. if the free end surface is the smaller one) or decrease (i. e. if the free end surface is the greater one) in the course of time. Such bodies may be used when during the treatment of a disease it is desirable to supply, for a time an increasing or decreasing amount of the preparation in question. If de-

sired, the small bodies may be composed of a number of conical and cylindrical portions and since the height of these portions may be made infinitely small, the body may be considered as formed by a rectilinear generatrix of any type which may be curved or broken, the only desirable limitation on form being that the area of the end surface or surfaces from which the resorption takes place will vary substantially in conformity with the requirement of the organism or the prescriptions of the physician, but differing from the parabolic variation produced when no covering is present.

Desirably in carrying out the invention, the protective layer or layers are applied in a layer thickness so small that they are not self-supporting but will collapse when they are no longer supported by the mass of the medical preparation. In this way, protruding edges are eliminated, which protruding edges might otherwise be formed around the mass of the pharmaceutical preparation, particularly in the case of small bodies in the shape of sticks, and which protruding edges might form an obstacle to the resorption and would in any case produce an incommoding foreign body in the organism after the preparation had been consumed. Where, however, protective layers of small thickness are used, such layers gradually collapse and are scarcely perceptible in the organism when the implantate has been completely consumed.

For the protective layer or layers, any material may be used which fulfills the conditions set forth above, namely, of being non-resorbable, non-poisonous, and mechanically harmless. It is particularly advantageous to use certain metals such as the noble, for example, gold, as well as other metals, namely, silver, and copper. These metals may be applied to the surface portions in question in any desired way, as for example, by pasting, spraying, or by a galvanic process. Among the metals gold seems particularly advantageous because it may be hammered or otherwise treated to form exceptionally thin foils having a thickness of, for example, $\frac{1}{10000}$ to $\frac{1}{1000}$ mm. Further these thin foils may be attached to the pharmaceutical preparation mass by molecular adhesion, and for example, with respect to gold foils as well as other metal foils, it is also possible if desired, to employ an agglutinant such as gum arabic or balsam of tolu. Such materials may also be used as the only protective layer.

While the pharmaceutical preparations, compressed for example into tablets, in the usual manner, and then coated with protective layers as described above, give marked improvement in the intended respects referred to, still further improvements may be carried out. Tablets produced in the usual manner are generally so porous that resorption does not take place at the surface only, but also to a certain degree within the depth of the material, whereby the effect to be obtained by means of the constant resorption surface is forfeited to some degree. Desirably therefore, the small bodies or the material from which they are made are subjected to such a pressure that porosity is eliminated and resorption then takes place from the surface only of the body. The pressure used for such purposes is much greater than that normally employed in the production of tablets in the prior art and should amount to at least 50 kg./cm.², and desirably substantially more, for example, from 100-150 kg./cm.², varying to some degree with the character of the prepara-

tion to be used and the individual case in which it is to be employed.

When pressures of the degree indicated are employed, so that resorption takes place superficially only, the rate of resorption may in some cases be smaller than desired with compositions of the usual type. Accordingly, it is desirable to incorporate in such cases a resorption accelerating agent, for example, $\frac{1}{8}$ per cent cacodylos natrici or other resorption accelerating agent, whereby the efficiency of the product is improved.

It is of decisive importance that day after day during the whole delivery period of the deposit, the resorption conditions should remain exactly predetermined, for example, substantially constant since any variation in the rate of solution of the medical preparation may produce immediately a corresponding variation in the state of the patient. Insofar as pressures of the order of those set forth above produce the highest possible firmness and reduction in porosity of the tablet, this result is achieved. It has, however, been found to be impossible to avoid cracks, pores or bubbles here and there in the bodies and their presence promotes dissolution with the result that the deposit is not broken down absolutely regularly with a plane or slightly curved surface of dissolution so that there may be irregularity in the resorption with resultant effect on the state of health of the patient.

