REVIEW ARTICLE

RECENT ADVANCES IN FREEZE-DRYING*

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In 1946, the Medical Research Council published their Special Report Series, No. 258, on "The Preservation of Proteins by Drying" (Greaves, 1946). This Report summarised the work of the M.R.C. Drying Unit which had been responsible for the preparation of dried plasma for transfusion purposes during the War.

The First International Symposium on Freezing and Drying (1951) was held in London in that year to be followed by a Second Symposium in 1958 (Parkes and Smith, 1960) and a Symposium organised by the New York Academy of Sciences, in 1959 (Review, 1960). During these post war years the technique of freeze-drying has been applied more and more widely and, with rapid technical improvements, has now reached the stage when it is becoming a commercial proposition in the preserved food industry.

In the pharmaceutical industry, freeze-drying has already become an important stage in the manufacture of certain products such as streptomycin and for the distribution of unstable products, such as hormone preparations, in a stable form. It has also enabled stable vaccines to be prepared, in particular B.C.G. (Obayashi, 1960; Muggleton, 1960) and vaccinia (Collier, 1955).

In the course of this review it is impossible to consider all the advances which have been made since the end of the war, and I shall limit myself to a discussion of those advances which I consider are of particular importance to the pharmacologist and the pharmaceutical industry. Advances in vacuum and refrigeration techniques, which have enabled drying chambers of almost any size to be made and have led to reliability and ease of operation, will not be discussed here. Instead, I wish to discuss Professor Louis Rey's work on Thermal Analysis (Rey, 1959, 1960a,b) which enables us to predetermine the optimal drying conditions for a particular substance. In addition, I wish to discuss the drying of living organisms and finally the application of heat in freeze-drying systems.

Thermal Analysis

If a simple solution of a salt such as NaCl is cooled, when it reaches 0° pure ice starts to separate as crystals. This removal of pure water from the system leads to concentration of the NaCl until a certain concentration known as the eutectic concentration is reached. The temperature then drops to −21·6°, at which temperature the eutectic concentrate freezes. This temperature of −21·6° is known as the eutectic temperature of NaCl.

* Based on two Special University of London lectures given at the School of Pharmacy, Brunswick Square, London, on March 6 and 8, 1962.

Obviously, if the material we wish to dry is in a solution of NaCl, and we dry at a temperature above $-21{\cdot}6°$, then there will be some drying from the liquid phase.

Again, many substances, such as glycerol-water solutions, do not crystalise entirely when they are frozen. The remaining fluid concentrates progressively and its viscosity becomes greater and greater until it hardens and becomes, at least partially, a glass. This glass, although it is metastable, may persist indefinitely. On warming the reverse process occurs, the glass progressively losing its high viscosity and returning to the liquid state. Many compounds which we may wish to dry may show these properties; in particular, sugars and alcohols and some vitamins. Such substances are very difficult to dry as the continuous softening of the glass leads to "puffing" of the product with some degree of melting and denaturation. But, thermal analysis will enable us to discover the devitrification temperature, and preliminary thermal treatment of the substance may enable a satisfactory freeze-drying of the substance to be accomplished.

The Optimal Drying Procedure

In the past we have faced the freeze-drying of a new product by the empirical method of trial and error. In the light of Rey's work, it is now possible to forecast the precise optimal drying procedure. The method is basically extremely simple; all that is necessary is to plot the temperature of the material when it is cooled and warmed at a constant rate and to compare its temperature with that of distilled water treated in an exactly

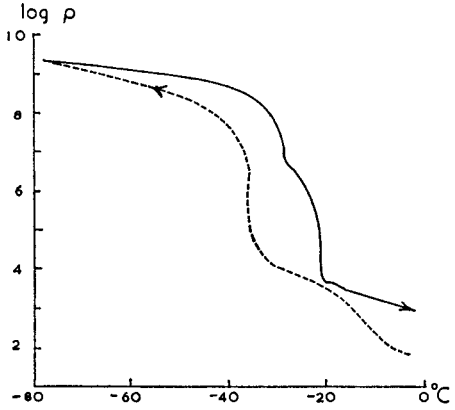

FIG. 1. Variation of the electric resistance with temperature of a solution of 10 parts per 1,000 of NaCl in distilled water. *Broken line* measurements taken during cooling. *Solid line* measurements taken during warming. *By courtesy of Professor L. R. Rey.*

similar way. At the same time the electric resistance of the product should also be measured. Single estimations may be plotted by hand, but when routine measurements are to be made, it is a great convenience to record them automatically.

