

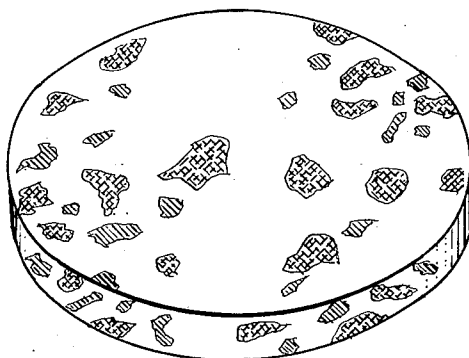
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SUSTAINED ACTION PHARMACEUTICAL TABLETS

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1

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SUSTAINED ACTION PHARMACEUTICAL
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1 Claim. (Cl. 167—82)

The present invention relates to sustained action pharmaceutical tablets and to the manufacture thereof.

There are many cases where it is desirable that medication administered to a patient be of brief and limited duration; this type of medication generally represents no problem. There are other cases where it is desirable that orally administered medication take effect at a particular place in the body. This type of problem is present where, for example, it is desired that the drug take effect in the intestine and not in the stomach. The problem is readily solved by providing the drug—usually a single drug—with an enteric coating which does not dissolve in the acid medium of the stomach, but does dissolve in the alkaline medium of the intestine. There are still other cases where it is desirable that a prolonged or sustained effect be obtained from a single dose of orally administered drug. For example, where a particular dose of a drug would normally exert its action for 4 hours—so that sustained action through the night, for instance, requires awakening of the patient at 4-hour intervals for re-administration of the medicament—it may be desirable to extend or prolong the action for a period of perhaps 8 or more hours—so that a dose taken just before retiring for the night, for instance, will exert its intended effect throughout the night and will obviate the necessity of awakening the patient for the purpose of administering additional medicament. In some cases, a medicament, if allowed to exert its entire effect at once, may give rise to undesired side-effects such as drowsiness or the like. Prolonging the action of such a drug, in the sense of stretching out the effect (including the side-effect or effects) over a period of time which is considerably longer than normal, may dilute the undesired effects to such an extent as effectually to obviate the sensation of their presence; the result thus, in effect, is to obtain the desired beneficial effect without undesired side-effect.

The present invention is concerned with the embodiment of medicaments—preferably in orally administrable form (compressed tablets)—of the prolonged or sustained action category. Medicaments of this type are known which involve periodic, timed, or repeated delayed disintegration products, wherein medication is contained in several layers, with the outer layer disintegrating first, followed by the disintegration of an inner layer (core) or layers, protective coatings or the like usually being provided between the several layers. In contradistinction to this type of prolonged action medicament, the products of the present invention are of the continuous disintegration type, i.e. they disintegrate gradually over a prolonged period of time, thus giving the desired sustained action.

The present invention is based upon the principle of incorporating into at least some portions of the medicament—which is itself constituted by an active ingredient or ingredients plus the usual pharmaceutical additaments or diluents—an ingredient which simultaneously functions as a disintegration-retardant (action-retardant) and as a binder. According to one aspect of the invention, a plurality of such special action-retarding and binding ingredients may be employed, severally incorporated into different portions of the final tablet or the like. According to still another aspect of the invention, the various portions of the medicament may be differently colored. Thus, where a per se known medicament is being con-

2

verted into sustained action form according to the present invention, the new tablet may comprise portions of such known medicament in unaltered form; if the normal color thereof is e.g. white, the portions of the new product constituted by such known medicament will continue to be white. Other portions of the new product which may contain one action-retardant according to the invention will be distinguished from the first-mentioned portions by being colored (e.g. with the aid of a pharmaceutically-tolerable coloring material). Still other portions which may contain another action-retardant will be distinguished from the already-mentioned portions by means of a different colorant.

Among other things, the multi-colored feature of the invention operates to identify the sustained action variant of the medicament from the normal variant thereof. It also tends to impress upon the patient the multi-component character—at least from the standpoint of period of activity—of the medicament.

As will hereinafter more clearly appear, the product of the invention is in effect an uncoated, non-enteric, multi-colored tablet comprising portions of different extents of action (different action periods), the differential action being due to the integral incorporation, into said portions of retarded action, of materials—essentially resinous in character—which function simultaneously, in such portions, as action-retardant and binding agent.

