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(54) Titre : **DISTRIBUTEUR D'UNE DOSE UNITAIRE D'UNE SUBSTANCE ACTIVE SOUS UNE FORME GALENIQUE SOLIDE**
(54) Title: **DISPENSER FOR DISPENSING UNIT DOSES OF AN ACTIVE DRUG SUBSTANCE IN A SOLID DOSAGE FORM**

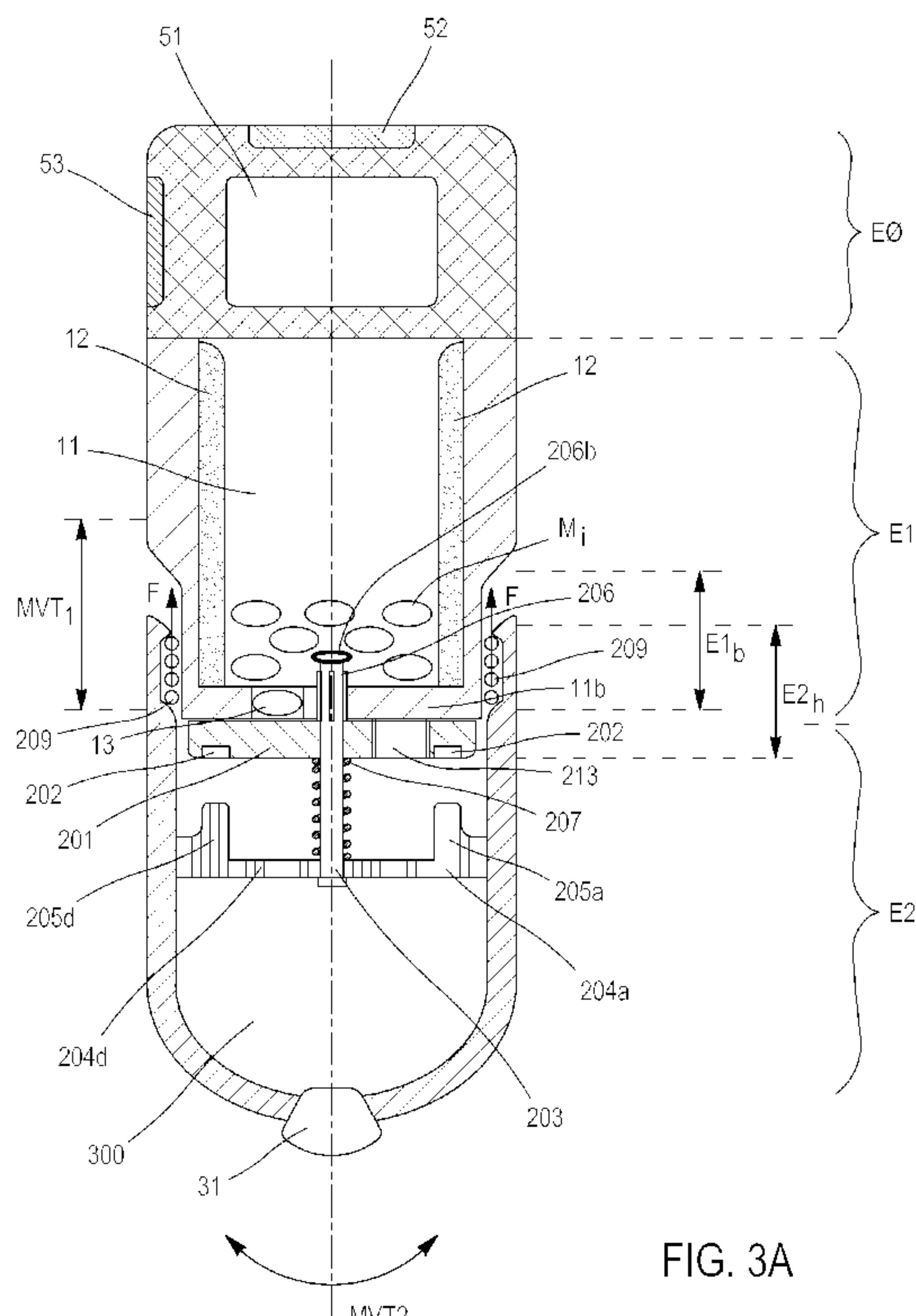


FIG. 3A

(57) Abrégé/Abstract:

The invention concerns a secure device for dispensing a unitary dose (Mi) of an active substance in solid dosage form. Such a device comprises means for preventing the chamber containing the unitary doses from being filled a second time. It can further accommodate (51) a treatment unit and means for communication with the outside world. Such a device is particularly effective for combating the counterfeiting of drugs. It further makes it possible to detect non-compliance of a patient during a clinical trial or non-compliance of a patient suffering from a chronic disease.

DESCRIPTIVE ABSTRACT

Dispenser for dispensing unit doses of active drug substance in a solid dosage form

The invention concerns a secure device for dispensing unit doses (Mi) of an active substance in a solid dosage form. Such a device comprises means to prevent refilling of the chamber containing the unit doses. It may further accommodate (51) a processing unit and means of communication with the outside world. Such a device is particularly effective when it comes to combatting the counterfeiting of medicines. It may further be used to detect patients' non-adherence during a clinical trial or the non-adherence of a patients suffering from chronic diseases.

Dispenser for dispensing unit doses of an active drug substance in a solid dosage form

The invention concerns devices for dispensing unit doses of a drug substance in a solid dosage form. Specifically, it concerns the fight against the 5 counterfeiting of medicinal products and patients' non-adherence towards clinical trials protocols or non-adherence of chronically ill patients.

The counterfeiting of medicines is a global phenomenon. Studies have shown that counterfeit medicines 10 account for over 10% of the global drug trade. In certain developing countries, as many as one drug in two might be a counterfeit. According to the World Health Organisation, counterfeiting generates a black economy worth over \$75 billion annually, highlighting the fact 15 that the so-called developed countries are not spared. Since 1992, a large number of World Health Organisation (WHO) Member States, Interpol, the World Customs Organization, the International Narcotics Control Board, the International Federation of Pharmaceutical 20 Manufacturers, the International Consumers organizations as well as the International Pharmaceutical Federation approved the following definition: "A counterfeit medicine is a product which is "deliberately and fraudulently mislabeled with respect to identity and/or 25 source". Counterfeiting can apply to both branded and generic medicinal products and counterfeit products may include products with the correct or the wrong ingredients or excipients, without active ingredients, with insufficient active ingredients or with fake 30 packaging."

Drug counterfeiting directly affects patients' health and safety. It also compromises the finances of companies operating in the sector as well as governmental agencies.

By way of example, the effects induced by a counterfeited medicine, which fails to reproduce the characteristics of the medicine that has been counterfeited may lead to treatment failure and can also 5 induce resistance to certain drug substances such as antibiotics. A counterfeit medicine can threaten a patient's health or cause the exacerbation of a disease via diverse complications. It can also directly cause the death of the patient, especially in the frailest 10 populations like children and the elderly.

The pharmaceutical industry is well aware of the dangers associated with malicious counterfeiting which is on the rise. It also measures the significant financial shortfall of the order of six billion euros a year for 15 French pharmaceutical companies only, and attempts to implement new strategies to combat counterfeiting, notably by trying to secure its packaging chains and distribution channels.

National agencies are also being mobilized to address 20 this phenomenon. Governments also suffer significant financial losses: the threat to public health engenders substantial expenses to cover the health care costs for people who may have been exposed to harmful products as well as for the replacement of stocks of counterfeit 25 drugs. Reinforcement of control and surveillance services for pharmaceutical supply channels on the ground is also consuming ever-increasing resources.

The solutions and strategies developed to date or 30 implemented by those concerned have proven to be expensive and relatively ineffective. Worse still, in the opinion of some observers, these strategies, although considered essential, could even curb investment devoted to research and limit the development of new molecules. Counterfeitors are particularly ingenious and they manage 35 to reproduce almost identical-looking bottles, vials, blister-packs, tablets and capsules, but obviously not

active ingredients. Some even recycle empty original containers; refill them with counterfeit medicines and reintroduce said containers on the market.

5 The pharmaceutical industry faces a second problem associated with the non-adherence of patients to clinical trials protocols. The objective of a clinical trial is to assess the effects of an active substance on patients who consent to follow a strict protocol, especially with
10 respect to drug regimen. They also have to make a precise report or fill in a clinical questionnaire about any positive or negative effects they have observed. Compliance with drug intake is crucial in clinical phases in clinical trials' phases because it is the only way of
15 establishing the most effective, non-toxic dose or the correct dosage to recommend in a specific therapeutic indication. Therefore, failure to comply with or adhere to a protocol by the patient, such as taking the medication at random, results in the collection of
20 inaccurate or insufficient data. Biased clinical trials can lead to the abandonment of a potentially effective drug or, conversely, to the approval of a drug of dubious efficacy or even one that is toxic at the established dosage. Patients' non-adherence towards clinical trial
25 protocols is unfortunately a widespread behavior. The average cost of developing a new drug is estimated at nearly one billion euros. The time required to obtain a Marketing Authorization or capitalize on research is of the order of twelve years (and sometimes longer).
30 Combatting patient non-adherence during clinical trials or at least detecting it constitutes a second challenge for the pharmaceutical industry. It is essential to reduce the costs and time associated with conducting clinical trials to improve the relevance and quality of
35 the results thereof by improving the adherence of enrolled subjects with the clinical protocols.