To avoid the presence of any cracks, pores or other irregularities it has been found that implantates capable of being broken down with absolute regularity so that the resorption surfaces remain plane or slightly curved as initially formed, can be produced by subjecting the substance to be incorporated in the deposit during the shaping thereof to a reduction of temperature from temperatures at which it is molten or semi-fluid to temperatures at which it has solidified in the desired shape. By such operation, the formation of any grain or crystalline structure at least of visible size is eliminated, the shaping being carried out at a pressure that is many times that necessary for the ordinary shaping operation. For example, the pressures used may be of the order of 1000 to 10,000 atmospheres, which pressure even exceeds the pressures suggested above for producing the deposits in the form of substantially non-porous tablets of the order of 50 to 150 atmospheres. It is well-known that practically no pressure is required for shaping the deposit in the fluid or semi-fluid condition.

By utilizing the means set forth immediately above, implantates or deposits are produced which are exceedingly compact and definitely free from cracks or bubbles or other undesirable structural defects. Owing to the compactness of the deposit, it retains a smooth and compact surface during all the time that it is breaking down under resorption and exactly the same quantity of the medical preparation will be dissolved per unit of time and per unit of surface during the whole dissolution process. The fluids of the body are not able to penetrate into the surface of a deposit body formed in this way to augment the rate of dissolution.

The omission of the formation of crystals which would cause a rough or grained surface is very desirable and may be obtained according to the embodiments of invention set forth above by subjecting the substances forming the deposit, during the decrease in temperature, through at least the range of temperatures within which crystal formation may occur, to ultra oscillations which

may be produced in any desired way, as for example, by means of electrical phenomena. The frequency of such oscillations may for example, be of the order of 30,000 to 40,000 oscillations per second.

In some cases, the dose of saturation to be administered will be considerably greater than the preserving dose and in such cases it is desirable that the initial rate of resorption should be greater than the subsequent constant rate of resorption maintained during the remainder of the treatment. While this may, of course, be obtained by supplementing the depot with a non-protected loosely compressed tablet, it is possible in the production of the small bodies according to the present invention to provide for this result, for example, by providing a small body of the same composition as that used for the given deposit, such small body having a non-protected protrusion or heightening of the same, or another composition or degree of compression than the remaining portion of the deposit.

The invention may be utilized in connection with implantates for depot purposes of any desired medical or pharmaceutical type illustrated for example, by the use of any of the various hormone preparations that are particularly valuable for utilization in accordance with the present invention. Such hormone preparations include for example, the male sexual gland hormone in its various chemical modifications, the female sexual gland hormones, for example, the corpus luteum hormone and the follicular hormone in all their various chemical modifications, the suprarenal hormone, desoxyorticosteron, insuline and the different hypophysis or pituitary hormones. While the use of hormones in this way is particularly valuable when carried out in accordance with the present invention, the latter is usable in connection with preparations of any kind that it is desired to introduce into the organism in the form of a depot implantate.

As pointed out above, it is possible according to the present invention in the production of the small bodies, to make allowance for the fact that the initial need of the body, as far as the medical preparation in question is concerned, is greater than the later continuing need. According to a further development of this principle, it is also possible to produce small bodies satisfying during a longer period of time, a cyclically varying need of one or more medical preparations, as for example, of the female sexual hormones.

In this case the small bodies may be built up in layers consisting of different preparations and preferably forming together a cylindrical block, the circumferential surface of which is coated with a protective layer as set forth above. For example, considering the female hormones, relatively thick layers of folliculin may alternate with relatively thin layers of folliculin plus lutein. Or if desired the difference between the different layers may not necessarily be a difference in kind as explained immediately above, but may be a difference in the nature of the chemical state in which the hormone or other material is produced, the degree of compression in the particular layer, the presence or absence of a catalyzer, or resorption accelerating agent, etc.

In order to obtain a predetermined rate of resorption, the coating must disappear in proportion as the free surface or surfaces exposed to resorption are consumed. If the coating does not disappear, the edge thereof will be left project-

ing like a collar and the resorption will then proceed predominantly by excavation of the central parts of the deposit body. If on the other hand, the coating disappears on places which have not yet been reached by the resorption of the free surface or surfaces, it is also impossible to ascertain a predetermined variation of the rate of resorption. To insure with certainty that the cover will be broken down in proportion as the resorption of the free surface or surfaces reaches the points of the covering material in question, variations in the application of the coating material may be utilized. Desirably to insure the result sought, the surfaces of the body should be treated by a covering material capable of intimately combining chemically or physically with the surface parts of the deposit. This means that the said covering substance should form with the surface of the body an interlayer in which the substance of the body as well as the substance of the cover occur in chemical combination or in physical mixture or initial solution. In this way it is assured that the covering substance will disappear with certainty at the time when the parts of the deposit body with which it is physically or chemically combined are resorbed. In such cases, the covering substance may itself form the layer protecting the deposit substance against resorption but on the other hand it may have the sole purpose of forming a support for another layer, protecting the deposit against resorption from the protected surfaces.

