

Process for the gravimetric filling in sterile conditions of solids in a pharmaceutical container.

Field of the invention

The present invention relates to a process of gravimetric filling in sterile conditions of pharmaceutical containers of small dimensions including syringes, vials, capsules, ampoules, single-dose devices, inhalers, bottles, carpules blister, sachets or bags with solid substances selected from the group formed by powder, lyophilizates, granules, pellets, nanoparticles or microparticles. More particularly, it relates to a process for the gravimetric filling of pharmaceutical containers with one or more sterile solid pharmaceutical substances or sterile excipients dosed and prepared in an aseptic environment.

10 State of the art

The legislation for the pharmaceutical industry imposes strict safety conditions on the filling of pharmaceutical containers with pharmaceutical substances. Currently, the filling of pharmaceutical containers of small dimensions such as syringes, vials or carpules among others, with pharmaceutical substances must comply with *Good Manufacturing Practices* (GMPs). To do this, a controlled air flow is generally used to work in sterile environments.

The movement of a fluid or gas when it is organized, stratified and gentle is called controlled air flow. In a laminar flow, the fluid moves in parallel laminas without mixing together and each fluid particle follows a trajectory called streamline. The controlled air flow may be considered as laminar or turbulent. Reynolds predicted the type of flow we have through an adimensional parameter called Reynolds number, which represents the ratio between the viscosity and inertia in the movement of a fluid, as is represented by the following equation:

$$Re = V_s \times D / V_c$$

25 where:

V_c = Kinematic viscosity.

V_s = Characteristic velocity of the fluid.

D = Diameter of the section wherethrough the fluid circulates.

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So that when:

- $Re < 2000$ it is called "Laminar flow", i.e. wherein the viscous forces are proportionally stronger than the forces of inertia and, therefore, the particles tend to move in streamlines.

- $Re > 4000$ is called “Turbulent flow”, i.e. wherein the viscous forces are weak compared with the forces of inertia and, therefore, the particles move in irregular routes.
 - $2000 < Re < 4000$ is called “Transitional flow”, i.e. that it cannot be modelled.
- 5 The reference legislation defines controlled air flow as that wherein the streamlines go in one direction, are approximately parallel and have a uniform velocity through the complete cross section of the clean zone. Thus, GMPs indicate velocities between 0.36 m/s and 0.54 m/s (i.e. $0.45 \text{ m/s} \pm 20\%$) and they define it as “Unidirectional flow”, according to Annex 1 relating to the manufacturing of sterile drugs of Good manufacturing practices for medicinal products
- 10 for human and veterinary use published by the European Medicines Agency (EMA) According to this guide, the laminar flow systems must provide a homogeneous velocity in the aforementioned range at the working point in an open environment, i.e. where the dosing is performed.
- 15 The main function of a unidirectional/laminar flow is to provide a working area free from particles and contamination where it guarantees the protection of critical processes, ensuring total protection of the products during their handling process and an isolation of the surrounding environment.
- 20 The protection is produced in the “process core”, i.e. in the location where the process and the interaction of the environment with the process occur. This is achieved thanks to the absence of particles by means of a type of filtration called HEPA. HEPA is the acronym of *High Efficiency Particle Arresting*. It is a high capacity filter which may trap a high quantity of microparticles, such as pollen, dust mites or tobacco smoke. After being filtered through a
- 25 HEPA filter, the discharged air must have a uniform velocity controlled according to the legislation to be fulfilled (according to the GMPs: 0.36-0.54 m/s). 3 factors intervene in this uniformity: the air diffusion screen used, the regulation of the fan velocity and the air channelling and return.
- 30 In accordance with the use and design of the laminar flow it is possible to guarantee the protection of the product, the protection of the operator or the protection of both. In any case, the controlled air flow allows control of the process in a sterile environment, which favours that it can do without additional processes such as terminal sterilization.

When the products that the containers are filled with are liquids, their filling is simpler than for solid products both if performed using a volumetric or gravimetric method. In any case, in the volumetric methods, wherein what is determined is the volume of product to be filled in the container instead of its weight, the product dosing is much simpler as it does not require the
5 presence of a weighing cell which conditions the filling or dosing accuracy, and which may also be altered by the impact of air flow.

Furthermore, when reference is made to the filling of solid substances such as microparticles, nanoparticles, granules, pellets, powder, etc., in pharmaceutical containers of
10 small dimensions, the problem is much greater, as in this case it is essential that the powder flows consistently and predictably, without any type of block or turbulence, thus guaranteeing that the volume or the weight of the solid pharmaceutical substance in the pharmaceutical container is appropriate. And if the filling is also performed under laminar air flow, the problem is even greater, as the laminar flow may influence both the precision of the
15 measurement by the balance, and the flow of solid particles as they are deposited in the container and, therefore, it may alter the result observed in the balance and, in consequence, the quantity of product filled in the container.

In this regard, it is necessary to consider that for the pharmaceutical industry, an error in the
20 filling of the active substance may cause patients to receive an inadequate dose of the product, which may have very harmful or even lethal effects in extreme cases. For this reason, in the processes described in the state of the art it is necessary to regularly check, by means of various previously qualified processes, the effective filling quantity of all the pharmaceutical containers and discard those wherein the quantity of pharmaceutical
25 substance, whether drugs, active substances or excipients, are outside the range.

These tests may be destructive or non-destructive. When they are non-destructive, a control is performed on 100% of the containers filled by gravimetric weighing methods, only discarding those units which are outside the pre-set specification. However, when the tests
30 are destructive, as generally occurs in volumetric filling processes, these controls are performed by means of statistical weighing every short time with the aim of controlling the dosing during the process, which greatly conditions the yield of the filling process since all control units are discarded despite the fact that they conform because of the destructive method.

In consequence, due to the high cost and value of the pharmaceutical substances handled and the fact that they are produced in large batches, it involves a very high financial cost for the pharmaceutical companies to be able to control the accuracy of product dosing, preferably using non-destructive control methods. However, contrary to this precept, the documents of the state of the art that allude to the filling process in small containers, allude to volumetric filling processes that generally perform destructive control processes, which lead to a loss of productivity, or which require multiple weighing controls in a multiplicity of stations or stages, which makes the process excessively expensive. Furthermore, the documents of the state of the art allude to dosing forms in devices or containers with dimensions greater than those used in the present invention.

Thus, we have the publication of the US patent US 2016/0200461 A1 applied for by VANRX Pharmsystems INC., which discloses a method for the volumetric filling and aseptic sealing of containers such as vials, bottles, syringes and ampoules with a liquid or lyophilized solid pharmaceutical product (which implies that the filling process is performed in liquid phase) in a controlled environment enclosure. This invention has the advantage of being able to fill a high number of containers at the same time, all of them located in the sealed enclosure. This sealed enclosure where the containers are found is introduced in a seal box, and at least the sealed enclosure or seal box must be decontaminated. The containers are sealed under vacuum or inert atmosphere conditions.

