Lyophilization Plant Control System

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***Abstract*— Lyophilization, or Freeze-drying is a low temperature dehydration process [1], [2] that involves freezing the product, very low pressure by which the ice is removed by sublimation. The plant is designed for the production of vaccines and immunostimulants. The control system is realized with a Siemens controller, operator panel and SCADA system.**

***Index Terms*— Freeze-drying system, Programmable Logic Controller (PLC), SCADA**

I. Introduction

The developed control system is designed to control a lyophilization plant, which is an element of the production of vaccines and immunostimulants. The control system is based on a Siemens controller S7-1200 CPU 1214C and the necessary signal modules. A 12” color touch panel and a SCADA system are used to connect to the operator.

There are three stages in freeze-drying process: freezing, primary drying and secondary drying.

In the first phase - freezing - the product is cooled to a temperature lower than the triple point (the temperature at which the solid, liquid and gaseous phases can coexist). Cooling is performed at normal atmospheric pressure. The freezing phase is critical to this process and should be done slowly. In this way, large crystals are formed, which form a network in the product and provide faster removal of water vapor during sublimation. There are cases in which the production of large ice crystals disrupts the structure of the product, which leads to poor texture and deterioration of nutritional qualities. In this case, freezing is done quickly (shock), thus avoiding the formation of large ice crystals. The product is frozen to temperatures from -50°C to -80°C.

The second phase is primary drying. The pressure drops to a few microbars, and the temperature rises gradually, at which point the ice begins to sublimate. At this stage, about 95% of the water in the product is released. This phase is slow, requiring the gradual addition of heat. The separated moisture is removed in two ways - with a vacuum pump and with a condenser chamber. Moisture condenses on the plates of the condenser and freezes.

Due to the extremely low pressure in the chamber, heat is transferred through thermal conductivity as convection is practically impossible.

The third phase is secondary drying. In this phase, the remaining unfrozen water is removed. The temperature rises above 0 degrees and the process is also carried out at greatly reduced pressure. At the end of the third phase, the process ends and the chamber is evacuated. As a result of the operation, the moisture content of the product is extremely low - about 1%.

The application of this method is large - it leads to significantly less damage to the product compared to high temperature dehydration methods. Lyophilization does not cause shrinkage or hardening of the product to be dried. Lyophilized products rehydrate quickly because pores of ice crystals remain in the dried product. Lyophilization can significantly extend the shelf life of the product.

In pharmacy, lyophilization is used to extend the shelf life of products such as live virus vaccines, biological or injectable preparations. After lyophilization, the product is sealed in glass vials, which are later very easily restored to their original form of injection. They may be in the form of capsules or powders for self-administration by patients. Probiotics are also produced by this technology by freezing live microorganisms.

The main method for microbial decontamination is low temperature dehydration. However, it is possible for some pathogens to remain in the product and if it is not stored properly, moisture can be absorbed to allow the pathogens to begin reproducing. This problem is solved by using very smooth stainless steel, from which the vacuum chamber is made, special disinfection procedures and hygiene procedures when working with these products.

The cost of lyophilization is several times higher than conventional drying methods, so it is suitable for products that significantly increase their value after this treatment. The main costs are for equipment, electricity and packaging.

Another problem may be a leak of silicone oil, which is used to heat and cool the system. Basically, these are the places where the hoses connect to the shelves. Mass spectrometers are used to detect silicone oil in the vapor.

II. Brief Description of the Installation

A general diagram of the installation is shown in fig. 1. There can be seen Chamber, Condenser, Hydraulic pump, Silicon pump, Vacuum pump, Water pump, Valves, Temperature and pressure sensors.

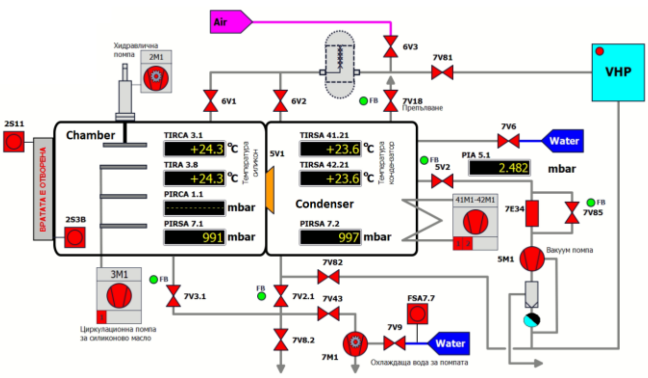

Fig. 1. General diagram of the installation

Two compressors are used to cool the chamber and the condenser. They are shown in fig. 2.

