July 6, 1965 J. R. A. SIMOONS 3,192,774

APPARATUS FOR DETERMINING THE RELEASE RATE OF DRUGS, WITH PROTRACTED OR DELAYED ACTION, OR OF OTHER SUCH SUBSTANCES

Filed Feb. 15, 1962 2 Sheets-Sheet 1

Fig. 1

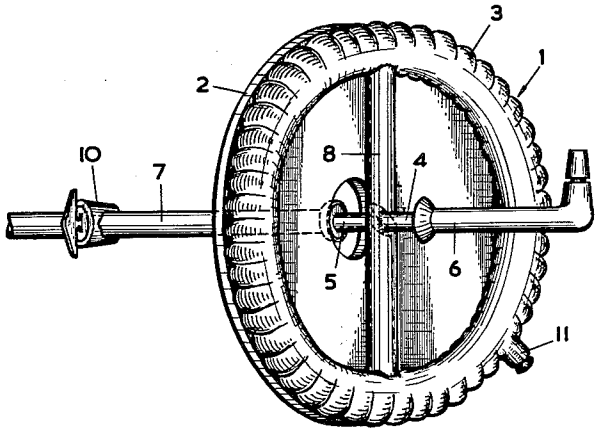
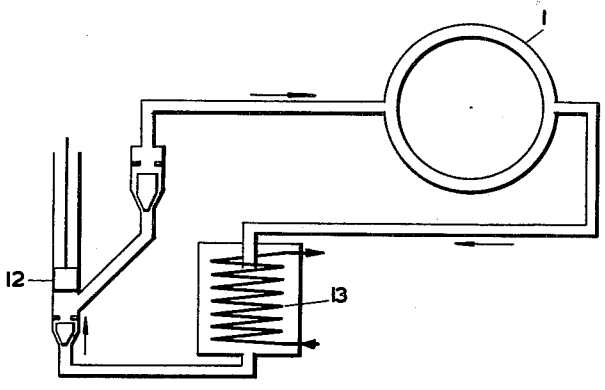


Fig. 2



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Fig. 3

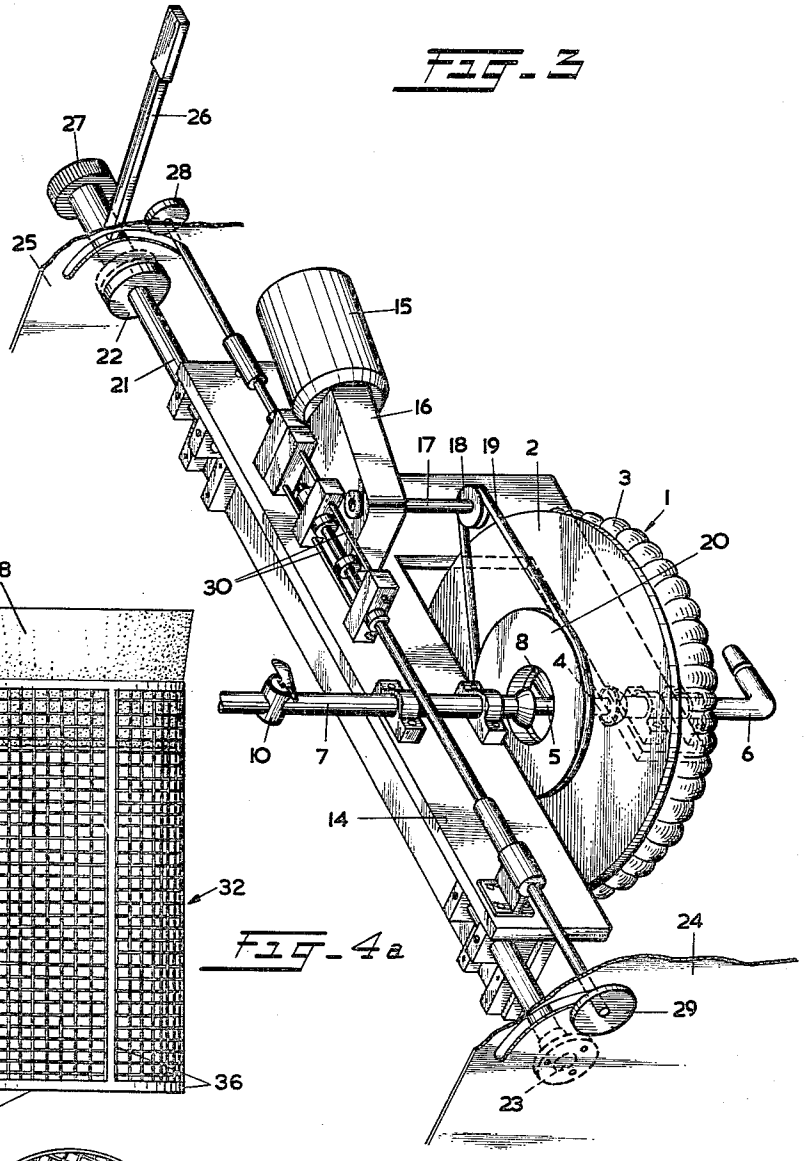


Fig. 4a

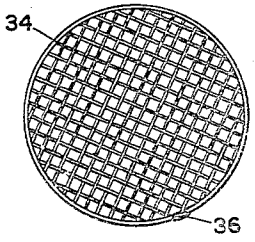


Fig. 4b

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APPARATUS FOR DETERMINING THE RELEASE RATE OF DRUGS, WITH PROTRACTED OR DELAYED ACTION, OR OF OTHER SUCH SUBSTANCES