Stakeholders, therefore try to raise patients' consciousness and commitment through informative pamphlets, hotlines, Web sites, etc. To help patients follow protocols and the clinician's recommendations, 5 some have tried to establish systems to remind them when to take their drug and their scheduled appointments with the clinician. Reminders might be through telephone calls, E-mails or electronic diaries. Others have developed new forms of "smart" pack, e.g. with a timer to 10 remind the patient when to take a dose. Such solutions are very expensive and do not allow to measure and therefore to detect patient's non-adherence to a clinical protocol.

15 The invention provides an answer to most of the disadvantages of current solutions.

Among the many advantages of the invention, the following can be singled out:

- To fight effectively against malicious counterfeit medicines attesting consistency between the content and the container
- it provides economical containers or dispensers adaptable to all solid dosage forms of drug substances ;
- according to variants embodiments:
 - o To deploy drug dispensers in regions with a high degree of atmospheric humidity thus, preserving the drug substances of medicines and their integrity;
 - o To prevent damage of drug dosage units, resulting from collisions between said doses within the dispenser;
 - o To limit the risk of accidents or drug poisoning by preventing the delivery of a dose to an unmonitored child while maintaining easy use by the elderly;

- o To assess patients' adherence with the clinical trial protocol or non-adherence in patients suffering from chronic disease;
- o To contribute to the implementation of patient assistance services during a therapeutic treatment.

5 To this end, a dispenser is notably intended to dispense a unit dose of an active substance in a solid dosage form. Such a device includes a chamber to hold multiple unit doses of said drug substance, a command mechanism that can be activated by the user, means for extracting from said chamber and delivering a single unit dose of the plurality in the chamber in response to 10 actuation of the command mechanism by the user, and a casing or housing cooperating with the chamber. To effectively combat drug counterfeiting, such a device is specially designed to prevent malicious refilling of the chamber. Moreover, it also controls the dispensing of a 15 unit dose to the patient

20 For this, the said envelope irreversibly encloses or encircles the chamber and includes means, which, if the envelope is damaged, attest, emphasize or accentuate the said alteration. Furthermore, the unit dose extraction and dispensing system includes a mechanism to prevent the 25 return of a unit dose back into the chamber.

By virtue of the invention, the chamber cannot be 30 refilled without damaging the envelope of the device or the mechanism designed to prevent reintroduction, such damage thereby bearing witness to fraudulent activity or forced entry.

To preserve active ingredients in certain substances, the quality of coatings, or to carry dispersible tablets in a device that can be used in a very humid country or 35 geographic area, a device according to the invention

could also include means of absorbing humidity to maintain a dry atmosphere inside the chamber.

To maintain the integrity of unit drug doses in the dispenser's chamber and protect them against alteration 5 resulting from collisions between said unit doses, a device according to the invention can advantageously include means to exert sufficient pressure on the unit doses inside the chamber to immobilize them.

To reduce the risk of drug intoxication, dispensing a 10 unit dose of a drug substance using a device according to the invention can be made easy for any patient (including the elderly) apart from young unattended children. With this in mind, the command mechanism of a device according to the invention can be designed so that it requires two 15 distinct actions by the user to activate the respective means for extracting and dispensing the unit dose.

To prevent a unitary dose taken out of the chamber being dispensed and possibly getting dirty, a device according to the invention can advantageously include a 20 receptacle to collect the unit dose extracted out of the chamber by the extraction and dispensing means. According to an advantageous embodiment, the chamber of a device according to the invention can be constituted by the envelope's inner wall.

25 In a variant, said chamber can be constituted by an insert.

According to a preferred embodiment, the means of extraction and dispensing of a device according to the invention can include a tube in the shape of a circular 30 helix which can carry one or more unit doses, the said tube being inside the chamber which has an orifice at its lower base, the lower distal portion of the tube opening of said chamber by said orifice.

To indicate that a device according to the invention 35 has never been used, it may advantageously comprise means indicating the absence of any initial distribution of a

unit dose. According to a first embodiment, such means showing that no unit dose has ever been dispensed before could consist of a stopper on the unit dose dispensing. Alternatively or additionally, they may consist of an 5 accessory that locks the command mechanism operable by the user.

To increase the fight against counterfeiting, fulfill the requirements of assistance services for patients suffering from chronic disease, or even to measure the 10 adherence of a patient to a clinical trial protocol, a device according to the invention could also contain a level with a processing unit cooperating with the command mechanism, and a source providing required electrical power to operate the said processing unit. Such a 15 processing unit may have a timer and a memory to timestamp and record every operation of the command mechanism that triggers the extraction and dispensing system.

In a variant, the extraction and dispensing system of 20 such a device can include a sensor for detecting the delivery of a unit dose. According to this variant, the device may have a level containing a processing unit cooperating with said sensor, and with an electrical power source to supply said processing unit which also 25 includes a timer and a memory to timestamp and record every dispensing of a unit dose detected by the sensor.

To protect the level and the elements it contains, the invention states that the envelope of a device according to the invention may advantageously enclose the 30 chamber as well as said level.

To exploit the memory of a processing unit in a device according to the invention, said processing unit can advantageously include a wireless interface for communication with the outside world. In a variant or as 35 a complement, the processing unit may include a hard-wired communication interface for communication with the

outside world. Similarly, a device according to the invention can include a human-machine interface capable of retrieving information stored in the memory or generated by the processing unit, the latter driving said 5 human-machine interface.

To trace a device according to the invention when it contains a processing unit, the unit's memory may include first and second identifiers, dedicated to the device and an operator who originally filled the chamber, 10 respectively. Said memory can also have an identifier characterizing an active drug substance in a solid dosage form contained in the chamber.

To prevent malicious and secondary exploitation of a device according to the invention or to prevent any 15 attempt to alter the contents of the memory of a processing unit enclosed in the device; the said memory could be advantageously designed to be non-erasable.

According to a second object, the invention concerns a process implemented by the processing unit of a device 20 in accordance with the invention when the latter encloses a processing unit having a communication interface with the outside world.

Such a process includes:

- a step to timestamp each unit dose extracted 25 from the chamber and dispensed;
- a step to encode and restore to the outside world information generated from the contents of the processing unit's memory.

According to a third object, the invention concerns 30 computer software containing one or more program instructions that, when interpreted or executed by the processing unit of a device according to the invention, launch the above-mentioned process.

Other characteristics and advantages will become 35 clearer from reading the following description and examining the accompanying figures, among which:

- figures 1A and 1B respectively describe the outer and inner views related to a first embodiment of a device according to the invention;
- 5 - Figures 2A and 2B describe a second embodiment of a device according to the invention which notably carries means to prevent any collision between the unit doses contained in the chamber; figure 2B is a partial enlargement of figure 2A to illustrate more accurately an example of a mechanism to prevent refilling of the device with unit doses;
- 10 - Figures 3A and 3B describe a third embodiment of a device according to the invention which notably encloses a processing unit.
- 15

The invention concerns the dispensing of drug substances, mainly medicines, packaged in a solid dosage form. In the sense of the invention, a unit dose of such active drug substance in a solid dosage form means (in a non-exhaustive manner):

- so-called "standard" tablets or "pills" intended to be swallowed by a patient: it dissolves within the body and can be absorbed throughout the gastrointestinal tract;
- 25 - chewable tablets which are not intended to be swallowed, but sucked by the patient: the drug substance passes into the bloodstream through the oral mucosa;
- orodispersible tablets which dissolve in the mouth of the patient within seconds;
- 30 - sublingual tablets which are not intended to be swallowed directly by the patient, but to be placed under the patient's tongue where they will dissolve: the drug substance passes into the bloodstream via the highly vascular mucosa underneath the tongue;
- 35

- effervescent or otherwise dispersible tablets which rapidly disintegrate or break up, preferably in a glass of liquid;
- coated or sugar-coated tablets, or film-coated tablets designed to obtain a specific effect, e.g. gastro-resistance, mask color or unpleasant taste, confer a "commercial" color or affix a logo or a reference to the company that markets the drug;
- coated or uncoated effervescent tablets: an effervescent tablet is one designed to break up and dissolve quickly;
- a capsule with a soft or a hard shell consisting of a hollow case containing a drug substance; among the various types of capsules can be distinguished:
 - o dipped capsules, oval-shaped and of varying size, referred to as capsules or capsulines;
 - o pressure-generated capsules, oval or spherical in shape, referred to as globules or beads, produced in a machine that uses high pressure to weld together two thin sheets of gelatin paste to create a cavity containing a liquid, paste or powder;
 - o soft or elastic capsules produced in a manufacturing process which is essentially the same as that used to make dipped capsules but with glycerin added into the formula to make the shell thinner and more flexible; these do not require drying before filling and are closed with a ring dipped in a gelatin solution: they usually contain oily substances;
- pills or lozenges, usually cylindrical or flattened spherical shape.