On the other hand, international publication WO 2006/074904 granted to IMA LIFE S.R.L., refers to the packaging of injectable liquid products in containers such as vials, syringes or more preferably bottles, in a sterile environment by means of sterilization and depyrogenating. More specifically, it relates to a complete and compact system for sterile packaging comprising a station for washing the containers intended for cleaning and decontamination of said containers, a sterilizing station to sterilize the containers that exit the washing station, this sterilizing station has two sterilizing modules, each module has in its upper part suitable conduits and separating baffles so that it achieves an airflow that impacts the bottles, said flow flows above the conveyor into a bell, under which are provided filtering means defined by a HEPA filter, both sterilization methods may work as cold or hot sterilisers and, finally, a filling and sealing station for filling said containers with said liquids which are later sealed.

Also, the publication of European patent EP 2 832 648 A1 in the name of Grifols Worldwide Operations Ltd. discloses a machine and a method for filling pharmaceutical containers with

liquid pharmaceutical compounds which make it possible to eliminate the problem of having to reject pharmaceutical containers, preferably vials, the quantity of pharmaceutical substance of which is outside the range specified in the legislation of the pharmaceutical industry, avoiding for said industry a significant additional cost in terms of investment in the machine proposed by said patent and increasing product productivity. The method of this publication is composed of the phases of weighing the empty container, filling the container with the pharmaceutical substance and later weighing of the full container in a full-container weighing station to confirm the quantity of pharmaceutical substance.

Furthermore, international application WO 2012/023118 A1 in the name of IMA Industria Macchine Automatiche S.P.A., refers to a filling machine comprising a total weight checking system and to a method for individually weighing units. More specifically, the publication discloses a filling machine suitable for filling capsules comprising a total weight check system of the capsules filled with a pharmaceutical product, containing a weighing apparatus for weighing all the capsules and transfer means for transferring the capsules from said filling machine to the weighing apparatus. This machine has, in the case of microdose weighing, an additional electronic balance, which has one or more load cells, for weighing the empty capsules, by means of transfer means the capsules are transferred to filling machines and the full capsules are transported to another weighing apparatus comprising electronic balances equipped with one or more load cells capable of measuring the weight of each full capsule. This patent in no case uses laminar flow during the process nor contemplates aseptic filling conditions.

US patent US4640322 applied for by Cozzoli Machine Co., discloses a machine for filling containers with particulate matter with certain fluidity, such as powder and similar matters. Principally, the machine applies sub-atmospheric pressure through a filter to suction the particulate material and then, after filling the measuring chamber or, sub-atmospheric pressure is applied through a filter to force the particulate matter downwards within the pharmaceutical container. This patent discloses a volumetric filling process which does not consider the specific properties of the product to be filled without mentioning the repercussion of the filling process subjected to laminar flow.

However, the present invention, offers an alternative to filling pharmaceutical containers with solid pharmaceutical substances, specifically by means of a gravimetric filling process with laminar flow in an aseptic environment.

- Within the documents of the state of the art, we also have international publication WO 02/092430 applied for by IMA Industria Macchine Automatiche SPA relating to the automated filling of bottles with solid substances in powder or granules, and in particular, it relates to a machine for filling bottles with dosed powdered pharmaceutical substances and to the filling propulsion mechanism which forms part of the machine. This process consists of several stages, the first relates to the weighing of the empty bottles in a first station, then, the bottles are filled in a filling station comprising powder dosing disks and a feed device of the pharmaceutical powder, these bottles pass to a second bottle weighing station for weighing the full bottles, and, finally, to a bottle capping station. All of this by means of a volumetric filling system. This system has the advantages of the quick and easy access to the dosing disks without having to remove the adjustment mechanisms, the ease of maintenance and cleaning of the machine, being a process to follow that is faster and less laborious. Logically, this process as it is volumetric only works for pharmaceutical powder with homogeneous granulometry and with a constant apparent density, since it does not guarantee in any way a specific particle size in addition to not allowing the filling of different batches of different chemical nature. Furthermore, despite the fact it mentions that it works in sterile conditions, it does not specify the method used to achieve said sterility, which presupposes terminal sterilization methods after the capping.
- European patent publication EP 2902327 B1 applied for by Harro Hofliiger Verpackungsmaschinen GmbH, relates to a dosing device for the volumetric dosing of pharmaceutical powder and the simultaneous filling of containers such as capsules and blisters among others, with the dosed powder. The device comprises a dosing station with a container for storing the powder, a filling station and a mobile measurement element wherein this measurement element is displaced from the dosing station to the filling station and vice-versa. It also has a sealing material which is elastically flexible, hermetic, porous and air-permeable. The measurement element moves from the dosing station to the filling station with a maintained negative pressure difference, where the dosing cavities are superimposed with the pharmaceutical containers. It eliminates the negative pressure difference and the powder passes from the dosing cavities to the pharmaceutical containers. The measurement element moves gain to the dosing station. In this case, the filling is volumetric so that the dosing is much simpler for those components that do not have specific granulometry to control.
- Furthermore, international publication WO 2010/128455 A1 in the name of IMA Industria Macchine Automatiche S.P.A., makes reference to a dosing apparatus and dosing unit

associable with an automatic filling machine to dispense pre-set and precise quantities of product in pharmaceutical containers, said machine has means for dosing both liquid and solid substances; for this purpose, said dosing means comprises: a volumetric piston pump, a peristaltic pump, a diaphragm or membrane pump, a time-pressure dosing system, a flow-control dosing system, a flowrate metre dosing system, a volumetric dosing system for powders or granules. In this case, the filling is volumetric so that the dosing is much simpler for those components that do not have specific granulometry to control.

Furthermore, international publication WO 2012/004606 A2 in the name of 3P Innovation Ltd discloses a powder doser for pharmaceutical substances comprising a dispensing system including a stirrer formed by flexible material and a hopper wherefrom the powder may flow. This hopper is divided in two parts, a first part formed by a flexible material and a second formed by a rigid material, a piezo-electric vibration device to make the hopper vibrate, and a device for weighing the pharmaceutical containers whilst they are being filled with the powder. 3P Innovation also has international patent application WO 2016/185230 A2 which discloses an apparatus and method for filling pharmaceutical containers such as syringes, vials, capsules, carpules and blisters with pharmaceutical matter in powder by means of vibration. This apparatus has a support for the pharmaceutical container, a reservoir to contain powdered pharmaceutical substances, which is in contact with a filling needle responsible for filling the pharmaceutical container with the powdered pharmaceutical substance, and a piezo-electric vibration device.

In any case, none of the documents published by 3P Innovation Ltd mentions the physicochemical and rheological properties of the formulation components and they are always centred on a vibration filling system, so that the solution proposed for the technical problem is exclusively limited to vibration filling machines and eliminating the impact of the harmful effects of said vibration in the drug dose. In no case does it mention any other filling type that is not vibratory since it discloses as essential element a vibration buffer part to be able to control the powder filling process.

Furthermore, said patent applications do not have examples of embodiment that enable validating the suitability of the claimed filling system; moreover, the degree of vibration to which the system is subjected together with the velocity and force of the airflow the filling process is subjected to make the precise powder filling process in the container absolutely unfeasible in addition to its weighing; since they have no elements that prevent the loss of verticality of the container so that it remains suitably so that the nozzle between the container

facilitating the dosing or that the container remains vertically suspended (without touching the walls of the vibration buffer part) so that the weighing device can guarantee the pre-set dose.