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4 Claims. (Cl. 73—432)

Heretofore tablets, pills, granules and other medicinal forms have almost invariably been composed in such a way that the drug, or the substance in question, is released fairly soon after administration, which results in shock like therapeutic action. In most cases the effect of the administered doses has rapidly ceased so that several doses are required per day to arrive at a therapeutic response over a longer period.

In view of the consequent disadvantages, more and more drugs are being supplied in dosage forms that effect delayed or repeat release after administration, so that their action may continue over several hours. An obvious consequence is that by this procedure a considerably higher amount of the drug is administered in a single dose than is customary under conventional administration; hence, it is of the utmost importance to be able to investigate how the quantitative drug release may be pursued "in vitro" over a definite period of time.

The present invention relates to an apparatus for determining the rate of release of drugs, or other substances. According to this invention tablets, in as far as this form is concerned, are submitted to a rotatory movement in a container through which a flow of artificial gastric or intestinal fluid circulates. A similar apparatus, which is known as the Gershberg-Stoll apparatus, has been described in the United States Pharmacopeia, No. XIV, and subsequent volumes; it comprises a beaker-shaped container, which holds a basket-rack assembly in which a number of tablets is being periodically raised and lowered in an immersion fluid. The up and downward movement of the tablets in the fluid causes a continuous flow alongside the tablets. The liquid is kept at the desired temperature by means of a thermostatic arrangement. The objection against the apparatus is that the tablets etc., are not treated in a manner comparable to the conditions normally existing in the gastro-intestinal tract. In particular their treatment is too gentle. The mechanical pressure on the tablets is not equally divided over all parts of the tablet surface which is undoubtedly the case with the peristaltic pressure in the gastro-intestinal tract.

It is an object of the invention to provide for an apparatus which is in much better agreement with natural human conditions. The object is reached, according to the invention, in that the container comprises a circular body which rotates around its own axis and whose inner surface has, at least partly, been provided with indentations or other such irregularities. The intestinal wall has, of course also an irregularly shaped inner surface. The tablets, etc., are introduced into the ring-shaped body which is being rotated; as a result of this movement the tablets are continuously rolled over the irregular inner surface, and are hence subject to much more intensive mechanical treatment during their stay in the immersion fluid. The rotating speed of the ring may be adapted to suit varying conditions. Via rotating axis and radial supply and outlet tubes the fluid is supplied to, or removed from, the ring shaped body.

An additional advantage of the apparatus according to

the invention over the Gershberg-Stoll apparatus is that the experiment is carried out in a closed system, which eliminates atmospheric influences, in particular deterioration caused by oxidation of the drug under examination.

According to the invention it is further preferable to provide the apparatus with the possibility to adjust the ring-shaped container within the range between vertical and horizontal positions. Thus the angle of inclination of the plane, in which the ring rotates, may be modified in order to obtain a still closer approximation to "in vivo" conditions. Thus, almost every form of tablet, etc., may be investigated; at regular intervals the tablets can be removed from the ring and analysed; the immersion fluid may further be investigated, by classical means, for its drug content and the stability thereof under the prevailing conditions. However, in the case of granular dosage forms this is unfeasible as the granules may be or may become so tiny that they pass through very fine sieves. The granules will escape from the container, so that the picture obtained becomes unreliable. According to the invention, investigation of such granules has now become feasible by using small perforated containers in which the granules are placed before being subjected to treatment in the ring-shaped body.

The perforations in such containers should of course be of such mesh size that the granules cannot leave the containers until they have released the drug. A gauze-like wall, of 0.3-mm. openings approximately, at a wire thickness of about 0.2 mm. (No. 50 mesh) is preferred.

It should be pointed out that there is another apparatus in use for investigating granular dosage forms, the granules being placed in appr. 90-ml. bottles, containing artificial gastric or intestinal fluid. The bottles are sealed and revolved in a thermostat bath. The seemingly intensified operation does not lead to the desired results, however, firstly because the granules are revolved in a constant amount of eluating fluid, which does not form a continuous flow as in reality; thus, the release of the drug is limited depending on its degree of solubility in the fixed amount of fluid.

Secondly, the movement of the granules in the bottles is determined by the fluid contents of the latter; usually the movements are rather restricted, due to the fact that the granules are more or less pressed against the bottom of the bottle as a result of the centrifugal force.

The invention provides for constant intensive treatment adequately approximating "in vivo" conditions through the possibility of varying rotating speed, angle of inclination and the liquid flow through the ring-shaped body.

The apparatus according to the invention will be further explained with reference to the attached drawings.