Furthermore, in the sense of the invention, such a unit dose may consist of one or more tablets or capsules, said plurality of units forming a unit dose to be taken by the patient for a given posology. A unit dose can 5 therefore consist of several units and be fully dispensed by actuating the command mechanism of a device designed to dispense drug substances to its user.

Figures 1A and 1B describe a first example of an 10 embodiment of a device 1 to dispense a unit dose of a drug substance in a solid dosage form. More specifically, Figures 1A and 1B describe in more detail the outer (fig. 1A) and inner (fig. 1B) views of such a device. This device contains a chamber 11 holding multiple unit doses 15 of active drug substance in a solid dosage form. As indicated in this example, chamber 11 is constituted, delineated or materialized by the inner surface 10i of envelope / envelope 10. Such a chamber could be cylindrical in shape as shown in the example described in 20 Figure 1B. Doses M1, M2, Mi—corresponding in the context of the example shown in figure 1B, to oval sugar-coated tablets—are present in the chamber 11. To extract and dispense a tablet (referenced M3 in figure 1B), the user activates a command mechanism. Referring to figure 1B, 25 this mechanism advantageously takes the form of a lid or a handle 20. In response to the action, the command mechanism triggers means to extract a unit dose from chamber 11. The dose M3 is thus dispensed to the patient. Advantageously, such a dispenser may include a receptacle 30 30 with a window so that, when it is dispensed, the unit dose will not be ejected with the risk of being dirty or contaminated before administration.

Referring to figure 1B, such means for the extraction and dispensing could advantageously take the form of a 35 hollow tube 28 shaped like a circular helix designed to deliver one or more unit doses. This tube is inside

chamber 11, which has an orifice at its lower base, the lower distal portion of tube 23 opening of said chamber by said orifice. Such a tube could be assembled to rotate around an axis substantially parallel to the axis of 5 rotation of chamber 11. In addition, the tube is integral to the lid or handle. Thus, an action to partially or fully rotate said lid causes the routing of the unit doses present in the chamber to move along tube 28 which, like a guide, will direct a unit dose (i.e. M3) towards 10 orifice 13 of the chamber. Such a unitary dose is thus extracted out of chamber 11 and dispensed to the patient, via the optional receptacle 30.

15 To combat the counterfeiting of medicines and more specifically to prevent secondary, fraudulent use of a container, the invention provides that envelope 10 of the device 1 can be designed to enclose the chamber 11 irreversibly after its original filling, thereby precluding any refilling of the chamber.

20 Referring to figure 1A, such an envelope 10 can for example be thermoformed. In a variant, it can result from the assembly of a plurality of parts that can be mutually welded or glued. Each part could include means for irreversible fitting (e.g. clips) so that by the end of 25 an assembly phase, all the parts form a single unit or confinement chamber for the unit doses.

30 To attempt using a device according to the invention in a fraudulent fashion, it becomes necessary to alter the integrity of the envelope to access chamber 11. According to a preferred embodiment, such an envelope 10 can be fitted with means that, if any attempt is made to breach it, indicate or attest said attempt. Envelope 10 could e.g. carry a series of either printed or engraved 35 guilloche motifs on the outer surface 10e. Alternatively or additionally, envelope 10 can also have--by virtue of its features or structure, areas of weakness or weak

breaking zones which, when an attempt is made to tamper with the envelope, automatically accentuate any damage inflicted to the envelope's physical structure. In addition, or as a variant, other techniques could be used 5 to render the chamber incompatible with holding the unit doses in response to the attempted tampering, e.g. by means of an ink projection system. The invention is not limited solely to these examples of methods to indicate any attempt to tamper with the integrity of the envelope 10. According to the example described in figure 1A, the envelope thus formed after its original filling may be rigid, flexible or semi-rigid according to the desired packaging, the device's planned use, required 15 specifications or local regulations. Any type of material can therefore be used, such as plastic, metal, polymers, etc.

The envelope and, therefore, chamber 11 can be substantially cylindrical as described in figures 1A and 1B. Variants of one or the other could be presented in 20 other geometrical configurations, e.g. a cone, a solid with a polygonal section, half-moon section, etc.

According to the example described in Figure 1B, the chamber is directly delineated by the inner wall 10i of envelope 10. To prevent any interaction between the 25 lining material of the envelope and the unit doses, the inner wall 10i of the envelope 10 can advantageously comprise a plurality of protective layers, e.g. food-grade varnish. Thus ensuring optimum neutrality of the inner surface of the envelope with respect to the 30 contents of chamber 11.

As a variant, chamber 11 can consist of an insert. e.g. a sleeve, cartridge or cassette (not shown in Figure 1B) can be enclosed within envelope 10. The insert is initially filled with unit doses. This variant notably 35 makes it possible to dissociate the unit dose batch constitution - filling the insert - from the final

packaging step - assembling a device according to the invention. This variant also precludes the need to deposit any protective material on the inner surface of the envelope to prevent any interaction between the 5 envelope material and the unit doses. The latter being protected by the insert.

Dispensing some drugs in countries or regions with high atmospheric humidity can be difficult: in contact with humidity, active ingredients of certain medicines, 10 the quality of coatings or the integrity of dispersible tablets can be quickly damaged in contact with humidity. To preserve unit doses stored in the chamber of a device according to the invention, the chamber can also advantageously further contain means to absorb humidity 15 12 to sequester ambient moisture and thereby maintain a dry atmosphere within the chamber 11. According to the example described in Figure 1B, the upper portion of the chamber 11 comprises a strip of blotting paper or any other material that sequesters or absorbs ambient 20 humidity or condensation inside the chamber. Additionally or alternatively, such means could be implanted at other points within the device 1.

As a complement, a device according to the invention can also include means to indicate that no unit dose has 25 been dispensed. By way of a non-exhaustive example, such means might consist of a stopper that blocks the dispensing of unit doses, e.g. a membrane seal that is well visible to the user of the device. Advantageously, such a stopper may cooperate with receptacle 30 to 30 obscure the window of said receptacle. It could alternatively cooperate with the envelope or constitute an extension or accessory to said envelope. The layout of the said stopper is advantageously designed so that its removal would be and remains visible to the user. e.g. 35 the removal of the stopper could leave visible damage on the envelope or receptacle in such a way at one glance

the user can see that the device has already been used. In a variant or as a complement, said means indicating the absence of any previous dispensing of a unit dose could consist of a mechanism or accessory designed to 5 lock the command mechanism 20 that is operated by the user in order to trigger the dispensing of a unit dose. Thus, to deliver the first unit dose, it becomes necessary to remove said lock to release the command mechanism. For example, such means can consist of a patch 10 or an adhesive strip, which removal could advantageously but not necessarily leave visible fragments on its support, or alternatively a strip cooperating e.g. together with the lid or the handle 20 and the device's envelope or body.

15

Figure 2A describes a second embodiment of a device 1 according to the invention. Such a device comprises a chamber 11 to contain a plurality of unit doses M1 to Mi. The device 1 advantageously consists of two or three 20 levels or modules. The upper level E1 consists of a hollow cylinder with a concave lower base E1b. In the hollow of said lower base, there is an opening 13, the shape of which substantially matches that of a unit dose. Furthermore, according to the example described in Figure 25 2A, the lower base of level E1 is laid out so that said opening 13 or the tip of inverted cone on the base is offset with respect to the axis of rotation all of the chamber constituted by the inner wall of said level. The unit doses can be arranged inside the chamber 11 at the 30 upper opening E1h of level E1. Once the chamber is filled with unit doses, the upper section of the chamber 11 is sealed with a (lid) 14. The latter irreversibly cooperates with the upper portion E1h, which may be bonded through welding, glue, clips, etc. The chamber 11 35 constituted by the inner wall of the upper level E1 would then have only one opening, namely opening 13.

To maintain a dry atmosphere inside the chamber 11, the lid 14 can include means to absorb ambient humidity such as blotting paper, etc. In addition, to prevent collision between said unit doses inside the chamber 11, 5 the lid 14 can comprise a set of spiral wicks 15 or any other equivalent system, such as, springs, elastic fibers, etc., the function of which is to apply sufficient pressure on the unit doses located at the top of chamber 11. Gradually, the unit doses are leaning 10 against each other and become immobilized. As shown in Figure 2A, a pressure disc 16 can advantageously be inserted between said spiral wicks 15 and the unit doses, the lower surface of which (i.e. the one in contact with the unit doses) has an inert coating to prevent any 15 direct contact between the spiral wicks 15 and the unit doses. As a variant, the pressure disc 16 can be entirely made of an inert coating or material. As for the device 1 described in Figure 1B, the inner surface of the chamber 11 can be coated with a protective varnish.