When a solution of an electrolyte is completely frozen, its electrical resistance becomes infinitely great. In order to measure this resistance, we need a resistance bridge measuring up to at least 100 megohms, and in order to avoid polarisation, this bridge must be fed with alternating current, preferably at about 1,000 cycles/sec., preferably square wave. Fig. 1 shows the resistivity measurements on cooling and warming a solution of 10 parts per 1,000 of NaCl in distilled water. The discrepancy between the two curves is due to supercooling on freezing so that a totally solid phase is not achieved until the temperature reaches −40°; the correct eutectic thawing temperature of −21·6° can be confirmed only on the warming curve.

This experiment shows the importance, when freeze-drying material containing NaCl, of first prefreezing to a very low temperature before drying at a temperature just below the eutectic, otherwise, at the same drying temperature, there might be some supercooled liquid present.

Automatic Control of Drying Temperature

This experiment also suggests a method of automatic control of the drying temperature. Just before the eutectic temperature is reached, there is a sudden fall in resistance. This fall could be made to cut off the heating circuit. This has a distinct advantage over control simply by the

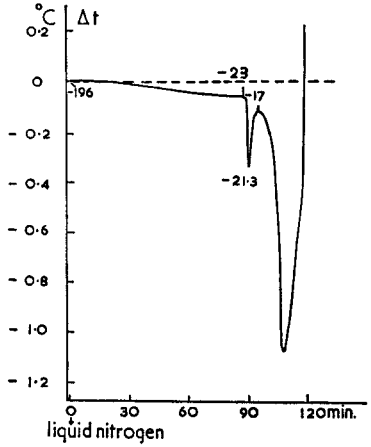

FIG. 2. Differential thermal analysis diagram of a solution of NaCl in distilled water. *By courtesy of Professor L. R. Rey.*

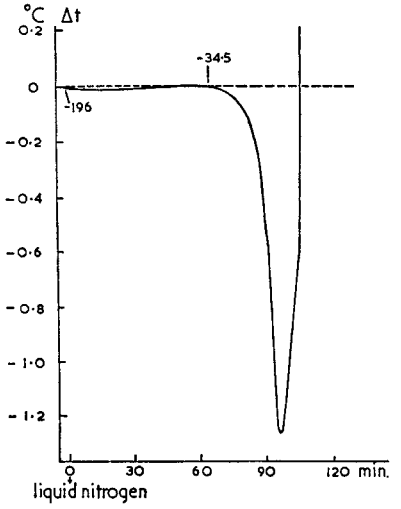

FIG. 3. Differential thermal analysis diagram of normal horse serum. *By courtesy of Professor L. R. Rey.*

temperature of the product. First, it enables drying to be carried out at the maximal permissible temperature and second, when the temperature starts to rise towards the end of the drying cycle, instead of the heat being automatically reduced as it would be if one were controlling by the temperature of the product, the heat will remain maximal. Thus, the duration

of the late stages of drying is greatly reduced, though a second relay controlled by the temperature of the product must operate to cut off the heat as soon as the dried product has reached its maximum safe temperature. This very elegant method of automatic heat control has been described by Rey (1961).

I have quoted only the example of a simple salt solution. With biological material, such as animal sera, the picture is much more complicated. The presence of proteins masks the salt eutectics and many of the salts are in very small concentrations. As a result, the electric resistance falls gradually with no very sudden steps.

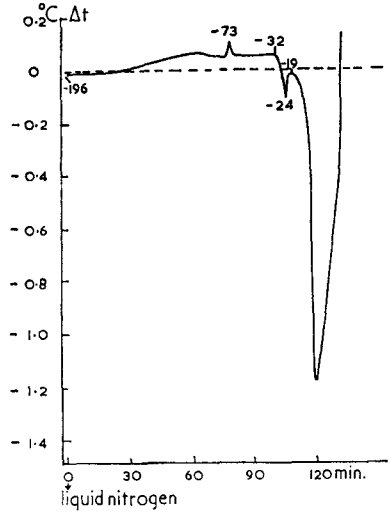

FIG. 4. Differential thermal analysis diagram of Earle's salt solution. *By courtesy of Professor L. R. Rey.*

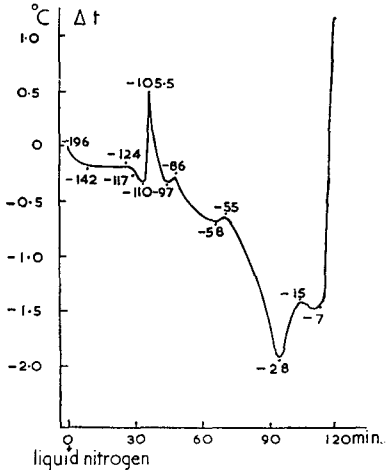

FIG. 5. Differential thermal analysis diagram of a 50 per cent solution of glycerol in Earle's salt solution. *By courtesy of Professor L. R. Rey.*