Continuing with the state of the art, we have European patent publication EP 2138447 A1, in the name of I.M.A Industria Macchine Automatiche S.P.A, which makes reference to a machine for the production of vials and bottles, particularly, for the filling of vials and bottles with doses of pharmaceutical product in liquid or powder form, this machine is formed by a station for feeding the open vials or bottles in an upper end or mouth, a filling station of the vials or bottles with predetermined product dose, a station for feeding a succession of seals for sealing the mouth of the vial or the bottle, a station for applying the seals to the vials or bottles and feeding them in a collection area and, optionally, there may be an additional weighing station of the vials or bottles. All the apparatus are located in a sterile environment, sealing units are used to create a sterile environment in the machine for the production of the vials or bottles. Again, this invention alludes to a filling system of powder in containers, generally bottles and vials, by means of a vibration filling process which does not consider the necessary granulometry of the formulation components.

Finally, international publication WO 2006/075227 A2 in the name of IMA Industria Macchine Automatiche SPA, refers to a unit for sterilizing and depyrogenating empty containers, mainly bottles. Said sterilization and depyrogenating is carried out by selecting as one wants the four possible combined sterilization modes, hot-cold, hot-hot, cold-hot and cold-cold, said process is performed with the empty bottles, which after said process will be transported to a filling phase with the material in liquid or powder, which is not mentioned in said document. Said publication, therefore, only refers to a sterilization and depyrogenating station for empty container suitable to be filled in a later process, which is not mentioned.

In general terms, the above publications disclose the filling of pharmaceutical containers but without considering the physicochemical or rheological properties of the products (so that they consider neither the filling of various products of different nature in the same dosing process or apparatus), nor the necessary and normalized process conditions for the aseptic filling of pharmaceutical products, particularly without considering those cases where the environment wherein the process is performed is an aseptic environment, with a gravimetric filling subjected to laminar flow. In the case of the above publications which largely use volumetric filling, this process has a series of drawbacks that are intensified when the dosed product is a solid, such as process inaccuracy, unreliability of substance dosing where there are substances of different granulometry or nature, the need to constantly calibrate the doser

depending on the material before each use and the incapacity of automatically compensating for the changes in the properties of the material, preventing filling several different products in the same apparatus or process, such as oscillations in the apparent density of the packaged products. Therefore, volumetric methods are unsuitable when there are variations
5 in the apparent density inter batch, or when in a single product there is heterogeneity in granulometry, as it cannot guarantee that the content throughout the batch is homogeneous. Furthermore, volumetric methods may alter the integrity of the substance dosed depending on the nature of the product, so it may form agglomerations, and more so if we consider that these processes are highly dependent on the filling temperature and viscosity of the product,
10 generating insurmountable fluctuations in the dose accuracy.

However, weighing and dosing control is vital for certain drugs, since they require a gravimetric filling process in the containers that respects the nature of the solid, in addition to the distribution of the particle size of the active agents and/or the solid excipients that form part of the formulation.

15 These aspects condition that for some types of drugs, such as sustained release drugs or inhalers, volumetric methods are discarded and they require gravimetric filling processes, with the aim that once the suitable quantity of each one of the components is dosed, there is a dispensing of the active substance in the composition in addition to an active diffusion
20 phenomenon of the agent within the release system originating a controlled-release phenomenon of the active substance in the formulation. If, furthermore, we consider the sustained-release systems and inhalers -which need to guarantee the correct release and/or activity of the formulation with the passage of time,- it make it more necessary if possible to control the dosing with the granulometric properties it has to guarantee the activity of the
25 formulation throughout the prescription time period, so that small dose variations give rise to more shorter or longer lasting activities than those prescribed, which obliges said formulations to be rejected from the production chain.

The invention described here is applicable to pulverulent solid compounds of any nature, although it is optimally applied to solids with the following distribution of particle sizes:

- 30
- no more than 10% of the total volume of particles is less than 20 microns,
 - no more than 10% of the total volume of particles is greater than 230 nor less than 140,
 - a value $d_{0.5}$ in the range of 60-160 microns,

where $d_{0.5}$ indicates the mean value of the particle size that divides the population exactly in
35 two equal halves, with 50% of the distribution above this value, and 50% below. In general,

throughout this specification, a value called "d0.X" represents the fraction in mass of the drug with particle sizes below the specified value, having a range from 0.0 to 1.0.

According to this definition, a value of d0.1 of 10 microns means that 10% of the total particle mass of the drug has a particle size less than or equal to 10 microns.

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Therefore, one object of the present invention is a process for the gravimetric filling or dosing of solid substances selected from the group formed by powder, lyophilizates granules, pellets, nanoparticles or microparticles in pharmaceutical containers of small dimensions including devices such as syringes, vials, capsules, ampoules, single-dose devices, inhalers, bottles, carpules blister, sachets and bags , and more particularly it relates to a process for the gravimetric filling in pharmaceutical containers of one or more sterile solid pharmaceutical substances dosed and prepared in an aseptic environment with controlled airstream so that the measurement of the weight is precise and is not influenced by the existence of a laminar flow.

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An additional advantage of the process of the present invention is that it does not need to weight the pharmaceutical before and after filling with the solid pharmaceutical substance in stations other than the dosing station, since the present invention defines a gravimetric filling process wherein the weighing cell is located in the container filling station, which means it can be confirmed that, after taring the container, the quantity of solid pharmaceutical substance it is filled with is precise.

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The present process is capable of being used in an aseptic environment in all its stages, filling the containers by a gravimetric process subjected to controlled laminar or turbulent flow, achieving that the air used does not alter the product weighing, thus avoiding the drawbacks produced by said flow such as the disturbance or prevention of the precise solid filing in the pharmaceutical containers.

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The process object of the present invention has the additional advantage of achieving precision in the filling of several substances of different nature in a single container from at least one filling station, in this way managing to fill more than two solid compounds of a different nature without interaction between them, since they are in solid form and the degree of humidity of the end product is less than 10%. This advantage is very important since the humidity may alter the weighing and cause the formation of agglomerations in the products, something which would alter the dose weighed in the container and which would alter the rheology of the compounds dispensed in the containers.

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And another additional advantage is that, throughout the process, it is possible to maintain an aseptic environment that guarantees the sterility of the finished pharmaceutical product. At present, to achieve the sterility of pharmaceutical products, pharmaceutical containers are
5 generally subjected to a terminal sterilization process generally carried out with humid heat in an autoclave, by means of which the pharmaceutical containers are steam sterilized. However, this process is unsuitable for sterilizing solid pharmaceutical products since, as water vapour is produced in this type of sterilization, it damages the integrity of the solid product that absorbs humidity. Furthermore, this type of sterilization does not manage to
10 penetrate in the powder, so that it would not give rise to the sterilization of the pharmaceutical product that there is within the pharmaceutical container.

Therefore, to be able to sterilize solid products included in a pharmaceutical container, terminal sterilization is required by means of dry heat. However, this other sterilization
15 process also has several drawbacks such as deterioration of the material used in the process, the difficult control monitoring during the process, in addition to the long period of time used in the sterilization that may alter the physicochemical properties of the product.

