LYOPHILIZING METHOD AND EQUIPMENT

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Filed Nov. 8, 1967, Ser. No. 681,525
Int. Cl. F26b 13/30
U.S. Cl. 34—92

ABSTRACT OF THE DISCLOSURE

In the process of freeze-drying or lyophilization of materials, especially pharmaceutical materials, the condensing surface is parallel with the surface of this material, or the plane connecting the middle parts of material-surfaces is parallel with the plane connecting the ends of the connecting surfaces. In such a way it is attained that the whole quantity of the material is exposed to the same freeze-drying effect and the results of tests made on small quantities can be readily used for lyophilizations in very large quantities.

The present invention relates to freeze-drying apparatus.

Freeze-drying or lyophilization is a process whereby materials are dried in frozen condition by means of sublimation of ice. It is particularly suitable for biological materials. In order to increase the speed of sublimation, sublimation is carried out under vacuum. To remove the vapour produced would require pumps of large sizes, as for example, 1 gram water vapour has a volume of several cubic metres at a pressure of 10⁻³ mm. Hg. Therefore, in known methods of lyophilization a cooled surface is placed in the way of the vapour resulting from sublimation, onto which the vapours condense and turn into ice. Thus, the vacuum may more easily be maintained by the pump.

Lyophilizing equipment which is available at present falls into two types. In one, the condenser is placed in the lyophilizing space and in the other the condenser is separated by a valve from the lyophilizing space.

For the first type a separate after-drier is necessary, as the vapour pressure of the ice formed on the condenser will decide to what ultimate pressure the space can be exhausted. By using a single-stage cooling machine for the condenser the temperature of the condenser cannot be cooled down readily to less than −50°C. At this temperature the ice on the surface of the condenser gives a vapour pressure in the lyophilizing space much in excess of 10⁻⁴ mm. Hg and vacuum value of diffusion pumps which therefore are useless. Thus, at this stage in drying the material must be moved over into a chamber without a condenser in which the 10⁻⁴ mm. Hg end vacuum can be obtained; this chamber is the after-drier and owing to its use the equipment is large and expensive.

Modern plant lyophilizing equipment is exemplified by the Unifroid (trademark) machine. The essentials are described in “Thermal Analysis of Eutectics in Freezing Solutions,” by L. H. Rey, “Conference on Freezing and Drying of Biological Material” (scientific communication published in the Annals of the New York Academy of Sciences, No. 40, page 62, 1960). Laboratory and plant lyophilizers differ from one another not only in capacity but also in behaviour. This follows from the fact that in plant equipment after a single load charges about 10 to 15 kg. ice is formed on the condenser, while in laboratory equipment only 1 to 12 kg. is formed and the difference in the size makes an extrapolation of the values obtained in the small equipment impossible. Thus, the plant equipment requires a considerably larger condenser pro rata than the laboratory equipment. If the lyophilization is carried out in ampoules, there is room for a large quantity of ampoules in the lyophilizing space, for instance, 5000 to 30,000, depending on the sizes of ampoules. The ampoules are placed on trays and the trays can be heated. The wall of the lyophilizing space can also be warmed. The cabinet is generally rectangular.

In the laboratory lyophilizer the space containing the ampoules (material) is ordinarily arranged in a chute-like cylindrical design. The material which is in the ampoules is placed on a separate tray system and is inserted into the chute-like space. For this laboratory design the condenser is formed either in spiral form at the inner wall of the cylindrical chamber or there is a separate cylindrical condenser in another chamber which is connected by a valve to the main chamber. These latter machines are generally used in biochemical, medical and biological research laboratories.

In pharmacies lyophilizing experiments on some pharmaceutical preparations are now often necessary. To determine time of operation, there ought to be known the changes in parameters (temperature, pressure, etc.) in advance, which it is useless to work out experimentally in large scale equipment for two reasons. Firstly, because when a small load for experimental purposes is charged into large scale equipment there is no possibility of producing the same conditions as if the lyophilizing space were completely charged; i.e., the conditions of heat capacity are completely different and, thus, the data of control and temperature changes for large scale conditions cannot be determined.

Secondly, if data are required for a large scale lyophilizing experiment with a full charge of expensive material are not feasible.

The present invention is suitable partly to eliminate the disadvantages of the above-mentioned two types of apparatus, and partly to permit the establishment of parameters for a large scale process using equipment of small dimensions and at a low cost. In addition, the equipment corresponding to the invention being simple and having a good efficiency will ensure good quality control and can be used on a laboratory scale or plant scale.

This invention makes the above-mentioned advantages possible in two different ways: on the one hand, the results obtained by the small equipment can be extrapolated, and on the other hand in large equipment there is a possibility of working with a few ampoules and validly using the data so obtained.

Accordingly, the present invention comprises lyophilization apparatus comprising a chamber capable of being exhausted, provided with means for holding material to be freeze-dried, and a condenser or condensers, the arrangement of the said means and said condenser being such that when the holding means is loaded with material the surface of said material lies essentially parallel with the condensing surface of the condenser.
The invention will be further understood by reference to the accompanying drawing, which illustrates in a schematic side view one embodiment of apparatus according to this invention, one side wall of the chamber of the apparatus being removed in order to make visible its interior.