The covering substance capable of combining intimately with the surface parts of the deposit, as for example, chemically or physically, may be used in such slight excess that the portions thereof that are not combined with the deposit substance form a coherent surface layer. It should in such cases, however, be so thin that it is not capable of supporting itself but collapses when the portions of it combined with the deposit substance disappear. If the surface layer thus formed yields sufficient protection against resorption of the deposit from the portions covered therewith, no further treatment of the deposit is required. However, this will frequently not be the case and the covering layer described will then serve solely for supporting another covering layer, as for example, a metal foil as set forth above, which metal foil is not itself capable of combining with the deposit substance and which accordingly is not used alone as advantageously as in connection with the covering material which combines intimately with the deposit material. In this case also, the second protecting coating is desirably applied in such quantity and form that even this layer will not be self-supporting but together with the protecting layer intimately combined with the deposit material, it will prevent access of the fluids of the organism to the protected portions of the deposit.

By thus employing two different covering substances or layers, one of which is capable of intimately combining, for example chemically or physically, with the surface portions of the deposit to serve as a support for the coating which does not have this characteristic, there is obtained a safe protection of the surface portions of the deposit insuring security in the breaking down of the totality of the covering layers in proportion as a resorption of the free surface or surfaces proceeds throughout the deposit. In this way it is possible to employ the outer covering, for example, from metals, particularly the noble metals, and other metals set forth above,

in combination with the inner coating material of the character set forth.

As covering materials to be intimately combined, for example chemically or physically, with the surface portions of the deposit, there may be utilized any substances soluble in a solvent capable of partially dissolving the deposit substance and thus penetrating into the surface of the deposit and leaving a pellicle or film on evaporation of the solvent. The choice of coating materials and solvents utilized necessarily depends on the nature of pharmaceutical or depot material being utilized. If the deposit substance consists, for example, of a substance of lipid character as in the case of the sex hormones, the covering substance utilized for producing an intimately bound layer may be any natural organic film-forming material such as a resin or balsam or similar natural substance soluble in a suitable lipid solvent. As solvents in such cases there may be used alcohol, mixtures of alcohol and ether, and other similar organic solvents, capable of dissolving to a limited degree and thereby penetrating into the deposit, consisting of sexual hormones, so as to form a thin surface layer, containing the deposit substance and the covering substance in intimate combination. In the case of deposits of other pharmaceutical substances, solvents having properties of the character set forth above may readily be found and the film-forming or pellicle-forming natural substance employed will depend on the kind of solvent utilized. Even water-soluble deposit substances are frequently partially soluble in organic solvents and thus permit the use of coating materials soluble in such solvents.

If the solution of the coating substance is used in a slight excess as compared with the amount penetrating into the surface of the deposit body, for example, by applying the solution several times and if desired in different concentrations, there may be formed on the surface of the deposit, a pellicle or film containing nothing of the deposit substance so that no resorption may take place through the surface thus protected. In such cases it is not necessary to employ additional or different protective layers but if the additional layers are not utilized, the covering layer employed should be insoluble in water or in the fluids of the organism in order to exert the necessary protective effect.

Since pellicles yielding sufficient protection will frequently, however, be tough and capable of supporting themselves, it is preferable generally to use the first or inner protective layer solely for supporting a further covering layer. The first layer in such cases will be so thin that it is safely not self-supporting and accordingly capable of disappearing when the portions of the deposit substance or of the chemical or physical combination of deposit substance and protective layer are resorbed.

In those cases where a multiplicity of layers is utilized, the outer covering layer may particularly be a metal, for example, a noble metal such as gold, copper, silver, etc., as set forth hereinabove. Desirably, in order to obtain a metallic covering layer yielding sufficient protection against resorption from the portion of the surface of the deposit covered thereby and at the same time certain of breaking down during resorption, the metal layer may be applied by distillation in vacuum or by cathode-atomization or by any analogous process, the deposit covered by the inner or initial protective layer being placed in

an evaporation or cathode-atomization chamber in which a high vacuum prevails and in which copper, silver or a noble metal is caused to evaporate or atomize.

