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ETHYL CELLULOSE COATINGS FOR SHAPED MEDICINAL PREPARATIONS

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Fig. 2

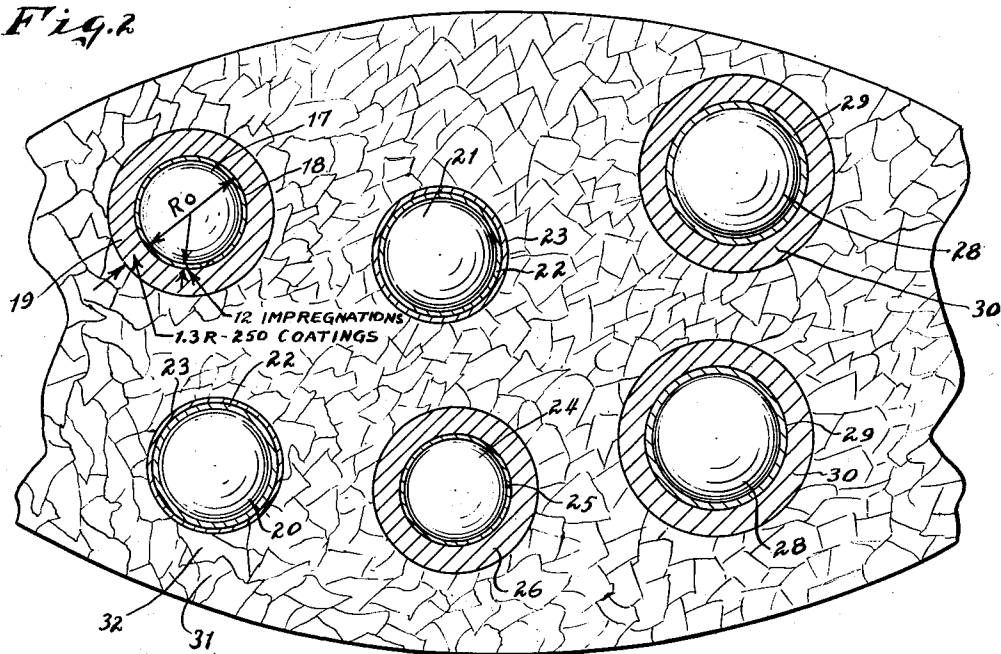
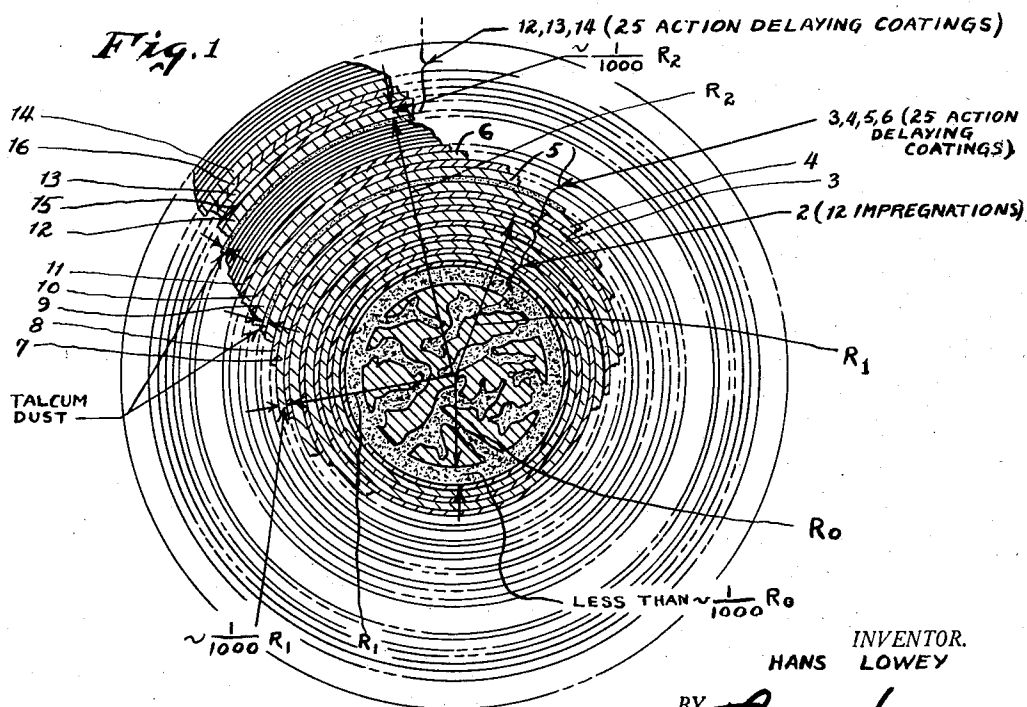