A chamber 1 is provided with condensers 5 whose condensing surfaces 6 are situated directly in front of the mouths of ampoules 7 held in stands or racks 8. For the sake of increasing the efficiency racks 8 containing the ampoules are in the vertical position. Ampoules 7 are held in the racks at an angle of about 30 degrees to the horizontal. In the ampoules the material to be dried is in frozen condition. The material cannot flow out from the ampoules even if it should melt following operational trouble.

A vacuum pump 10 is connected via duct 3 to chamber 1. Condensers 5 may be cooled down by refrigeration means (not shown) to about —40° C. The condenser surfaces 6 are on ribs and may be covered by close fitting covers 11, which are illustrated in the withdrawn position.

The ampoules 7 may be warmed by heaters 9.

In operation, ampoules 7 containing frozen material are placed in the racks 8 within chamber 1, and the condensers 5 are cooled to about —40° C. Vacuum pump 10, connected to a pre-vacuum pump 2, is then started, and pressure in chamber 1 drops to about 10⁻⁴ mm. Hg. Thus, in frozen condition the contents of the ampoules lose water by lyophilization.

In the final stage of the drying process, shutters 11 are released to cover surfaces 6. Thus vapor from ice collected on these surfaces no longer limits the attainable vacuum, which consequently is reduced still further by pump 10 thus leading to substantially complete drying of the material in the ampoules.

In known apparatus the essence of the process is that sublimated ice again turns into a solid phase on the condenser surface. In such apparatus, however, the condenser is situated around the wall of the chamber as a spiral. Thus, the distance of individual ampoules, etc. from the condenser varies. This different distance affects the speed of sublimation of the material in the ampoules, thus leading to variations in drying times in different ampoules.

Consequently, the construction corresponding to the invention imparts a change of fundamental importance which can be measured by the surprising improvement in the efficiency of the equipment. In the case of apparatus according to the invention the distance between a condensing surface 6 and the mouths of the ampoules in front of it is the same for each of the ampoules, and advantageously this can be as little as 1 cm. In a very advantageous embodiment shown in the drawing the plane connecting the ends of the ribs bearing surfaces 6 is parallel to the plane connecting the centers of the surfaces of the material in the ampoules, and the ribs are perpendicular to this latter plane.

In apparatus known so far, the distance of the farthest ampoule from the condenser surface may be 50 times the distance of the nearest ampoule, and may be some meters away.

The constructions corresponding to the invention permit a reduction of the distance between the condensing surface and the material to be dried and this distance is the same for all of the containers holding the said material.

In another embodiment of the invention the condenser is situated horizontally or vertically and can be inserted or removed from the chamber by means of a suitable rail system and seals through openings in the wall of the lyophilizing space. Thus the last stage of the drying process can be carried out following removal of the condensers.

Experiments have shown that compared with conventional apparatus the time for lyophilization can be considerably reduced. In addition, the drying process can be regulated more exactly, because the longitudinal plane of the condensing surface is parallel to the tray system containing the material, thus, the distance between the surface of the material in each ampoule and the condenser is absolutely the same and, therefore, the conditions of temperature, etc. can be made optimal.

During drying of biological material, denaturation takes place to a certain extent. The reason for this is partly because of the actual freezing process, and partly because of the fluctuations of temperature arising during the course of the sublimation. These fluctuations of temperature depend on the regularity of the sublimation. These can be reduced to a minimum by means of the apparatus of the invention because it is rapid, can be well regulated, responds instantly, and is stable and independent of the number of ampoules.

Of course, not only materials stored in ampoules can be dried but other containers or objects which are placed on suitable holders can also be put into the lyophilizing space, or they can be attached to it and sublimation can be performed with good results.

A further advantage of the invention is that the laboratory equipment and the equipment made on a large scale can be made with an identical construction and the thermodynamic relationships are also the same. Thus, if only a few ampoules are put into a machine having a capacity of say 50,000 ampoules, or it is compared with a small machine, the flow conditions of vapour, the temperature ratio, etc. will be the same. Thus it is possible to evaluate large scale lyophilizing conditions economically in advance. Additionally, the work is performed in a very short time and the construction of the machine is simple and has a low cost of production.

It may also be mentioned that the equipment corresponding to the invention can be made on the basis of units, i.e. the equipment can be assembled from unit members to the desired size.

What we claim is:

1. Lyophilization apparatus comprising an evacuable chamber, a condenser in upright position within said chamber, two upright stands for holding the material to be freeze-dried one on each side of said condenser, and a source of heat adjacent each of said stands but remote from said condenser, said condenser, said two stands and the two said sources of heat being substantially parallel to each other.

2. Lyophilization apparatus as claimed in claim 1, in which said condenser has horizontal parallel ribs and the contour of the ends of the ribs is parallel to said stands and to said sources of heat.

3. Lyophilization apparatus as claimed in claim 1, and means for selectively segregating said condenser from said stands.

4. Lyophilization apparatus as claimed in claim 3, said segregating means comprising removable covers interposable between said condenser and said stands.

References Cited

UNITED STATES PATENTS

2,380,339 7/1945 Siedentop 34-5
2,312,930 5/1964 Abbott 34-5
2,242,575 1/1966 Manaresi 34-92
2,299,525 1/1967 Those 34-92
2,382,585 5/1968 Blake 34-92

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