In the first phase of lyophilization - freezing process, the chamber is cooled. The heat carrier is silicone oil, and the circulation is carried out with the silicone pump. Up to a

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temperature of -20 °C, only compressor 41 operates, and at lower temperatures, compressor 42 is switched on. Cooling control is performed by valves which are switched with PWM.

In the primary and secondary drying phases, the compressors cool the condenser on which the water vapor condenses and freezes.

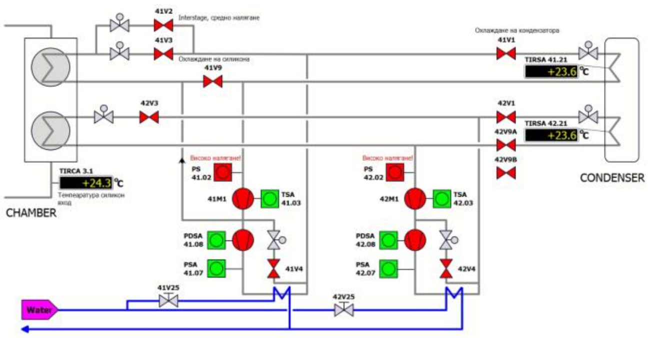

Fig. 2. Compressors

During the primary and secondary drying, the temperature in the chamber must rise. An electric heater is used, which heats the silicone. Power control is performed with a contactor that switches with PWM.

During the second and third phases of the process, it is necessary to maintain a deep vacuum in the chamber. For this purpose, a vacuum pump and a vacuum valve are used, which regulates the required pressure. The pressure measurement in the chamber is performed with a logarithmic absolute pressure sensor.

The scheme of the hydraulic system is shown in fig. 3.

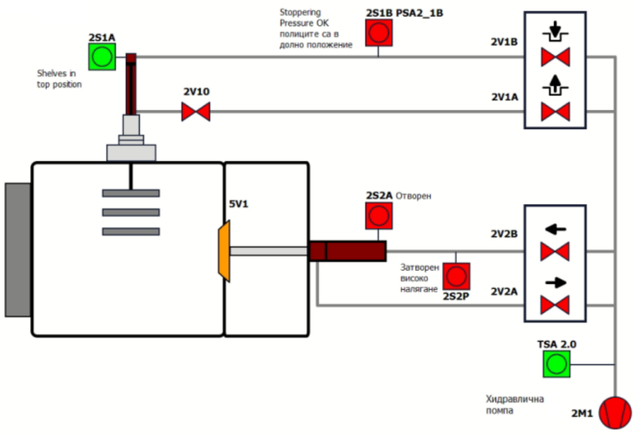

Fig. 3. Hydraulic system

The hydraulic system moves the shelves up and down and opens and closes the valve between the chamber and the condenser (5V1). Two groups of valves (2V1 and 2V2), position sensors and pressure relays are used for control. Energy is provided by the hydraulic pump.

After completing the process, opening the door and removing the dried product, it is necessary to equalize the pressure in the chamber with the external pressure. For this purpose, valves are used, through which air passing through a sterile filter is sucked.

Hot water is used to defrost the condenser. It is then emptied and dried using a water seal pump and a vacuum pump.

The system is controlled by a SCADA system and a 12” touch operator panel. The operator can set the following operating modes (Fig. 4):