Fig. 1



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1

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ETHYL CELLULOSE COATINGS FOR SHAPED MEDICINAL PREPARATIONS

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8 Claims. (Cl. 167—82)

This invention relates to shaped medical preparations and especially to the coating of medicating carriers.

One of the objects of the invention is to provide on granulated carriers of predetermined shape, one or more action affecting multi-coat layers of predetermined structure and dimensions, and of high elasticity so as substantially not to be affected in their action by the further handling of the granules and especially during shaping or compression of several granules into capsules or tablets of predetermined shape, structure and dimensions.

A preferred object of the invention is to provide so many coatings or a layer of such thickness while maintaining a predetermined solidity and elasticity as to permit complete postponement or exclusion of action for such a great period, i. e., several hours, as to insure any action to occur only after a predetermined delay, for example, after passage through the stomach. Such relatively thick layers are in contrast to relatively thin layers which merely cause medication to start slowly but immediately, with the result of a more sustained action instead of a delayed action.

Another object of the invention is to provide a multi-coat layer on a granulated medication containing carrier having so many coatings as to insure the occurrence of a predetermined action delaying or action sustaining effect, within certain permissible tolerances, even in case some of these coatings would be inhomogeneous or imperfect due to inaccuracies which may be incidental or accidental to existing production methods or facilities.

Still another object of the invention is to provide multi-coat layers each including a large plurality of successive coatings, and wherein each plurality of coatings gradually decreases in thickness from the bottom to the top layer of such plurality, while the bottom layer of each plurality of coatings may be caused to increase in thickness, in a manner preferably proportional to its radius or to the distance of the coating from the center of the granule.

A further object of the invention is to insure or enhance elasticity and occurrence of the desired action delay after consumption of a finished tablet or capsule by applying the multi-coat layer or layers to a medically active, round granulated carrier, and reducing the thickness of each individual coating to a thickness which is not more than one percent of its radius or a fraction thereof, preferably for a granule of a diameter of .05", the thickness of each individual coating should be reduced to the order of magnitude of .000025".

Still further an object of the invention is to provide on granulated round carriers multi-coat layers of a pH-wise substantially neutral structure, so as to reduce to a minimum the effect of the usually varying individual acid or alkaline conditions prevailing in the part or parts of the human body receiving the tablet or capsule, whether such tablet or capsule is to be effective in the stomach or in the intestines or in both, thereby maying the effect of the stomach or intestinal juices, whether alkaline or acid, more closely proportional to the number of coatings and thus more accurately predeterminable than it would be with the use of pH-wise non-neutral, or acid or alkaline coatings.

2

At the same time as a further object of the invention, imperfections in such substantially neutral coatings such as varying thickness or even ruptures or fissures will have less effect upon the desired action delay, in contrast to imperfections in acid or alkaline coatings which once broken at one point would permit either the acid stomach fluid or the alkaline intestinal fluid, as the case may be, to break through rather quickly to the granulated medicinally active core, thus causing it to act prematurely thereby destroying any intended predetermined actional sustaining or action delaying effect of these coatings.

As a more specific object of the invention, therefore, the individual coatings in a multi-coat layer are substantially separated from each other or from any preceding or succeeding coating.