Another approach is by direct temperature measurement during constant warming. The principle behind these measurements is the continuous comparison on a warming curve between the solution being investigated and distilled water ice. Phenomena such as devitrification of a glass involving crystalisation will be shown as an exothermic reaction, the curve rising, whilst thawing of a eutectic mixture will be shown as an endothermic reaction, the curve falling. These changes are correlated with an absolute measurement of temperature.

Fig. 2 shows such a curve for NaCl with its eutectic at −21·3°. Fig. 3 shows a similar curve for horse serum with eutectic melting starting at −34·5°, and the curve for chick embryo extract shows eutectic melting starting at −17·5°.

Fig. 4 shows the more complicated thermal analysis of Earle's solution. Note particularly the exothermic reaction at −73° due to crystalisation followed by eutectic melting starting at −32° and being maximal at −24°.

Fig. 5 shows an even more complex picture of Earle's solution containing 50 per cent of glycerol. The first endothermic reaction is due to a vitrous transformation at −117°; at −105° there is devitrification to cubic ice. At −86° there is an exothermic crystallisation from cubic to hexagonal ice. At −58° there is thawing of the glycerol: water eutectic and final thawing at −28°.

Since nearly all biological solutions contain salts and undergo considerable supercooling during freezing, and since many form glasses on freezing, difficulties are likely to be encountered unless a complete thermal analysis has previously been made. Some general rules can, however, be devised. First, it is wise to prefreeze to a very low temperature, at least to −80° in "dry-ice", preferably to −196° in liquid nitrogen, to be certain that no supercooled liquid remains. Second, if glass is formed, it is necessary to ensure devitrification before drying starts; this is done by raising the temperature to a point above the lowest temperature at which exothermic reactions can be observed, and holding at this temperature sufficiently long for crystallisation to occur. Third, after the previous treatment, drying must be carried out below the lowest eutectic temperature. If the electric resistance of the material is known, then this resistance may be used to control the heat input during drying.

The Drying of Living Organisms

In the M.R.C. Report No. 258 (Greaves, 1946) there was no reference to the preservation of living organisms by freeze-drying. Several papers had appeared by that time, notably by Elser, Thomas and Steffan (1935), suggesting that the method was of value for this purpose. Since the war, however, a considerable amount of work on the preservation of viruses and bacteria by freeze-drying has been published. The position up to 1954 has been admirably reviewed by Fry (1954).

The most important factor in deciding the percentage survival both immediately after drying and for long term storage is undoubtedly the medium in which the organisms are suspended for drying. Very many different media have been reported to have been used successfully, such as serum, broth, skimmed milk and gelatin, but seldom has success been verified by viable counts on a variety of organisms. In 1949, Fry and Greaves suggested that a medium consisting of 75 per cent serum and 25 per cent broth, containing 7·5 g. of glucose per 100 ml. gave satisfactory viable counts with a number of organisms, including such delicate organisms as *Neisseria gonorrhoeae* and *Vibrio cholerae*, both immediately and also after long term storage at room temperature. At that time they suggested that the serum acted as a protective colloid and as a support medium to give a final dried cake, and that the glucose exerted its effect by acting as a buffer of the residual moisture content preventing the organisms from becoming too dry. They had no explanation why broth was so necessary. They also showed that the glucose effect was shared by many other sugars such as lactose and sucrose. Since its description, this medium has been used widely and successfully for the drying of many different species of organism.

But this medium is not suitable for all purposes. For instance, neither serum nor broth would be very suitable for human injection of a living vaccine. Moreover, although this medium gives excellent long term survival at room temperature, and we have results now of up to 15 years duration, at high ambient temperatures survival is poor. Consequently, over the years, the Fry–Greaves medium has been considerably modified.

It was Obayashi (1960) who first showed that the use of sodium glutamate greatly increased the stability of B.C.G. vaccine at high temperatures. Muggleton (1960), also working with B.C.G., found that the effect of sodium glutamate was neutralised by glucose and not by sucrose. He therefore suggested that a B.C.G. vaccine for human use should be dried in a mixture of 5 per cent glucose-free dextran, 1 per cent sodium glutamate and 5 per cent sucrose. He showed that the dextran was a satisfactory non-antigenic substitute for the serum and the sodium glutamate a satisfactory substitute for the broth in Fry and Greaves' medium, and that 5 per cent sucrose buffered the residual moisture content at 1 per cent.

