(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 101 131 A1

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
16.09.2009 Bulletin 2009/38

(51) Int Cl.:
F26B 5/06 *(2006.01)*

(21) Application number: **07425840.1**

(22) Date of filing: **31.12.2007**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR
Designated Extension States:
AL BA HR MK RS

(71) Applicant: **Terruzzi Fercalx S.p.A.**
20121 Milano (IT)

(72) Inventor: **The designation of the inventor has not yet been filed**

(74) Representative: **Long, Giorgio et al**
Jacobacci & Partners S.p.A.
Via Senato 8
20121 Milano (IT)

(54) **Lyophilization method and system therefor**

(57) The object of the present invention is a lyophilization method for food or pharmaceutical substances and, in particular, a continuous lyophilization method of said substances comprising the following successive steps:
- providing a mixture containing at least one substance to be lyophilized, and at least one vehicle substance to be sublimed;
- causing said mixture to undergo a nebulization treatment in order to form fine droplets;
- flash freezing said mixture droplets so as to form solid particles having discrete dimensions containing said at least one substance to be lyophilized and said at least one vehicle substance;
- sublimating said frozen particles;
- recovering the sublimation product in the form of solid aggregates having dimensions ranging between 5 and 500 microns.

In addition, the invention relates to an equipment for the production of lyophilized substances so designed as to be capable of being operated in an essentially continuous manner.

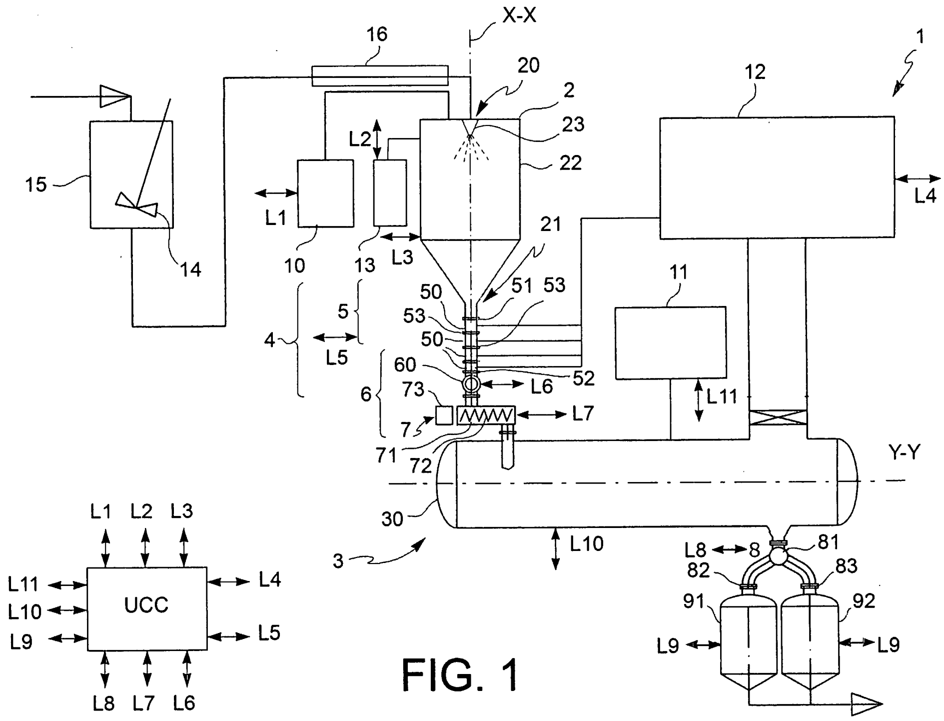


FIG. 1

EP 2 101 131 A1

Description

FIELD OF THE INVENTION

[0001] The object of the present invention is a lyophilization method for substances such as, in general, food or pharmaceutical substances and, in particular, a method for the continuous lyophilization of said substances. In addition, the invention relates to a system for the production of lyophilized substances which is designed such as to be capable of being operated in an essentially continuous manner.

BACKGROUND ART OF THE INVENTION

[0002] It is known that any lyophilization method is carried out by following a batch operational scheme. In general, the lyophilization comprises a deposition step of a solution or suspension into special vessels, called trays, so as to form a layer having a thickness which can range between 1 and 3 cm in relation to the substance to be lyophilized. Subsequently, the trays content is deep-frozen at temperatures usually ranging between -40° C and -60° C, according to the type of product to be processed. Once the cryostatic stability has been reached, one starts to generate a micrometric vacuum and, concomitantly, to supply heat to the frozen mass which is contained in the trays. The heat is conventionally provided by means of thermostated plates which the trays rest on.

[0003] The heat supplying step to the trays is of crucial significance, since it must take place in an accurately controlled manner so as to ensure the vehicle substance sublimation, without affecting the molecular structure of the substance of interest.

[0004] The sublimation, beside depending on the known intrinsic characteristics of the product to be processed, also depends on external factor, such as the heat conduction from the tray bottom plate and, therefrom, to the product, on the heat radiance from a plate towards the inferiorly arranged tray, and on the heat conduction inside the product to be processed or, in other terms, on the particle-to-particle heat transmission between those particles which are contained in the trays. The latter condition is particularly slow due to the particle arrangement on the trays plane which undergoes the heating.

[0005] In fact, it shall be noticed that, while the trays are so shaped as to contain a solution or suspension layer to be processed having a reduced thickness (1 to 3 cm), in any case, due to the slow heating process, the heat takes a considerable period of time in order to pass through said thickness and cause the vehicle substance sublimation in all the particles, also in those which are immersed in the solution or suspension, that is those particles which are far both from the bottom and the surface of the tray. All these conditions make the duration of the lyophilization operation possibly ranging between 12 and 24 hours.

[0006] Alternatively, one could consider enlarging the solution or suspension receiving surface in order to decrease the thickness of the layer to be subjected to sublimation. It shall be apparent that such a solution is not convenient at all from the industrial application point of view, where the amounts of product to be processed are considerable, therefore they would require huge trays and relative equipment dimensions, with onerous structural drawbacks.

[0007] In addition, the whole process is further burdened with batch operations such as the restoration of the atmospheric pressure conditions in the freeze-dryer, with optional heating of the substance of interest to a near-room temperature to recover the lyophilizate from the equipment without damaging it, the trays drawing from the lyophilization chamber, and the discharge of the lyophilizate they contain into special vessels intended for a successive processing, the cleaning of each tray, of the lyophilization chamber, and the plates, as well as the waiting time for the unfreezing of the condensers for successive operations.

[0008] The sum of the partial times which are necessary for all the above-mentioned operations is such as to make the batch lyophilization method as an operation heavily burdening on the production time. To date, this problem has been faced by adopting a lyophilization method in which the product to be processed is fed, frozen, lyophilized, and recovered by employing tunnel freeze-dryers. It consists in a long linear path along successive lyophilization chambers which are mutually interconnected by means of insulating gates. This technology employs lyophilization chambers having an average length of 40/50 or more meters, and enlarge while the receiving ability increases.

[0009] In order to solve the above-mentioned drawbacks, relevant improvements have also been proposed, the commonest among which involving the exchanging surfaces between thermal plates and trays, robot-assisted loading systems for the trays.

[0010] Notwithstanding the above-mentioned improvements, the currently available lyophilization methods are in any event very lengthy and batch processes.

SUMMARY OF THE INVENTION

[0011] Therefore, the technical problem underlying the present invention is to devise a lyophilization method which allows considerably accelerating the production times, while allowing simplifying the processing steps as well as the production equipment.

