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

(11) EP 4 105 585 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
21.12.2022 Bulletin 2022/51

(21) Application number: **21180228.5**

(22) Date of filing: **18.06.2021**

(51) International Patent Classification (IPC):
F26B 5/06 $^{(2006.01)}$ ***F26B 25/22*** $^{(2006.01)}$

(52) Cooperative Patent Classification (CPC):
F26B 5/06; F26B 25/22

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME
Designated Validation States:
KH MA MD TN

(71) Applicant: **CRYOGENIC AND VACUUM SYSTEMS, SIA**
3601 Ventspils (LV)

(72) Inventors:
- **Kravchenko, Sergey**
  3601 Ventspils (LV)
- **Kulesovs, Nikolajs**
  1003 Riga (LV)
- **Panova, Natalia**
  3601 Ventspils (LV)
- **Bratarcuks, Sergejs**
  1079 Riga (LV)
- **Voleina, Dmitrijs**
  3601 Ventspils (LV)

(74) Representative: **Fortuna, Jevgenijs**
Foral Patent Law Office
Kaleju iela 14-7
1050 Riga (LV)

(54) **FREEZE-DRYING METHOD AND APPARATUS**

(57) The invention relates to devices and methods for freeze-drying. According to the proposed method and device for freeze-drying, the process control of sublimation of a substance uses the temperature *T,* pressure *P,* and the Clausius-Clapeyron equation as control parameters to determine the values of control actions. Controlling influences on the sublimation process is determined by their ratio. The temperature was selected as the main parameter, and pressure was selected as the correcting control parameter.

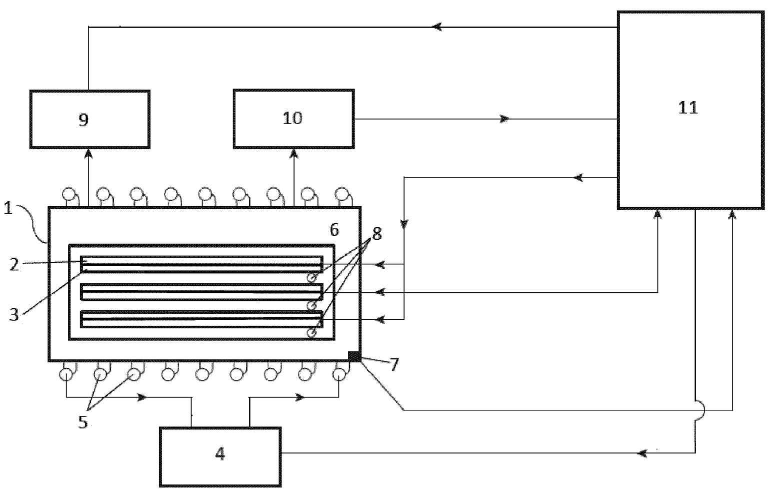


Fig. 1

Description

Technology area

[0001] The invention relates to devices and methods for freeze-drying.

Prior art

[0002] Freeze-drying refers to the removal of moisture from frozen materials, such as food, medicine, and others, by sublimation of ice. Freeze-drying is based on the ability of ice to evaporate under certain conditions, bypassing the liquid phase. In industrial conditions, the drying process is carried out in a vacuum at a pressure of the vapor-gas medium below the pressure corresponding to the triple point of the substance phase transformation.

[0003] Freeze-drying has several advantages over traditional preservation methods: there is no need for refrigeration since dry food can be stored for a long time at positive temperatures; the sales system of such goods is simplified and the time of their sale is increased; in addition, the taste of the product remains virtually unchanged.

[0004] A known method and device for freeze-drying (US9459044). The known method includes reducing the pressure to the first vacuum pressure, as a result of which the control system automatically activates the heater. Further, the method includes increasing the pressure to the second value of a vacuum pressure exceeding the value of the first pressure, where, as a result of reaching the value of the second pressure, the control system automatically turns off the heater. The result is a decrease in pressure, reactivation of the heater, sublimation of water, and an increase in pressure, which leads to the next turn-off of the pressure-activated heater. Another freeze-drying method involves lowering the temperature in the chamber of the device to -45.5 °F or below using a refrigeration system with a one-stage vacuum pump and sublimation under reduced pressure in the chamber of the device. The freeze dryer includes a chamber, a vacuum pump, a heater, and a control system programmed with instructions in effect to cycle through the pressure-activated heater. The main disadvantage of the known solution is the occasional shutdown of the heating elements, which leads to a decrease in the supply of thermal energy to the sublimated product, that is, the intensity of sublimation decreases. This mode of operation of the device leads to an increase in the time of its operation until the desired result is achieved, thereby reducing its performance.

[0005] A known method for monitoring and controlling the process of lyophilization of a solution of a frozen product using a wireless sensor network (US2020340743). The method includes arranging one or more wireless pressure sensors configured to fit into a lyophilization vial tray located in a lyophilization chamber having a plurality of product vials, wherein the wireless pressure sensors are distributed between the lyophilized product vials, thereby providing spatial pressure measurement, collection information on the spatial pressure from the specified wireless pressure sensors, calculation of the sublimation rate of the solution, and regulate the pressure and/or temperature in the lyophilization chamber so that the calculated sublimation rate remains within the specified ranges of parameters. Thus, the known process of the device operating modes control is based on the solvent evaporation rate control, and the process control is designed in such a way that the sublimation process should be the real sublimation process, and not a vacuum drying process (drying at low pressure and possibly at low temperature, but not lower than pressure and temperature of the triple point of the phase transformation of the substance). This protects the base substance from degradation, which is very important, for example, for pharmaceutical and cosmetic substances. The Navier-Stokes equation is used as a tool for determining the control actions on the sublimation process and some parameters in the sublimation chamber required to solve this equation are measured by the abovementioned sensors. The parameters required are the temperature of the gases, and precisely the gradient of the gas's temperature, which is flowing away and carry out the sublimated substance, and the pressure of the gases, in the places where the corresponding gas pressure and temperature sensors are installed. The main disadvantage of the known solution is the use of the gas temperature gradient to control the sublimation process, which only indirectly characterizes the temperature of the sublimated product, and since the solutions of substances in the sublimated products have a complex composition and the intensity of their evaporation depends not only on the temperature and pressure of the gases inside the chamber but also on the fractional the composition of the evaporated substances and their differences even for one type of sublimation products. At the same temperature and pressure of the air-vapor medium inside the chamber, the evaporation rate of the products depends on the fractional composition of the product, and over time the evaporation rate changes, since the lighter fractions volatilize easily; an example of a solution of alcohol in water - first alcohol begins to evaporate intensively, and only then, as the temperature rises, water begins to evaporate, or another example - oil rectification. Failure to take these circumstances into account leads to distortion of control actions, which reduces the quality of the sublimated product and reduces the productivity of units.