A preferred object of the invention, is to separate the individual coatings by a thin layer of extremely finely ground filler particles such as talcum, which serve to maintain an effective separation of adjacent coatings even though the bottom coating may not be completely dry when a succeeding coating is applied. In fact such complete dryness is not desired firstly because it would unduly extend time of manufacture, and, secondly, the succeeding coating would have difficulty adhering to a completely dried out bottom surface.

On the other hand, the direct application of a succeeding coating on a wet or humid bottom coating would tend to make the two adjacent coatings structurally one, causing one coating to share its defects with the other one in more or less the same manner and location, and thereby destroying or impairing the safety in effect, achieved by separating a great number of thin coatings in accordance with the invention.

In accordance with another feature of the invention, the powder layer applied to a not-completely-dried-out and therefore still somewhat soft bottom layer will cause a roughening of its surface, which while holding the two adjacent coatings substantially separate and apart from each other, will cause a succeeding coating safely to adhere to its bottom coating while at the same time imparting to its top coating a structure substantially independent from that of the bottom coating. Thus, for example, openings in one coating will not necessarily communicate with openings in the other coating, and therefore the probability of a break-through, through a number of coatings of the juices affecting the multi-coated granule is reduced, or rather limited to single coatings only.

Still another object of the invention is to provide multi-coat action sustaining or action delaying layers on non-granulated carriers and even medical substances in powder and even tablet form such as aspirin powder or tablets.

Still further another object of the invention is to provide action sustaining or action delaying coatings on immediate action substances other than those of a medical nature such as biologically active substances or carrier of such substances, such as fertilizers, herbicides or insecticides in powder or tablet form.

All these features of the invention, especially those resulting from the specific coating structures and procedures applied in this disclosure permit wide and predetermined variations in the effectiveness of medical preparations such as tablets and capsules.

These and other objects of the invention will be more fully disclosed in the drawings annexed herewith in which Fig. 1 represents cross section through a granulated carrier embodying certain principles of the invention and Fig. 2 a combination of granules differentially coated also in accordance with the invention.

According to Fig. 1 a granulated carrier of round shape such as produced in the usual manner in a rotating pan

from sugar or corn starch is schematically indicated at 1. It may either contain or be impregnated with a medicating substance such as nitroglycerin.

In the latter case, granule 1 is provided in accordance with the invention, first, with a medicating impregnation 2 containing, for example, a medically active substance such as nitroglycerin compound in an amount of say 50% of the weight of the granule 1.

Impregnation 2 is applied in one impregnation step or preferably in several steps of a number which may be somewhat less than the number of coating steps involved in the application of action sustaining or action delaying coatings.

In the present case medicating impregnation or coating 2 has been applied in twelve successive steps each involving a medicating layer of substantially not larger dimensions than the subsequent action sustaining or action delaying layers, with the difference that the resulting medicating layer 2 forms, at least partially, not only a coating but also an impregnation for the granule 1.

Since preferably substantially the same coating is used to apply the medicating substance as in the application of the subsequent action sustaining or action delaying coatings, the penetration of the medically active coating into the interior of granule 1 causes a diminution in the thickness which for that reason and depending upon the internal structure of granule 1, may be thinner than the corresponding action sustaining or action delaying coatings, all this without departing from the scope of this invention.

Upon medicating impregnation or impregnations 2, a great number of extremely thin action sustaining or action delaying coatings are applied schematically indicated as an example at 3, 4, 5 and 6 of Fig. 1 without, however, being limited to such number. Each of these coatings should have a dimension not exceeding a few percent of the radius of the granule and generally each coating should have a thickness not exceeding a few percent of its radius.

It has also been found from experiments underlying the invention that a great number, preferably at least ten coatings must be applied in order to give the resulting multi-coat layer a predetermined action sustaining effect, and at least twenty coatings must be applied to obtain a predetermined time delaying effect.