[0012] Such problem is solved by a lyophilization method in which the product to be processed is essentially continuously fed as a mixture, frozen, lyophilized, and recovered due to the provision of technical contrivances which allow obtaining a production flow between the various steps without major discontinuities.

[0013] Therefore, a first object of the present invention is a continuous lyophilization method for substances such as food, flavours, and pharmaceutical industry products.

[0014] A second object of the invention is a system for the continuous production of lyophilized substances.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Further characteristics and the advantages of the present invention will be more clear from the following detailed description of some embodiments, given by way of non-limiting example, with reference to the Figures, in which:

- Fig. 1 illustrates a schematic view of a lyophilization system in accordance with a first embodiment of the invention;
- Fig. 2A illustrates a detail of the lyophilization equipment according to an embodiment variation of the invention;
- Fig. 2B illustrates a detail of the lyophilization equipment according to a second embodiment variation;
- Fig. 3 illustrates a schematic view of a lyophilization equipment in accordance with a further embodiment variation.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The thought underlying the present invention is the observation that, in order to be able to considerably increase the lyophilization process productivity, it is important to intervene during the heating step of the frozen products. In fact, as previously mentioned, this step is particularly crucial and slow.

[0017] It has been noticed that in order to accelerate the heating of a substance deposited in the trays, one could make use of the principle of the directly proportional relationship between exchange surface and sublimation ability of the product, that is, the larger is the thermal exchange surface of the product to be processed, the higher is the product-carrying substance sublimation. In other terms, the larger is the surface of a substance which is exposed to the environment, the higher is the possibility that the vehicle substance is free to leave the product without hindrances.

[0018] Differently from what has been proposed to date, the idea was to increase not much the collecting surface of the product to be processed, so as to disperse it on a very thin layer, as much to provide the product in such a shape that the product itself has the largest exposure surface possible, independently from the support which it undergoes the processing on.

[0019] In the present description, by the term "mixture" is meant both a homogeneous liquid phase and a suspension liquid phase, in other terms, it indicates both a solution and a suspension.

[0020] On the basis of these assumptions, the method in accordance with the invention comprises the following consecutive steps:

- providing a mixture containing at least one substance to be lyophilized, and at least one vehicle substance to be sublimed;
- causing said mixture to undergo a nebulization treatment in order to form fine droplets;
- flash freezing said mixture droplets so as to form solid particles having discrete dimensions containing said at least one substance to be lyophilized, and said at least one vehicle substance;
- sublimating said frozen particles;
- recovering the sublimation product in the form of solid aggregates having dimensions in the range between 50 and 500 microns.

[0021] The mixture which has to undergo the inventive method can be any mixtures which are usually employed in a lyophilization method. For example, the mixture can be a solution or a suspension of one or more pharmaceutical, food, cosmetic substances, fragrances, preservatives, substances for veterinary or agronomic use.

[0022] In particular, the mixture can be a solution or suspension of substances such as: antibiotics, enzymatic derivatives, fruit juices, natural extracts, substances in a vehicle substance, such as the commonest solvents, for example, water, alcohols, aromatic derivatives.

[0023] The preparation of such mixtures depends on the type of substances which are meant to be lyophilized, and it is, in any case, within the skills of those of ordinary skill in the art. Consequently, the preparation of solutions or suspensions will be not further detailed herein.

[0024] Preferably, the mixture is provided under stirring before the nebulization step, so as to keep the best homogeneity possible during all the drawing time for the nebulization. In this way, also the lyophilized end product can continuously ensure a high degree of homogeneity.

[0025] The method of the invention can further comprise a pre-cooling step before undergoing the nebulization. Aim of this step is to decrease the mixture temperature by bringing it nearer to that of start freezing at the cost of the cold nitrogen gas stream exiting the freezing chamber, resulting in an energetic recovery. Preferably, said step will be performed by means of a recovery chamber in which the mixture supply tube is lapped by the exiting nitrogen gas stream, as it will be better described herein below with reference to the equipment.

[0026] Next, the nebulization step can be carried out also through any one of the methods which are known in the art. For example, it can be carried out by nozzle nebulization with spraying through compressed gas, nebulization through rotating dynamic heads where small toothed rotor and stator turbines cause the dispersion as droplets of the liquid passing through the gaps of the toothing (the more the cutting actions for each rotation of the turbine, the smallest the droplets), or sonic or ultrasonic energy nozzles in which a ultrasonic head, such as the one manufactured by the Austrian firm DUMAG, comprises a resonance chamber which is passed through by a spraying compressed gas while exerting a variable pressure power at the typical 20 KHz frequency, so as to atomize the liquid into micrometric droplets.

[0027] As regards the ultrasonic nebulization, atomizers may be employed such as those described in the U.S. patent 5,707,636, herein incorporated by reference in its entirety. Briefly, the atomizer exploits the vibrations of resonant metallic members, or suitable nozzles, so as to produce droplets having a diameter ranging between 5 and 500 microns. Such members may comprise an axially-perforated nozzle, a member without nozzle with an angulated reflecting end, a member with vibrating planar plate.

[0028] The freezing step can be implemented in accordance with any one of the technologies which are known to those of ordinary skill in the art. Preferably, the freezing takes place by free fall of the mixture droplets inside a freezing chamber, during which said droplets are hit, usually countercurrently, by a cooling fluid.

[0029] The most commonly used cooling fluid is, without limitations, the nitrogen gas which is employed at a temperature of about -60° C. Other gases for cryogenic system can be suitable to this aim, such as, for example, CO_2.

[0030] Anyhow, independently from the method type which is employed for the freezing, the treatment must be carried out so as to allow the formation of solid particles having discrete dimensions in which one or more substances to be lyophilized and one or more vehicle substances to be sublimed are contained, according to the type of mixture which has been prepared for the lyophilization treatment.

[0031] The particles which have to be produced will also depend on the nebulization step which, as previously explained, can take place in accordance with conventional nebulization or atomization methods.

[0032] However, it results in the frozen particles being composed by constituents which not necessarily are spherical, and small enough to ensure, in the successive heating step for the sublimation, an increase of the heating speed inside each member compared to the heating speed inside the solution or suspension layer which is usually deposited on the conventional trays.

[0033] From what has been described, it results that the above-mentioned heating increase inside each particle allows accelerating the volatile substance sublimation.

[0034] In addition, just thanks to the provision of the product to be lyophilized in the form of discrete particles, this allows increasing the exposure surface by volume unit, resulting in that the vehicle substance can sublimate much more easily. In fact, having a larger exposed surface, in other terms, a free surface, a vehicle substance molecule encounters much less obstacles to the sublimation, therefore it can leave more quickly the particle compared to a vehicle substance molecule which is trapped inside a compact layer which is deposited on the trays.

[0035] The sublimation step can be carried out with any one of the conventional methods.

[0036] In particular, it can be performed vertically, where the discrete solid frozen particles fall by gravity inside a chamber under high vacuum and are passed through by thermal and/or electromagnetic energy, so that, upon falling, the particles are invested with a suitable energy dose such as to induce the heating and, therefore, the vehicle substance sublimation without damaging the molecular structure of the substance of interest.

[0037] Alternatively, the sublimation can take place horizontally on the conventional trays, or within structures which are designed so as to further accelerate the sublimation method, as it will be explained herein below. In any case, also for the horizontal sublimation, the particles are subjected to a suitable heating in a sublimation, or lyophilization, chamber under high vacuum.

[0038] As regards the sublimation vertically performed, three different approaches can be adopted.

[0039] The first one consists in the free fall, under the action of the force of gravity only, the discrete frozen particles along the cavity of the lyophilization chamber, and recovering the lyophilized product essentially consisting in said at least one substance of interest on the same chamber bottom.