Disclosure of the invention

[0006] The invention aims to eliminate the disadvantages of prior art. This goal is achieved by the proposed method and device for freeze-drying, according to which, to control the process of sublimation of the substance, temperature T, pressure P, and the Clausius-Clapeyron equation are used as control parameters and to determine the values of control actions. Controlling influences on the sublimation process is determined by their ratio. The temperature was selected as the main parameter and the pressure was selected as the correcting control parameter. More specifically, the objective is achieved due to the technical features indicated in the independent claims.

Brief Description of Drawings

[0007]

Fig. 1 is a schematic diagram of an embodiment of a freeze-drying device;
fig. 2 is a schematic diagram of one embodiment of a freeze-drying method;
fig. 3 is a schematic diagram of another embodiment of the freeze-drying method.

Detailed description of the invention

[0008] The proposed device and method for freeze-drying and the control of the sublimation process of a substance use temperature *T*, pressure *P*, and the Clausius- Clapeyron equation to determine the values of control actions as control parameters. Controlling influences on the sublimation process is determined by their ratio. As the main parameter, the temperature was selected as a more inertial process, and as the correcting control parameter, the pressure was selected as a faster process.

[0009] The proposed device (Fig. 1) contains:

- a vacuum chamber-desublimator 1, in which one or more shelves 2 are located, adapted to accommodate the product to be freeze-dried; the shelf or shelves 2 are equipped with one or more heaters 3, adapted to heat the shelves 2 and maintain the predetermined temperature of the shelves 2;
- a refrigeration unit 4 connected to a heat exchanger 5, which is installed in such a way as to ensure heat transfer from the desublimating surface 6 located in the vacuum chamber-desublimator 1; moreover, the desublimating surface 6 can be represented as walls of the vacuum chamber-desublimator 1, or one or more plates connected to the heat exchanger 5 with the possibility of mutual heat transfer (for taking heat from the desublimating surface 6 and cooling it);
- at least one temperature sensor 7 of the desublimating surface 6, installed and configured to take temperature readings from the desublimating surface 6;
- one or more temperature sensors 8 of the shelves 2, adapted to take temperature readings from the shelves 2 and, preferably, protected by housing to protect against the influence of the temperatures of other elements of the device;
- at least one vacuum pump 9, installed with the possibility of pumping out gases from the vacuum chamber-desublimator 1;
- at least one pressure sensor 10 was installed with the possibility of obtaining pressure readings in the vacuum chamber-desublimator 1.

[0010] Shelf temperature sensors 8, desublimating surface temperature sensor 7, pressure sensor 10 are connected to the control computer 11 with the possibility of transmitting a signal representing the data received by sensors 7, 8, 10. Vacuum pump 9, refrigeration unit 4, shelf heaters 3 are connected with a control computer 11 with the possibility of receiving and transmitting a signal to control the said elements of the device.

[0011] Moreover, the control computer 11 is connected to computer-readable hardware that storing a computer program containing machine-executable instructions (or the control computer 11 itself contains these machine-executable instructions), the execution of which causes the processor to control the freeze-drying device according to steps (iii) - (vi) of the freeze-drying method described below.

[0012] The freeze-drying process according to this invention comprises (Fig. 2 and 3):

- determination of the product to be sublimated and selection of the appropriate operating mode of the device, that is, the determination of the program for the sublimation of the product filler, which contains data on the thermophysical properties of the product filler;
- according to the specified mode, information about the sublimation mode is loaded into the sublimation program from the long-term memory of the control computer 11: the pressure $P0$ of the triple point of the product's filler substance phase transformation, the temperature of its triple point of phase transformation $T0$, its heat capacity ΔH, as well as the temperatures of the thermostatting levels of the shelves T_j $j = 1, ..., n_T$, and T_D desublimating surface 6, the temperature of the beginning $T_B = T0$, as well as the number of thermostatting levels n_T,
- the implementation of the loading of the product on one or more shelves 2 of the vacuum chamber-desublimator 1 (the product can be placed in trays, open cans, etc.);
- the implementation of the sealing of the vacuum chamber-desublimator 1;
- freezing the desublimating surface 6 to a temperature $T_D < T0$;
- carrying out freezing of the shelves 2 to a temperature T_B, so that $T_D < T_B = T_0 < T0$;
- the implementation of the evacuation of the vacuum chamber-desublimator 1 by pumping out the air-vapor medium to a pressure p_0, so that $P_D < p_0 < P0$, below the pressure p_1 corresponding to the temperature T_1 of the first level of thermostatting of the substance sublimation. Moreover, the values of the pres-

sure parameters are determined by Clausius-Clapeyron equation according to the set temperature values and the initial data of the sublimation mode

$$p_2 = p_1 exp\left[-\frac{\Delta H_{субл,mol}}{R}\cdot\left(\frac{1}{T_1}-\frac{1}{T_2}\right)\right]$$