FIG. 1 gives a perspective picture of the ring-shaped container in which the process of drug release takes place.

FIG. 2 represents a diagram of the entire apparatus.

FIG. 3 gives a perspective view of the entire apparatus according to the invention, seen from an oblique rear angle.

FIGS. *4a* and *4b* illustrate the before-mentioned perforated container **32**, a preferred embodiment being a cylinder about 8.5 mm. in diameter and 17 mm. high. The bottom **34** and the sides are made of 20 to 40 mesh wire screen with the joints **36** being soldered together and a rubber stopper **38** closing the top.

The ring shaped body depicted in FIGURE 1 forms the main section of the apparatus according to the invention for determining the release rate of oral protracted action medications or other such substances. The ring-shaped body is fitted on a plate-shaped carrier, **2**, which has been provided with means to rotate the carrier and hence the ring-shaped body **1**. The outer wall of this body has, on the inside, been provided with indentations

which may be visible on the exterior. The ridges may cover part of the side walls of the body, and are desirable on at least one of them in view of the possibility to shift the whole ring-shaped body from the vertical position, as shown in the diagram, to a more or less inclined position.

Through the centre of ring-shaped body **1** extend two rotatable tubes **4** and **5**, rotatably supported by fixed tubes, **6** and **7**; via these tubes supply or removal takes place through radial extensions **8** and **9**, respectively, which are separated on the site where tubes **4** and **5** join. Supply takes place via cock **10**, tubes **7**, **5** and **9**, removal via tubes **8**, **4** and **6**.

Ring-shaped body **1** has, at **11**, been provided with an opening for the introduction or removal of tablets, etc., to be investigated, which can be closed by a ground-in stopper.

The tablets are introduced into the ring-shaped body **1**, which is next made to rotate. The tablets are carried in an upwards direction under the influence, of the indentations on the inside of the ring wall. At a certain point the tablets will start rolling downwards, around their own axis, in a continuous movement since the ring-shaped body is rotated at a constant speed.

This action will cause mechanical pressure on all sides of the tablets while, at the same time, they are submitted to a constant flow of the immersion fluid.

FIGURE 2 gives a schematic outline of the action of the apparatus as a whole. The ring-shaped body has again been indicated by **1**. At **12** there is a peristaltic or circulation pump, while causes the liquid to circulate in the direction indicated by the arrows.

At **13** there is a thermostat bath for controlling or maintaining the temperature level of the substrate; the bath also serves as a storage tank for the substrate.

FIGURE 3 shows operation and assembly of the ring-shaped body and its carrier **2**. It appears from the drawing that tubes **6** and **7** are fixed immovably on a plate-shaped foundation **14**; ring-shaped body **1**, rotatable by means of tubes **4** and **5**, is fitted, water-tight, in the facing ends of tubes **6** and **7**.

On plate-shaped foundation **14** there is an electromotor **15**, which operates an axis **17** via reduction and assembly cabinet **16**; at the axis end there is a belt-pulley **18**, which operates the larger belt-pulley **20**, via belt **19**; the latter belt-pulley has been fixed to carrier **2** of ring-shaped body **1**. Plate-shaped foundation **14** has, at the bottom, been provided with means to fix axis **21**, which at **22** and **23**, respectively, has been fitted in plate-shaped supports, **24** and **25** respectively, which arise from a holder which is not visible in the diagram. Axis **21** has been provided with an adjustable lever **26** and an adjustable nut **27** by means of which the axis may be fixed in the position indicated by lever **26**.

The apparatus is shown with the ring-shaped body in vertical position; it will be clear that if lever **26** is shifted to the left, the axis with plate-shaped foundation and all the parts affixed thereto, including ring-shaped body **1** will be adjusted to an inclined position.

28 indicates means (which have not been mentioned in detail) by which to control the speed at which axis **17** and, consequently, the ring-shaped body rotates.

29 indicates a belt release whose rotation will shift electromotor **15**, along sliding rods, **30**, in the direction of **29**, so that belt **19** is released; ring **1**, with carrier **2**, may then be removed after cock **10** has been closed.

What I claim is:

1. Apparatus for determining the release rate of drugs, with protracted or delayed action, said apparatus comprising: a container in the form of a hollow ring-shaped body having an irregularly contoured inner surface; means supporting said ring-shaped body so that it is rotatable about its own axis; a pair of radially inwardly extending tubes each carried by said supporting means and connecting the interior of said ring-shaped body with a supply-tube and a discharge-tube respectively, said supply- and discharge-tubes being located concentrically with the axis of the ring-shaped body; an opening in said ring-shaped body for the introduction or removal of said drugs and a closure for said opening.

2. Apparatus according to claim **1** including in addition fluid-tight sealing means between said axially extending discharge- and supply-tubes and means for rotatably supporting said tubes.

3. Apparatus according to claim **1** wherein the means for supporting said ring-shaped body includes a frame which may be adjusted to vary the plane of rotation of the ring-shaped body to any position between a vertical and a horizontal position.

4. Apparatus according to claim **1** for determining the release rate of drugs in granule form wherein said ring shaped body contains at least one perforated container to hold said drug in granule form.

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