[0040] The second approach consists in the treatment of the particles along a guided vertical path in which the particles slide on a sloped plane under the action of the force of gravity. In particular, the inner part of the lyophilization chamber will be provided with a guided path for the particles which is such as to increase their residing time therein. The advantage of such approach is to ensure a higher degree of lyophilization, moreover for those particles which comprise substances which are particularly slow to be sublimed.

[0041] The third approach provides for a treatment which takes place also along a vertically guided path, but, in addition, such path undergoes a vibration in order to allow a higher agitation for the particles and, therefore, to further promote the same particles exposure to the heated and vacuumed environment, thus still improving the sublimation extent.

[0042] As regards the sublimation which is horizontally performed, in this case also there are different implementation approaches.

[0043] A first approach simply consists in the exploitation of the conventional technology, that is the lyophilization chambers in which the products to be processed are deposited on the trays. In this case, the sublimation statically occurs on a horizontal plane.

[0044] Alternatively, the treatment can be carried out by sliding on a sloped plane so as to reduce the thickness of the product to be sublimed, in order to promote the exposure of the particles to the heat source and to the vacuum. Such solution will be able to be efficiently adopted when particularly flowable or rotatable particles must be processed.

[0045] A further variation can be represented by a sliding and vibrational treatment in which the particles, beside sliding or rotating down along a more or less sloped plane, are also subjected to a vibrational motion, so as to make the particles jump upon sliding along the plane. The advantage conferred by this variation is the fact that the particles are subjected to an agitated motion, which causes the continuous turnover thereof in order to avoid their build-up and ensure the maximum exposure to the heat of the whole surface of the particles. In fact, in the most difficult cases, in which the vehicle substance is dammed inside the particle structure, the more is the exposure extent of the particle to the heated environment, or, in other terms, the less is the obstacle on the particle surface, the higher is the possibility or ease to come out from the same particle.

[0046] A further variation is represented by a treatment on a conveyor belt which the particles are deposited on. This variation has the advantage to be able to very easily adjust the residing time for the lyophilization, in the event that the sublimation is particularly troublesome.

[0047] With reference to the Figures, a system for the production of lyophilized substances in accordance with the present invention will be now described.

[0048] In Fig. 1, a system for the production of lyophilized substances is indicated with the reference numeral 1.

[0049] The system 1 comprises a nebulization or atomization and freezing equipment 2 of a mixture comprising at least one substance to be lyophilized, and at least one vehicle substance to be sublimed, which is coupled to a lyophilization equipment 3 of the particles produced by said nebulization or atomization and freezing equipment so as to essentially continuously perform a lyophilization.

[0050] In particular, the nebulization and freezing equipment 2 can be any equipments which are known in the art such as, for example, the one which is described in the previously mentioned U.S. patent.

[0051] Preferably, the nebulization and freezing equipment 2 comprises a closed container 22 equipped with an inlet 20 to allow the inlet of a mixture of substance to be processed, and an outlet 21 to discharge the mixture transformed into fine frozen droplets. In particular, the equipment 2 further comprises a nebulization or atomization device 23 so arranged at said inlet 20 as to receive the mixture and continuously dispense it inside the container in the form of minute droplets.

[0052] The device 23 can be represented by any nebulizing or atomizing nozzle which is known in the art. For example, nozzles with spraying through compressed gas, small toothed rotor and stator turbines, the ultrasonic head manufactured and patented by the Austrian firm DUMAG.

[0053] Furthermore, the vessel 22 can be arranged along a vertical axis X-X, as represented in Fig. 1, so that the freezing of the droplets produced by the nebulizer or atomizer 23 can occur simply by falling.

[0054] Preferably, the container 22 may comprise therein a path (not shown) along which the droplets are constrained in order to extend the residing time thereof in the nebulization and freezing equipment 2, thus promoting a better freezing degree or, anyhow, allowing a more accurate checking for the method.

[0055] In particular, the path can be represented by a helical plate on which the mixture droplets are sprayed which slide upon the plane thereof, while being run over by the cooling fluid. Advantageously, such helical plate can be subjected to a vibration, so as to stir the droplets during the fall thereof in order to allow a homogeneous freezing extent for each droplet. Vibrating means (not shown) allowing such agitation can be represented by conventional vibrating means which confer a sussultatory movement with longitudinal and vertical component to the plate, so that the material is induced to go forward and, concomitantly, to vertically jump. To this aim, the vibrating means will typically comprise, without limitations, an eccentric driving system.

[0056] Alternatively, such vibrating means can be omitted in the case that the mixture to be frozen turns out to be easily processable.

[0057] Preferably, the nebulization and freezing equipment 2 may comprise a recovery chamber (16). The recovery chamber is a kind of jacket covering a variable length of the mixture feeding line, as already described, having the function to recover the cooling gas and sending it along the feeding line in order to pre-cool the mixture to be frozen. In addition, a conventional system for an even distribution of the cooling gas in the chamber 22 beneath can be provided.

[0058] The lyophilization equipment 3 may comprise, as illustrated in Figs. 1, 2A, and 2B, a container or chamber 30 which extends along a horizontal axis Y-Y inside which handling means 31 for the frozen particles to be processed are housed.

[0059] The handling means 31 can comprise a support 32 which the frozen particles coming from the nebulization and freezing equipment 2 are discharged on. Such support can be composed, as represented in Fig. 2A, by one or more trays 33 suitably shaped and arranged in series upon handling, for example, by a conveyor belt 34. Alternatively, the support can be a single plane with adjustable sloping (not shown) which extends almost for the entire container 30 length so as to receive the frozen particles at a first end and let them slide towards the opposite end, simply under the action of gravity.

[0060] Advantageously, as represented in Fig. 2B, the support 32 can be subjected to a vibration, thanks to vibrating means 35 which confer a sussultatory movement with longitudinal and vertical components to the receiving and transporting surface 36 of the frozen particles of said support, so that the material is forced to go forward and, concomitantly, to vertically jump. To this aim, the vibrating means 35 will typically comprise an electromagnetic transmission system or an eccentric transmission system similar to the one described with reference to the nebulization and freezing equipment 2 helical plate.

[0061] With reference to the Fig. 3, a variation of the lyophilization equipment 3 is illustrated.

[0062] In particular, the equipment 300 comprises a container 310 similar to that of the equipment 3, but arranged along a vertical axis Z-Z. Furthermore, handling means 311 comprising a support 321 which extends essentially along the whole container so as to support the frozen particles during the fall thereof are housed inside said container. Such support can be a helical plate. Such plate also can be handled by vibration, as previously explained in order to advantageously improve the lyophilization treatment quality.

[0063] In other terms, the vibration which is conferred to the particles by vibrating means allows exposing the individual particles as more as possible to the environment inside the container 310 in which thermal or electromagnetic energy is applied, so as to induce the heating of the frozen particles and, therefore, the desired sublimation.

[0064] It shall be noticed that the lyophilization equipment in the two variations 3 and 300 is so designed as that the container 30, 310 inner surface is electrolytically polished.

[0065] In addition, all the connection points to the several devices and equipments are provided with a high vacuum connection of the smooth surface type, and with "O"-rings if a static seal is necessary, and a rotating one if a double mechanical seal is required.

[0066] Preferably quartz infrared-transparent accesses, both to supply of the electromagnetic energy from outside, and to allow the control of the particle surface temperature by means of contactless readers; visible spectrum transparent accesses for the visual check of the evolution of the process inside; vacuum sealing connections for instruments necessary to the sensing of operative parameters such as room temperature, inner pressure, microwave field data are also provided (not shown).