Briefly stated, and taking a three-portion medicament by way of example, the products of the invention may be constituted as follows:

Medicament M is first made up in essentially conventional manner, for example by admixture with usual additaments, such as corn starch, milk sugar and the like, and is then granulated and sized, keeping only granules of desired or preferred size. A second batch of medicament M is then made up in essentially similar manner, except that there are included as further additaments, a first action-retardant and binding agent AB and a coloring material D. This batch is also granulated and sized. A third batch of medicament M is then made up after the manner of the second batch, except that a different action-retardant and binding agent AB' and a different coloring material D' are employed. This batch is also granulated and sized. The final tablets are then made up, on a conventional tableting machine or in other convenient and essentially conventional manner, from various proportions—for example, equal parts by weight—of the several batches. The products will be multi-colored tablets, the several differently colored portions of which are of differential disintegrability in the body liquids, e.g. gastric juices. The result will be that—due to the retardant action of the additaments AB and AB'—the corresponding portions will exert their action over a longer period of time than will the portions free from such action-retardants. Moreover, due to the differential retardant action of the agents AB and AB' with respect to each other, these will also be assimilated into the body at different rates, so that a sustained action results.

A number of concomitant action-retardant and binding agents may be employed for the purposes of the present invention. Where more than one such agent is employed, it is of course desirable that they be different in their disintegration retarding action. Presently preferred agents of this character are vinyl acetate (e.g. Bakelite Vinyl Resin AYAC) and refined shellac (so-called pharmaceutical glaze).

The coloring materials are preferably certified food colors; any of these may be employed. Where the untreated medicament is white, good contrast is obtained when the other portions are green and orange respectively. In this connection, use may be made, if desired, of F. D. & C. Green No. 3 and D. & C. Orange No. 4, both

of which are certified food colors (specifications for both of these dyes are found in the bulletin issued September 1940—S.R.A., F.D.C. 3, published by the Federal Security Agency on coal-tar color regulations). However, other non-toxic and pharmaceutically approved coloring materials may just as well be employed.

The invention is applicable to a wide variety of pharmaceuticals, as will be evident from the representative embodiments set forth in the following illustrative examples. In these examples the parts are by weight.

Example 1

This example illustrates the application of the invention to produce a sedative and antispasmodic tablet of sustained action.

Into a mixture of conventional pharmaceutical tablet ingredients consisting for example of 48 parts of corn starch, 145 parts of milk sugar and 15 parts of powdered sugar, there are incorporated, as active ingredients, about 50 parts of phenobarbital and about 0.25 part of belladonna (e.g. in the form of Bellafoline). The mass is intimately and homogeneously admixed. To the resultant mixture, there is then added 0.8 part of gelatine dissolved in a small quantity (e.g. about 5 parts) of water, and 1 part of stearic acid dissolved in a small quantity (e.g. about 9 parts) of ether. Distilled water is then added until the mass has achieved the proper consistency for granulating. The mass is then granulated through a 5-6 cm. screen (5 to 6 meshes per centimeter), the thus-sized material being then dried, advantageously at 45° to 50° C. If desired, the dried material—which may be designated as the white granulation—may be further sized by being passed e.g. through a 4-5 cm. screen.

A second batch of material—which may be designated the green granulation—is then made up from about 50 parts of phenobarbital, about 0.25 part of belladonna, about 157 parts of powdered sugar, and 2 parts of stearic acid, using as wetting agent a 50% by weight solution of about 50 parts of vinyl acetate (preferably as Bakelite Vinyl Resin AYAC) in methanol, which solution also contains 1 part of F. D. & C. Green No. 3. After the material is thoroughly mixed, it is broken up into lump form and dried at 55° to 60° C. Following elimination of all the methanol, the material is allowed to stand at room temperature (about 20° to 30° C.) until the granulation becomes hard. It is then broken up and sized through a 5-6 cm. screen, discarding any fine powder.

A third batch of material—which may be designated the orange granulation—is then made up from about 50 parts of phenobarbital, about 0.25 part of belladonna, about 167 parts of powdered sugar, and 2 parts of stearic acid, using as wetting agent a 60% by weight solution of about 40 parts of refined shellac (pharmaceutical glaze) in methanol, which solution also contains 1 part of D. & C. Orange No. 4. The material is worked up essentially after the manner of the green granulation.

