FREEZING AND DRYING

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REPORT OF A SYMPOSIUM HELD

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FOREWORD

THIS report contains all the papers read at a Symposium of the Institute of Biology which was held in London in June, 1951. In addition it was possible to record the whole of the discussion which followed the papers and this has also been included.

The Institute greatly appreciates the facilities for holding the Symposium which Professor E. N. da C. Andrade, F.R.S., and the Managers of the Royal Institution made available.

The Editor wishes to thank Mrs. L. O. Butler, Mrs. E. Roberts and the Misses H. Allen, P. Kelsey, S. Pirkis, M. Taylor and G. Woodhatch who so competently recorded and transcribed the discussion and also Mr. D. J. B. Copp, the General Secretary of the Institute and the Church Army Press for their assistance in the production of this report.

R. J. C. HARRIS,
Editor.

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CHAIRMAN: Dr. C. H. Andrewes, F.R.S.

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CHAIRMAN: Professor J. F. Danielli

INTRODUCTION

IN opening the Symposium the Chairman of the first session, Dr. R. I. N. Greaves, said:

" It is my great pleasure to welcome you all to this Symposium on ' Freezing and Drying ', which is the first to be held—I rather expect anywhere—but certainly in this country.

That such a meeting was wanted is clearly shown by the large number of you who are present to-day, which I am told is close on 400.

I am sure that you would wish to join with me in thanking the Institute of Biology for calling this meeting, and especially I know that you would like me, on your behalf, to thank Dr. R. J. C. Harris, who has been personally responsible for most of the hard work.

This first session is to be devoted to the ' Industrial Applications of Freeze-drying '—I personally prefer the term ' Drying by Sublimation '. As a laboratory technique it has been known for fifty years or more, but it was the last war which caused this somewhat retiring infant to blossom forth into maturity, when first the dried plasma and later the penicillin programme was met by the production of plants, the size of which had never previously been imagined.

This war-time mushroom growth was, of necessity, built up on somewhat insecure foundations, and it must be confessed that our detailed knowledge is at times rudimentary. It is here that I hope that this meeting may be of real value.

Nevertheless the virtues of this technique are now becoming widely recognized and its vices are better known. Its applications in the medical and veterinary fields are numerous and increasing daily, and to-day there can scarcely be a biological laboratory not equipped with freeze-drying apparatus.

I regret to say that one still hears remarks such as:—' the material should be as dry as dust '; or ' less than 1% residual moisture is satisfactory '—as though this applied to every material under all circumstances; or ' quick freezing is essential '—with no qualifications; or ' pack in dry nitrogen '—with no attempt to discover just how dry the nitrogen was.

One could extend these remarks very considerably, but I hope that these post-war years have enabled us to define more exactly the criteria for satisfactory drying, and I hope, by pooling our ideas at this meeting, our knowledge of this most useful technique may be advanced."

SESSION I

INDUSTRIAL APPLICATIONS OF FREEZE-DRYING: DESIGN OF EQUIPMENT

LARGE-SCALE FREEZE-DRYING AS CURRENTLY CARRIED OUT IN THE WESTERN HEMISPHERE

By

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THE general procedures and the types of equipment used for freeze-drying, as carried out on an industrial scale in commercial enterprise, are quite different from what is to be found in the research laboratory. This is not only because the scale of operation is larger, but also because the requirements and objectives are different.

No products produced on an industrial scale are freeze-dried with final sealing of the containers under the original processing vacuum. In every case, the vacuum is released and the containers are then sealed either under air, an inert gas, or under secondary vacuum.

With some products, all-glass ampoules to be sealed by fusion with a flame are used. The vast majority of products are dried in moulded-glass bottles of appropriate size and closed with a rubber stopper. This is finally covered with an aluminium cap. The cap serves a dual function. One is general mechanical protection of the stopper and the other is retarding the diffusion of water-vapour and air through the rubber during storage. Although the closure is not fully hermetic and all diffusion is not stopped, for all practical purposes it has been found to be fully satisfactory.