[0067] The nebulization and freezing equipment 2 is advantageously coupled to the lyophilization equipment 3 by means of a continuously transferring device 4 of the discrete frozen particles produced in said equipment 2.

[0068] In particular, the transferring device 4 comprises in turn a vacuum generating chamber 5 and a collection and continuous, gradual release device 6 of the particles.

[0069] The vacuum generating chamber 5 can be advantageously represented by a channel which is continuous with the outlet 21 of the nebulization and freezing equipment 2, and closed in the proximity of said outlet by a first controllably openable gate or lid 51 to allow the fall therein of the discrete frozen particles. Furthermore, the chamber 5 is closed at its end opposite said outlet by a second controllably openable gate or lid 52 to allow the discharge of the particles inside the collection and release device 6.

[0070] Preferably, the vacuum generating chamber 5 is divided in a number of sectors or compartments 50 by further gates or lids 53. In this way, the vacuum chamber 5 can be divided in a number of sectors inside which the vacuum is increased to increasingly higher values upon reaching the lyophilization equipment 3. Therefore, the sector which is more proximate to the equipment 2 will not have very high vacuum pressure values, while the sector which is more proximate to the equipment 3 will have values which are equal to or near the high vacuum generated in said equipment.

[0071] The provision of a vacuum chamber 5 has the advantage to prepare the discrete frozen particles in the best way for the reception by the equipment 3 and already treated in the suitable conditions. In fact, if the particles were forced to directly pass through the slightly overpressurized environment of the equipment due to the presence of the nitrogen which is inputted for the countercurrent freezing 2 to a high vacuum environment, such as the inner part of the heated equipment 3, they will undergo, by one hand, a pressure and thermal shock which could cause alterations to the aggregative structure of the particles and, on the other hand, it would result in a so-called "blow-by effect". The blow-by effect consists in a continuous inflow of the inert gases which are used for the freezing step in the vacuum chamber, consequently having to oversize the vacuum generation system power because of the excess of said inert gases.

[0072] The collection and gradual continuous release device 6 of the particles can be represented, for example, by a simple funnel or hopper (not shown) in which a collecting portion is relatively large, so as to collect the particles coming from the vacuum chamber 5, while a discharge portion is restricted, so as to allow a constant, continuous release of said particles inside the lyophilization chamber 30.

[0073] Alternatively, said device comprises collecting means 60 of the particles coming from the vacuum chamber 5, and discharge means 7 so as to discharge said particles in the lyophilization chamber 30.

[0074] Preferably, the collecting means 60 consist in valve means such as, for example, controlled flow rate rotative valves. These types of valves can be implemented so as to allow a further removal of optional gas residues by suction at these valves.

[0075] The discharge means 7 can be represented by any member which is able to receive the particles which are collected by the collecting means 6, and to deposit them in an essentially continuous manner inside the freeze-dryer.

[0076] Preferably, said means 7 comprise a chamber 71 sealingly connected at one end to the discharge means 6 and, at the other end, to the lyophilization equipment 3, a coil 72, and a movement system 73 adapted to control the movement of said coil. Such means not only continuously operate, but also so as to move a constant amount of particles. In particular, the means consist in a open coil screw, the movement of which allows meeting the requirement of an essentially continuous deposition of prefixed amounts of material.

[0077] The system 1 of the invention can further comprise a discharge device 8 for the lyophilized material. The device preferably comprises a "diverter" valve 81 to direct the exiting lyophilizate flow to two alternately operating collecting volumes/tanks 91 and 92. Two closures 82 and 83 arranged in series on the two valve 81 outlets ensure a perfect sealing against the room pressure.

[0078] Downstream said closures 82 and 83, the system 1 is equipped with two collecting tanks 91 and 92 for the lyophilized product.

[0079] Preferably, the tanks 91 and 92 are kept at a constant temperature with dry, optionally sterile, air or nitrogen atmosphere blanketing during the lyophilizate collecting step.

[0080] Furthermore, the tanks 91 and 92 can be dimensioned so as to have such a volume that allows performing suitable quality tests by drawing samples from the mass without interrupting the whole process or parts thereof.

[0081] Alternatively, the device can be equipped with systems with a single tank having the function to allow the above-mentioned test and dosing operations for the supply of successive manufacturing processes directly connected to the production line. For example, such processes can comprise the packaging step.

[0082] In addition, a pressurized tank 13 is connected to the freezing device 2 for the liquid nitrogen which is employed as a freezing fluid, or other cryogenic liquid, as stated before.

[0083] In addition, also a container 15 is in communication with the inlet 20 of the device 2 so as to continuously supply it with the mixture of the substances to be lyophilized and to be sublimed. Preferably, the mixture is kept under agitation by means of conventional stirrers 14.

[0084] The system 1 of the invention can be equipped with a cooling unit 10, a powering unit 11, and a vacuum unit 12.

[0085] In particular, the nebulization and freezing equipment 2 can be coupled to a cooling unit 10 of the conventional type so as to receive a cooling fluid which countercurrently run over the mixture nebulized particles which fall by gravity from the inlet 20 to the outlet 21 of said equipment 2.

[0086] The powering unit 11 is employed to supply energy to the particles to be subjected to sublimation. The powering unit can be connected to several energy sources for the transmission to the particles, so as to induce the heating thereof and the sublimation of the vehicle substances. Powering units of this type are broadly known, therefore they will not be set forth in detail herein.

[0087] Among the energy types which may be employed, the thermal energy is the most spread. The thermal energy can be supplied by plates or electric resistances (not shown) which are superiorly, inferiorly, and/or laterally arranged in relation to the trays or any of the support and handling systems of the discrete frozen particles previously described.

[0088] Alternatively, the employed energy can be energy from electromagnetic waves, such as microwaves or infrared waves. Furthermore, the above-mentioned upper, lower, and/or side arrangement can be adopted also in the case of said alternative sources.

[0089] In particular, the microwave energy can be generated by a magnetron with adjustable power, 10% to 100%, according to the type, flow rate, and characteristics of the vehicle substance which must be treated. The magnetron is sized according to the geometric parameters of the lyophilization device 3 and the specific consumption for the vehicle substance sublimation. These equipments are available in the market from specialized firms. Furthermore, the employment thereof on the basis of the above-mentioned substance types is within the skill of those of ordinary skill in the art.

[0090] As regards infrared energy, it can be used by itself, or associated to microwaves. In fact, the infrared radiations can be employed to heat the particles surface, thus allowing the sublimation of the surface molecules of the vehicle substance, while the microwaves heat more quickly the inner part of the particles, thus allowing the sublimation of the vehicle substance entrapped after that the surface has been at least partially cleared.

[0091] Appliances for infrared radiation emission of are well known, such as, for example, lamps provided with power adjusting means in order to meet different needs.

[0092] The transferring equipment 4 of the mixture discrete frozen particles is handled in each of the components thereof by conventional handling means (not shown) of the hydraulic or pneumatic type and which are synchronically controlled in order to ensure the proper continuous operation of the whole lyophilization method, as it will be explained herein below.

[0093] The vacuum unit 12 may comprise a conventional vacuum pump such as a mechanic, fluid jet, condensation, adsorption, or ionization pump. Such unit is mainly connected to the lyophilization equipment 3 for the generation of vacuum therein, but also to the vacuum chamber 5 of the transferring device 4 of the particles from the nebulization and freezing device 2 to the lyophilization equipment 3.