20 With such a layout of the upper level, the unit doses are naturally pushed by gravity and the effect of the spiral wicks towards opening 13 of the chamber 11 when the device is held in a more or less vertical position.

The device 1 comprises a second level E2 which 25 function is to extract one unit dose among the plurality of unit doses contained in the chamber 11 and to dispense the dose extracted to a patient or more generally to a device 1 user.

Level E2, below level E1 when the device 1 is held 30 more or less vertical, includes a dispensing channel 25 substantially parallel to the axis of rotation a11 of the chamber 11. The axis of rotation a25 of said channel 25 is also substantially parallel to axis a13, which is perpendicular to the cross-section of opening 13. Axes 35 a13 and a25 are offset in such a way that channel 25 does not emerge facing opening 13. The distance between axes

a₁₃ and a₂₅ is greater than or equal to the maximum dimension of the unit dose in chamber 11. In connection with the example described in figure 2A, level E2 looks like a cylinder with an external diameter substantially 5 identical to that of level E1.

The upper portion of level E2 further comprises a transversal groove 29 perpendicular to the axis of rotation of level E2. Groove 29 also intersects with the channel 25, which emerges in said groove 29. Such groove 10 29 only opens at one end. It constitutes a groove in which a command mechanism 20 can slide along. For a groove 29 with a circular section, the mechanism 20 advantageously looks like a full cylinder arranged to slide in said housing. The housing and mechanism 20 could 15 have sections that are not circular but would be matched so that the mechanism can slide inside the housing. The command mechanism 20 is long enough so that its distal part 21 thereof remains projected out. The mechanism 20 can advantageously include a shoulder 20a so that its 20 course is limited in the groove 29, the shoulder acting as a stop against the inner surface of level E2. The command mechanism 20 cannot therefore be removed after assembly of the device 1. The groove 29 also features a spring or cylinder 26 cooperating with the inner surface 25 of level E2 and the proximal part (i.e. internal) of the command mechanism 20. The command mechanism 20 thus resembles to a push button, the course of which inside the level is limited by the shoulder 20a and the resistance of the spring 26. The command mechanism 20 30 advantageously has a full structure apart from a traversing recess 20e with a cross-section similar to that of the opening 13. Like a cradle, the mechanism 20 can thus convey a unit dose inside groove 29. The traversing recess is laid out so that a single unit dose 35 is extracted by gravity out of chamber 11 and received in said recess when the mechanism 20 is in its resting

position (the spring 26 pushing said mechanism back until the shoulder 20a is stopped against the inner surface of level E2) and when the device 1 is held so that level E1 is positioned above level E2.

5 When the command mechanism is actuated by a user of the device 1, said mechanism 20 enters the groove 29 and stretches the spring 26. The traversing recess 20e transports the unit dose, the latter resting on the lower wall of groove 29. When the recess 20e is facing channel 10 25, the unit dose is released and dispensed by simple gravity. During the path of the command mechanism 20, the opening 13 of the chamber 11 is blocked by the body of the command mechanism 20. When the user of the device releases the command mechanism 20, the spring 26 pushes 15 it back to its resting position. In turn, the body of the mechanism 20 blocks the channel 25. The opening 13 of the chamber is again facing the recess 20e and a unit dose can therefore take place within the recess 20e. To make sure that only one unit dose can be conveyed, the height 20 of the recess 20e is close to that of one unit dose.

 To join or seal together levels E1 and E2, said levels advantageously include irreversible, matching joining points. Thus, the lower part of level E1 and the upper part of level E2 are laid out to cooperate with one 25 another in an irreversible manner, using, e.g. means of a weld, glue, clips, etc. The respective outer walls of levels E1 and E2 as well as that of the upper lid 14 constitute the envelope 10 of the device 1. Thus enclosing not only the chamber 11 but also the unit dose 30 extraction and dispensing system.

 So that the extracted, dispensed dose does not fall straight out, the device 1 may include a receptacle 30. This constitutes the lower level E3 of the device 1. In contrast to the other two levels that are mutually and 35 irreversibly assembled, receptacle 30 cooperates with the lower base of level E2 reversibly, e.g. through a thread

or an adjustment affording enough friction to keep the receptacle in position. Thus a user can remove the receptacle 30, recover the unit dose and then reposition said receptacle 30 on the lower base of the level E2. The 5 lower part of the channel 25 is again closed. The use of the receptacle makes it possible to associate to the actuation of the mechanism a second operation required for dispensing a unit dose. Young children are thereby protected because they should be unable to reproduce 10 these two consecutive actions. In a variant or as a complement, the invention provides for the possibility of associating a complementary mechanism to block/release the path of the command mechanism 20. By way of example, there could be a split pin or a second push button (not 15 shown in Figure 2A) that can be actuated by the user to release the path of the mechanism 20 inside the groove 29. This constitutes a mixed meta-command mechanism, which requires two distinct actions by the user to extract a unit dose from chamber 11 and dispense said 20 unit dose to the user of the device 1.

Such a layout can dispense only a single unit dose per actuation of the command mechanism. To dispense a plurality of tablets or capsules that together constitute a plural unit doses, simply adjust the dimensions, 25 particularly the depth-of recess 20e, so that the latter can accommodate the relevant number of tablets or capsules.

To prevent fraudulent refilling of the chamber 11, the envelope of the device resulting from the assembly of 30 levels E1 and E2, and possibly lid 14, can include any means, such as those described above referring to a device 1 according to Figure 1A and 1B, the function of which consists in emphasizing any tamper attempt or even exacerbating the damage caused by such an attempt. Such a 35 device can also include means to bear witness that no unit dose has ever been dispensed before. Thus, following

the example of the device illustrated in Figures 1A or 1B, such so-called "tamper-evident" means can advantageously consist of a shutter means for dispensing a unit dose. By way of example, such a shutter could 5 consist of a seal or adhesive strip joining the receptacle 30 and the lower surface of the level E2 until it is deliberately removed. As a variant, such means confirming that no unit dose has ever been dispensed before could also consist of an accessory to block the 10 command mechanism 20 as long as said accessory has not been removed or altered.

In addition, in order to prevent filling of the chamber via the channel 25, a device according to the 15 invention could include means to prevent any "return" of a unitary dose back into the chamber 11.

By way of a non-limiting example, such means could consist of one or more flaps designed to close the opening 13 of the chamber 11 or the channel 25. Thus, as 20 it is notably described in Figure 2B, the inner proximal wall of the recess 20e, i.e. the wall closest to the end remaining inside the groove 29 of the mechanism 20, can cooperate with a flap 27. This operation can be achieved by means of a pivot link positioned in the upper part of 25 the recess with a length more or less equal to the breadth of said recess 20e. Such a flap is naturally kept flattened against the inner wall of the recess 20e when a unit dose initially present in the chamber 11 occupies the recess. Even if no unit dose is present in said 30 recess 20e or the chamber, the flap 27 remains flat against the wall of the recess for as long as the device is kept more or less vertical, i.e. when the level E1 is above level E2. Once the orientation of the device varies, the flap 27 closes all or part of the opening 13. 35 It closes completely the latter if the device is held vertically "upside down", i.e. when the level E2 is

positioned above level E1. Rotation of the flap 27 is restricted by the presence of a small stop 27' on the opposite inner wall in the recess 20e. Said stop 27' is advantageously disposed so as not to hinder passage of a 5 unit dose through the opening 13 and its accommodation in the recess 20e. This simple flap 27 prevents any attempt to fill the chamber 11 via the dispensing channel 25. To try to achieve such an operation, it is necessary to turn the device upside down with the distal part 25b of the 10 dispensing channel 25 pointing up, to introduce a "fraudulent" dose in said channel 25, to actuate the command mechanism 20 so that the recess 20e comes in front of the channel 25 and thus introduce said dose into the recess 20e. By releasing the mechanism 20, the recess 15 is positioned at the opening 13 of the chamber 11. The flap 27 remains positioned between the injected unit dose and the opening 13. The unit dose cannot enter the chamber. Other techniques or flaps could be positioned to block displacement of the command mechanism 20 or to 20 block the transfer of a dose into the channel 25 when a dose moves from the distal part 25b of the channel 25 towards the groove 29. To keep the atmosphere dry in the optional receptacle 30, it could contain means of absorbing humidity and/or condensation (not shown in 25 figure 2A).

Figure 3A described a third embodiment of a device for dispensing a unit dose according to the invention. A first level E1, substantially cylindrical and hollow, 30 encloses a chamber 11 designed to store unit doses M1, M2, Mi. The cylinder E1 is closed at its lower base 11b. Said base carries an opening 13, with a configuration that substantially matches the dimensions of a unit dose. The thickness of the cylindrical wall of level E1 tapers 35 towards the bottom over a height E1b, in such a way that level E1 can be inserted into the upper part of a lower

level E2 (described hereafter). The upper part of level E1 can be closed using a lid or, as will be seen later, by an upper level E0. Said lid or the lower part of the said optional upper level E0 cooperates with the upper 5 part of level E1 and is sealed to the latter in a permanent and irreversible link by welding, glue, clips, etc. The chamber 11 is therefore delineated by the inner surface of level E1. This inner wall can advantageously include a layer of food-grade varnish or any other 10 protective layer to prevent interaction between the unit doses and the material composing E1. The inner wall of the chamber 11 can also include one or more strips of some material that absorbs humidity or condensation 12 to dry out the atmosphere within the chamber 11.