In a preferred embodiment of the invention, the diameter of the granules has been found to be of the order of .05" and a thickness of each coating applied thereon of the order of $\frac{1}{1000}$ of a percent of its radius or .000025".

In a preferred embodiment of the invention further the number of coatings forming one action sustaining or delaying layer and which are indicated in Fig. 1 from 3 to 6 consists of the order of 25 and similarly each successive layer has been established as of the order of 25 coatings. Such 25 coatings of the dimensions indicated above have been found to provide a sustained action effect of the duration of approximately one hour, provided the granules contain a medicating substance or coating or are to be medically active; or, as the case may be, an action delaying effect of two hours provided there are 50 coatings applied in succession.

In a particular example, it has been found that on a granule of a diameter of .05" the application of 250 coatings of an average thickness of .000025" will increase the diameter of each granule by about 30% from .05" to .065". By manufacturing in this manner ten types or batches of granules containing ten different multi-coat layers of different multiples of 25 coatings, each of these multi-coat layers will provide an action sustaining effect for a predetermined multiple of hours. In this way a substantially continuous action sustaining effect is obtained, which, in accordance with this invention can be made to extend altogether over 10 hours with a considerable degree of accuracy and within economically reasonable production tolerances.

In order to produce such action sustaining or action delaying effects of relatively long duration, in one example of the invention, the following procedure is applied:

The object of this procedure was to obtain a nitroglycerin containing tablet releasing the nitroglycerin gradually and practically proportionally during a period of approximately ten hours and in such a manner as not to become destroyed when released in the patient's stomach and not produce any shock effect upon the patient when released in his intestinal tract.

In order to achieve such a gradual release in a first step of procedure, a predetermined amount of say 100 pounds of granulated material is worked in a rotating pan in otherwise well known manner, into substantially round granules which, after sieving and, if necessary, regranulating of the residues, are transformed into 200 pounds of granules of substantially equal size, for example, of between ten to twenty mesh or a diameter of approximately .05 each.

These 200 lbs. of granules are now subjected to a great number of coating operations in a rotating pan, in otherwise well known manner, except that in accordance with the invention the coating solution applied is of a substantially lower concentration than usual and the speed of the rotating pan is of a substantially higher order than the usual.

Both these features cooperate to produce an extremely thin coating of extremely high elasticity and solidity, especially when superimposed in large numbers.

In a particular example of such coating operation the 200 pounds of .05" diameter granules are first coated with a lesser number of say, 12 medicating coatings increasing the weight of the granules from 200 to 201.5 lbs. and thereafter with one or several multiple coatings each consisting of 25 separate coatings, whereby each of these coatings is produced by one pound of a coating solution containing a very high percentage of solvent, weighing at least several times as much as the coating material itself. In a particular example the solution is an 85% alcohol solution containing 15% of a cellulose compound containing at least one of the following substances: methyl cellulose, ethyl cellulose, and cellulose acetate, phthalate or derivatives thereof; this solution also includes a few percentages (of the order of about 10%) of beeswax and castor oil which add to increase plasticity and elasticity of the coatings, respectively.

The alcohol solvent may be replaced by chloroform, if necessary; all this without exceeding the scope of the invention, although ethyl cellulose has been found as contributing a maximum of elasticity to the final coatings and a minimum of inaccuracies and imperfections.

It has also been found of importance for the effects characteristic of the invention that the coating solution be substantially neutral or of the order of 7 pH.

It should be noted that in order to obtain exactly predetermined coatings the solvent must be applied immediately before coating.

The coating itself is effected in a rotating pan of usual construction of a diameter of around 38 inches but rotating with a speed of 50 to 60 R. P. M. in contrast to the usual 30 R. P. M.

The coating operation itself and the rotation of the pan occurs for a duration of around five minutes until the entire one pound solution is transformed into coatings; then a drying operation of around 10 minutes or twice as much as the coating time is applied. Thereafter a separating layer is applied to the dry yet still soft coating in the form of very fine talcum powder estimated to be of not more than the order of coating thickness, or between about 1000 and 10,000 mesh.