[0013] Moreover, the sublimation process is carried out in several levels of thermostatting *j* from 1 to n_T, and at each of the levels of thermostatting, several cycles *i* from 1 to n_{Tc} of pressure change inside the vacuum chamber - desublimator (1) are performed. The current parameters of the sublimation process, i.e., temperature T_c and pressure p_c inside the vacuum desublimator chamber, is checked for each level and cycle of the sublimation process and compare with the parameter T_j and p_j. And further, the cycle of operation of the sublimation device vacuum pump (9) means the repeated process of pumping out the vapor-air mixture by the vacuum pump (9), from the limiting value pressure p_j, to the lower value of the pressure p_{j-1}, and then its subsequent growth to the value p_j due to the sublimation process. The range of cycle pressure changes is determined by control computer (11) for each thermostatting level based on the thermostatting temperature of the shelves 2 of the current T_j and the previous T_{j-1} levels. For the first step, i.e., $j = 1$, the previous step is zero-step $T_{j-1} = T0$, and, accordingly, $p_{j-1} = p_0$. Transition to another thermostatting lavel is possible both by a change in the magnitude of the pressure increase over the given time, when it does not reach the given level, i.e., p_j, or when current number n_c of sublimation cycle reaching the limiting value of the repetitive operating cycles number n_{Tc} of the vacuum pump, i.e., $n_c \geq n_{Tc}$.

[0014] The pressure p_0 and the temperature T_0 of the lower-level and the temperature T_1 of the first level of sublimation $j = 1$, of the first cycle $i = 1$ coincide with the parameters of the lower level of sublimation P_B and T_B, that is, $T_D < T_B = T_0 < T_1 < T0$ and $P_D < P_B = p_0 < p_1 < P0$.

[0015] Since the initial pressure in the chamber p_0 is lower than the saturated vapor pressure at the temperature of the first thermostatting level p_1, that is, $p_0 < p_1$, according to the specified sublimation parameters, the filler substance begins to sublimate from the product, and since the temperature of the desublimating surface 6 T_D is below the temperature of the first level of thermostatting T_1, and at the same time the initial pressure in the chamber p_0 is higher than the saturated vapor pressure P_D corresponding to the temperature of the desublimating surface 6 T_D according to the given parameters of the sublimation mode, then the filler substance is desublimated on the desublimating surface 6 as follows as $T_D < T_0 < T_1$.

[0016] If the intensity of the sublimation process exceeds the intensity of the desublimation process, then the current pressure p_c in the chamber rises, and if, for a given duration $t_{1,1}$ of the sublimation process, the pressure in the vacuum chamber-desublimator 1 reaches a pressure corresponding to the temperature of thermostatting, that is, $p_c = p_1$, then the control computer 11 turns on the vacuum pump 9 and reduces the pressure in the vacuum chamber-desublimator 1 to the initial level p_0. The process is carried out until one of two events occurs:

- either the current number of sublimation cycles n_c do not less than the specified value for this first stage, the first cycle of the sublimation process $n_c \geq n_{1,1}$,
- either for a given time $t_{1,1}$, the pressure in chamber p_c will not be able to reach the value of p_1.

[0017] The condition is checked that the current number n_c of sublimation cycles do not exceeded the specified value for the given, first stage, the first cycle of the sublimation process $n_c \leq n_{1,1}$:

- if the condition $n_c \leq n_{1,1}$ is not met, then the control computer 11 transmits the sublimation device to the next level of thermostatting, which is set by the temperature T_2 of shelves 2 of the vacuum chamber-desublimator 1.
- if the condition $n_c < n_{1,1}$ is satisfied, then the transition to checking the condition $p_c < p_1$.

[0018] The fulfillment of the condition is checked that for a given time $t_{1,1}$ the pressure p_c in the vacuum chamber-desublimator 1 did not reach the value p_1, that is, $p_c < p_1$:

- if the condition $p_c < p_1$ is not met, then the control computer 11 turns on the pump 9 and lowers the pressure inside the vacuum chamber-desublimator 1 to the value p_0, and the process is repeated;
- if the condition $p_c < p_1$ is fulfilled, then the control computer 11 transmits the device to the next level of thermostatting, which is set by the temperature T_2 of the shelves 2 of the vacuum chamber-desublimator 1.

[0019] Then, the next thermostatting level is carried out. For this, with the help of heaters 3, the shelves 2 with the product are heated, followed by their thermostatting T_j = *const*, and then the current pressure p_c of the sublimation process is measured by the pressure sensor 10, and the control computer 11 checks its compliance to the parameters of the *i-th* cycle of *the j-th* level of the sublimation process. That is, compliance of the current pressure value p_c to the limit value of the *i-th* cycle of sublimation of the *j-th* level of thermostatting, i.e., with p_j.

[0020] The temperature of the shelves 2 is stabilized, and, suppose, if the chamber is not equipped with some kind of vapor removal system, then the saturated vapor current pressure $p_c < p_j$ will increase, tending to the value of p_j corresponding to the temperature T_j.

$$p_2 = p_1 exp\left[-\frac{\Delta H_{субл,mol}}{R}\cdot\left(\frac{1}{T_1}-\frac{1}{T_2}\right)\right]$$

[0021] However, the filler substance desublimates on the desublimating surface 6, since $T_D < T_c \leq T_j$ for all $i=1,...,n_{Tc}$ and $j=1,...,n_T$, decreasing the rate of current pressure p_c growth. But if the intensity of the sublimation process exceeds the intensity of the desublimation process, then the pressure in the vacuum chamber-desublimator 1 increases, and if, for a given duration $t_{i,j}$ of the sublimation process, the current pressure p_c in the vacuum chamber-desublimator 1 reaches or exceeds the pressure *pj,* that is, $p_c \geq p_j$, then the control computer 11 turns on the vacuum pump 9, which reduces the pressure in the vacuum desublimator 1 to the initial level p_{j-1}. The process is carried out until one of two events occurs:

- the current number of sublimation cycles n_c has reached or exceeded the specified amount $n_{i,j}$ of the cycle number of this level of the sublimation process $n_c \geq n_{i,j}$;
- for a given time $t_{i,j}$, the current pressure p_c in the chamber do not reach the specified value of pressure p_j, that is, $p_c<p_j$.