[0094] The operation of the whole system 1 of the invention is controlled and operated by means of a system comprising a controlling and operative unit (UCC) which is connected, through electrical cables lines, or wireless transmissions, to sensors (not shown) which are mounted at each handling device or member. The connections are implemented through dedicated lines, which are adapted both to receive and send electrical signals for each system equipment or device which needs to be checked.

[0095] In particular, as represented in Fig. 1, the line L1 connects the controlling and operative unit to the freezing unit 10, the line L2 to the nitrogen tank 13, the line L3 to the nebulization and freezing equipment 2, the line L4 to the vacuum unit 12, the line L5 to the vacuum chamber 5 and to each correposnding compartment and gates, the line L6 to the collecting device 6 of the frozen particles, the line L7 to the discharge device 7 of the frozen particles, the line L8 to the valve 81, the closures 82 and 83 of the discharge device 8, the line L9 to the tanks 91 and 92 of the lyophilizate, the line L10 to the lyophilization equipment 3, the line L11 to the energy unit 11 for the transferring of energy to the lyophilization equipment 3, and the line L12 to the stirring tank 15 of the mixture to be lyophilized.

[0096] Furthermore, the controlling and operative unit comprises an electronic processor (not shown), such as a personal computer, equipped with hardware and software suitable to receive electrical signals from the sensors of said devices and members and to convert them into values. These values are representative of the operational status of each member or device, or are indicative of the inner conditions of said devices or instruments. Furthermore, the processor is equipped with a memory in which baseline values can be present for the operative parameters which are intrinsic of each equipment or device and preset on the basis of the kind of substance which must be lyophilized. Such values are continuously compared to the values continuously sensed by the above-mentioned sensors and, in the case that some deviation should be reported compared to the baseline values, the processor intervenes, by sending control signals to the equipment or device, in order to bring the operative values back within the baseline ones.

[0097] During the operation of the system 1 for the continuous production of lyophilized substances, a mixture of at least one substance of interest and at least one vehicle substance is prepared and put into the container 15, where it is kept under stirring by the stirrer 14.

[0098] From the container 15, the mixture is continuously transferred to the inlet 20 of the nebulization and freezing equipment 2 simply by gravity, or by means of a pump (not shown), the flow of which is controlled by the above-mentioned controlling and operative unit. Once the equipment 2 has been reached, the mixture passes through the nebulizer 20, which transforms the liquid mixture into minute droplets. The droplets fall inside the container 2 towards the outlet 21, and are concomitantly countercurrently run over by the cooling fluid which has been put into by a pump (not shown) which draws in the tank 13.

[0099] When the frozen particles reach the outlet 21 of the nebulization and freezing device 2, they build up at the first gate 51 of the vacuum chamber 5. At preestablished intervals, which are set by the controlling and operative unit, for example, when a preset amount of nebulized frozen particles has been reached, the gate 51 is opened to make the particles fall into the first compartment 50 of the chamber 5, then it is immediately closed again. At this point, some amount of vacuum is generated, which is not too high in order not to create a sudden pressure differential, which could damage the molecular structure of the substance of interest. Subsequently, the next gate 53 is opened downstream said first gate, to make the particles pass into a further compartment 50 in which, once said further lid has been closed again, a higher degree of vacuum is generated. Further steps, which are identical to the one just described, can be provided in the downstream compartments until reaching a vacuum extent which is similar to the one which is present in the lyophilization equipment 3.

[0100] As previously explained, the flow of nebulized particles and the opening of the vacuum chamber lids are synchronically controlled and operated by the operative and control unit, so as to ensure an essentially continuous flow of particles. Furthermore, the flow rate of the nebulization flow, the freezing temperature, the freezing fluid flow of the vacuum degree in each compartment of the vacuum chamber are always controlled and operated by said controlling and operative unit.

[0101] For example, the opening and closing of the gates 51, 52, and 53, of the vacuum chamber 5 must be operated so that the compartments 50 are mutually insulated when the vacuum has to be applied. In fact, as previously described, the compartments are subjected to increasing vacuum degrees from the equipment 2 to the equipment 3, where there is a high vacuum. Therefore, the control and operational unit operates the activation of the pump, to generate the device 12 vacuum inside a particular sector of the vacuum chamber and concomitantly generate increasing vacuum degrees in the different compartments.

[0102] When the nebulized and frozen particles have reached the gate 52 dividing the chamber 5 from the collection and release device 6, this opens to make the particles fall into the collecting means 6. As previously explained, the collecting means can be such as to collect the particles and continuously release them (funnel) or at regular intervals (rotative valves) to the deposition member 7 in a continuous manner inside the lyophilization equipment 3.

[0103] Then, the particles are essentially continuously deposited inside the lyophilization equipment 3 so as to fall onto the support 32. At this point, the frozen particles are subjected to a vacuum heating to induce the vehicle substance sublimation. In particular, the powering unit 11 supplies energy to the particles in the form of thermal energy and/or electromagnetic energy in preset amounts, on the basis of the type of product which is desired, and operated by the operative and control unit. Concurrently, the vacuum unit 12 generates an extent of vacuum, also preestablished and controlled, again by the operative and control unit.

[0104] After a period of time which varies according to the product type under processing, the particles sublimate, that is, the lyophilizate of the substance of interest, are discharged from the support 32 to the discharge device 8. As previously explained, the discharge device 8 discharges the lyophilizate alternatively in the tanks 91 and 92 kept at the same degree of vacuum as the lyophilization equipment 3.

[0105] From what has been so far described, it shall be apparent that the system in accordance with the invention advantageously allows producing a substance which is lyophilized in an essentially continuous manner. This involves a considerable advantage from the productive point of view, since the downtimes represented by the above-mentioned equipment and component handling and preparation operations are minimized. Meanwhile, possible contacts with the outside are avoided, which could cause a contamination of the products, above all when substances for pharmaceutical use are being processed, just thanks to the closed system of the above-mentioned system. In addition, the system allows implementing the method previously described, thanks to which not only the drawbacks present in the prior art systems are avoided, but, above all, the production time is drastically reduced and the end product quality is drastically improved.

[0106] Other advantages are a reduction of the overall dimensions compared to the current technologies, in particular if the required production is substantial, the conventional systems must have considerable dimensions in order to meet such needs. The continuous processing also allows for an optimization of the specific energetic consumptions.

[0107] Consequently, the method and the system of the present invention allow meeting the needs set forth in the introductive part of the present description, and concurrently providing the several advantages which have been described before compared to the methods and the equipments of the prior art.

[0108] However, those of ordinary skill in the art will be able to make further variations to the invention, all of which are in any case to be considered within the protection scope of the following claims.

Claims

1. A method for the production of lyophilized substances comprising the following successive steps:

- providing a mixture containing at least one substance to be lyophilized, and at least one vehicle substance to be sublimed;
- causing said mixture to undergo a nebulization treatment in order to form fine droplets;
- flash freezing said mixture droplets so as to form solid particles having discrete dimensions containing said at least one substance to be lyophilized and said at least one vehicle substance;
- sublimating said frozen particles;
- recovering the sublimation product in the form of solid aggregates having dimensions ranging between 5 and 500 microns.

2. The method according to claim 1, wherein such mixture is a solution or suspension of one or more pharmaceutical, food, cosmetic substances, fragrances, preservatives, substances for veterinary or agronomic use.

3. The method according to claim 1 or 2, comprising a pre-cooling step of said mixture.

4. The method according to any claim 1 to 3, wherein the nebulization is performed by nozzle nebulization with spraying using compressed gas, nebulization through dynamic rotative heads, or sonic or ultrasonic energy nozzles.

5. The method according to any claim 1 to 4, wherein the nebulization is carried out with atomizers exploiting the vibration of resonating metallic elements or nozzles comprising an axially-perforated nozzle, a member without nozzle having an angulated reflecting end, a member with vibrating planar plate.