To freeze the products, the containers may be placed in a low temperature vault to form a solid plug at the bottom of the vial. This is generally the simplest and is satisfactory provided the depth is not too great. If too great a depth occurs in this way, it is necessary to shell-freeze by rotating the bottle on its horizontal axis. A typical shelling machine in which the refrigerant is dry-ice, is illustrated in Figure 1.

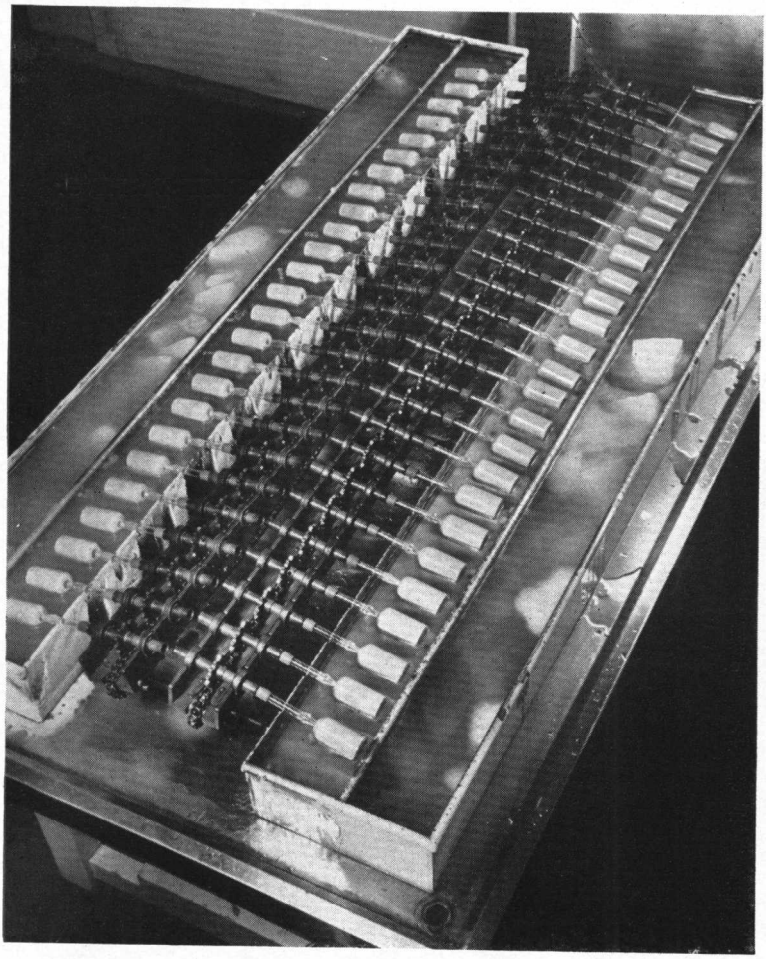

FIG. 1. Dry-ice type Shelling Machine for ampoules.

For the drying, the containers are placed in special racks on shelves in vacuum-drying chambers like those illustrated in Figures 2 and 3. The shelves are usually heated with hot water. The water is forced through the shelves with a motor-driven pump and is thermostatically controlled to supply the latent heat of sublimation as fast as possible without melting the product. In some dryers, the shelves are electrically heated, but this has not been found to be generally satisfactory for, after the completion of drying a batch, too long a

FIG. 2. Drying Chamber being loaded with racks for supporting plasma bottles and for supporting small vials of antibiotics. No protective covering is provided in this case.

time is required to chill the shelves again before reloading with the next batch. With water-heated shelves, this is easily taken care of by circulating cold water and the " down time " is reduced to a minimum.

In a few installations, heating is carried out by means of infra-red. Use of this means of heating is not widespread. It is more difficult to control because of local overheating, particularly at fringed edges where thinly-dried regions of product are situated, before the main bulk of drying has been completed.