[0022] The condition is checked by the control computer 11, that the number of sublimation cycles n_c is more or equal to the specified value $n_{i,j}$ for a given cycle of the sublimation process, that is, $n_c \geq n_{i,j}$:

- if the condition $n_c \geq n_{i,j}$ the condition is not met, then the control computer 11 of the device turns on the heaters 3 of the shelves 2 and goes to the next thermostatting level, which is set by the temperature T_{j+1} of the shelves 2 of the device.
- if the condition $n_c \geq n_{i,j}$ is satisfied, then the transition to checking the condition $p_c < p_j$ is carried out.

[0023] The fulfillment of the condition is checked that for a current time $t_{i,j}$ the current pressure p_c in the chamber has not reached the value p_j. i.e., $p_c < p_j$

- if the condition $p_c < p_j$ is not met, then the control computer 11 turns on the vacuum pump 9 and lowers the pressure inside the desublimator chamber 1 to the value p_{j-1}, and the process is repeated;
- if the condition $p_c < p_j$ is satisfied, then the device turns on the heaters 3 of the shelves 2 and goes to the next level of thermostatting, which is set by the temperature T_{j+1} of the shelves 2 of the device.

[0024] The parameters of the upper level of the last thermostatting level, i.e., $j = n_T$, of the last cycle $i = n_{Tc}$ coincide with the parameters of the upper level of the sublimation process, that is, $T0 \geq T_{nT}$ = const and $p_c \leq p_{nT} \leq P0$.

[0025] The shelves 2 with the product are heated with the heaters 3, followed by thermostatting at the temperature $T_{nr} = const.$ The temperature of the shelves 2 stabilizes, the current pressure p_c begins to increase, tending to the value of p_{nT} corresponding to the temperature T_{nT}:

$$p_2 = p_1 exp\left[-\frac{\Delta H_{субл,mol}}{R}\cdot\left(\frac{1}{T_1}-\frac{1}{T_2}\right)\right]$$

[0026] In this case, the filler substance desublimates on the desublimating surface 6, since $T_D < T_{nT}$. If the intensity of the sublimation process exceeds the intensity of the desublimation process, then the current pressure p_c in the desublimator chamber 1 increases, and if, for a given duration $t_{i,nT}$ of the sublimation process, the current pressure p_c in the desublimator chamber 1 reaches pressure p_{nT}, then the control computer 11 of device turn on the vacuum pump 9 is turned on, which lowers the pressure in the desublimator chamber 1 to the initial level p_{nT-1}. The process is carried out until one of two events occurs:

- the current number of sublimation cycles n_c reach or exceed the specified value of the cycle number of the thermostatting level $n_c \geq n_{nT}$, or
- for a current time t_c, the current pressure p_c in the desublimator chamber 1 does not reach its limitation value, i.e., $p_c < pnT$.

[0027] The fulfillment of the condition is checked that the current number of sublimation cycles n_c lower the specified value for the given thermostatting level $n_c < n_{nT}$.
- if the condition $n_c < n_{nT}$ is not met, then the device switches its mode of operation to the completion of the sublimation process, that is, bringing the pressure inside the desublimator chamber 1 to the ambient pressure and the temperature of the shelves 2 to the set value, and gives a signal about the end of the sublimation cycle.

[0028] - if the condition $n_c < n_{nT}$ is satisfied, then the transition to the verification of the condition $p_c \leq p_{nT}$ is made.

[0029] The fulfillment of the condition is checked that for a current time $t_{c,nT}$ the current pressure p_c in the chamber lower than the value p_{nT}, that is, $p_c < p_{nT}$.

- if the condition $p_c < p_{nT}$ is not met, then the control computer 11 turns on the vacuum pump 9 and lowers the pressure inside the desublimator chamber 1 to the value of p_{nT-1}, and the process is repeated.
- if the condition $p_c < p_{nT}$ is satisfied, then the control computer 11 switches the mode of its operation to complete the sublimation process, that is, to bring the pressure inside the desublimator chamber 1 to the ambient pressure and the temperature of the shelves 2 till a predetermined value and gives a sig-

nal about the end of the goods sublimation.

[0030] Next, the desublimator chamber 1 is depressurized, the desublimator chamber 1 is unloaded, and the device is turned off.

Claims

1. A freeze-drying device containing a vacuum chamber-desublimator (1), in which one or more shelves (2) are located, adapted to accommodate the product to be freeze-dried; the shelf or shelves (2) are equipped with one or more heaters (3) adapted to heat the shelves (2) and maintain a predetermined temperature of the shelves (2); a refrigeration unit (4) connected to a heat exchanger (5), which is installed in such a way as to provide heat transfer to the desublimating surface (6) located in the vacuum desublimator chamber (1); moreover, the desublimating surface (6) is connected to the heat exchanger (5) with the possibility of providing mutual heat transfer for cooling the desublimating surface (6); at least one temperature sensor (7) of the desublimating surface (6) is installed and configured to take temperature readings from the desublimating surface (6); one or more temperature sensors (8) of the shelves (2) adapted to take temperature readings from the shelves (2) and, preferably, protected by a housing to protect against the influence of the temperature of other elements of the device; at least one vacuum pump (9) installed with the possibility of pumping out gases from the vacuum desublimator chamber (1); at least one pressure sensor (10) installed with the possibility of obtaining pressure readings in the vacuum desublimator chamber (1); the control computer of the device (11), connected to the sensors (7, 8 and 10) with the possibility of receiving a signal from these sensors, and also connected to the vacuum pump (9), the refrigeration unit (4) and the shelf heaters (3) with the possibility of receiving and transmitting a signal for providing control of the mentioned elements of the device; moreover, the control computer (11) contains computer-executable instructions or the control computer (11) is connected to a computer-readable hardware storing a computer program containing computer-executable instructions, the execution of which causes the control computer (11) to perform the following steps:

(iii) freezing the desublimating surface (6) to a temperature $T_D < T0$;
(iv) freezing one or more shelves (2) to a temperature of the sublimation process beginning T_B, so that $T_D < T_B \leq T0$;
(v) evacuation of the desublimator chamber (1) by evacuating the air-vapor medium with a help of vacuum pump (9) to the pressure of the onset of sublimation P_B so that $P_D < P_B < P0$, moreover, the pressure $P0$ and P_D determined for the given values of $T0$ and T_D according to the Clausius-Clapeyron equation

$$p_2 = p_1 exp\left[-\frac{\Delta H_{субл,mol}}{R}\cdot\left(\frac{1}{T_1}-\frac{1}{T_2}\right)\right]$$

where:

p_2 is the saturated vapor pressure of the filler substance at temperature T_2, for the all-possible values of T_2 (for example $T_2 = T_B$, $T_2 = T_D$ or others; in this case $p_B = p_2$, $p_D = p_2$ or other will be determinates in accordance of equation result);
p_1 - the pressure of saturated vapors of the filler substance at temperature T_1, for the beginning of the sublimation process $p_1 = P0$;
$AH_{subl,mol}$ - molar latent heat of the phase transition taking place at temperature T, where $T=(T1 + T2)/2$;
T_1 - temperature of the previous thermostatting mode, for the beginning of the sublimation process $T_1 = T0$;
T_2 is the temperature of the subsequent thermostatting mode, for the beginning of the sublimation process $T_1 = T_B$;
$R = 8.314 \cdot J \cdot K^{-1} \cdot mol^{-1}$-universal gas constant;

(vi) to determine the pressure p_j according to the Clausius-Clapeyron equation, thermostatting temperature T_j of the shelves (2) is used, and then p_j is used to comparing it with the current pressure p_c in the vacuum desublimator chamber (1) that is measured by the pressure sensor (10) for the current time;

(a) if the current pressure is equal to or more than the preset pressure - the pressure is lowering by a vacuum pump (9) to a predetermined level; if less than the preset one -
(b) determining the cycle time of the pressure increase from the initial value, after pumping out the vapor-air mixture by the vacuum pump (9), to the calculated pressure value of the sublimation process, calculated based on the thermostatting temperature T_{j-1} the shelves (2); if the current cycle time is less than the specified one - return to the step (vi), if equal to or greater than the specified one -
(c) determining the number of cycles; if the number of cycles is less than the specified

one - go to step (e), if equal or more -

(d) determining the current pressure; if the current pressure is not less than the preset one - return to step (v), if less than the preset one -

(e) determining the number of thermostatting levels; if the number of thermostatting levels is less than the specified one, heating the shelves (2) by heaters (3) to the next thermostatting level, determining the upper-pressure limit of the next thermostatting level according to the Clausius-Clapeyron equation; if the number of thermostatting levels is greater than or equal to the specified one, the device is shut down.

2. The device according to claim 1, is **characterized in that** steps (c) and (d) of said computer-executable instructions are combined into one step, which forces the processor to determine the number of cycles and the current pressure in the vacuum desublimator chamber (1); if the number of cycles not less than the specified one or the current pressure is lower than specified one - go to step (e); if the number of cycles is less than the specified one or the current pressure is not less than the specified one - transmit to the mentioned step (a) determining the current pressure; pumping down the pressure to the previous level; if the current pressure is lower than the preset one, transmit the sublimation process to perform next thermostating level: heating of the device shelves (2) to the next level of temperature, determination of the upper-pressure limit corresponding to this temperature using Clausius-Clapeyron equation, and transmit the sublimation process to the step (vi), if it is not less than the preset one, the pressure is lowered by the vacuum pump (9) to the preset level and returns to step (vi) if it is lower than the preset one, go to step (e).

3. The device according to any one of claims 1-2, is **characterized in that** the desublimating surface (6) is made in the form of the walls of the vacuum desublimator chamber (1) or in the form of one or more plates connected to the heat exchanger (5) with the possibility of providing mutual heat transfer.

4. A freeze-drying method comprising the following steps:

(i) loading the product onto one or more shelves (2) of the vacuum desublimator (1);

(ii) sealing the vacuum desublimator chamber (1);

(iii) freezing the desublimating surface (6) to a temperature $T_D < T0$;

(iv) freezing one or more shelves (2) to a temperature of the sublimation process beginning T_B, so that $T_D < T_B \leq T0$;

(v) evacuation of the desublimator chamber (1) by pumping out the air-vapor medium with a vacuum pump (9) to the pressure of the onset of sublimation P_B so that $P_D < P_B < P0$, moreover, the pressure P_B and P_D is determined for the given values of T_B and T_D according to the Clausius-Clapeyron equation

$$p_2 = p_1 exp\left[-\frac{\Delta H_{\text{субл}.mol}}{R}\cdot\left(\frac{1}{T_1}-\frac{1}{T_2}\right)\right]$$

where:

p_2 is the saturated vapor pressure of the filler substance at temperature T_2, for the all-possible values of T_2 (for example $T_2 = T_B$, $T_2 = T_D$ or others; in this case $p_B = p_2$, $p_D = p_2$ or other will be determinates in accordance of equation result);

p_1 - the pressure of saturated vapors of the filler substance at temperature T_1, for the beginning of the sublimation process $p_1 = P0$;

$AH_{subl,mol}$ - molar latent heat of the phase transition taking place at temperature T, where $T=(T1 + T2)/2$;

T_1 - temperature of the previous thermostatting mode, for the beginning of the sublimation process $T_1 = T0$;

T_2 is the temperature of the subsequent thermostatting mode, for the beginning of the sublimation process $T_1 = T_B$;

$R = 8.314 \cdot J \cdot K^{-1} \cdot mol^{-1}$-universal gas constant;

(vi) thermostatting temperature T_j of the shelves (2) is used to determine the pressure p_j according to the Clausius-Clapeyron equation; p_j is used to compare it with the current pressure p_c in the vacuum desublimator chamber (1) that is measured by the pressure sensor (10) for the current time;

(a) if the current pressure is greater than or equal to the preset pressure - pumping down the pressure to the previous level, if less than the preset one -

(b) determining the cycle time of the pressure increase from the initial value, after pumping out the vapor-air mixture by a vacuum pump (9), to the calculated pressure value of the sublimation process, calculated based on the thermostatting temperature of the shelves (2); if the current cycle time is less than the specified one - return to the step (vi), if equal to or greater than the spec-

ified one -
(c) determining the number of cycles; if the number of cycles not less than the specified one - go to step (e), if equal or more -
(d) determining the current pressure; if the current pressure not less than the preset one - the pressure is lowered by a vacuum pump (9) to a predetermined level and return to step (vi), if less than the preset one -
(e) determination of the number of thermostatting levels; if the number of thermostatting levels is less than the specified one, heating the shelves (2) by heaters (3) to the next thermostatting level, determining the upper-pressure limit of the next thermostatting level according to the Clausius-Clapeyron equation; if the number of thermostatting levels is greater than or equal to the specified one, the device is shut down.