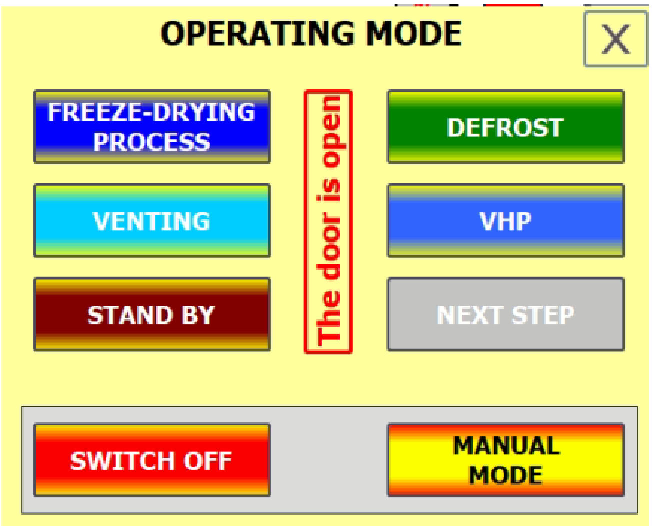

Fig. 4. Operating modes

The main mode of operation is freeze-drying process. The other modes are auxiliary, e.g. defrosting, ventilation, standby mode. The VHP mode is used to decontaminate the installation. In this case, it is connected to an additional device (VHP) that injects a disinfectant. The plant and VHP control systems are connected via a communication interface to control the disinfection process. In „Manual mode“, all elements can be switched on and off by an operator. This mode is dangerous because some of the locks do not work. The main application of this mode is in settings and troubleshooting.

The required recipe must be selected before starting the lyophilization process. A separate screen is used to create, edit and select recipes (Fig. 5):

	Phase	Total time		SNº	Segment time		Temperature	Pressure	Status
1	Loading	000 HH	05 MM	01	000 HH	05 MM	001.0 °C	- - - - - - -	
2	Freezing	000 HH	35 MM	01	000 HH	30 MM	001.0 °C	- - - - - - -	
3	Freezing	004 HH	35 MM	02	004 HH	00 MM	-20.0 °C	- - - - - - -	
4	Freezing	005 HH	05 MM	03	000 HH	30 MM	-50.0 °C	- - - - - - -	
5	Freezing	005 HH	35 MM	04	000 HH	30 MM	-50.0 °C	- - - - - - -	
6	Primary Drying	007 HH	05 MM	01	001 HH	30 MM	-50.0 °C	0.030 mbar	
7	Primary Drying	007 HH	50 MM	02	000 HH	45 MM	-08.0 °C	0.400 mbar	
8	Primary Drying	009 HH	50 MM	03	002 HH	00 MM	-08.0 °C	0.400 mbar	
9	Primary Drying	009 HH	55 MM	04	000 HH	05 MM	-03.0 °C	0.400 mbar	
10	Primary Drying	012 HH	55 MM	05	003 HH	00 MM	-03.0 °C	0.400 mbar	
11	Primary Drying	013 HH	00 MM	06	000 HH	05 MM	003.0 °C	0.400 mbar	
12	Primary Drying	018 HH	50 MM	07	005 HH	50 MM	003.0 °C	0.400 mbar	
13	Primary Drying	018 HH	55 MM	08	000 HH	05 MM	010.0 °C	0.400 mbar	
14	Primary Drying	020 HH	55 MM	09	002 HH	00 MM	010.0 °C	0.400 mbar	
15	Secondary Drying	021 HH	45 MM	01	000 HH	50 MM	050.0 °C	0.200 mbar	
16	Secondary Drying	023 HH	15 MM	02	001 HH	30 MM	050.0 °C	0.200 mbar	
17	Unloading	023 HH	20 MM	01	000 HH	05 MM	045.0 °C	0.000 mbar	
18	- - - - - -	- - - - - -							

Fig. 5. Part of the screen for creating, editing and selecting recipes

From this screen the type of phase, its duration, set temperature and pressure are selected. The execution of the recipe is monitored in the "Status" column. As it can be seen (Fig. 5) the system must maintain temperatures in the range from -50°C to +50°C for a set time. Depending on the type of phase, the pressure in the chamber must be maintained between 30 µbar and 400 µbar. The system allows each recipe to contain up to 30 phases. Up to 30 recipes can be created and stored in the controller's memory.

III. Control system

The control system is implemented with a Siemens PLC CPU 1214 and the necessary signal modules. About 250 signals (discrete and analog) are used. The TIA Portal V15.1 environment is used for the development of the system, and the programming language is SCL.

The correct operation of all elements of the system is constantly checked - engine overload, elevated pressures or temperatures, correctness of temperature and pressure measurements. Algorithms for reaction in case of failure in some of the elements are developed.

Temperature control is one of the main processes in lyophilization. The change of temperature is done on a ramp, as the start and end point (temperature and time) are set in the recipe. The set point of the temperature controllers is taken from the ramp, which is calculated for each sampling time.