15

The level E2, below the level E1, consists of a hollow cylinder, the external diameter of which is substantially identical to that of the upper part of level E1. The thickness of the cylindrical wall of the 20 upper part of level E2 is reduced over a height E2h substantially equal to the above-described height E1b. The two levels E1 and E2 can therefore cooperate, the lower part of E1 sliding into the upper part of E2 over a distance substantially equal to heights E1b and/or E2h, 25 respectively. An internal shoulder on the upper section of level E2 can be used to fix a spring 209 inserted between the inner surface of E2 and the outer wall of E1. This spring 209 exerts a force F that tends to mutually push back both levels.

30

Level E2 further comprises an internal structure, e.g. a star-shaped structure having four arms 204a, 204b, 204c, 204d substantially orthogonal to the axis of rotation of level E2. The invention is not limited to the said number of arms or to this configuration of the 35 structure. Said arms meet substantially at a point intersecting with the axis of rotation of level E2. Said

junction of the arms also cooperates according to a fixed link with a torsion shaft 203, the axis of rotation of which substantially coincides with that of level E2. Said shaft is of such a length that it can emerge through an 5 opening inside chamber 11 of level E1 after assembly of the two levels. Each arm 204a through 204d has a prominent lug following a direction close to that of the torsion shaft 203.

The invention provides that a disc 201 with an 10 opening 213 similar to the opening 13 of the chamber 11, should be mounted to rotate on the torsion shaft 203. The disc 201 is positioned on the shaft 203 to be applied substantially against the outside wall of the lower base 11b of level E1. A coil spring 207 around the shaft 203 15 keeps the disc 201 substantially flattened against the lower base of level E1 so that it slides along the torsion shaft 203. The lower side of said disc 201, i.e. the side opposite that in front of the level E1, carries as many recesses 202 (four in our example) as there are 20 arms on the star-shaped structure in level E2. Each recess 202 is laid out to receive the distal part of the lugs or protuberances 205a through 205d, the length of said lugs being set so that their distal parts only cooperate with the recesses 202 when the spring 209 is 25 contracted. Advantageously, the respective ends of said spring 207 are joined on one side to the disc 201 and on the other to the base of the torsion shaft 203 to keep the recesses 202 aligned to the protuberances 205a through 205d. The distal part of the shaft 203 -after 30 assembly- is fixed to the lower part of the chamber 11, e.g. by means of one or more longitudinal lugs or prominent stoppers 206 on the distal part of the shaft 203, cooperating with an appropriate opening in the lower surface of the level E1. Such an E1-E2 layout allows a 35 first "sliding"-type MVT1 movement of the lower part of level E1 in the upper part of level E2. The shaft 203

acts as a guide. It also restricts the course of level E1 by means of a stop 206b located at the end of the shaft 203 emerging into the chamber 11. The E1-E2 arrangement described in Figures 3A and 3B also allows a second 5 rotatory-type MVT2 movement of the level E2 with respect to the level E1. In practice, the torsion shaft 203 allows this MVT2 movement, e.g. through the action of a user. The torsion shaft 203 automatically brings levels E1 and E2 into relative resting positions by virtue of 10 the spring function exerted by the shaft as soon as the user releases the mechanism.

The opening 213 of the disc 201 is similar to the opening 13 of the chamber 11. It is advantageously located at a distance or radius of the shaft 203, 15 substantially equal to that separating the opening 13 of the said shaft. In contrast, the disc 201 is initially located, i.e. when levels E1 and E2 are in their relative resting positions, in such a way that the openings 13 and 213 face each other only when the torsion shaft reaches 20 maximum torsion and when the disc 201 is blocked by the lugs 204a through 205d, these having entered the recesses 202 under the effect of sufficient pressure to squash the spring 209. A unit dose can therefore not be taken out of the chamber 11 and dispensed unless both movements—MVT1 25 and MVT2—are combined. This arrangement therefore offers an answer to the risk of unattended young children using the unit dose dispenser. In practice, two distinct operations are required to trigger the dispensing of a unit dose. The latter is extracted and dispensed by 30 gravity, said unit dose coming out of the chamber 11 via the opening 13, crossing the opening 213 temporarily in alignment with the opening 13 and falling through the arms 205a through 205d into the lower part 300 of level E2, all provided that the device is held substantially 35 vertical, level E1 being positioned above level E2. Thus, the command mechanism—in the sense of the invention—

consists of the combination of the two levels E1 and E2, which can be actuated with respect to one another by a user of the device 1.

The level E2 can be opened at its lower base 300. It 5 may alternatively have an inverted conical shape or dome to form a receptacle intended to receive an extracted unit dose To be able to use said unit dose, a user can remove a cap 31 designed to close an opening in the lower part of the level E2. The lower part of E2 can also 10 include means to absorb any humidity or condensation present in the receptacle 300.

The assembly of levels E1 and E2 can be made irreversible, on one hand by setting or machining the stop 206b located on the distal part of the shaft 203 and 15 by closing the upper part of the chamber 11 after it has been filled via the cover or the optional upper level E0. The device described in figures 3A and 3B has an overall cylindrical configuration. As a variant it could include levels with polygonal or other-shaped sections.

20 To improve the fight against counterfeiting, satisfy the requirements of assistance services for patients suffering from chronic diseases and even measure the adherence of a patient to the clinical trial protocol, a 25 device according to the invention, whatever its embodiment, may also include electronic means to identify the device or even the active substances contained in the composition of the unit doses in the chamber, or again to timestamp and record every time a unit dose is dispensed.

30 To accommodate such electronic means, a device according to the invention could comprise a dedicated level.

The example described in figure 3A illustrates such an alternative embodiment. This contains a level E0 with 35 a special housing 51 to house or contain a processing unit that cooperates with the command mechanism and a

source of electrical power to drive said processing unit. By way of example, such a source might be a battery carried in said housing 51 or a photovoltaic cell 52 that cooperate with said processing unit. Such a processing 5 unit (not shown in figure 3A) advantageously incorporates a timer and memory to timestamp and records every actuation of the command mechanism to trigger the unit dose extraction and dispensing system. Referring to the example illustrated in figure 3A, the level E1 can 10 contain a stop that cooperates with the lower level to limit the torsion of the shaft 203. The processing unit can exploit this contact as a piece of information transmitted by the command mechanism, constituted by the combination of the two levels E1 and E2, confirming that 15 a unit dose has been dispensed. The processing unit can use any protocol to relay this information, e.g. if levels E1 and E2 are made of materials that conduct electricity, contact between the two levels by means of the stop could constitute grounding or electrical 20 repository detectable by the processing unit.

According to a second example, a device 1 described in figure 2A can be fitted with an end-of-run sensor to detect the force exerted by a user on the mechanism 20. Such a sensor could be located in the groove 29. As soon 25 as said sensor is solicited by the proximal part of the mechanism 20, i.e. when the user has pushed said mechanism 20 into groove 29, said end-of-run sensor transmits the delivery information to the processing unit.

30 As a variant, the unit dose extraction and dispensing means could include a sensor to detect the dispensing of a unit dose as such. According to the example described in figures 3A and 3B, such an optical or inductive sensor could be located on the disc 201 close to the opening 35 213. According to this variant, the processing unit no longer cooperates directly with the command mechanism but

with the said sensor which transmits the information as soon as a unit dose crosses the opening 213.

Whichever solution is chosen, the processing unit can timestamp and record every time a unit dose is dispensed.

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To preserve the integrity of housing 51 and all the components inside it, the invention provides that the envelope of a device according to the invention can advantageously enclose the chamber 11 and said housing 10 51. For this, referring to figure 3A, levels E1 and E0 can be sealed, i.e. cooperate via a fixed and irreversible link, e.g. by means of welding, glue, clips, etc. This envelope is materialized by the outer walls of the two levels E0 and E1. Selecting the level E0 to cover 15 and thereby close the chamber 11 precludes the need for a special lid. The said envelope resulting from the assembly of levels E1 and E0 can contain any appropriate means attesting or even exacerbating any tamper attempt as mentioned above referring to the preceding embodiments 20 described with reference to figures 1A and 2A. The housing 51 can advantageously contain a non-conductive resin or foam to protect electronic components against humidity and condensation in said housing.

25

In order to be able to exploit the contents of the memory of a processing unit contained in a device according to the invention, said processing unit could advantageously include a wireless communication interface to communicate with the outside world. In a variant or as 30 a complement, the processing unit can include a hard-wired communication interface to communicate with the outside world. In this way, communication can be established with a reader or terminal to collect, process and send back through an adequate human-machine interface 35 the information that has been memorized or generated by the processing unit. The reader or terminal would be

capable of implementing a communication protocol with the device's processing unit.