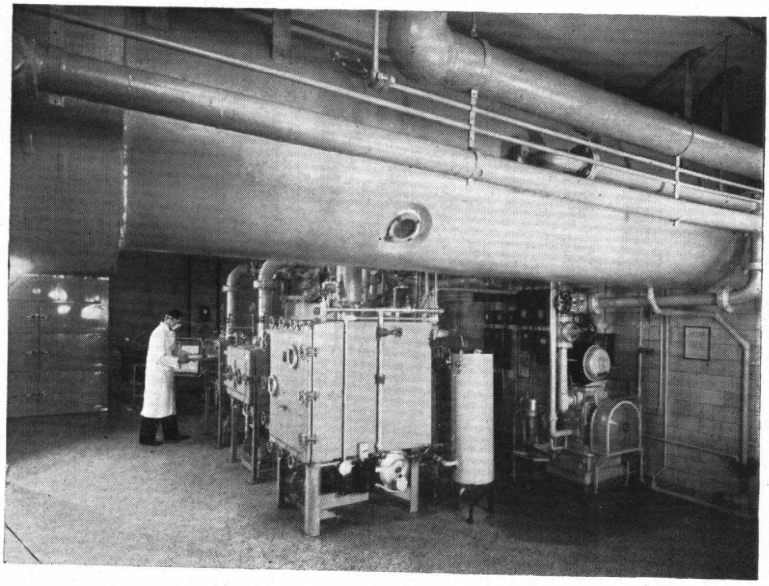

FIG. 3. Miscellaneous size Drying Chambers with large vapour condenser in the upper foreground for trapping out water-vapour.

With certain products produced in large volume like antibiotics, drying is frequently carried out in bulk, either in stainless-steel trays covered with lids or in large-size bottles. In the former the lids are arranged for the vapours to escape by a tortuous path to prevent contaminants from falling into the material. In either case the dried solids must be pulverized, weighed and transferred under aseptic conditions and with the atmosphere controlled at low relative humidity.

In some drying chambers the supporting shelves may be chilled to sub-freezing temperatures with a secondary refrigerant like trichlorethylene so that plug-freezing may be carried out readily in the racks on the drying shelves. Then, after freezing is completed, evacuation takes place and there is no opportunity for thawing before the proper degree of vacuum is obtained for freeze-drying. Following this the source of cold trichlorethylene is cut off and hot trichlorethylene is fed in at proper temperature.

The trays for supporting the small vial type of bottle or larger bottles must be arranged for good conditions of transfer of heat. This is necessary both for freezing within the chamber, when carried out there, and for supplying the latent heat of sublimation rapidly and uniformly during drying.