All these drawbacks of both types of terminal sterilization are also resolved with the present
20 invention as this type of sterilization is not necessary, since in the present invention, an aseptic environment is maintained whilst the pharmaceutical containers are filled with sterile solid pharmaceutical substances, which guarantees sterility of the end pharmaceutical product during the process and at the end thereof.

25 **Brief description of the figures**

Figure 1 shows a general view of the container (1) used in the present invention, consisting of a body (2) and a ridge (3).

Figure 2 shows a general view of the hollow cylinder (4) used also in the present invention, showing its inner cavity (5) and the recess (6) situated in the upper area of said inner cavity
30 (5).

Figure 3 shows a view of the container (1) inserted in the cylinder (4), so that the ridge (3) of the container (1) rests on the recess (6) of the cylinder (4), so that that it is the only area of contact between container (1) and cylinder (4).

Figure 4 shows a view of the cylinder (4) and container (1) unit which is inserted therein, when both parts are about to be located above the weighing cell (9) which is equipped, on its weighing surface (10), with a projection (11). When the cylinder (4) and container (1) unit lowers on said projection, the container (1) is slightly raised from its position resting in the
5 recess (6) of the cylinder (4) so that it is totally in suspension above the projection (11), resting all its weight thereon, so that the weighing cell (9) can accurately measure the weight of the container (1). It also shows the lid (12) designed to cover the unit so that it is hermetically isolated from the outside.

Figure 5 shows a illustrative diagram of the different stages which may be present in the
10 filling process according to the invention and which may comprise, according to the illustrative example shown in the figure, the following components: (1): Neutralization of electrostatic charges of the container by means of an ionizing bar; (2): Neutralization of electrostatic charges of the container by means of an ionizing needle; (3) Neutralization of electrostatic charges of product A to be dosed, and dosing thereof; (4): Neutralization of
15 electrostatic charges of the container after the dosing of product A; (5) Neutralization of electrostatic charges of product B to be dosed, and dosing thereof; (6): Neutralization of electrostatic charges of the container after the dosing of product B; (7): Capping of the container.

20 Detailed description of the invention

The filling process of a solid pharmaceutical formulation in a pharmaceutical device or pharmaceutical container must overcome several difficulties. In first place, it is necessary in many cases to dose a very small quantity of product with great accuracy. To this first point we have to add the need to comply with the legislation indicated in the different international
25 pharmacopoeias for aseptic fillings where the presence is necessary of large air flow streams (unidirectional or turbulent flow), which guarantee the elimination of any particle foreign to the process that may contaminate the end product.

These two conditions are essential for achieving the proposed aim (aseptic filling of solid in pharmaceutical devices) but achieving this is unfeasible on many occasions, since the
30 presence of large airstreams harms and alters the precise dosing.

This fact is further complicated if possible when we refer to a gravimetric filling process, wherein the only unit of measurement and dose control is the weight. And the incidence of airstream inside the device, during or after the dosing, may cause the displacement of the

solid, impregnating the walls thereof and even escaping to the outside (preventing the accuracy of the dose). This harm is aggravated if the filling is performed by gravimetric control (by weight) since the air will affect the sensor element and also distort the measurement.

- 5 This fact is important, since the basic function of industrial filling systems is to dose predetermined quantities of solids in a specific time period and precisely. Therefore, the important thing is not the volume but the mass of the product to dose. In contrast, the result of dosing does depend on other variables such as the physicochemical characteristics of the bulk product, the granulometry of the solid, the conditions of the environment and the dosing
- 10 process in relation to the selected dosing body. With respect to the process, the principle of volumetric dosing should be differentiated from gravimetric dosing.

In volumetric dosing, the expulsion of the material is exclusively produced in accordance with the volume and, with the quantities. In other words, the volume is defined before the powder dosing starts. In this way, as the dosers that work volumetrically do not measure the mass,

15 their dosing bodies will have to be calibrated depending on the material before each use: it is necessary to determine what quantity of must be dosed by the body in a defined time period. The same is also applied when the material and the batch are changed. Furthermore, volumetric dosing systems cannot automatically compensate for the changes in material properties, such as oscillations in apparent density, viscosity, distribution of particle size, and

20 even the nature of the different solid products. Thus, with the aim of compensating for the possible oscillations in the pouring weight, volumetric systems often operate with overdosing since its operation depends on the volume so that the doser body is always uniformly filled. It is for this reason that a weighing of the volumetric dosing system is more compatible with the laminar flow system, it becomes totally unfeasible in the case of sophisticated drugs that

25 have determined granulometric and physicochemical properties.

Hence, volumetric filling has a series of drawbacks that are intensified when the dosed product is a solid, such as the inaccuracy of the process, the unreliability of the substance dosing when there are substances of different granulometry or nature, the need to constantly calibrate the dose depending on the material before each use and the inability to

30 automatically compensate for the changes in the material's properties, preventing filling several different products in the same apparatus or process, such as oscillations in the apparent density of the packaged products. Therefore, volumetric methods are unsuitable when there are variations in the apparent density inter batch in a single product, or when in a single product there is heterogeneity in the granulometry as it may not guarantee that the

content in all the production batch is homogeneous. Furthermore, the volumetric methods, may alter the integrity of the dosed substance depending on the product nature as agglomerations may form and more so if we take into consideration that these processes are highly dependent on the filling temperature and product viscosity, generating insurmountable
5 fluctuations in the dose accuracy.

However, in the principle of gravimetric dosing or in accordance with the weight, one or several weighing cells integrated in the process measure (weigh) the material that one wants to dose. Therefore, the only unit of measurement is the weight. So that the actual weight regulates the dosing, meaning that gravimetric systems can automatically compensate for
10 the possible deviations in apparent density, in addition to other characteristics intrinsic to the product such as the distribution of particle size of the solid. Logically, the gravimetric dosing system is practically incompatible with the laminar flow system, since the incidence of an airstream inside the device, and in particular in, on or in the surrounding area of the weighing cell during or after dosing, may cause several drawbacks in the process: the displacement of
15 the solid impregnating the walls thereof and even escaping to the outside (preventing accuracy of the dose), the impact of the airstream in the sensor element or weighing cell, distorting the measurement, affecting the cleaning of the inside of the device, alteration of the integrity of the dose filled and consequent contamination, alteration of the distribution of particle size since the flow disperses the particles of smaller size varying the homogeneity of
20 batches, etc.

Therefore, one of the challenges to overcome when performing an aseptic filling is the protection of the filling process from the incidence of airstreams that the aseptic conditions require in the case of drugs, preferably, parenteral drugs. Hence, it is necessary to create an area of exclusion where the dosing process is protected from said streams. Thus, both the
25 sterility of the process and the accurate dosing by weight are preserved, since on the one hand it isolates the weighing cell (allowing the correct gravimetric dosing) and on the other hand, around this small area of exclusion (limited environment around the pharmaceutical device during the filling) the effect of the airstream continues to prevail (of turbulent or unidirectional flow) avoiding the access of any viable particle (with capacity to generate
30 microbiological colonies or not) or infeasible (any impurity or particle foreign to the product product) to the interior of the device or container.

This area of air exclusion around the filling process must only exist during said filling process, so that the incidence of the streams on all the system surfaces is possible the rest of the time. Thus, it preserves the aseptic character provided that this is possible, minimizing the

risk of contamination and eliminating microbial contamination from the pharmaceutical formulation.