Temperature control is performed with elements with relay characteristics - valves and contactor. With this type of elements there are restrictions on the minimum time for on and off state. PI regulators with PWM are used to control these elements. These restrictions lead to the insertion of a dead zone in the output of the regulators. Two refrigeration compressors are used for cooling. The main compressor is used for cooling to a temperature of -20°C. At temperatures below -20°C, the second compressor is switched on. The required cooling capacity varies depending on the temperature in the chamber, the amount of product, as well as the cooling of the condenser. Simultaneous control of both independent compressors with continuous change of the set point and the required refrigeration capacity requires the use of a modified PI controller, in which the second compressor is switched on if necessary. An additional slave controller is used. A change in the parameters of the controller depending on the mode of operation of the system is also used.

At the beginning of the second phase of the process - primary drying, it is necessary for the condenser to be cooled to a temperature of -40°C. This requires a lot of cooling power, because the temperature in the chamber must be maintained at -50°C. In this case, additional slave regulators are used, which ensure the distribution of the cooling power from the two compressors to the condenser coils and to the chamber. Used refrigeration technology requires a defined sequence of switching valves, which further complicates the implementation of the control of cooling.

During the second and third phases of lyophilization, it is necessary to control the pressure in the chamber. This requires precise measurement of this pressure. Two absolute pressure transmitters are used. The first is a standard type with a linear scale from 0 to 2000 mbar. With it, pressures below 1 mbar cannot be measured, a range that is essential for the lyophilization process. This requires the use of an absolute pressure transmitter with a logarithmic scale (Fig. 6). In this way, pressures in the range of 500 μbar can be accurately measured. A 16-bit ADC is used to ensure measurement accuracy.

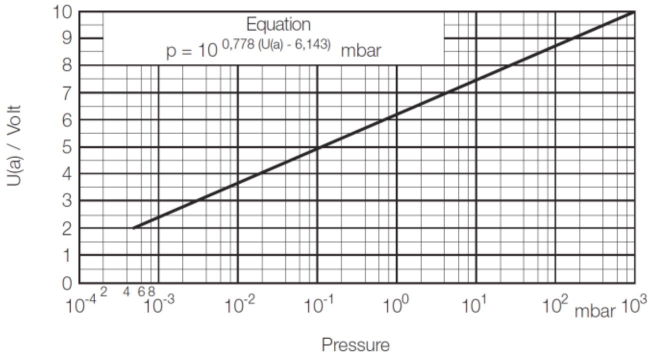

Fig. 6. Logarithmic scale for pressure measurement

A vacuum pump and pressure control valves are used to reduce the pressure in the chamber. In the first segment of the primary drying phase, it is necessary to reduce the pressure in the chamber from atmospheric (about 1000 mbar) to 50 - 30 μbar. At the same time, the valve between the chamber and the condenser opens. The time necessary for lowering the pressure is 30 - 40 minutes.

In the following segments of the lyophilization, the temperature of the product must be raised according to the set recipe. The temperature of the silicone oil is raised with an electric heater. A contactor is used to turn the heater on and off. The control is performed with a PI controller, and the contactor works with PWM (the problems for this control are the same as with the compressors described above).

After sublimation begins, the pressure in the chamber starts to increase. The pressure regulator is a PI that controls with a PWM valve (the problems for this are described above). The pressure set point is taken from the recipe.

In this case, sublimation and evaporation are random processes and depend on a combination of many factors - the type of product, its quantity, its distribution in trays or vials, the temperature of the product and its change. This is a factor that further complicates the process of adjusting the parameters of the controller.

IV. SCADA and HMI

The SCADA system uses a standard computer configuration with a Windows operating system. The same computer is also used for an engineering station: the software developed and the programming environment are also on it. This approach makes it easy to update the software as well as to detect system problems. There is a connection to this computer via the Internet, which allows for a quick response when troubleshooting - you do not always need a physical presence when a problem occurs.

The control of the processes by the operator is performed by the SCADA system or by the operator panel. The main screen of the SCADA system is shown in fig. 7. The SCADA system is bilingual - English and Bulgarian, which allows operators of different nationalities to work.

The system is designed so that work with it is intuitive to support the operator to have easy access to the necessary information about the process. All elements of the system, as well as the pipeline are animated, and their color and form change depending on the mode of operation.

There is a separate screen for each controller, which graphically shows the control of the process, the operating mode and the parameters of the controller. This is enough to adjust the parameters, which can change during the process.