6. The method according to any claim 1 to 5, wherein the freezing step occurs by free fall of the mixture droplets produced in the nebulization step, inside a freezing chamber, during which said droplets are countercurrently run over by a cooling fluid.

7. The method according to any claim 1 to 6, wherein the sublimation step is vertically carried out, wherein the discrete solid frozen particles fall by gravity inside a chamber which is under high vacuum and is passed through by thermal and/or electromagnetic energy, or it is horizontally performed on heated supports (trays).

8. A system (1) for the production of lyophilized substances comprising a nebulization or atomization and freezing equipment (2) of a mixture comprising at least one substance to be lyophilized, and at least one vehicle substance to be sublimed, which is coupled to a lyophilization equipment (3; 300) for the particles produced by said nebulization or atomization and freezing equipment so as to essentially continuously carry out a lyophilization.

9. The system (1) according to claim 8, wherein said nebulization and freezing equipment (2) comprises a closed container (22) equipped with an inlet (20) to allow the inlet of a mixture of substance to be processed, and an outlet (21) so as to discharge the mixture transformed into fine frozen droplets, and a nebulization or atomization device (23) arranged at said inlet (20).

10. The system (1) according to claim 9, wherein the container (22) comprises therein a path along which the droplets are constrained in order to expand the residing time thereof in the equipment.

11. The system (1) according to claim 10, wherein said path is a helical plate which the mixture droplets are sprayed on, which, upon falling, slide on the plane thereof, while being run over by the cooling fluid, such helical plate being optionally subjected to a vibration.

12. The system (1) according to claim 11, wherein said plate is handled by vibrating means which confer a sussultatory movement with longitudinal and vertical component to the plate.

13. The system (1) according to any claim 8 to 12, wherein said equipment (2) comprises a recovery chamber (16) and an even distribution system of the cooling fluid.

14. The system (1) according to any claim 8 to 13, wherein said equipment (3) comprises a container or chamber (30) which extends along a horizontal axis (Y-Y), and inside which handling means (31) of the frozen particles to be processed are housed.

15. The system (1) according to claim 14, wherein the handling means (31) comprise an optionally heated support (32) which the frozen particles coming from the nebulization and freezing equipment (2) are discharged on.

16. The system (1) according to claim 15, wherein such support (32) is represented by one or more trays (33) which are suitably shaped and arranged in series, for example, handled by a conveyor belt (34).

17. The system (1) according to claim 15, wherein said support (32) is a single plane with adjustable sloping, which extends almost for the whole container (30) length so as to receive the frozen particles at a first end, and let them slide towards the opposite end under the action of gravity.

18. The system (1) according to claim 15, wherein said support (32) is subjected to vibration thanks to vibrating means (35) which confer a sussultatory movement with longitudinal and vertical components to the frozen particles, so that the material is forced to go ahead and concomitantly to vertically jump.

19. The system (1) according to claim 18, wherein said vibrating means (35) comprise an electromagnetic transmission system, or an eccentric transmission system.

20. The system (1) according to claim 8, wherein said equipment (300) comprises a container (310) arranged along a vertical axis (Z-Z), inside which handling means (311) comprising a support (321) which extends essentially along the whole container are housed, so as to support the frozen particles during the fall thereof.

21. The system (1) according to claim 20, wherein such support (321) is a helical band, optionally handled by vibration.

22. The system (1) according to any claim 8 to 21, wherein the nebulization and freezing equipment (2) is coupled to the lyophilization equipment (3; 300) by means of a continuously transferring device (4) of the discrete frozen particles which are produced in said equipment (2).

23. The system (1) according to claim 22, wherein said transferring device (4) comprises a vacuum generating chamber (5) and a collecting and gradual continuously release device (6) of the frozen particles.

24. The system (1) according to claim 23, wherein said vacuum generating chamber (5) is a duct which is continuous with the outlet (21) of the nebulization and freezing equipment (2) and is closed in the proximity of said outlet by a first controllably openable gate (51) to allow the fall therein of the discrete frozen particles.

25. The system (1) according to claim 24, wherein said chamber (5) is further closed at its end opposite said outlet (21) by a second controllably openable gate (52) to allow the discharge of the particles inside the collecting and releasing device (6).

26. The system (1) according to claim 24 or 25, wherein said vacuum generating chamber (5) is divided in a number of compartments (50) by further gates (53) or lids.

27. The system (1) according to any claim 23 to 26, wherein said collecting and gradual continuous releasing device (6) is a funnel or hopper wherein a collecting portion is relatively large, so as to collect the particles coming from the vacuum chamber (5), while a discharge portion is reduced, so as to allow a constant and continuous release of said particles inside the lyophilization chamber (30; 300).

28. The system (1) according to any claim 23 to 26, wherein said device (6) comprises collecting means (60) of the particles coming from the vacuum chamber (5), and discharge means (7) so as to discharge said particles in the lyophilization chamber (30; 311).

29. The system (1) according to claim 28, wherein said collecting means (60) consist in valve means such as, for example, controlled flow rate rotative valves.

30. The system (1) according to claim 28 or 29, wherein discharge means (7) comprise a chamber (71) sealingly connected at one end to the discharge means (6), and at the other end to the lyophilization equipment (3), a coil (72), and a magnetic sealing and movement system (73).

31. The system (1) according to any claim 8 to 30, further comprising a discharge device (8) for the lyophilized material.

32. The system (1) according to claim 31, wherein said device (8) comprise a valve "diverter" (81) to direct the exiting lyophilizate flow to two alternatively operating lyophilizate collecting tanks (91, 92).

33. The system (1) according to claim 32, wherein two closures (82, 83) are arranged in series on the two valve (81) outlets in order to ensure the perfect sealing against the room pressure.

34. The system (1) according to claim 32 or 33, wherein said tanks (91, 92) are kept at a constant temperature with dry, optionally sterile, air or nitrogen atmosphere blanketing during the discharge of the lyophilized substances.

35. The system (1) according to any claim 8 to 34, further comprising a cooling unit (10) coupled to the nebulization and freezing equipment (2).

36. The system (1) according to any claim 8 to 35, further comprising a powering unit (11) to supply energy to the particles to be subjected to sublimation.

37. The system (1) according to any claim 8 to 36, wherein said powering unit (11) is connected to thermal energy or electromagnetic wave energy sources.

38. The system (1) according to any claim 8 to 37, further comprising a system comprising a controlling and operative unit (UCC) connected, though electric cables lines or wireless connections, to sensors which are mounted at each handling device or member.

39. The system (1) according to claim 38, wherein said controlling and operative unit comprises an electronic processor which is equipped with hardware and software suitable to receive electrical signals from the sensors of said devices and members, and to transform them into values representative of the operational status of each member or device, or indicative of the inner conditions of said devices or equipments, said processor being equipped with a memory in which there are baseline values for the typical operative parameters for each equipment or device and which are preset on the basis of the type of substance which must be lyophilized.

40. The system (1) according to claim 39, wherein said processor is so configured as to compare in a continuous manner said baseline values in relation to the continuously sensed values by the above-mentioned sensors and, in the event that some amount of deviation in relation to the baseline values should be sensed, the processor intervenes, by sending control signals to the equipment or device, in order to bring the operational values back within the baseline ones.