The drying is preferably effected in a flow of warm air of slightly above room temperature, preferably at around 70° Fahrenheit.

Thus in accordance with the invention, upon the medicating impregnation or impregnations 2 the first action

5

sustaining or delaying coating is applied in the form of a one pound alcohol solution as mentioned above and immediately after drying after talcum dusting, the second coating 4 is applied in the form of a 1 lb. solution substantially identical with the previous solution whereafter another dusting procedure takes place. This process is continued until 25 coatings have been applied, always using a 1 lb. alcohol solution of cellulose compound.

Thus this first action sustaining or delaying coating procedure will increase the weight of the granules from 201.5 to 204.5 pounds.

Thereafter one-tenth of the granules corresponding to an action sustaining period of one hour, namely, 20.45 lbs. are removed and stored separately and the balance of the granules, i. e. 184.05 lbs. is subjected to another coating procedure again involving 25 separate coating operations, each using again a 1 lb. 85% cellulose compound coating solutions, resulting in coatings 12, 13, 14 etc. with intermediate talcum dust layers 15, 16, etc.

The result will be 187.05 pounds of granules each granule containing 50 coatings of predetermined thickness and providing an action sustaining period of two hours.

In a third operation, now, one-ninth of this amount, namely 20.75 pounds of granules, is removed and put aside; the balance, namely an amount of 166.30 pounds of granules, is subjected to 25 successive coating operations each involving a 1 lb. 85% cellulose compound solution. As a result of this third operational step 169.3 pounds of granules are obtained containing granules having each a three hour action sustaining effect.

This coating procedure is now continued until, finally, ten batches of granules are obtained, representing ten different multiples of 25 coatings corresponding to ten different action sustaining periods, extending from one to ten hours, respectively.

By combining one or preferably several granules, in the abovementioned example 20 granules, of each batch, into a tablet or capsule, this tablet or capsule will provide an action sustaining or delaying effect gradually extending over ten hours.

Part of such a tablet in cross section is shown in Fig. 2 where granule 17 is shown carrying a 12-coat impregnation 18 and a 250-coat action delaying layer 19. Granules 20 and 21 are shown to have in addition to and on top of the 12-coat medically active impregnation 22, a 25-coat action delaying layer 23, while granule 24 carries in addition to medicating impregnation 25, a 50-coat action delaying layer 26, and granules 27, 28 carrying in addition to medicating layers 29, a 100-coat action delaying layer 30.

There may be combined, of course, in a tablet, any desired number of granules having any desired number of coatings in accordance with the invention and in addition to medically active granules such as shown at 17, 20, 21, 27 and 28, a number of medically inactive filler granules preferably of irregular shape such as shown in Fig. 2, at 31, 32, which protect the medically active granules from breakage or any other action distorting effects.

In another example of the invention only four such batch steps are involved. In this case, in a first step, a time delaying action is intended, i. e., an action in which for a predetermined time, for example, during the passage of the tablet through the stomach, no medicating effect at all is produced, while thereafter, namely, in the intestines, a medicating effect, for example, a sustained action medicating effect is to be realized.

In this particular case and in this particular example two hundred pounds of granules or powder particles of any shape not necessarily round but preferably of the general diametrical dimensions mentioned above, are coated in a first operational step with fifty separate coatings preferably of the dimensions mentioned above, each involving an intermediate dusting and a one pound coating solution similar to that mentioned above in its first

6

step. In this way the first 50 coatings cause a delay time of approximately two hours, i. e., for a duration sufficient to permit a tablet or capsule containing such granules or powder particles to be passed through the acid stomach and to the alkaline intestines, provided, of course, that in accordance with the invention the coatings are of a pH-wise substantially neutral structure.