It is thus possible to trace a device according to the invention by consulting certain information recorded in the processing unit's memory, e.g. first and second identifiers respectively dedicated to the device and the operator who originally filled the chamber (e.g. a pharmaceutical company or any sub-contractor responsible for packaging the unitary doses of a drug), or alternatively an identifier characterizing an active substance in a solid dosage form contained in the chamber.

It is also possible to recover the history of unitary doses dispensing.

15

A device according to the invention can include a specific human-machine interface that is capable of sending back information recorded in the memory or generated by the processing unit, the latter controlling said human-machine interface. By way of example, the device 1 described in figure 3A can include a flexible display 53, e.g. an LCD screen. According to a preferred variant, the processing unit can implement a reversible hashing or compression function in response to solicitation by a user through a special command button or possibly after a predetermined number of unit dose dispensing operations. Instead of an electronic reader or a terminal capable of communicating with the device (which might be too costly for some customers), information in the memory or generated by the processing unit could be collected by a human being, e.g. notably linked with the history of unit dose dispensing. To do this, the user reads a short alphanumeric code preferably between four and sixteen characters to limit the user's effort and the risk of returning incorrect information by consulting the device's human-machine interface 53. The

user can then communicate this code by telephone, fax, E-mail, etc. The invention provides that the human-machine interface may additionally or alternatively consist of a loudspeaker or more generally any means enabling a human 5 being to perceive information. The invention provides that all communication with the processing unit should be protected through conventional techniques, e.g. by coding and/or signature and/or authentication, etc.

To preclude the possibility of malicious secondary 10 use of a device according to the invention or to prevent any attempt to alter the content of the memory of a processing unit housed in a device, said memory can advantageously be designed to be non-erasable.

So that the processing unit notably generates a 15 history of unit doses dispensing, the invention also concerns a process implemented by the processing unit of a device according to the invention. Such a process notably includes a step to timestamp every unit dose taken out of the chamber and dispensed. To do this, the 20 processing unit cooperates with the command mechanism that triggers the dispensing of a unit dose or with a sensor that detects such dispensing. The presence of a clock within the processing unit allows it to timestamp a dispensing operation. Any timestamp technique can be 25 employed, e.g. using GMT as a reference or any other reference that can be used by the processing unit to increment a counter of time units. The processing unit can also implement a process comprising a step to encode and transmit to the outside world information generated 30 from content of the processing unit's memory, e.g. the dispensing history.

So that a processing unit can implement such a process, its initialization or programming can 35 advantageously involve computer software containing one or more program instructions which, when interpreted or

executed by the processing unit, launch a process as mentioned above. Such software could be downloaded or preloaded in a memory cooperating with the processing unit at the time of assembly of the device or during its
5 personalization process.

CLAIMS

1. Device (1) to dispense unitary doses (M3) of an active substance in a solid pharmaceutical form, including a chamber (11) to house a plurality of unit doses (M1, M2, ..., Mi) containing said active substance, a command mechanism (20) that can be actuated by a user, means (28, 20e, 25, 201) to extract a single unit dose (M3) out of said chamber and dispense a single dose out of the plurality doses stored in the chamber (11) in response to actuation of the command mechanism (20) by the user, an envelope (10, 10a) cooperating with the chamber (11), said device being characterized in that:
 - said envelope (10, 10a):
 - irreversibly encloses the chamber (11);
 - comprises means which, during an alteration of the integrity of the envelope, attest, emphasize or accentuate said alteration;
 - means for extracting and dispensing include a mean (27) to prevent the return of a unit dose back into the chamber (11).
2. Device according to Claim 1, further comprising means of absorbing humidity (12) to maintain a dry atmosphere inside the chamber (11).
3. Device according to any of the preceding Claims, comprising means (15, 16) to exert sufficient pressure on unit doses contained in the chamber

(11) to immobilize every unit dose contained in the chamber.

4. Device according to any of the preceding 5 Claims, wherein the command mechanism is arranged to require two distinct user actions to trigger the means for extracting and dispensing a unit dose.
5. Device according to any of the preceding 10 Claims, comprising a receptacle (30, 300) to collect a unit dose extracted from the chamber by the extraction and dispensing means.
6. Device according to any of the preceding 15 Claims, wherein the chamber (11) is constituted by the inner wall (10i) of the envelope.
7. Device according to any of Claims 1 to 5, wherein 20 the chamber is constituted by an insert.
8. Device according to any of the preceding 25 Claims, wherein the extraction and dispensing means comprise a circular spiral-shaped tube (28) designed to transport one or more unit doses, said tube being inside the chamber (11), the latter having an orifice (13) on its lower base, the lower distal part of the tube (23) emerging from said chamber through said orifice.
9. Device according to any of the preceding 30 Claims, wherein the envelope is thermoformed around the chamber.

10. Device according to any of Claims 1 to 8, wherein the envelope contains a plurality of elements joined together in pairs by welding, glue or clips.
5
11. Device according to any of the preceding Claims, wherein the means attesting, highlighting or exacerbating an alteration of the integrity of the envelope, consist of one or more engraved or printed guilloche motifs in areas of weakness or weak breaking zones.
10
12. Device according to any of the preceding Claims, comprising means attesting that no unit dose has ever been dispensed before.
15
13. Device according to the preceding Claim, wherein the means attesting that no unit dose has ever been dispensed before consist of a stopper of the means dispensing the unit dose.
20
14. Device according to Claim 12, wherein the means attesting that no unit dose has ever been dispensed before consist of an accessory to lock the command mechanism (20) that can be actuated by the user.
25
15. Device according to any of the preceding Claims, further comprising a housing (51) accommodating a processing unit that cooperates with the command mechanism and a power source (52) that supplies required electrical energy for the operation of said processing unit, said unit further includes a
30

clock and a memory to respectively timestamp and record every time the command mechanism is solicited to trigger the means to extract and dispense.

5

16. Device according to any of Claims 1 to 8,
- for which the extraction and dispensing means comprise a sensor detecting a unit dose dispensing;

10

- said device including a housing (51) accommodating a processing unit cooperating with said sensor and a power source supplying necessary electrical energy for the operation of said processing unit, said unit also comprise a clock and a memory to respectively timestamp and record each delivery of a unit dose detected by the sensor.

15

17. Device according to Claims 15 or 16, wherein the envelope encloses the chamber (11) and the housing (51).

20

18. Device according to any of Claims 15 to 17, wherein the processing unit comprises a wireless interface to communicate with the outside world.

25

19. Device according to any of Claims 15 to 18, wherein the processing unit includes a hard-wired interface to communicate with the outside world.

30

20. Device according to any of Claims 15 to 19, comprising a human-machine interface (53) capable of returning information stored in the memory or

generated by the processing unit, the latter controlling said human-machine interface.

21. Device according to any of Claims 15 to 20,
5 wherein the memory comprises first and second identifiers respectively dedicated to the device and an operator who filled the chamber before the envelope was sealed.

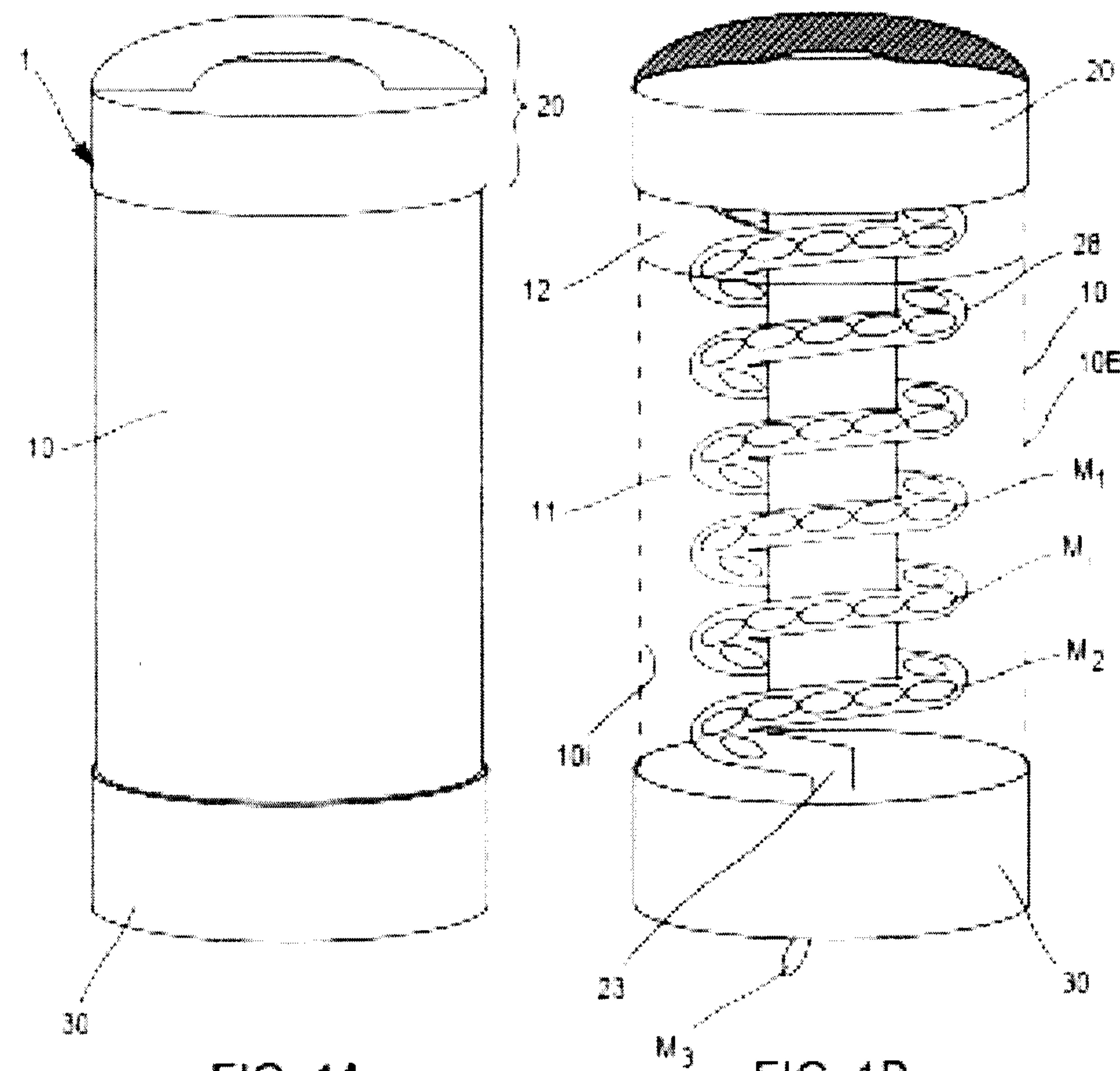
- 10 22. Device according to any of Claims 15 to 21, wherein the memory includes an identifier characterizing the active substance in a solid dosage form that is housed in the chamber.

