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PRODUCING CHRONOACTIVE PHARMACEUTICAL GRANULES

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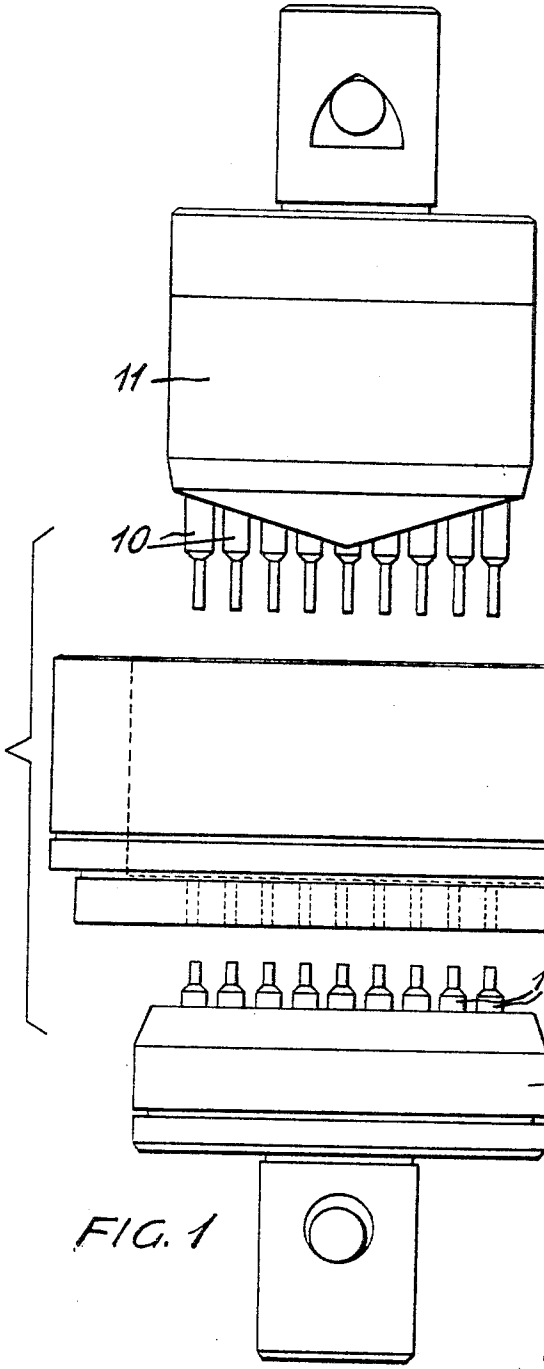

FIG. 1

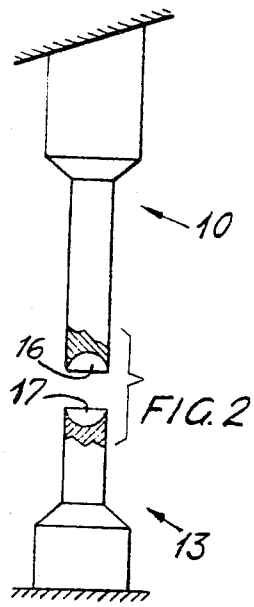

FIG. 2

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PRODUCING CHRONOACTIVE PHARMACEUTICAL GRANULES

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ABSTRACT OF THE DISCLOSURE

Chronoactive granules are mechanically produced from granulated powders having a high concentration of active materials of up to 95% and more while the excipients amount to 5% or less of the total mixture. Minute tablets having a diameter of about 1–2 mm. are prepared from such powders using multiple tablet making machines having a plurality of top-dies and bottom-dies, said small tablets being introduced into a pan where they are coated with at least one layer of materials adapted to form the finishing of the chronoactive granules.

Expensive and delicate methods are used at present in producing chronoactive granules for the delayed transfer of medicines generally prepared in gelatine capsules, such methods substantially involving the operator's empiricism and skill.