The result of such coating procedure will be an amount of 206 pounds of granules, or particles, each providing a two hour delayed action period. Thereafter one fourth of this batch is removed from the pan and the balance is subjected to a second coating step whereas an amount of coating solution proportional to the remaining weight of the granules or particles is added, and 50 successive coating operations are applied in a manner similar to that of the first operation.

After two further and successive coating steps, two further batches of a size substantially equal to the first removed batch are removed from the coating pan.

As a result of these four coating steps each including fifty individual coating operations, four batches of granules or particles are obtained each batch corresponding to two, four, six and eight hours of action delaying periods.

The final product of these four coating operations each containing 50 coating steps will be a mixture of four batches of granules or particles containing equal amounts of two, four, six and eight hour action delaying coatings.

In other words a tablet or capsule made with a mixture of such granules or particles will produce no action whatever in the stomach but will produce action delaying effects for a period of approximately eight hours in the intestinal tract.

In order to achieve a more pronounced or prolonged preliminary action delaying effect, in another example of the invention the different batches of granules are produced in simultaneous coating steps instead of in successive coating steps as before.

In order to explain this matter still further an example of this type of procedure will be given.

A first batch of 50 pounds of granules or particles of a general size such as mentioned above is provided in a rotating pan with fifty coatings of dimensions such as mentioned above and in the manner stated above and with the use of a coating solution such as exemplified in one of the previous examples.

Thereafter in another successive coating operation a second 50 lb. batch of equal character is added to the first batch and fifty further coatings are applied to both batches with corresponding amounts of solution in accordance with the invention.

The result will be 100 lbs. of granules or particles, 50 lbs. thereof providing an action delay of two hours and another 50 lbs. thereof providing an action delay of four hours.

Now, in a third step of this procedure, a third 50 lb. batch of granules or particles is added and the three batches are coated in the pan in substantially the same manner as stated above with fifty appropriate coatings, dimensioned in accordance with the invention.

Thereafter, in a fourth coating step, a fourth 50 lb. batch of granules or particles is added and the pan is rotated and fifty further coatings are applied to these four batches in accordance with the invention. The result of these four process steps will be a 200 lb. mixture of granules or particles, containing in equal proportions action delaying coatings for two, four, six and eight hours respectively.

This mode of procedure has the advantage that the last or top layer of multiple coatings which are applied to all four batches and to every one of the 200 lbs. of granules or particles, can be made of any desired thickness corresponding to any amount of predetermined action delaying time such as several hours, while the underlying coatings may be relatively thinner corresponding

only to action sustention periods such as durations of one hour only or multiples thereof.

In a fourth mode of coating procedure, four separate 50 lb. batches of appropriately shaped granules or particles are processed completely separately. Each of these batches is treated separately, the first batch with 50 coatings, the second batch with 100 coatings, the third batch with 150 coatings and the fourth batch with 200 coatings, all applied in accordance with the invention. A tablet or capsule made of a mixture of equal quantities of these four granules or particles and derived from each of these four batches will have no effect whatever for two hours and therefore it will be able to pass the stomach substantially unaffected; it will only be effective after two hours, i. e., in the intestinal tract, and in this location it will be gradually effective for a duration of altogether eight hours one granule being effective over each pair of successive hours.

The invention is not limited to the exact coating procedures, amounts and structures shown and described but may be applied in any proportion and sequence whatsoever. It is especially possible in accordance with the invention to obtain wide variations and mixtures for action delay and action sustention in a predetermined manner, to increase one or the other of these effects.

I claim:

1. In a medically active shaped preparation, a number of substantially round medically inactive granulated carriers, each having an impregnation of a solution of therapeutically active material in ethylcellulose and upon said impregnation a number of action-delaying ethylcellulose coatings, the number of coatings on at least some of said carriers being different from the number on the remaining carriers by at least 25; said 25 coatings containing a total amount of coating material of the order of 1% of the weight of the inactive carrier substantially equally divided among said 25 coatings, and each of said coatings being substantially not thicker than .1% of its radius.