By utilizing such multilayer protective coatings, the breaking down of the unprotected surfaces of the deposit body proceeds so regularly that in case said surfaces are originally given a curved shape (for example, in the case of deposit bodies in the form of small sticks, the sides of which are covered by protective layers) the breaking down takes place exactly at right angles to the said unprotected surfaces so that the deposit body during the entire breaking down period continues to have its uncovered surfaces curved. Ultimately there will remain a lenticular body so that the delivery of the deposit substance does not suddenly cease but decreases at that time from the normal, constant value to zero during the time of the existence of the said remaining lenticular body. Thus a respite for implanting another deposit or for accommodation to another hormonal level is provided.

It has been found that in the case of hormones of the class comprising oestron, testosterone, progesteron, and corticosteron the resorption from the uncovered part of the face of the deposit body will advance about 0.2-0.3 mm. per month (that is, a layer of 0.2-0.3 mm. thickness will be resorbed per month) if the body has been prepared at a pressure of 1000-10,000 atm. whereas it will advance about 0.6 mm. per month if the body has been prepared at a pressure of 100-150 atm. Knowing the amount of the pharmaceutical preparation in question, which it is desired to supply to the organism per month it can be calculated what surface area there is required for the resorption. Thus in the case when 0.2 mm. is resorbed per month and the surface from which resorption takes place has an area of 1 cm.² this will correspond to a resorption of about 180,000 I. U. of oestron or 180 I. U. of androsteron or 1200 I. U. of testosterone or 18 I. U. of progesteron. If for instance in a certain case 60,000 I. U. of oestron has to be supplied per month there will be required a surface area of about 0.3 cm.² and if the body is formed like a stick, which is uncovered by the coating only at one end, its diameter must be about 3 mm. Again, in the case of progesteron when 15 units are to be supplied per month the surface area, from which resorption can take place must be about 1 cm.². If the body is in the shape of a stick both end surfaces of which are uncovered, its diameter must be about 8 mm. Again, in the case of testosterone if 2000 I. U. are to be supplied per month the surface area, from which absorption can take place must be 2.0 cm.² which means that 2 sticks of 8 mm. diameter and free at both ends may be used when the material has been compressed to 1000-10,000 atm. In the place thereof only 1 stick of testosterone, which has only been compressed to a pressure of for inst. 150 atmospheres may be used.

Thus it is an easy matter to calculate from these approximate values what kind of body has to be used and the dimensions thereof. The rate of absorption of other sterol like compounds than those described above will be of the same order and any sterol like compound, which is non-poisonous may therefore be used for the dilution of the medical preparation if such dilution be necessary.

In connection with the embodiments of the invention illustrated in the drawing, as shown in

Figures 1 and 2, the body 1 has a shape of a small stick, which is shown in Figure 1 in an axial or longitudinal section and in Figure 2 in cross section. In this case the depot material constituted in the body 1 is covered by a single layer of the coating 2.

In Figure 3 a body of substantially the same shape as that shown in Figure 1 is shown in longitudinal section. The depot material 3 is surrounded in this case by two coatings, an inner and an outer coating, 4 and 5 respectively. Both end surfaces 6, 7 are free and exposed.

In Figure 4 the depot material 8 as shown may consist of layers of different character. For instance in the case of the female sex hormone there may be used alternate layers 8 of 0.6 mm. thickness of oestron and layers 9 of 0.05 mm. thickness of oestron plus lutein. In this case only one end surface 10 of the stick is free, whereas the other end surface is coated as shown at 11 in the same manner as the cylindrical surface of the depot material.

In Figure 5 a longitudinal section through the depot body 12 is shown, such body having a greater cross sectional area 13 at one end, after which the body continues as a comparatively elongated portion 14 of substantially constant cross section, terminating in a portion 15 having decreasing cross section. The only portion of the surface left free is that one end 16, that is at the portion having the greater exposed area, the remainder carrying the coating 17. This type of body is adaptable for use in the case where initially a comparatively great amount of the medical preparation is to be supplied, following which the supply remains substantially constant and after that the supply gradually decreases.