It is the object of said methods to provide minute pills containing the pharmacologically active materials, said pills being coated in the coating pans with films of gastric juice resistant materials so as to obtain the delayed transfer of the active material within the pill. The so-called sweetbread or granule nucleus is obtained by empiric methods carried out in said coating pan, or by granulating devices provided with selecting sieves providing granulated compounds formed of equally sized particles which are then placed in the pan for the delaying re-treatment, as previously mentioned.

In addition to the above disadvantages, the known method allows very low yields as to the amounts of active materials being used, owing to the numerous passages and hence to the possible alteration of the most transient active materials due to process length and necessity of particularly minute and repeated controls; moreover, it is the feature of the methods still in use and from which the present process particularly differs to require a high weighing ratio of the excipients to the active materials and thus the inability of effecting high dosages of active materials: only in some cases concentrations of 50% could be experimentally obtained. Generally, concentrations of 20–30% can be considered as good concentrations. This novel method for producing chronoactive granules differs from the methods heretofore used in that powders of a high active material concentration (up to 95% and more) are prepared, while the excipients amount to 5% or less of the total mixture, small tablets being prepared from such powders with a diameter of about 1–2 mm. by using reciprocating or rotary multiple tablet making machines having a plurality of substantially hemispherical cup dies and bottom-dies, and in that the small tablets being produced are introduced into a pan wherein they are coated with at least one layer of materials adapted to form the finishing of the chronoactive granule, materials which for example may be such as to avoid the disintegration of the active materials by gastric juices, or to delay the absorption of the active materials in the intestine section.

This novel method clearly differs from all the other present methods in using a multiple tablet making machine provided with small dies, while the other methods make use of long and delicate manual pan processes prior to coating.

Granules or nuclei obtained according to the present method are of a larger size than those obtained by known manual methods, while chronoactive granules being produced do not differ as to therapeutic effect; the granules obtained by the present method firstly show the advantage of having very high concentrations of active materials (up to 95% and more) which could not be absolutely obtained by the other methods in which, due to manual working, it is necessary to resort to a high weighing ratio of the active materials to the excipients associated therewith.

In fact, the conventional technique for preparing chronoactive granules requires the interleaving of films of active and supporting materials. Each layer of active material being added by panning for granule forming must have an underlying layer of sugar syrup: in turn, the active material has to be absorbed on levilite, talc, or another excipient. Accordingly, the granule will be mostly (at least 50% in weight) and necessarily formed of excipients. This avoids high concentrations of active materials to be obtained with resulting disadvantages of a technical and practical character:

(1) High amount of granules required to attain the desired dosages.

(2) The empiric character of the above operations requires long working times, continuous and expensive controls and does not give absolute guarantees of dosage.

Also the possibility of using a sweetbread already containing an active material, instead of using a sugar sweetbread (initial nucleus of the granule) will not alter the terms of the problem, since the highly reduced size of said sweetbread does not allow an active material addition in such amounts as to substantially modify the weighing ratio of the excipients to the active material.

Instead by the novel method according to the present invention, the high pressures of the tablet making machine on the granulated powders of the active materials will allow compact and stable tablets to be obtained, said tablets being almost entirely formed of active materials.

The following important advantages of the methods are thus obtained:

The working period is reduced to about one-tenth, with a minimum possible alteration of the most transient active materials since the manufacturing process is greatly simplified and shortened;

Resort to highly empirical specialized staff is avoided; analytical dosage control of the products in which said granules are used is facilitated; wastages of active materials are avoided; the same final effects are provided both as to therapeutic activity and as to capability of a manufacture as gelatine capsules, the same being on the contrary improved in that the capsule size can be reduced.

The advantages provided by the present invention relative to the other methods are due to the embodiment based on the application of a multiple minute die tablet making machine in the production process of chronoactive granules, by operating said machine with powders prepared with very high concentrations of active materials, which could not be absolutely feasible by means of the known methods at present being used.

In order to illustrate the machine allowing the fulfilment of the method according to the invention, there is shown in the accompanying drawings:

In FIGURE 1 an explanatory diagram of the machine; and

In FIGURE 2 the enlarged partial cross-section of the end of a die and bottom-die thereof.