5. The method according to claim 4, is **characterized in that** steps (c) and (d), i.e., determination of the number of cycles and determining the current pressure are combined into one step, which determines the number of cycles and the current pressure in the vacuum desublimator chamber (1); if the number of cycles not less than the specified number or the current pressure lower than the specified one - go to step (e), if the number of cycles less than specified one or the current pressure not less than the specified one - lowering the pressure in the vacuum chamber-decublimator (1) to the lower preset level and return to step (vi); (j) determining the current pressure; if the current pressure is equal to or more than a given one - the pressure the pressure is lowered by a vacuum pump (9) to a predetermined level and return to step (vi), if less than a given one - go to step (e).

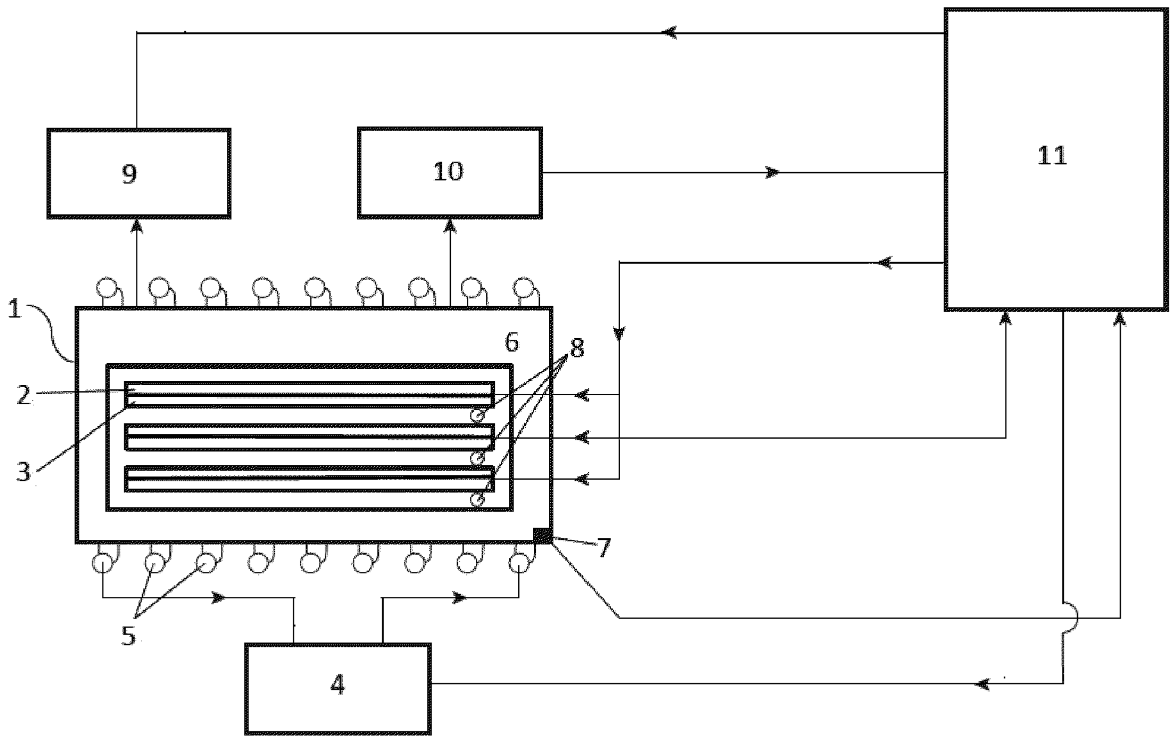
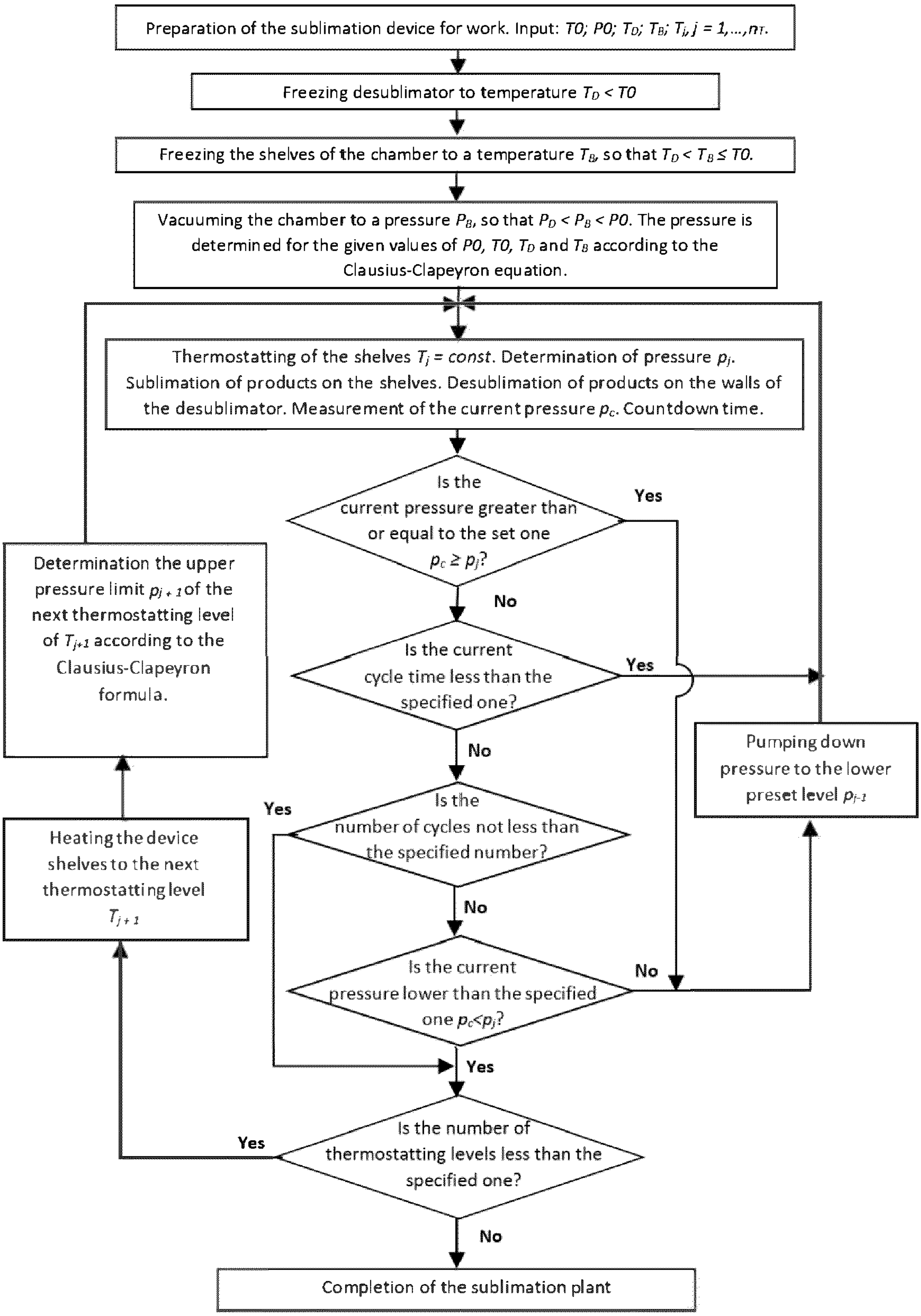
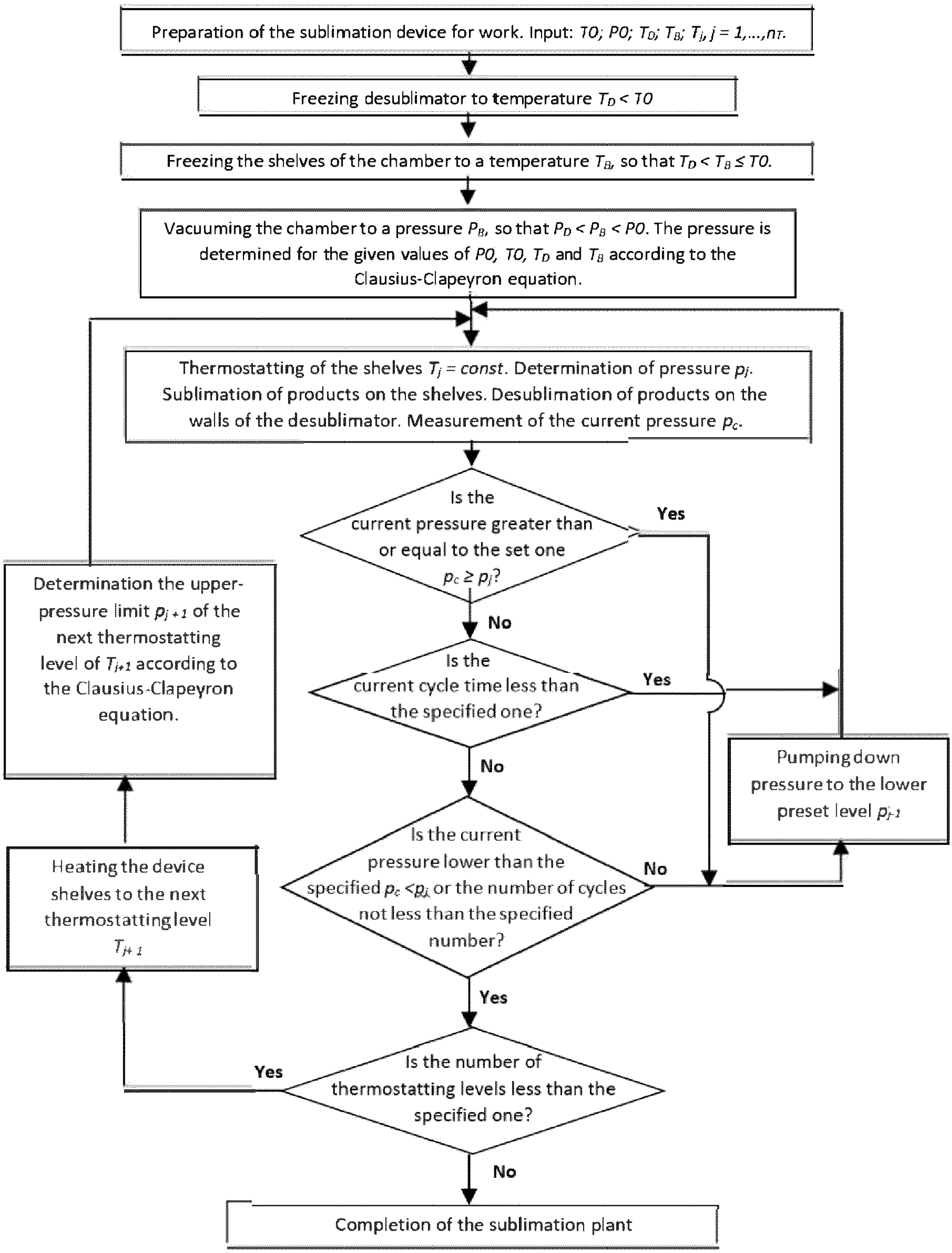