In consequence, the problem to be resolved by the present invention is to provide a process for the gravimetric filling or dosing of solid substances selected from the group formed by
5 powder, lyophilizates, granules, pellets, nanoparticles or microparticles in a pharmaceutical container of small dimensions including devices such as syringes, vials, capsules, ampoules, single-dose devices, inhalers, bottles, carpules, blisters, sachets and bags, and more particularly it relates to a process for the gravimetric filling in pharmaceutical containers of one or more sterile solid pharmaceutical substances dosed and prepared in an aseptic
10 environment with controlled airstream so that the measurement of the weight is precise and is not influenced by the existence of a laminar flow.

The solution is based on a method of gravimetric filling of a solid product in a container comprising the following stages, which are illustrated in attached Figures 1 to 4:

- 15 a) providing a container (1) comprising a generally cylindrical body (2) and which is equipped in its upper part with a ridge (3) of diameter slightly greater than the diameter of the body (2) of the container (1),
- b) inserting the container (1) in a hollow cylinder (4), the inner cavity (5) of which has a diameter slightly greater than the diameter of the body (2) of the container (1), and which is
20 equipped with a recess (6) in the upper area of the inner cavity (5), so that the ridge (3) of the container (1) rests in the recess (6) of the upper area of the inner cavity (5) of the cylinder, and with the contact area between the ridge (3) of the container (1) and the recess (6) of the upper area of the inner cavity (5) of the cylinder being the only area of contact between container (1) and cylinder (4), so that the container (1) it is in suspension within the inner
25 cavity (5) of the cylinder (4) and with its upper surface (7) located slightly underneath the upper surface (8) of the cylinder;
- c) disposing the cylinder (4) and container (1) unit above a weighing cell (9) which is provided on its weighing surface (10) with a projection (11) which has a diameter less than
30 the diameter of the inner cavity (5) of the cylinder (4) and a suitable height to raise the container (1) by the sufficient height (h) so that the ridge (3) of the container is no longer in contact with the recess (6) of the upper area of the inner cavity (5) of the cylinder (4) but without the upper surface (7) of the container (1) exceeding the height of the upper surface (8) of the cylinder (4), so that the container (1) is completely suspended above the projection

(11) provided on the surface (10) of the weighing cell (9) and therefore resting all its weight thereon;

5 d) covering the upper surface (8) of the cylinder (4) hermetically by means of a lid (12) equipped with an orifice (13) wherethrough it is possible to add the solid product by means of a dosing element (14) or nozzle;

10 e) weighing with the desired precision the container (1) whilst it is suspended above the projection (11) provided on the surface (10) of the weighing cell (9) and resting all its weight thereon, and

f) filling the container (1) with the solid product through the orifice (13) of the lid (12), gravimetrically controlling the quantity of product added thereto by means of the weighing cell (9).

15 The lid of stage d) must be understood in general terms as any element which may hermetically cover the cylinder (4), so that, for example, said lid may be implemented in the practice in the form of the lower walls or of a flexible hopper which incorporates a dosing element or nozzle, provided that this hopper is adapted to the cylinder so that that it does not allow the access of air flow therein.

20 Stages e) and f) are preferably performed in the same dosing station with the object that the precision of the weighing is optimum, although nothing would prevent it from being performed in different dosing stations.

Through the stages of the method described the verticality or suspension of the container (1) is achieved so that the container (1) is vertically suspended without touching the walls of the
25 cylinder (4), so that the weighing device may precisely guarantee the pre-set weight of added solid product. Furthermore, said verticality facilitates that the dosing element (14) or nozzle may enter the container (1) facilitating the dosing. All of this may occur even in the presence of vibration provided by an external vibrating element, which in embodiments of the invention may help correctly dose the product in the container (1).

30

In a preferred embodiment, the process is carried out in an isolator. In another preferred embodiment the process is carried out in a sterile open room complying with in both cases Grade A according to the classification of clean air rooms and devices commonly accepted by standard EN ISO 14644-1.

In the case of isolators, and according to a preferred embodiment, before the dosing operation stated in the present invention, it requires a sterilization with nebulized or vaporized hydrogen peroxide or a mixture of hydrogen peroxide with peracetic acid.

The following advantages are achieved through the indicated process:

- 5 1) Thanks to the provision of the cylinder with the described characteristics, containing the container in suspension and which is hermetically closed before the weighing, it achieves that the container is hermetically isolated from the laminar air flow in the measurement cabin and, therefore its weighing, both of the full and empty containers, may no longer be affected by the existence of laminar flow;
- 10 2) Likewise, the product to be filled in the container, in addition to its access channel thereto, is also isolated from the outside hermetically, so that the laminar flow in the measurement cabin cannot affect the falling of the solid product in the container either;
- 15 3) The empty container is exactly weighed with the same conditions and normally only with seconds of difference before it starts to be filled with the solid product, so that it avoids the errors present when the weighing is performed at different moments and/or circumstances of the process.
- 20 4) Thanks to the provision of the container it is possible to very precisely dose solids that have certain characteristics such as apparent density, intrinsic viscosity, specific distribution of particle size of the solid, etc. aseptically in laminar flow conditions.

For the person skilled in the art, it will be clear that the process indicated may be implemented in different embodiments of the invention, all included within the scope of the
25 invention according to the content of the attached claims. For example, and without limiting character, the present invention includes the following particular embodiments, all independent from one another but they may be combined together without limitation:

In one embodiment, between container and cylinder it is possible to provide one or more intermediate parts by way of "sleeves" of the container insofar as the presence of said
30 sleeves do not alter the described process, which may provide additional advantages such as a better balance of the container with the cylinder cavity. Illustratively, a "sleeve" of this type between container and cylinder may have a height of between 0.5 mm and 10 mm, and preferably between 0.5 and 5 mm in height. This "sleeve" achieves the suitable verticality or suspension of the container so that it remains in a suitable form so that the dispenser needle

(nozzle) enters the container facilitating the dosing, in addition to que the container is suspended vertically (without touching the walls of the vibration buffer part) so that the device of weighing can guarantee the pre-set dose.

5 In another embodiment, the cylinder may be equipped, for practical reasons, with additional external surfaces, such as an outer ridge of a certain thickness, designed so that the cylinder can be rest without the risk that the cylinder can slide and fall, or also so that the cylinder provide with said ridge can be displaced from one place to another within the different points of the filling stations by means of a series of elevated rails.

10 In a further embodiment, the projection provided on the weighing surface may have a generally cylindrical form but may also adopt other forms such as square, hexagonal or others. Its upper surface may also be flat or may end in other geometric forms, such as conical or truncated cone shaped. All these variations may be possible as long as the project continues to fulfil its function of raising the container, optionally covered by one or more sleeves, sufficient so that the ridge thereof is separated from the recess of the upper surface
15 of the cylinder so that all the weight of the container, with or without product, rests on the projection of the balance and therefore on the actual balance, which guarantees a correct weighing thereof. It is also important that the height of the projection is not too high so that the upper surface of the container will remain above the upper surface of the cylinder, which will prevent the hermetic sealing thereof by means of the indicated lid. Therefore, it is
20 important to precisely control the height of the balance surface projection.