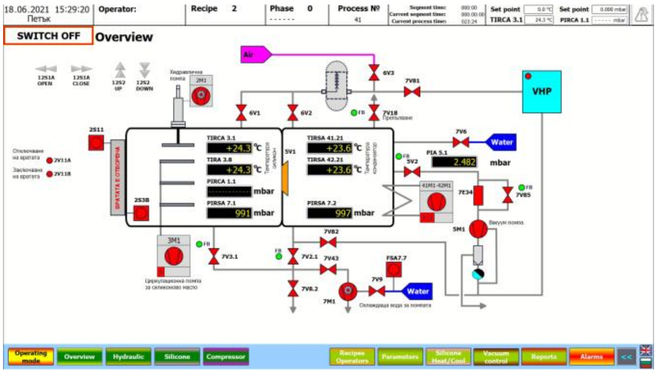

Fig. 7. Main screen

Buttons located at the bottom of the screen can open other screens where additional process data can be seen or parameters can be entered. Creating and editing recipes is one of the main screens of the system. From it the recipe to be executed is selected, this recipe can be edited, a new recipe can be created. This screen also sets additional parameters, including a comment on the current recipe (fig. 8).

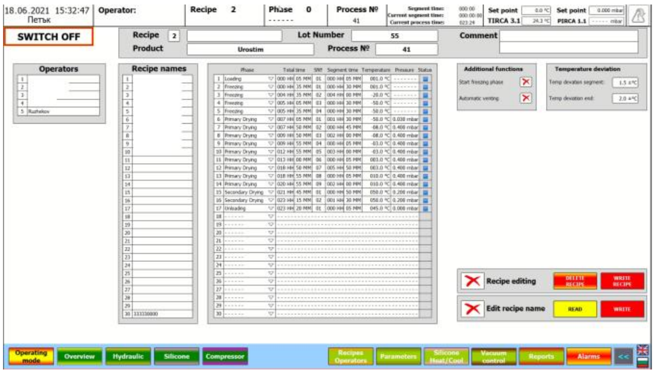

Fig. 8. Recipe screen

When creating or editing a recipe, the type of phase, the duration of the segment, the set temperature at the end of the segment, and the pressure in the chamber are set.

One of the main screens is the Alarm. In the event of a fault in any of the elements of the system, the alarm screen displays the cause of the alarm. The operator must decide how to continue the process. It is possible that if the damage does not prevent the process from continuing, it will be masked and the process will continue. It is also possible to temporarily suspend the process until the damage is repaired.

Continuous records of the main parameters of the process are made during the execution of the recipe. Based on these data, reports are prepared (Fig. 9) on the progress of the process. These reports can be printed, signed and stored as proof of the specific process. The reports are of two types: text-based recipe and main points of it and graphical - temperatures and pressures during the process.

Fig. 10 shows one of the main graphs of the report: pressure and temperature in the chamber. It can be seen that the task and the execution of the parameters are very close. The random nature of the sublimation process can be seen in the green graph.

Fig. 9. Report screen

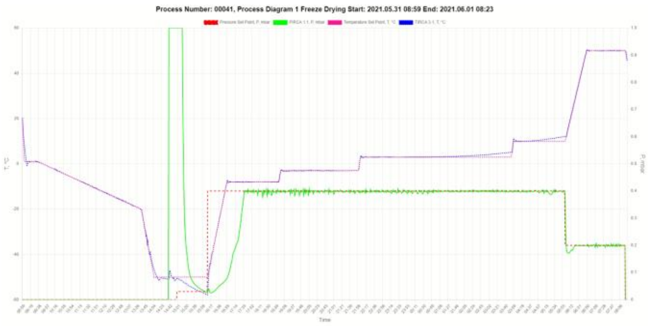

Fig. 10. Pressure and temperature in the chamber

V. Conclusion

A control system for lyophilization installation is developed and put into operation. It is part of the process of making vaccines and immunostimulants. It is developed on the basis of Siemens PLC 1200, HMI 12” touch operator panel and SCADA system. The main elements of the system and the methods for their control are shown. The main problems that need to be solved and the selected solutions for the specific case are described. Some of the sensors and actuators, the regulators used and their setting are briefly described.

The developed SCADA system, through which the installation is managed, its possibilities are concisely presented, some of the main screens are shown.

Attention is also paid to the creation of reports on past processes.

References

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