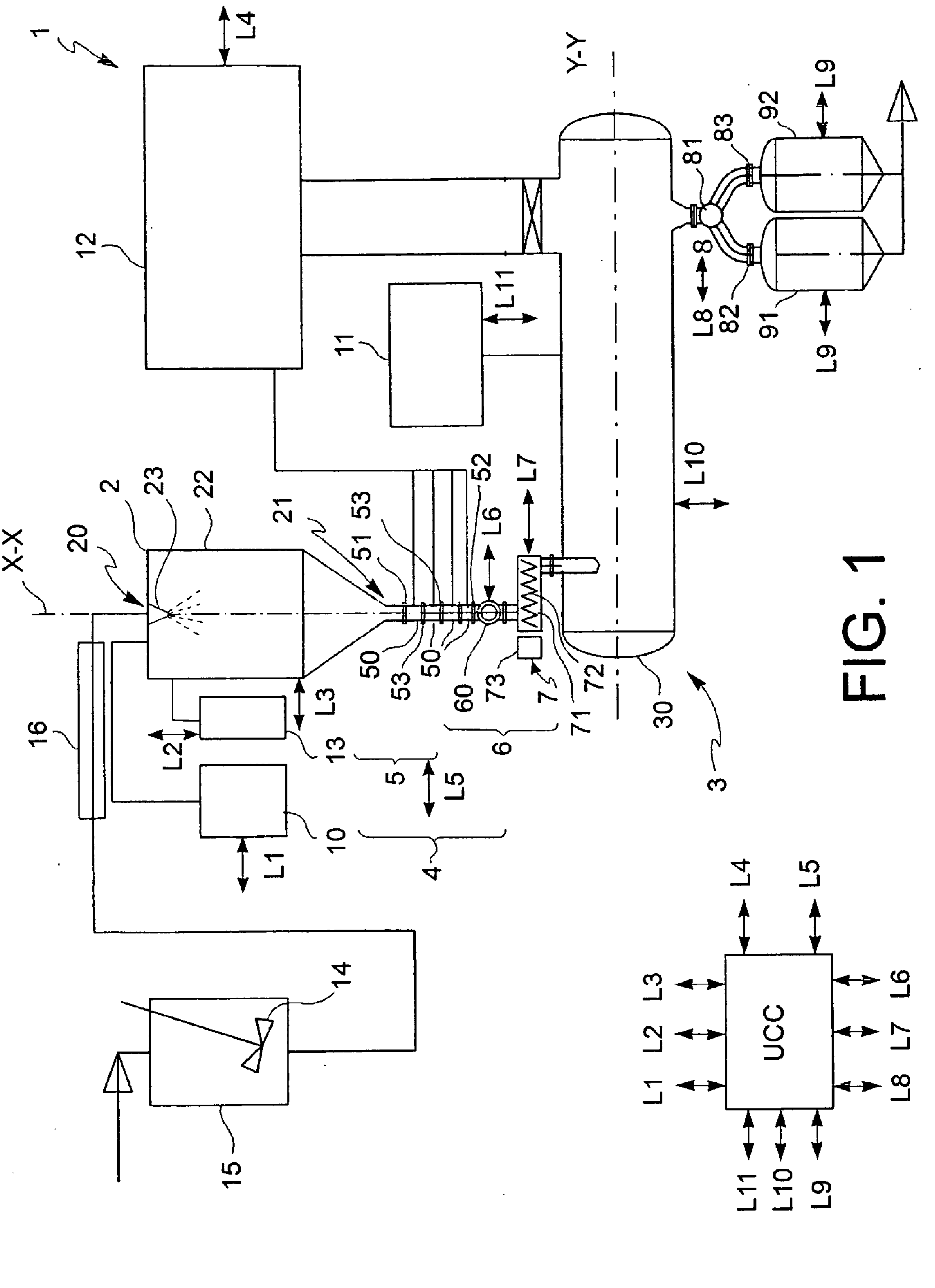

1
12
L4
Y-Y
X-X
11
L11
2
20
22
23
21
51
53
52
50
60
L6
L7
L10
73
7
71
72
30
3
6
5
L5
4
13
L2
L3
10
L1
16
14
15
8
81
82
83
91
92
L8
L9
UCC
L1
L2
L3
L4
L5
L6
L7
L8
L9
L10
L11

FIG. 1

FIG. 2A

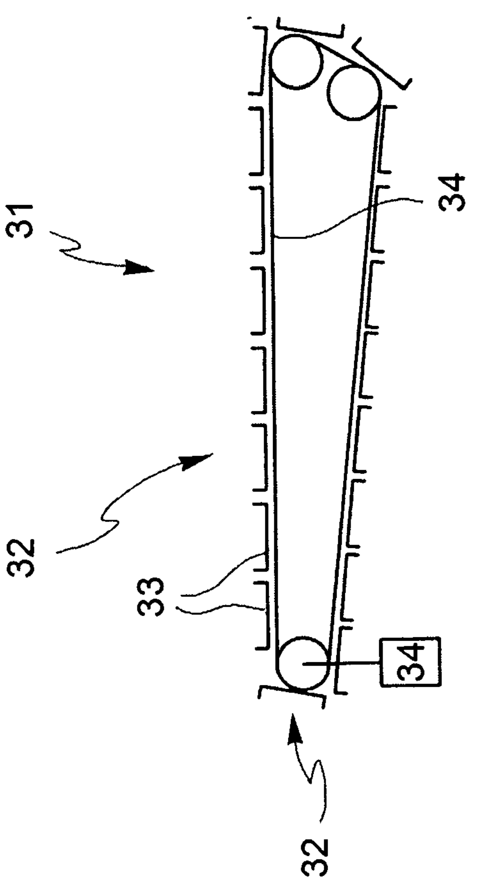
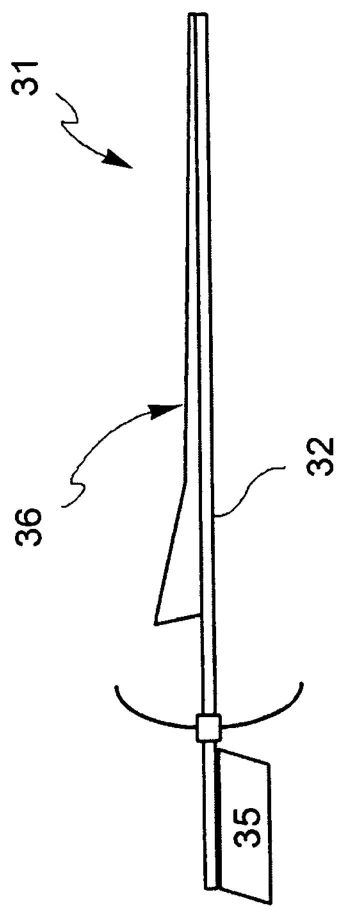