In yet another embodiment, the product filling stage may be repeated as many times as necessary, for example if more than one different product is filled in the container, in which case the different products will be filled in the container in different filling stages. Alternatively, if were no reasons to keep the different solid products in differentiated stages, it
25 would also be possible to previously mix the different products and fill the mixture in a single filling stage and weighing in a single weight measurement.

In another additional embodiment, the filling stages may be accompanied, previously, subsequently and/or simultaneously, with ionization stages of the container to neutralize its electrostatic charges, for example, through bar, needle, curtain, filter, ring ionizers, etc. This
30 process achieves that as the solid product falls in the form of powder in the container, particularly when it is of plastic material, the powder particles do not adhere to the inner or outer wall of the container but fall to the bottom thereof.

In yet another embodiment, the filling of the product or products may be simultaneously accompanied with an airstream which is preferably N₂ or compressed air, both sterile to help the dosing and provide the necessary sterility conditions required by the process. Furthermore, when the airstream is N₂ it displaces the oxygen present inside the container, preventing oxidation of the product and consequently its subsequent degradation.

In a further embodiment, the filling of the container may be performed by a dosing process with endless screw, with a gravimetric doser due to weight loss equipped with a hopper and a high-precision nozzle, with single-thread doser, with double-thread doser, with doser with vibrating channel or with vibrating hopper, with doser with equipped with conveyor belt, with doser equipped with a compacting system, etc. For products that do not easily slide, it is necessary to add a stirrer in the upper hopper to guarantee constant supply of the solid.

In yet another additional embodiment, the doser may be equipped with a mixer.

In another embodiment, the weighing cell may be multiple so that it can fill a multiplicity of containers, so that the cylinder of the present invention may be equipped with a multiplicity of inner cavities each and every one of them with a diameter slightly greater than the diameter of the body of the container, and which are in turn equipped with a recess in the upper area so that the ridges of the containers rest in the recess of the upper area of the cavities of the cylinder, and with the contact area between the ridge of each container and of each recess of the upper area of the cavity of the cylinder being the only area of contact between container and cylinder, so that each container is in suspension within each cavity of the cylinder and with its upper surface located slightly underneath the upper surface of the cylinder;

In another embodiment, the weighing cell must be high-precision, preferably impermeable to water, environmental dust, vapours, disinfecting agents, etc.

The pharmaceutical container is preferably filled with the container in vertical position preferably by its wider part, although it can also be filled by its narrower part, provided that its diameter allows access of the filling needle or nozzle inside the container.

A possible overall diagram of the process, shown solely with illustrative purposes, can be that shown in attached figure 5.

The container may adopt the form of syringes, vials, capsules, ampoules, single-dose devices, inhalers, bottles, carpules blister, sachets and bags designed to contain solid substances, although it is preferably a syringe or a carpule as they have the aforementioned upper ridge. In said case, the ridge described above is the ridge that the syringes or the carpules usually have in their upper end, i.e. at the end whereby the plunger or plug of the

carpule, respectively, is introduced. Although, as specified, the invention also includes the possibility that the container can be filled by the opposite end, i.e. by the end with the more reduced diameter wherethrough the needle would normally be coupled. In any of the aforementioned cases, the material of the container may be formed by plastics of different composition, such as polyolefins and cyclic polyolefins, polypropylene, polybutadiene, polyethylene, polystyrene, vinyl polychloride, polyacrylonitrile, polyamides etc., polyesters (containing the ester functional group in its main chain: poly(ethylene terephthalate), polycarbonate), acrylic polymers (poly(methyl methacrylate), polyacrylonitrile), thermoplastic resins (polyacetals and polyhaloethylenes), polyurethanes, formaldehyde resins (phenol resin, urea resin), phenoplasts, aminoplasts, thioplasts, duroplastic resins (unsaturated polyester, polyurethanes), silicones, polyvinylidenes, cellulose derivatives, polycarbonates, and mixtures of all of them, etc. Alternatively, the receptacle may also be metal, e.g. of steel or titanium suitable for the administration of drugs, of glass, of crystal, etc.

In turn, the cylinder shall be preferably composed of a metal material such as steel or titanium, although it contemplates the possibility that it can be made from various materials, such as different plastics, glass, stone, resin, crystal, etc.

Both the materials used for the container and the cylinder materials must be airtight, inert, impermeable and not absorb and/or adsorb the product contained.

Preferably, the containers of the present invention are both syringes and carpules with the nozzle finished in a threaded cone (male or female) or in a simple cone.

The invention described here is applicable to pulverulent solid compounds of any nature, although optimally it is applicable to solids with the following distribution of particle sizes:

- no more than 10% of the total volume of particles is less than 20 microns,
- no more than 10% of the total volume of particles is greater than 230 nor less than 140,
- a value $d_{0.5}$ in the range of 60-160 microns,

where $d_{0.5}$ indicates the mean value of the particle size that divides the population exactly in two equal halves, with 50% of the distribution above this value, and 50% below. In general, throughout the present specification, a value called " $d_{0.X}$ " represents the fraction in mass of the drug with particle sizes below the specified value, having a range of 0.0 to 1.0.

In a preferred embodiment of the invention, the distribution of particle sizes is:

- no more than 10% of the total volume of particles is less than 20 microns,
- no more than 10% of the total volume of particles is greater than 230 nor less than 140,
- a value $d_{0.5}$ in the range of 60-130 microns.

5 According to another preferred embodiment:

- no more than 10% of the total volume of particles is less than 20 microns,
- no more than 10% of the total volume of particles is greater than 325 nor less than 245,
- a value $d_{0.5}$ in the range of 100-155 microns.

10 Examples of this type of compounds may be risperidone, paliperidone, fentanyl, olanzapine, letrozole, aripiprazole, anastrozole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, quetiapine, ziprasidone, among others including any derivative, metabolite or salt (such as pamoate or palmitate) alone or in combination.

The invention described here is applicable to pulverulent solid compounds of any nature,
 15 although optimally it is applicable to solids of polymeric nature, generally lactic or glycolic acid copolymers (PLGA) with a ratio of lactic/ glycolic monomer ratio in the range of 40:60 to 70:30, preferably in the range of 45:55 to 75:25. It also preferably uses polylactic acid polymer (PLA), in addition to also other materials, such as polydioxanone, poly(trimethylene-
 carbonate in the form of copolymers and homopolymers, poly(ϵ -caprolactone) copolymers,
 20 polyanhydrides and polyorthoesters, which have been accepted as materials of biomedical use.

The preferred polymers in this invention are selected from copolymers with an intrinsic inherent viscosity preferably in the range of 0.16-0.60 dl / g, and more preferably between 0.25-0.55 dl / g, measured in chloroform at 25°C and a concentration of 0.1%. The
 25 concentration of the polymeric component in the compositions of the invention is preferably included in the range of 25-50%, (expressed as the percentage of polymer weight based on the total polymer solution component) and more preferably between 30-40%.