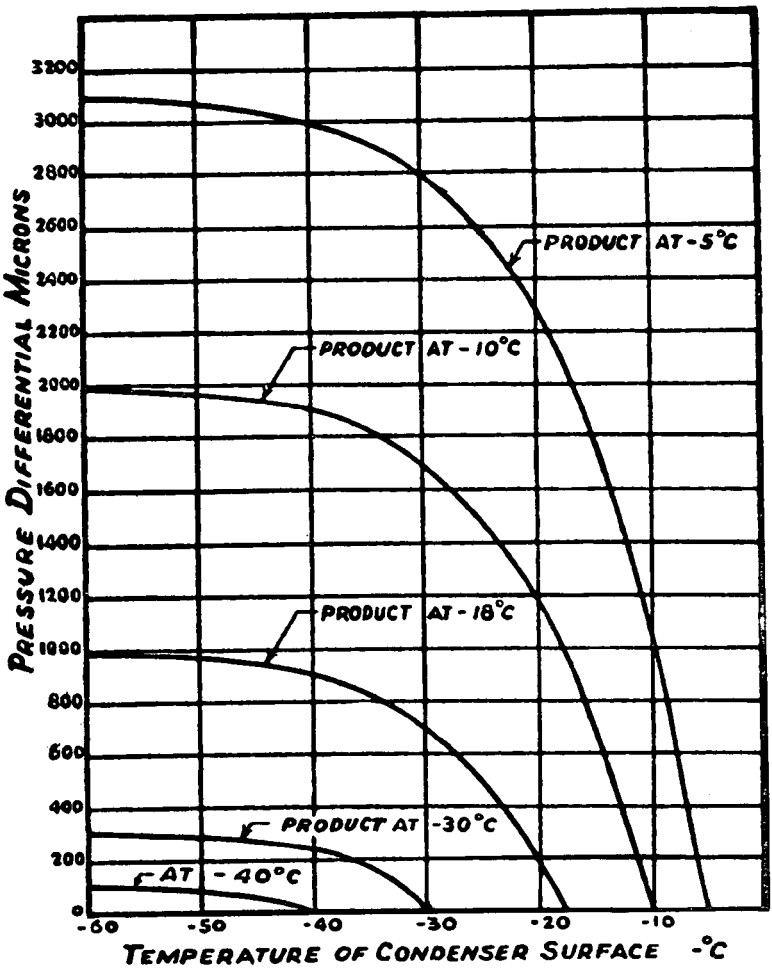

FIG. 4. Relation between temperature of condenser and the driving force for drying the product. The curves show the conditions for products being dried at different temperatures. The actual temperature in drying varies, depending on the product being dried.

The temperature at which the product must be held during drying varies widely because of differences in eutectic composition. Extreme examples are A.C.T.H. (adrenocorticotrophic hormone) and streptomycin where the temperature must be held as low as -35 to $-40°$ C. The effect this has on the vacuum requirements and the temperature of condensers is illustrated in the curves in Figure 4.

FIG. 5. Compact Single-packaged Unit. Two lower shelves refrigerated with Freon for prefreezing and to act as condenser plates. Top shelves used for drying and are hot water heated.

For production of vacuum, oil-sealed rotary mechanical pumps are mostly used. Where the product requirements call for a higher degree of vacuum in order to maintain lower temperatures, diffusion pumps are used to advantage because of their greater efficiency below

50 microns. In almost all installations, the water-vapour is trapped out in a mechanically-refrigerated condenser. Compound ammonia refrigeration or Freon refrigeration is used. In smaller sizes, Freon is more economical and in the larger, ammonia is preferred. In a few plants, direct pumping is carried out by means of multi-stage steam ejector pumps. Requirements of steam and cooling water are expensive unless certain ideally-situated locations provide for these at lower than normal cost. Then direct pumping can provide the simplest means for evacuation of non-condensables and for removal of the water-vapour. Mechanical oil-sealed rotary pumps may be used in a limited way for both functions, too, particularly where the temperature requirements for the product are not low. It is necessary, however, for the oil in the vacuum pump to be continually clarified of condensed water-vapour, which is done by means of a continuous centrifuge.

An interesting type of unit which is quite efficient and easy to operate for limited production of small volume items is illustrated in Figure 5. The two lower shelves are refrigerated by means of direct expansion Freon and the two upper shelves are heated by means of water containing an anti-freeze. For plug freezing, the trays with the containers of product are placed on the lower shelves. Then, for drying, they are transferred to the upper shelves, the door closed and