As an example illustrating the manner in which a body of a pharmaceutical preparation can be made in accordance with the invention there is described in the following the production of such a body from a hormone such as oestron, testosterone, progesteron and corticosteron. The hormone is placed in a small cylinder, having the dimensions of the body to be produced. One end of the cylinder is closed and the other end is open to receive a piston. The cylinder is surrounded by a chamber in which there is a fluid, the temperature of which can be exactly regulated. The piston is in connection with a screw by means of which it can be placed under great pressure. In the case of oestron for instance the temperature controlling chamber is heated to about 260° C. after the cylinder with the oestron placed therein has been placed therein and the piston closing one end of the surface has been connected with the screw. When the oestron has been heated for some time to 260° the pressure in the cylinder is increased by means of the screw to 10,000 kgs. per cm.², and a source of ultra-sonic vibration is started. The pressure and the sound are maintained until the temperature has decreased to about 200° C. and then the whole is allowed to cool. The cylinder is removed and the stick formed therein is taken out and sprayed with a solution of coloconium-free shellac in ethyl alcohol and ethyl ether. This solution is produced by extracting 100 g. shellac in the cold with a mixture of 1000 g. 100% ethyl alcohol and 100 g. ethyl ether. The extracting fluid is left to stand over night and then the undissolved part of the shellac is removed by filtering.

Spraying is only continued until the stick has a moist appearance which, when the stick is placed at a distance of 15 cm. from the spraying

11

device and rotated, will be the case in course of for instance 60 seconds.

The stick is then placed in a chamber, which is evacuated in order to remove any trace of alcohol. After this the stick is covered by metal cathode atomization. For this purpose after drying, the stick is placed in a vacuum chamber, so as to form one electrode of a cathode atomization apparatus, the other electrode of which consists of silver, gold, platinum or copper. The chamber is evacuated to a pressure of $\frac{1}{100}$ to $\frac{1}{1000}$ mm. mercury and a little argon is allowed to enter the chamber. This is repeated once or twice. When a vacuum of about $\frac{1}{1000}$ mm. mercury has been attained the apparatus is placed under a tension of 1000 to 15,000 volts for about 10 minutes until the stick has a completely metallic appearance. In order to obtain an even distribution of the metal either the sticks or the electrodes may be rotated.

Before metallizing the stick a cap of paraffine or the like can be placed upon the end or ends of it in order to prevent the metal from adhering on the end surfaces. The paraffine can be removed after metallization has been performed.

In place of metallizing by cathode atomization the stick may also be metallized by evaporation of metal to it in a vacuum chamber. Such methods are well known and there will be no use in describing the manner in which they are carried out at this place.

The metallization may also be carried out by placing a gold foil of extreme thinness upon the surface or surfaces to be covered. This may be made by hand. In this case it is not necessary to apply a covering of shellac upon the stick before metallization.

In place of using a solution of shellac for applying the first cover there may be used a mixture of 75 parts of shellac and 25 parts of mastics. The solvent may be ethyl alcohol and ethyl ether as mentioned above or acetone, chloroform or carbon tetrachloride.

Having thus set forth my invention, I claim:

1. A depot implantate comprising a discrete

12

body of a therapeutic preparation having a surface coating of non-resorbable, non-poisonous and mechanically harmless material of such thinness that it will disintegrate when not supported by said therapeutic preparation, a portion of the body of the therapeutic preparation being exposed, from which exposed portions resorption may take place.

2. The product of claim 1, in which the small body has its cylindrical shape and the coating is circumferentially thereon.

3. The product of claim 1, in which the surface coating is a metal foil having a thickness of from about .001 to .0001 mm.

4. A depot implantate comprising a small body of therapeutic preparation having at least two coatings, one of which is intimately combined with the surface of the therapeutic preparation and the other is of non-resorbable, non-poisonous and mechanically harmless material of such thinness that it will disintegrate when not supported by said therapeutic preparation, portions of the body of the therapeutic preparation being exposed from which exposed portions resorption may take place.

5. The product of claim 4, in which the inner coating is of a natural organic film-forming material and the other coating is metallic.

CARL VÆRNET.

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