For the purpose of the present invention, throughout this specification, the term intrinsic or inherent viscosity (η_{inh}) of the polymer is defined as the ratio of the natural logarithm of
 30 relative viscosity, (η_r), with respect to the polymer mass concentration, c , i.e.:

$$\eta_{inh} = (\ln \eta_r) / c$$

considering that the relative viscosity (η_r) is the ratio of the viscosity of the solution η with respect to the viscosity of the solvent η_s , i.e.:

$$\eta_r = \eta / \eta_s$$

Furthermore, it shall be understood that the values of intrinsic viscosity throughout the present specification are measured at 25°C in a chloroform solution with a concentration of 0.1%. The term of the intrinsic viscosity is commonly considered an indirect indicator of the polymer's molecular weight. In this way, a reduction in the intrinsic viscosity of a polymer, measured at a given concentration in a certain solvent, with the same composition of monomer and terminal groups, is an indicator of the reduction in molecular weight of the polymer (IUPAC. Basic definitions of terms relating to polymers 1974. Pure Appl. Chem. 40, 477-491 (1974)).

The polymers may be of synthetic, semi-synthetic and natural origin. They also include cellulose derivatives (for example, cellulose acetate, ethylcellulose, cellulose acetate phthalate, cellulose ethers such as, for example, hydroxypropyl methylcellulose), acrylate derivatives (for example Eudragit, poly(methyl methacrylate), cyanoacrylates) and biocompatible and biodegradable polymers such as polyanhydrides, polyesters, polyorthoesters, polyurethanes, polycarbonates, polyphosphazenes, polyacetals, polyoxyethylene-polyoxypropylenes. Polyesters such as polylactic, polyglycolide, polycaprolactone, polyhydroxybutyrate or polyhydroxyvalerate are important. Furthermore, polysaccharides such as sodium alginate, chitosan or chitin or proteins may also be used. In the bibliography it has described a large number of support materials and all of them are potentially considered for the preparations according to the invention.

EXAMPLES

Several examples of container filling by means of the process of the present invention are shown below, which must be considered with solely illustrative purposes and not limiting of the scope of the invention. To explain said examples, it should be mentioned that syringes are going to be used as pharmaceutical containers with a female or male connection system indifferently, and PLGA and PLA excipients, and Risperidone and Letrozole, respectively, as active compounds.

Example 1: Filling of letrozole in a syringe at a dose of 50 mg.

In the first example, the compound to be filled is the active compound Letrozole, for a filling dose in a 50 mg prefilled syringe. It should be highlighted that the filling process takes place within a Tesltar Azbil® rigid-walled aseptic isolator. Before starting with the filling process, all equipment must be clean and sterile, to do this, firstly, sterilization is performed with
5 nebulized or vaporized hydrogen peroxide or a mixture of hydrogen peroxide with peracetic acid.

To commence the filling, we start by taking the sterile syringes and caps, giving said caps to an operator who is in the capping station.

In first place, each syringe is organized underneath an ionized nitrogen stream, preferably,
10 although it may also use a compressed airstream, to achieve its ionization and elimination of the electrostatic charge. Then, the syringe is moved to the filling station to introduce it in the cylinder (4). The syringe shall be placed above the weighing cell, which tares the weight of the empty syringe, recording the data in the weight tracker of the control system. After this, it starts with the filling of the syringe with a quantity of 50 mg $\pm 30\%$ of letrozole by means of a
15 nozzle. The syringe is weighed as it is filled during the filling, so that the system can be controlled to stop the filling when the desired weight is reached, in this case 50 mg $\pm 30\%$ of letrozole.

Subsequently, if we want to fill a second substance, such as an excipient, the cylinder (4) and the syringe filled with letrozole shall be transported to a second filling station, performing
20 the same steps described above.

After filling with letrozole, the cylinder (4) together with the syringe pass to the capping or sealing station, after passing through an ionization stage of the full syringe. Once the syringe filling process has concluded, and having sealed it, it can be positioned on a tray with the other filled and sealed syringes.

25 This example has been performed for doses of 50, 75, 100, 200, 300, 400 and 500 mg of letrozole, operating suitably and precisely dosing.

Example 2: Filling of risperidone in a syringe at a dose of 100 mg.

In this example, the compound to be filled is the active compound risperidone, for a filling dose in a 100 mg prefilled syringe. It should be highlighted that the filling process takes place within a Tesltar Azbil® rigid-walled aseptic isolator. Before starting with the filling process, all
30 equipment must be clean and sterile, to do this, firstly, sterilization is performed with nebulized or vaporized hydrogen peroxide or a mixture of hydrogen peroxide with peracetic acid.

To commence the filling, we start by taking the sterile syringes and caps, giving said caps to an operator who is in the capping station.

In first place, each syringe is organized underneath an ionized nitrogen stream, preferably, although it may also use a compressed airstream, to achieve its ionization and elimination of the electrostatic charge. Then, the syringe is moved to the filling station to introduce it in the cylinder (4). The syringe shall be placed above the weighing cell, which tares the weight of the empty syringe, recording the data in the weight tracker of the control system. After this, it starts with the filling of the syringe with a quantity of 100 mg $\pm$ 30% of risperidone by means of a nozzle. The syringe is weighed as it is filled during the filling, so that the system can be controlled to stop the filling when the desired weight is reached, in this case 100 mg $\pm$ 30% of risperidone.

Subsequently, if we want to fill a second substance, such as an excipient, the cylinder (4) and the syringe filled with the risperidone shall be transported to a second filling station, performing the same steps described above.

After filling with risperidone, the cylinder (4) together with the syringe pass to the capping or sealing station, after passing through an ionization stage of the full syringe. Once the syringe filling process has concluded, and having sealed it, it can be positioned on a tray with the other filled and sealed syringes.

This example has been performed for doses of 50, 75, 100, 200, 300, 400 and 500 mg of risperidone, operating suitably and precisely dosing.

Example 3: Filling of polylactic acid (PLA) in a syringe at a dose of 90 mg.

In the first example, the compound to be filled is the excipient PLA for a medicine formulation, in a filling dose in a 90 mg prefilled syringe. It should be highlighted that the filling process takes place within a Teslar Azbil® rigid-walled aseptic isolator. Before starting with the filling process, all equipment must be clean and sterile, to do this, firstly, sterilization is performed with nebulized or vaporized hydrogen peroxide or a mixture of hydrogen peroxide with peracetic acid.

To commence the filling, we start by taking the sterile syringes and caps, giving said caps to an operator who is in the capping station.

In first place, each syringe is organized underneath an ionized nitrogen stream, preferably, although it may also use a compressed airstream, to achieve its ionization and elimination of the electrostatic charge. Then, the syringe is moved to the filling station to introduce it in the

cylinder (4). The syringe shall be placed above the weighing cell, which tares the weight of the empty syringe, recording the data in the weight tracker of the control system. After this, it starts with the filling of the syringe with a quantity of 90 mg $\pm$ 30% of PLA by means of a nozzle. The syringe is weighed as it is filled during the filling, so that the system can be controlled to stop the filling when the desired weight is reached, in this case 90 mg $\pm$ 30% of PLA.

After filling with PLA, the cylinder (4) together with the syringe pass to the capping or sealing station, after passing through an ionization stage of the full syringe. Once the syringe filling process has concluded, and having sealed it, it can be positioned on a tray with the other filled and sealed syringes.