Fig. 1


Preparation of the sublimation device for work. Input: $T0$; $P0$; T_D; T_B; T_j, $j = 1,...,n_T$.
Freezing desublimator to temperature $T_D < T0$
Freezing the shelves of the chamber to a temperature T_B, so that $T_D < T_B \leq T0$.
Vacuuming the chamber to a pressure P_B, so that $P_D < P_B < P0$. The pressure is determined for the given values of $P0$, $T0$, T_D and T_B according to the Clausius-Clapeyron equation.
Thermostatting of the shelves $T_j = const$. Determination of pressure p_j. Sublimation of products on the shelves. Desublimation of products on the walls of the desublimator. Measurement of the current pressure p_c. Countdown time.
Is the current pressure greater than or equal to the set one $p_c \geq p_j$?
Yes
No
Determination the upper pressure limit p_{j+1} of the next thermostatting level of T_{j+1} according to the Clausius-Clapeyron formula.
Is the current cycle time less than the specified one?
Yes
No
Pumping down pressure to the lower preset level p_{j-1}
Yes
Is the number of cycles not less than the specified number?
Heating the device shelves to the next thermostatting level T_{j+1}
No
Is the current pressure lower than the specified one $p_c < p_j$?
No
Yes
Yes
Is the number of thermostatting levels less than the specified one?
No
Completion of the sublimation plant


Preparation of the sublimation device for work. Input: TO; PO; T_D; T_B; T_j, $j = 1,...,n_T$.
Freezing desublimator to temperature $T_D < TO$
Freezing the shelves of the chamber to a temperature T_B, so that $T_D < T_B \leq TO$.
Vacuuming the chamber to a pressure P_B, so that $P_D < P_B < PO$. The pressure is determined for the given values of PO, TO, T_D and T_B according to the Clausius-Clapeyron equation.
Thermostatting of the shelves $T_j = const$. Determination of pressure p_j. Sublimation of products on the shelves. Desublimation of products on the walls of the desublimator. Measurement of the current pressure p_c.
Is the current pressure greater than or equal to the set one $p_c \geq p_j$?
Yes
No
Is the current cycle time less than the specified one?
Yes
No
Is the current pressure lower than the specified $p_c < p_j$ or the number of cycles not less than the specified number?
No
Yes
Pumping down pressure to the lower preset level p_{j-1}
Determination the upper-pressure limit p_{j+1} of the next thermostatting level of T_{j+1} according to the Clausius-Clapeyron equation.
Heating the device shelves to the next thermostatting level T_{j+1}
Is the number of thermostatting levels less than the specified one?
Yes
No
Completion of the sublimation plant

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 21 18 0228

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	US 6 971 187 B1 (PIKAL MICHAEL J [US] ET AL) 6 December 2005 (2005-12-06) * the whole document * -----	1-5	INV. F26B5/06 F26B25/22
A	EP 2 674 712 A1 (KYOWA VACUUM ENG [JP]) 18 December 2013 (2013-12-18) * the whole document * -----	1-5	
A	Narlin Beaty ET AL: "Lyophilization: Heat and Mass Transfer", , 2 February 2006 (2006-02-02), XP055372760, Retrieved from the Internet: URL:http://www.sublimationscience.com/Publications/Heat_Mass_Transfer.pdf [retrieved on 2017-05-15] * the whole document * -----	1-5	
A	GENIN ET AL: "A method for on-line determination of residual water content and sublimation end-point during freeze-drying", CHEMICAL ENGINEERING AND PROCESSING: PROCESS INTENSIFICATION, ELSEVIER SEQUOIA, LAUSANNE, CH, vol. 35, no. 4, 1 January 1996 (1996-01-01), pages 255-263, XP005464039, ISSN: 0255-2701, DOI: 10.1016/0255-2701(95)04131-1 * the whole document * -----	1-5	TECHNICAL FIELDS SEARCHED (IPC) F26B
A	US 4 547 977 A (TENEDINI KENNETH J [US] ET AL) 22 October 1985 (1985-10-22) * the whole document * ----- -/--	1-5	

1 The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	29 November 2021	Villar Fernández, R

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

PO FORM 1503 03.82 (P04C01)

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 21 18 0228

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	WO 2012/016301 A1 (HOSPIRA AUSTRALIA PTY LTD [AU]; WENSLEY EMMA J [US] ET AL.) 9 February 2012 (2012-02-09) * the whole document * -----	1-5	

TECHNICAL FIELDS SEARCHED (IPC)

1 The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	29 November 2021	Villar Fernández, R

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

PO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 21 18 0228

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.

29-11-2021

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6971187 B1	06-12-2005	NONE	
EP 2674712 A1	18-12-2013	EP 2674712 A1	18-12-2013
		ES 2814824 T3	29-03-2021
		JP 5876424 B2	02-03-2016
		JP WO2012108470 A1	03-07-2014
		US 2014026434 A1	30-01-2014
		WO 2012108470 A1	16-08-2012
US 4547977 A	22-10-1985	NONE	
WO 2012016301 A1	09-02-2012	AU 2011286179 A1	28-02-2013
		AU 2016208368 A1	18-08-2016
		BR 112013002936 A2	24-12-2019
		CA 2807601 A1	09-02-2012
		CN 103209898 A	17-07-2013
		CN 103770967 A	07-05-2014
		CN 106966036 A	21-07-2017
		CY 1119634 T1	04-04-2018
		DK 2601105 T3	02-01-2018
		EP 2601105 A1	12-06-2013
		EP 3208202 A1	23-08-2017
		ES 2651489 T3	26-01-2018
		ES 2773781 T3	14-07-2020
		HU E035235 T2	02-05-2018
		JP 5993853 B2	14-09-2016
		JP 2013532566 A	19-08-2013
		KR 20130103489 A	23-09-2013
		KR 20180119687 A	02-11-2018
		MX 345215 B	19-01-2017
		MY 166078 A	23-05-2018
		NZ 606713 A	24-04-2015
		PL 2601105 T3	30-03-2018
		PT 2601105 T	06-12-2017
		SG 187766 A1	28-03-2013
		SG 10201506066X A	29-09-2015
		SI 2601105 T1	29-12-2017
		US 2013205719 A1	15-08-2013
		WO 2012016301 A1	09-02-2012

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 9459044 B **[0004]**
- US 2020340743 A **[0005]**