- 15 23. Device according to any of Claims 15 to 22, wherein the processing unit's memory is non-erasable.

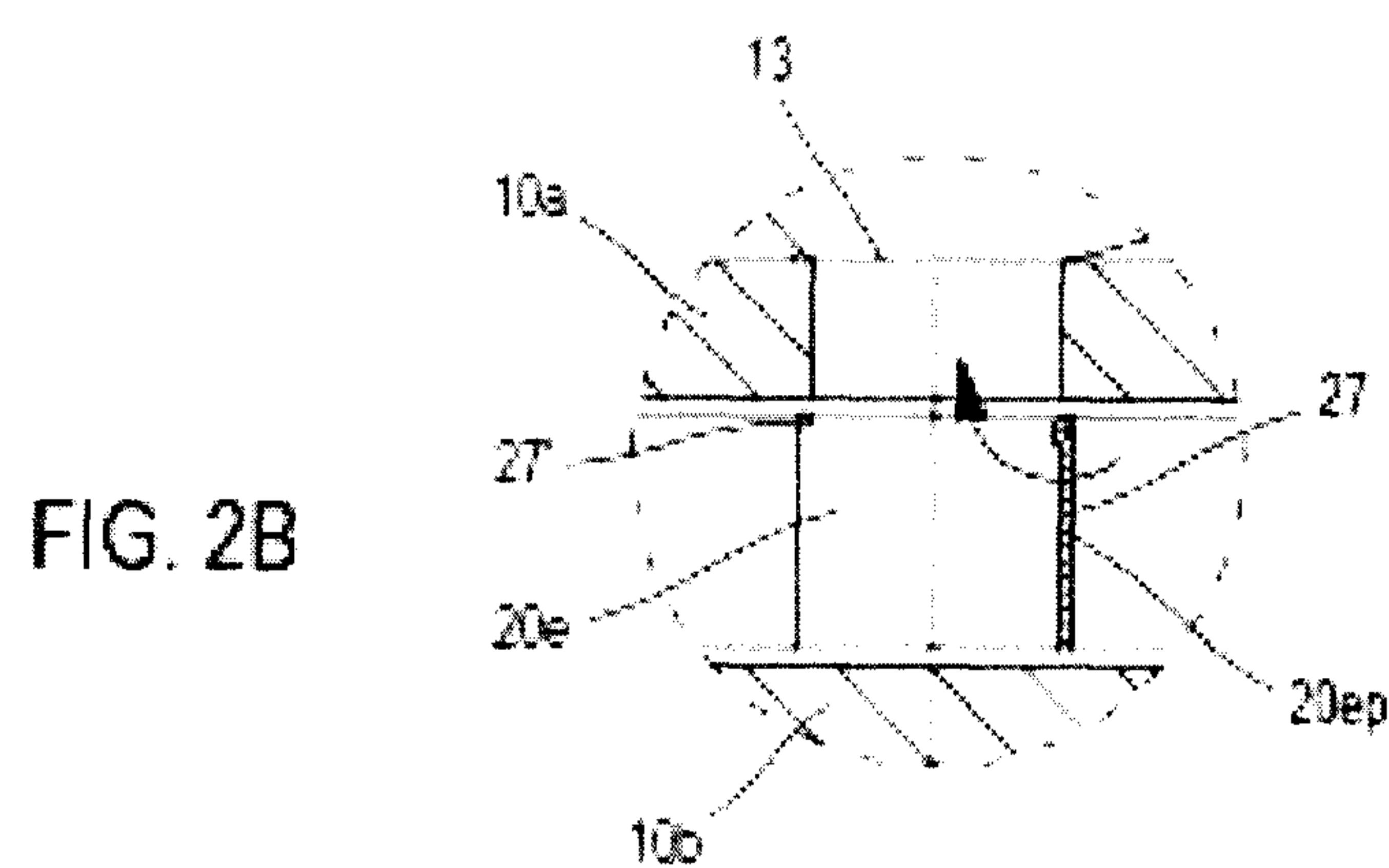
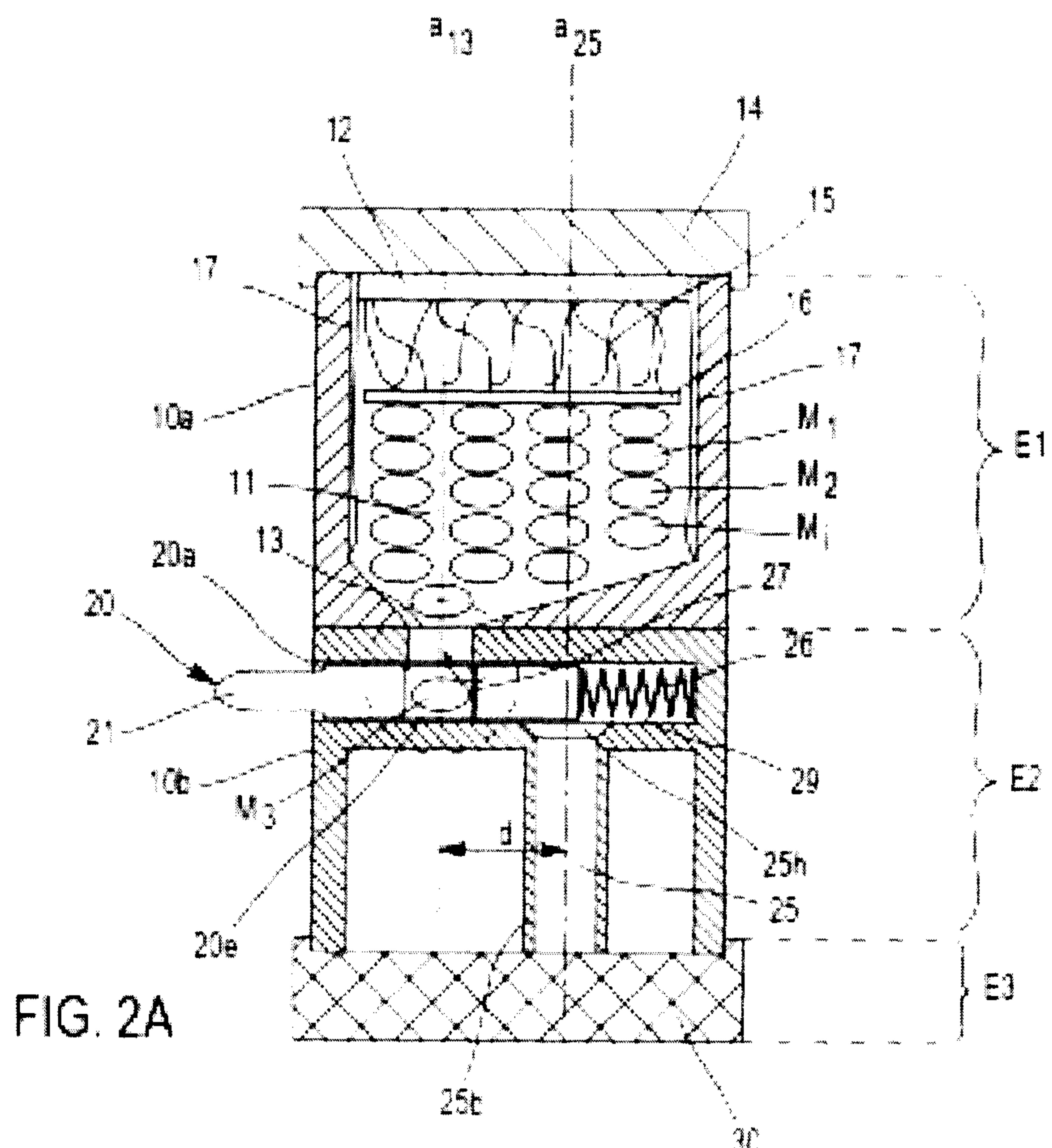
- 20 24. Process implemented by the processing unit of a device according to any of Claims 18 to 23, characterized in that it comprises:
 - a step to timestamp each unit dose extracted from the chamber and dispensed;
 - a step to encode and return to the outside world information generated from the contents of the processing unit's memory.