This example has been performed for doses between 90 and 1000 mg of PLA, operating suitably and precisely dosing.

Example 4: Filling of PLGA in a syringe at a dose of 100 mg after example 2 (filling of risperidone).

After performing the stages of example 2, the syringe passes to a second filling station within the cylinder (4). The syringe shall be placed above the weighing cell, which tares the weight of the empty syringe, recording the data in the weight tracker of the control system. After this, it starts with the filling of the syringe with a quantity of 100 mg $\pm$ 30% of PLGA (Resomer 503®) by means of a nozzle. The syringe is weighed as it is filled during the filling, so that the system can be controlled to stop the filling when the desired weight is reached, in this case 100 mg $\pm$ 30% of Resomer 503®.

Subsequently, if we want to fill with a third substance, such as an excipient or another active compound, the cylinder (4) and the previously filled syringe shall be transported to the next filling station, performing the same steps described above as many times as necessary.

After filling with PLGA, the cylinder (4) together with the syringe pass to the capping or sealing station, after passing through an ionization stage of the full syringe. Once the syringe filling process has concluded, and having sealed it, it can be positioned on a tray with the other filled and sealed syringes.

This example has been performed for doses of 100 to 500 mg of PLGA, operating suitably and precisely dosing.

CLAIMS

1) Method of gravimetric filling of a solid product in a container (1) comprising the following steps:

a) providing a container (1) comprising a generally cylindrical body (2) and which is equipped in its upper part with a ridge (3) of diameter slightly greater than the diameter of the body (2) of the container (1),

b) inserting the container (1) in a hollow cylinder (4), the inner cavity (5) of which has a diameter slightly greater than the diameter of the body (2) of the container (1), and which is equipped with a recess (6) in the upper area of the inner cavity (5), so that the ridge (3) of the container (1) rests in the recess (6) of the upper area of the inner cavity (5) of the cylinder, and with the contact area between the ridge (3) of the container (1) and the recess (6) of the upper area of the inner cavity (5) of the cylinder (4) the only area of contact between container (1) and cylinder (4), so that the container (1) is in suspension within the inner cavity (5) of the cylinder (4) and with its upper surface (7) located slightly underneath the upper surface (8) of the cylinder;

c) disposing the cylinder (4) and container (1) unit above a weighing cell (9) which is equipped, on its weighing surface (10), with a projection (11) which has a diameter less than the diameter of the inner cavity (5) of the cylinder (4) and a suitable height to raise the container (1) by the sufficient height (h) so that the ridge (3) of the container is no longer in contact with the recess (6) of the upper area of the inner cavity (5) of the cylinder (4) but without the upper surface (7) of the container (1) exceeding the height of the upper surface (8) of the cylinder (4), so that the container (1) is completely suspended above the projection (11) provided on the surface (10) of the weighing cell (9) and therefore resting all its weight thereon;

d) covering the upper surface (8) of the cylinder (4) hermetically by means of a lid (12) equipped with an orifice (13) wherethrough it is possible to add the solid product by means of a dosing element or nozzle (14);

e) weighing with the desired precision the container (1) whilst it is suspended above the projection (11) provided on the surface (10) of the weighing cell (9) and resting all its weight thereon, and

f) filling the container (1) with the solid product through the orifice (13) of the lid (12), gravimetrically controlling the quantity of product added thereto by means of the weighing cell (9).

2) Method according to claim 1, wherein between container (1) and cylinder (4) is provided at least one sleeve covering the container (1) designed to guarantee the verticality and suspension of the container (1) within the inner cavity (5) of the cylinder (4) so that neither the container (1) nor its covering sleeve touch the inner walls of the cylinder (4).

3) Method according to claims 1 or 2, wherein stages c) to f) are repeated the necessary times in the case that more than one solid product is to be dosed in the container (1).

4) Method according to any of claims 1 to 3, wherein previously, subsequently or simultaneously to any of stages a) to f) an ionization stage of the container (1) and/or of the cylinder (4) is introduced to neutralize its electrostatic charges.

5) Method according to claim 4, wherein the ionization stage is carried out by introducing an ionizing bar, needle or ring in the container (1) and/or in the cylinder (4).

6) Method according to claims 4 or 5, wherein a stream of compressed air or sterile N₂ is introduced in the container (1) and/or the cylinder (4) simultaneously to the ionization to help the dosing and provide the required sterile conditions.

7) Method according to any of the preceding claims, wherein the filling of solid product in the container (1) of stage f) is performed by means of an endless screw, a gravimetric doser by weight loss equipped with a hopper and a high-precision nozzle, a single-thread doser, a double-thread doser, a doser with vibrating channel or with vibrating hopper, a doser equipped with conveyor belt, or a doser equipped with compacting system.

8) Method according to claim 7, wherein the hopper is equipped with a stirrer to guarantee a constant and fluid supply of the solid product in the container (1).

9) Method according to any of the preceding claims, wherein the cylinder (4) is equipped with a multiplicity of inner cavities (5), each one of which is capable of receiving a container (1).

10) Method according to claim 9, wherein the weighing cell (9) is multiple with the aim of being able to weigh the multiplicity of containers (1) equipped in the multiplicity of inner cavities (5) of the cylinder (4).

11) Method according to any of the preceding claims, wherein the container (1) is a syringe, vial, capsule, ampoule, single-dose device, inhaler, bottle, carpule blister, sachet or bag designed to contain solid substances.

12) Method according to claim 11, wherein the container (1) is a syringe or carpule.

13) Method according to any of the preceding claims, wherein the cylinder (4) is a metal cylinder of titanium, steel, plastic, crystal, glass, stone or resin.

14) Method according to claim 13, wherein the cylinder (4) is equipped with an outer ridge designed so that the cylinder (4) can be supported by means of pliers or clamps, or also so that the cylinder (4) can be displaced by means of rails elevated from some points to others of the filling stations.

15) Method according to any of the preceding claims, wherein the projection (11) provided on the surface (10) of the weighing cell (9) has generally cylindrical form and its upper surface has substantially flat, conical or truncated cone shape.

16) Method according to any of the preceding claims, wherein the solid product to be filled in the container (1) has the following distribution of particle sizes:

- no more than 10% of the total volume of particles is less than 20 microns,
- no more than 10% of the total volume of particles is greater than 230 nor less than 140,
- a value $d_{0.5}$ in the range of 60-160 microns,

where $d_{0.5}$ indicates the mean value of the particle size that divides the population exactly in two equal halves, with 50% of the distribution above this value, and 50% below.

17) Method according to any of preceding claims 1 to 15, wherein the solid product to be filled in the container (1) has the following distribution of particle sizes:

- no more than 10% of the total volume of particles is less than 20 microns,

- no more than 10% of the total volume of particles is greater than 325 nor less than 245,
- a value d_{0.5} in the range of 100-155 microns,

18) Method according to claims 16 or 17, wherein the solid product to be filled in the container (1) is selected from the group consisting of risperidone, paliperidone, fentanyl, olanzapine, letrozole, aripiprazole, anastrozole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, quetiapine, ziprasidone, including any derivative, metabolite or salt thereof, alone or in combination.

19) Method according to any of the preceding claims, which is performed in an aseptic environment in a laminar air flow cabin.