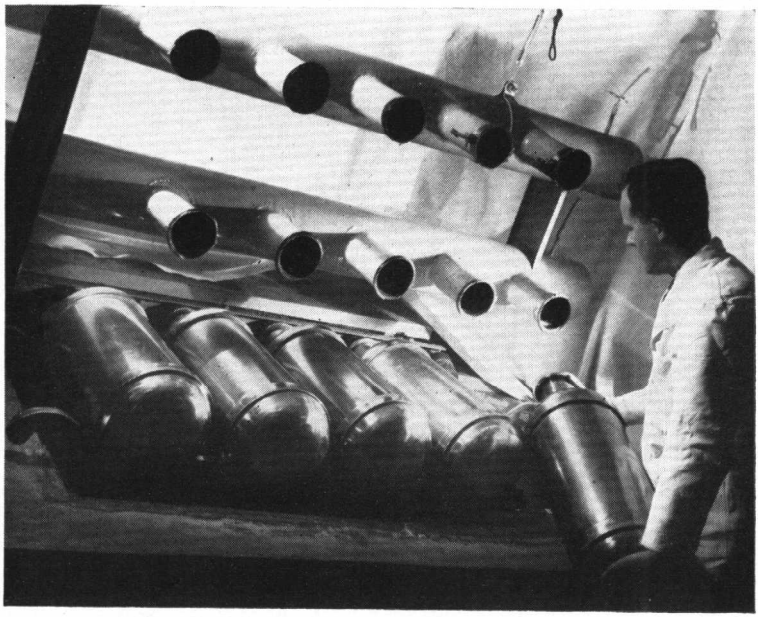

FIG. 6. Old style bulk drying equipment.

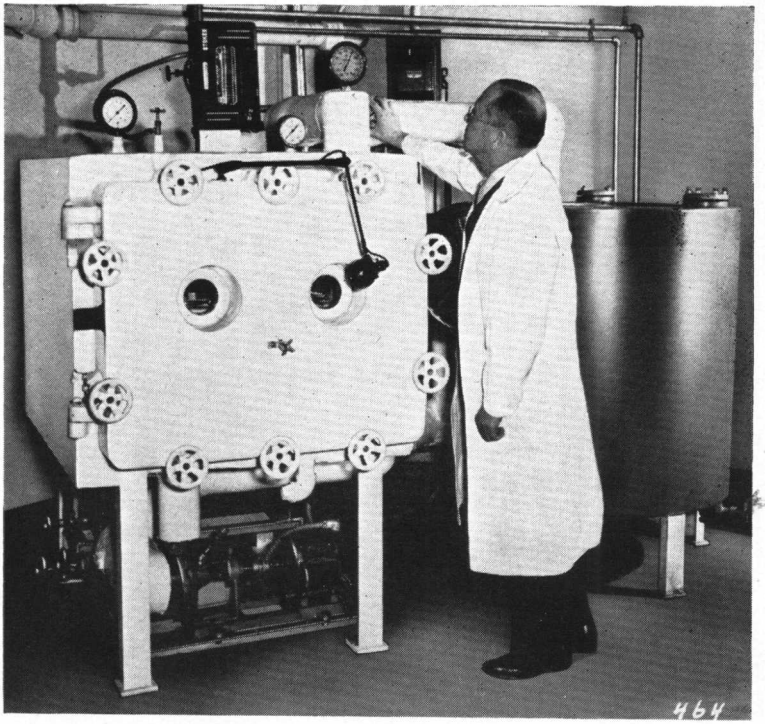

FIG. 7. Later type equipment with dry-ice refrigerated trap.

the vacuum pump turned on. The two lower cold plates then serve as the cold condenser. This eliminates the necessity of external vapour lines and valves. The refrigeration and all of the general equipment is contained within the panels under the drying chamber.

For comparison with modern equipment, 1935–1940 types of bulk dry-ice apparatus will be found illustrated in Figure 6. In this one earlier Pyrex glass balls are replaced with stainless steel bulbs. A later type of dry-ice condenser with chamber used for production of convalescent serum, as installed at the Children's Hospital in Philadelphia, is illustrated in Figure 7. The shelves of the chamber may be chilled to $-50°$ C. as well as heated.

Below is a list of some of the products produced by various companies in the United States for general distribution and sale. Many of these are also produced in Canada, Mexico and various South American countries. The ones produced most widely outside the United States are human blood-plasma, antibiotics and vitamin preparations.