Equal weights of each batch—white granulation, green granulation and orange granulation—are then thoroughly mixed together in a blender, after which the material is tableted in conventional manner.

Each thus-prepared tablet will correspond essentially to the tablet illustrated (on enlarged scale) on the accompanying sheet of drawing, the respective parts being cross-hatched to designate color, the white portions being free of cross-hatching.

Such a tablet will provide a sustained action—as compared to a tablet made exclusively of the white granulation. Moreover, the physician may prefer that the patient take the latter type of table during the day, and the sustained type of tablet only before retiring; the variegated coloring of the sustained action tablet will thus enable the patient to distinguish between the two types.

Example 2

If it is desired to prepare a sustained action tablet

with antispasmodic action but no sedative action, the procedure according to Example 1 is followed except that the phenobarbital is omitted throughout.

Example 3

A sustained action tablet may also be prepared essentially according to the procedure of Example 1, but omitting the orange granulation entirely. In this case, each tablet is conveniently constituted of equal parts by weight of the green granulation and of the white granulation.

Alternatively, the green granulation may be omitted and the tablets composed of equal parts by weight of the white and the orange granulations.

Example 4

In some cases, the normal granulation may also contain a color. This is exemplified for instance in the case of 5-ethyl-3-methyl-5-phenylhydantoin tablets, used for instance as an antiepileptic for grand mal seizures and psychomotor equivalents.

The first batch is prepared essentially after the manner described for the first batch in Example 1. It will here be a pink granulation, due to the incorporation of a small quantity of Erythrosine Dye Solution ¼%.

A second batch is prepared as a green granulation using vinyl acetate and green colorant after the manner described for the second batch in Example 1.

Finally, an orange granulation is prepared after the manner described for the orange granulation of Example 1, using refined shellac and orange colorant.

In each batch, the active ingredient—preferably in the form of Mesantoin (Sandoz)—constitutes 50% by weight of the material.

Example 5

A sustained action tablet which is useful as an oxytocic and for migraine can be prepared essentially after the manner described in Example 1, using as active ingredient ergotamine tartrate, preferably as Cynergen (Sandoz), in an amount constituting about 2% by weight of each batch.

Example 6

Sustained action is frequently desirable in connection with antihistaminics. A sustained action tablet comprising white, green and orange granulations can be prepared after the manner of the foregoing examples using any desired antihistamine as the active ingredient. Thus, use may for example be made of 1-methyl-4-amino-N'-phenyl-N'-(2-phenyl)-piperidine tartrate, about 25 mg. per 220 mg. tablet, advantageously in the form of Sandostene (Sandoz).

It is evident from the foregoing that the principle of the invention is applicable to practically all types of tablet medication. In each case where the retardant-binder is used according to the invention, it is noteworthy that it is incorporated in dissolved form, so that such retardant-binder becomes just as much part of the respective mass or granulation as the medicaments or diluents themselves which are contained in such granulation. In other words, the mass of material in each such granulation is permeated by the wetting solution in which the retardant-binder has been previously dissolved, the material being manipulated so that a uniform mass results. On evaporating off the solvents, the retardant-binder becomes an integral part of the granulation and eventually of the tablets. No enteric coating action is hereby involved, as is evidenced inter alia by the fact that at least one granulation involves no retardant-binder at all. Even in the granulations which contain such retardant, the homogeneous character thereof distinguishes them from the enteric type of material.

Having thus disclosed the invention, what is claimed is:

A sustained action pharmaceutical tablet containing an active pharmaceutical ingredient and being con-

5

stituted by a tableted intimate and substantially uniform admixture of groups of granules, each granule of each group of granules comprising said active ingredient, the active ingredient in each granule of at least one group of granules being uniformly impregnated throughout with a disintegration retardant-binder selected from the group consisting of vinyl acetate resin and refined shellac, and the active ingredient in each granule of at least one group of granules being uncoated with, unimpregnated with and free from disintegration retardant additament, whereby each granule of the last mentioned group of granules may, upon coming into contact with body fluid, exert its function in normal manner and at normal rate, and the surface of said tablet comprising portions of differential disintegrability when in contact with said fluid.

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6

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,044,938

July 17, 1962

Stanley G. Halley

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 4, line 40, for "Cynergen" read "Gynergen --.

Signed and sealed this 5th day of February, 1963.

(SEAL)

Attest:

ERNEST W. SWIDER
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