2. Preparation according to claim 1 wherein said medically active impregnation contains nitroglycerin and said total amount of ethylcellulose coating material is approximately 1.5% of the weight of the medically inactive carrier, and wherein each of said coatings has a thickness of the order of .000025 inch; said carriers having a granule diameter of .05 inch; the diameter of the largest medically active coated carrier being approximately 30% greater than the diameter of the smallest medically active coated carrier.

3. Preparation according to claim 1 in the form of a tablet wherein each of said medically impregnated ethylcellulose coated carriers is additionally provided with at least 25 ethylcellulose top coatings containing a total amount of coating material of the order of 1.5% of the weight of the medically inactive carrier; said amount being divided substantially equally among said 25 top coatings, and each of said top coatings being substantially not thicker than .1% of its radius.

4. In a coating process, the steps of coating medically inactive granules in a rotating pan to a substantially round shape, sieving the granules to a substantially equal size, impregnating said granules with a medicating substance in an ethylcellulose solution and coating thereon an action delaying ethylcellulose layer in the form of at least 25 substantially separate successive coating steps; the 25 coatings containing a total amount of coating material of the order of 1% of the weight of the medically inactive granule substantially equally divided among said 25 coatings; each coating being followed by an intermediate drying step and each action delaying coating having a thickness of the order of $\frac{1}{10}$ % of the radius of the medically inactive granule.

5. Process according to claim 4 wherein said medically active impregnation contains nitroglycerin and said total amount of ethylcellulose coating material is approximate-

ly 1.5% of the weight of the medically inactive granule and, wherein said granules are of the order of .05 inch diameter, each coating being of the order of .000025 inch; and wherein there are a further number of medically impregnated granules coated in said pan and provided with so many successive ethylcellulose coatings as to increase the diameter of the coated granules to approximately 30% of the diameter of the medically impregnated granules containing only 25 ethylcellulose coatings; the thickness of all the coatings on different granules being a multiple of the thickness of all the coatings on said granules containing only 25 ethylcellulose coatings.

6. Process according to claim 4 wherein said granules are coated with a highly evaporative solution of ethylcellulose and in a coating pan rotating at a speed of around 50 to 60 R. P. M., the ethylcellulose being dissolved, immediately prior to rotation, in said solution; said solution containing as a solvent at least 85% of at least one of the group consisting of alcohol and chloroform.

7. Process according to claim 4 wherein a predetermined batch of granules is placed in the rotating pan and rotated at a speed of about 50 to 60 R. P. M. for a duration of five minutes, the operation being repeated 25 times whereby each time substantially the same amount of ethylcellulose is applied in a solution containing fractions of beeswax and castor oil and as a solvent at least 85% of at least one of the group consisting of alcohol and chloroform, each time followed by a fifteen minute drying period, and wherein thereafter a predetermined fraction of said batch is removed from said pan and a coating solution is applied to the remaining batch in an amount substantially in the same proportion to the remaining batch as applied previously to the entire batch, and the pan is again rotated in twenty-five separate operations each lasting five minutes; followed by fifteen minute drying periods; whereupon again a fraction of granules substantially equal to the fraction previously removed is removed from the pan, and the granules remaining in the pan are coated in the previous manner, said removing and coating operations being repeated until a desired number of batches of granules is obtained; the coatings of each batch representing multiples of twenty-five coatings, there being interposed after each coating step a powder dusting step consisting of the application of talcum of about 1,000 to 10,000 mesh and of an amount substantially not higher than that of the ethylcellulose in one finished coating; whereupon predetermined amounts of granules of each batch are formed into a predetermined shape providing a predetermined amount of action delay.

8. Process according to claim 4 in the manufacture of a tablet wherein each of said medically impregnated ethylcellulose granules is additionally provided with at least 25 ethylcellulose top coatings containing a total amount of coating material of the order of 1.5% of the weight of the medically inactive granules; said amount being divided substantially equally among said 25 top coatings, and each of said top coatings being substantially not thicker than .1% of its radius.

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