At the top, FIGURE 1 shows a bank of minute dies or punches **10** parallelly mounted on a single piston **11**,

which is common to all the dies. Beneath such dies **10**, the vessel **12** containing the powder mixture (about 95% active and about 5% excipient) is arranged and at the bottom the bank of bottom-dies **13** coaxially mounted and facing the dies **10** on a single back- or end-piston **14**, which is common to all the bottom-dies.

Both the banks of dies **10** and bottom-dies **13** may be movable, or only one of them may be movable. Each top die and bottom-die terminates in a small hemispherical cup **16** or **17** so as to form substantially in the form of about 1 mm. After being introduced into a pan, coating and manufacturing thereof as gelatine capsules are conventionally carried out.

The fulfilment of the method, utilizing the machine diagrammatically shown in the drawing, is as follows:

The main active materials intended to make up the composition of the small tablets are first processed by mechanical procedures in order to convert the same in an as far as possible uniform granulated form to facilitate the compression of the powders which will be accomplished in second step in the tablet making machine.

The proportion of active materials of the granulated product may reach 95% and more, while the remainder is formed of excipient materials and lubricants.

Therefore the proportion of active materials of small tablets produced by means of the multiple tablet making machine may reach 95% and more, which could never be obtained by any system at present used for preparing similar pharmaceutical forms having the same purpose.

The granulated product is compressed in the desired form and size within said machine, the piston **11** of which carrying the bank of dies **10** is driven by a connecting rod and cam (not shown). Piston **11** falls back in vessel **12**, wherein a mechanically moving hopper of a conventional type (not shown) stores the desired amount of granulated product. Top punches **10** mounted on piston **11** fall back in apertures of bed die bottom **15**, which apertures form die cavities. From the bottom a back or end-piston **14** with a bank of bottom-dies **13** ascends with the same speed as and in synchronism with the top dies **10**, thus allowing a plurality of small tablets having a desired and predetermined diameter and thickness to be obtained at each stroke. The dies are provided by special, high strength steel punches having a diameter of 2 mm. and being slightly hollowed out at the end. The concavity of the top dies and bottom-dies will allow substantially spherical small tablets to be obtained.

Precompressed powder is driven into the die cavities by the punches moving through a reservoir. In a uniform direction of flow, the tablets are removed from the lower ends of the cavities. Therefore, the punches may be driven through a confined mass of powder and the powder precompressed as it is being driven into the cavities. This precompression is in turn responsible for the ability to manufacture tablets with such high concentration of pharmaceutically active ingredients.

The small tablets being produced are then transferred to a copper pan for a short period of time and are agitated in the pan, the friction between the pan and the tablets and between the tablets themselves enhances the spherical form thereof and rendering the groups of tablets more flowable and more readily measurable.

While the small tablets are in a pan, spray guns apply coatings of gastric juice resistant materials. While the tablets are in the pan, other coatings, colors, etc., may be applied. Finally, the packaging of the small tablets in as gelatine capsules is carried out.

What is claimed is:

1. The method for producing chronoactive tablets comprising: confining a mass of loose powder within a stationary vessel having a vertical confining wall surrounding the mass of loose powder and having a bottom supporting said mass of loose powder on its upper face and provided with vertically disposed apertures forming die cavities underlying said powder mass and extending through said bottom from its top face to lower ends terminating in its lower face, moving a plurality of first punches having concave end faces through the confined mass of powder into the die cavities, thereby filling and compressing the powder in the die cavities, while concurrently moving a plurality of second punches having concave end faces into the die cavities from their lower ends, thereby compressing powder in the die cavities to form compressed tablets.

2. The method of claim **1** wherein the powder and compressed tablets comprise about 95% pharmaceutically active material and about 5% excipient material.

3. The method of claim **1** further comprising coating the tablets with a layer of material slowly soluble in gastric juice.

4. The method of claim **1** wherein the concave end faces of the first and second punches are hemispherical.

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