- 25 25. Computer software comprising one or more program instructions which, when they are interpreted or executed by the processing unit of a device according to any of Claims 18 to 23, launch a process according to Claim 24.

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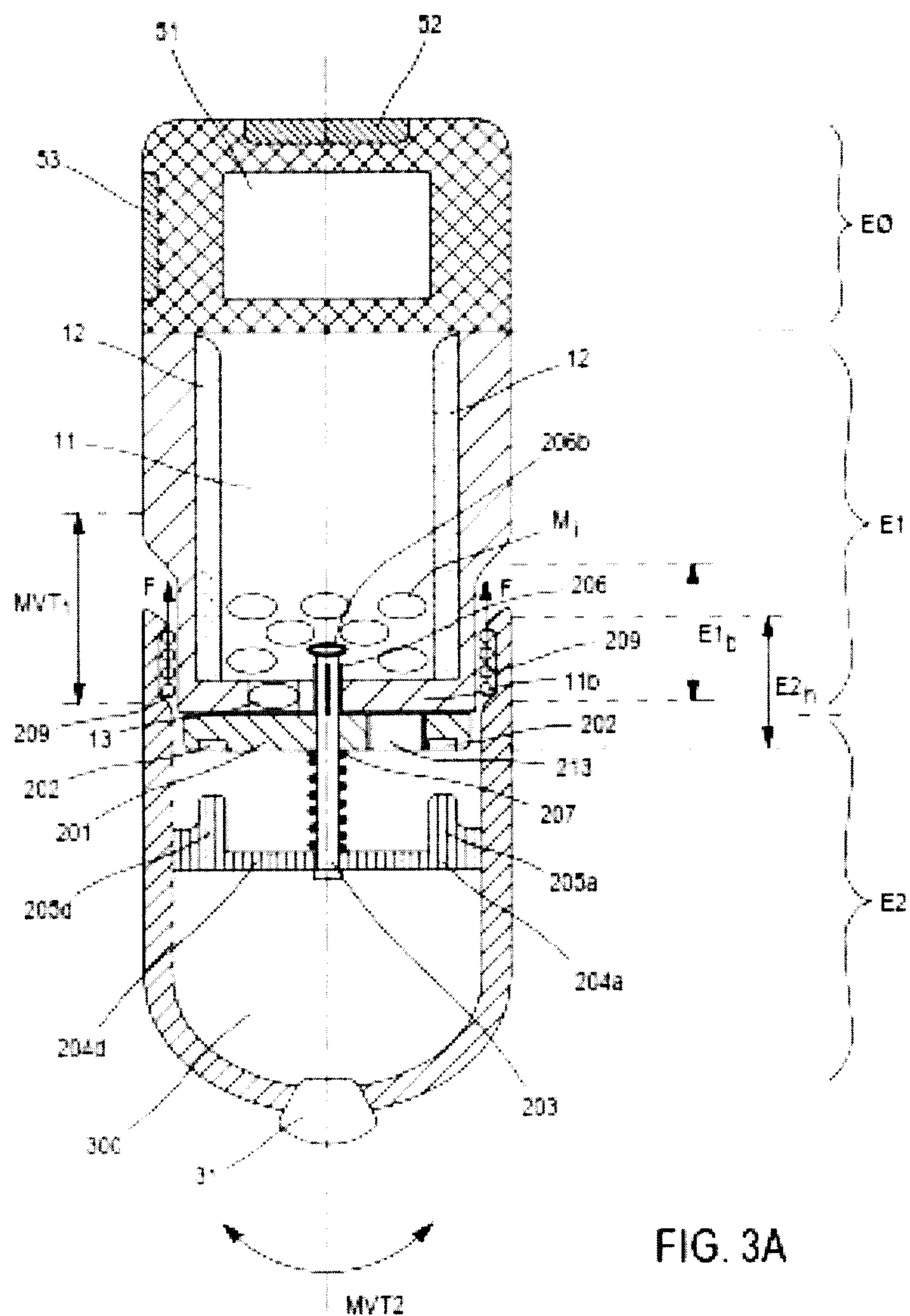


FIG. 3A

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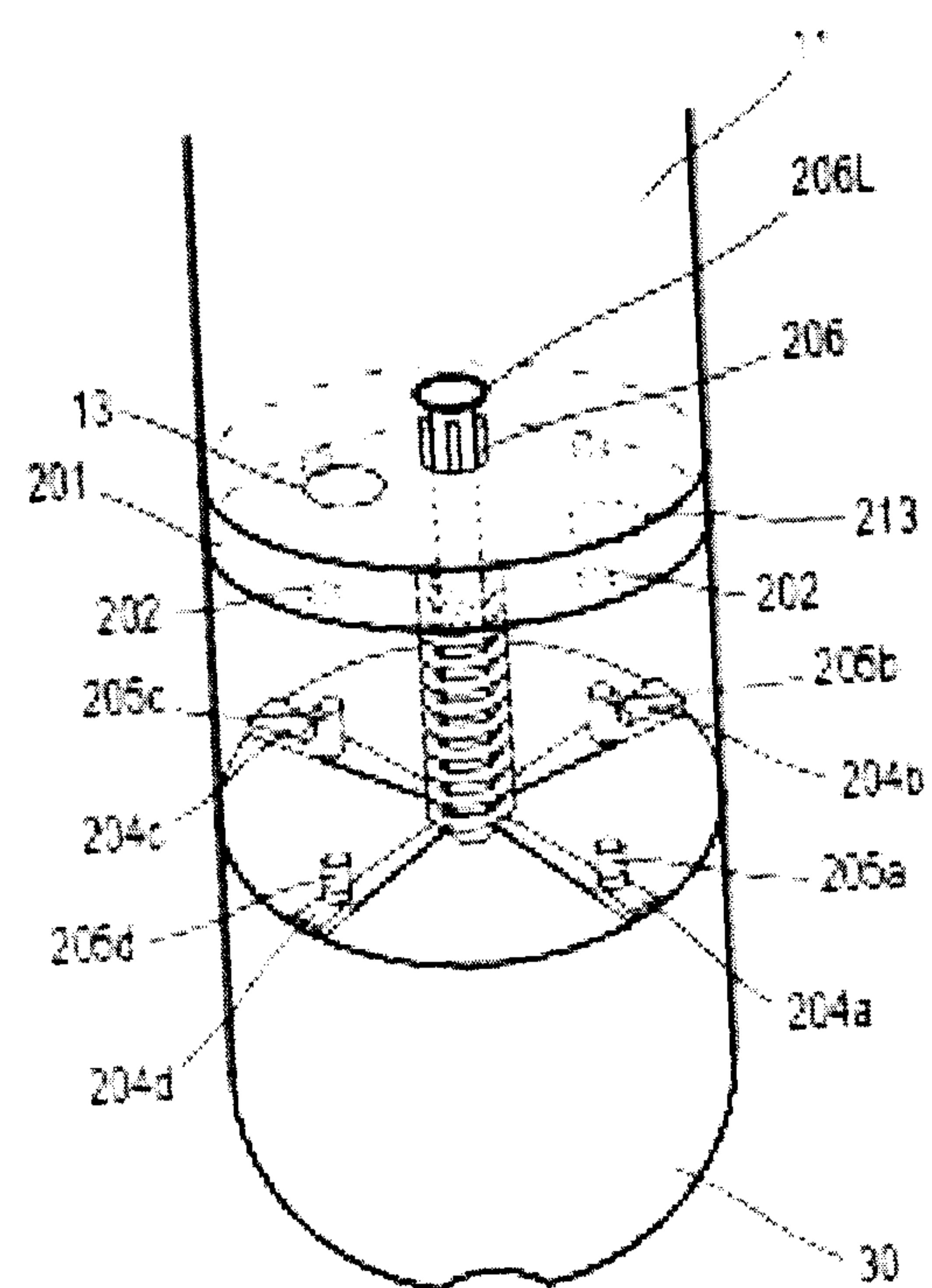


FIG. 3B