FIG. 2B



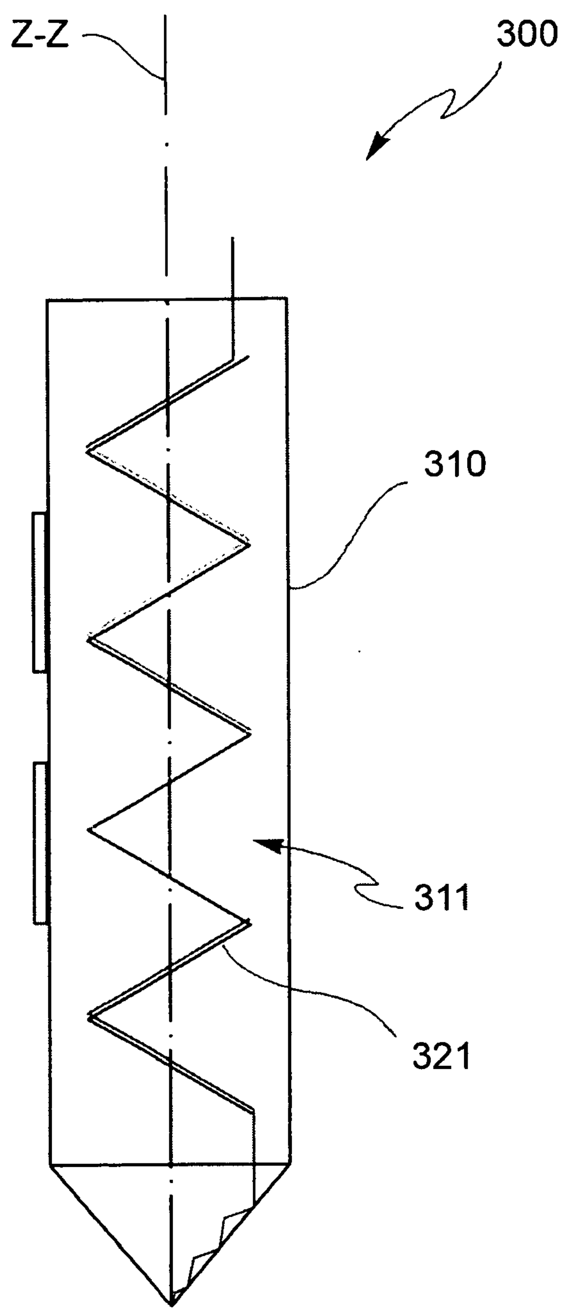


FIG. 3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 07 42 5840

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 2005/105253 A (AGRES LTD [NZ]; CARSON JAMES KENNETH [NZ]; HILL HAROLD KEITH [NZ]; GRA) 10 November 2005 (2005-11-10)	1-4,6-9, 13-19, 22,31, 35-37	INV. F26B5/06
Y	* the whole document *	5,20,21, 23-26, 28,29	
D,Y	US 5 707 636 A (RODRIGUEZ LORENZO [IT] ET AL) 13 January 1998 (1998-01-13) * column 5, lines 9-31 *	5	
Y	US 3 574 951 A (OETJEN GEORG-WILHELM ET AL) 13 April 1971 (1971-04-13) * the whole document *	20,21	
Y	US 3 431 655 A (GROVER KENNETH M ET AL) 11 March 1969 (1969-03-11) * column 2, lines 19-36; figure 1 *	23-26, 28,29	
X	US 5 230 162 A (OYLER JR JAMES R [US]) 27 July 1993 (1993-07-27)	1,2,4, 7-9,13, 22,31, 35-37	TECHNICAL FIELDS SEARCHED (IPC)
Y	* the whole document *	10,11, 32-34	F26B
Y	US 4 608 764 A (LEUENBERGER HANS [CH]) 2 September 1986 (1986-09-02) * column 12, line 55 - column 14, line 4; figure 3 *	10,11	
Y	GB 1 027 176 A (HUPP CORP) 27 April 1966 (1966-04-27) * page 5, lines 24-36; figure 1 *	32-34	

-/--

The present search report has been drawn up for all claims

1

Place of search	Date of completion of the search	Examiner
The Hague	19 June 2008	Silvis, Henk

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons
& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 07 42 5840

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 3 362 835 A (ERIK THUSE ET AL) 9 January 1968 (1968-01-09) * the whole document *	1,2,4, 7-9, 14-19, 22,31	
A	GB 952 920 A (VICKERS ARMSTRONG LTD) 18 March 1964 (1964-03-18) * the whole document *	12,20, 27,30	
A	US 3 616 542 A (RADER EARL L) 2 November 1971 (1971-11-02) * column 11, lines 46-68; figure 2 *	34	
A	US 3 621 587 A (SMITH HORACE L JR) 23 November 1971 (1971-11-23)		
A	US 5 208 998 A (OYLER JR JAMES R [US]) 11 May 1993 (1993-05-11)		
A	FR 1 356 477 A (BARBARESCHI) 27 March 1964 (1964-03-27)		TECHNICAL FIELDS SEARCHED (IPC)
A	DE 10 2004 005660 A1 (RHEINISCHE FRIEDRICH WILHELMS [DE]) 25 August 2005 (2005-08-25)		
A	US 4 033 048 A (VAN IKE CLAYTON) 5 July 1977 (1977-07-05)		
A	US 3 300 868 A (FRITZ ANDERWERT) 31 January 1967 (1967-01-31)		
A	US 3 313 032 A (MALECKI GEORGE J) 11 April 1967 (1967-04-11)		

The present search report has been drawn up for all claims

1

Place of search	Date of completion of the search	Examiner
The Hague	19 June 2008	Silvis, Henk

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 07 42 5840

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

19-06-2008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005105253 A	10-11-2005	AU 2005237933 A1	10-11-2005
		BR PI0510529 A	30-10-2007
		CA 2565136 A1	10-11-2005
		EP 1742716 A1	17-01-2007
		JP 2007535652 T	06-12-2007
		KR 20070047239 A	04-05-2007
US 5707636 A	13-01-1998	AT 202279 T	15-07-2001
		AU 693539 B2	02-07-1998
		AU 2113795 A	04-03-1996
		BR 9506305 A	05-08-1997
		CA 2173221 A1	15-02-1996
		CN 1135175 A	06-11-1996
		DE 69521406 D1	26-07-2001
		DE 69521406 T2	02-05-2002
		DK 726765 T3	15-10-2001
		EP 0726765 A1	21-08-1996
		ES 2159632 T3	16-10-2001
		GR 3036548 T3	31-12-2001
		WO 9603979 A1	15-02-1996
		IT BO940379 A1	05-02-1996
		JP 9503441 T	08-04-1997
		PT 726765 T	28-12-2001
		RU 2142792 C1	20-12-1999
US 3574951 A	13-04-1971	FR 2006889 A5	02-01-1970
US 3431655 A	11-03-1969	BE 728116 A	07-08-1969
		GB 1195363 A	17-06-1970
US 5230162 A	27-07-1993	NONE	
US 4608764 A	02-09-1986	CH 664005 A5	29-01-1988
		DE 3516967 A1	21-11-1985
		JP 1988709 C	08-11-1995
		JP 7018645 B	06-03-1995
		JP 60253783 A	14-12-1985
GB 1027176 A	27-04-1966	GB 1027177 A	27-04-1966
US 3362835 A	09-01-1968	DE 1604879 A1	14-01-1971
		GB 1086251 A	04-10-1967
GB 952920 A	18-03-1964	CH 384471 A	15-11-1964
US 3616542 A	02-11-1971	CA 920502 A1	06-02-1973

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 07 42 5840

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

19-06-2008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3616542 A		DE 2008098 A1	10-09-1970
		FR 2032371 A5	27-11-1970
		GB 1275381 A	24-05-1972
		GB 1275382 A	24-05-1972
		GB 1275383 A	24-05-1972
		IE 34012 B1	08-01-1975
		IL 33928 A	30-06-1974
		JP 54031068 B	04-10-1979
		SE 363889 B	04-02-1974
US 3621587 A	23-11-1971	NONE	
US 5208998 A	11-05-1993	NONE	
FR 1356477 A	27-03-1964	NONE	
DE 102004005660 A1	25-08-2005	NONE	
US 4033048 A	05-07-1977	NONE	
US 3300868 A	31-01-1967	CH 408781 A	28-02-1966
		DE 1604768 A1	29-01-1970
		ES 312609 A1	01-01-1966
		GB 1066938 A	26-04-1967
		NL 6505303 A	25-10-1965
US 3313032 A	11-04-1967	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 5707636 A **[0027]**