Meanwhile, Scott (1960), in Australia, was approaching the problem from a different angle. He dried his cultures in a papain digest broth and then stored at varying water activities over salts at varying hydration values, and at various temperatures, in vacuum, air and nitrogen. He found that at low water activities and low temperatures the good initial survival with glucose was well maintained, but that such dried cultures were unstable at high temperatures. Sucrose gave much better protection at high temperatures; ribose was poor at all temperatures and water activities. Scott concluded from his experiments that the instability of dried cultures at high temperatures was due to the presence of carbonyl groups, that the amino-acids of the broth in Fry and Greaves medium neutralised carbonyl groups, but that glucose added carbonyl groups whereas sucrose did not.

In testing a drying medium, a good initial survival and long term storage at room temperature is not enough. A slightly less good initial survival if it gave better long term survival at higher temperatures would be preferable. For this reason I introduced the empirical method of heating in which the dried material was subjected to a temperature of 100° and the time necessary to reduce the viable count to half was estimated.

Under these conditions the Fry and Greaves medium showed up very poorly at high temperatures. 5 per cent peptone was poor for immediate survival, but excellent at high temperatures, which supported Scott's hypothesis. Sodium glutamate alone worked best at 5 per cent; at lower percentages, as used by Obayashi, the initial survival was poor, suggesting that the cultures were too dry; at higher percentages the glutamate appeared to have the dual effect of neutralising carbonyl groups and also acting as a buffer of the final moisture content. The glutamate was greatly improved by adding a colloid such as 5 per cent glucose-free dextran.

These studies, Greaves (1960), led to the conclusion that a drying medium for bacteria should contain (1) a protective colloid, i.e. 5 per cent

dextran containing no glucose. (2) A buffer to control the residual moisture content around 1 per cent, i.e. 5–10 per cent sucrose or 5–10 per cent sodium glutamate. (3) A neutraliser of carbonyl groups, i.e. broth or 1 per cent sodium glutamate.

Recently Obayashi, Ota and Shiro (1961) have suggested the use of polyvinylpyrrolidone as the protective colloid instead of dextran. From a limited experience, I have had good results using the K 30 fraction of polyvinylpyrrolidone with a mean molecular weight of 45,000 and also with Bayer's New Periston with a mean molecular weight of 11,500. When made up, the polyvinylpyrrolidone is acid and, in my experiments, was neutralised before use.

Obayashi and his colleagues in the same paper have used my high temperature survival experiments and consider that for a particular organism it is possible to get a fair idea of the likely storage time at any temperature by extrapolation from the results obtained at high temperatures.

An important paper is that of Collier (1955), who recommends the use of 5 per cent peptone alone for preparing dried vaccinia virus. As already stated, this is not very good for bacteria, for the organisms get too dry. But I have confirmed Collier's findings with other viruses, in particular influenza virus, and the virus of *Herpes simplex*.

Could there be a fundamental rule of nature here that the more simple the form of life the more water it is possible to remove without causing death? Some of my recent work would confirm that this is so.

Drying Higher Forms of Life

Two possible break-throughs in the search for a method of drying higher forms of life have occurred in recent years. The first was a paper by Annear (1956a), in which he claimed an 80 per cent recovery on drying *N. gonorrhoeae* as opposed to the more usual 10–15 per cent of freeze-drying techniques. He obtained a similar recovery with *V. cholerae* and also claimed the successful drying of leptospira (1956b) and the protozoon *Strigomonas oncopelti* (1956c). In his method he first freeze-dried plugs of 10 per cent peptone, 7 per cent glucose and 0·5 per cent soluble starch. Onto the freeze-dried plug he placed a small drop of his culture and immediately placed the ampoule on a vacuum manifold and evacuated it. The drop of culture liquified part of the plug, and when a vacuum was applied this liquid foamed in the ampoule and the foam rapidly dried. Unfortunately, Annear made no measurements of temperature so it was impossible to decide whether this was freeze-drying or rapid drying of a liquid film.

The second break through was a paper by Meryman (1959), in which he claimed the successful freeze-drying of bovine sperm. The basis of his method was the very rapid freeze drying of the sperm which was suspended as a thin film on nylon mesh. Freezing was by evaporation, and he stated that the time taken to bring the specimen temperature from ambient to $-35°$ was critical, and for sperm was between 2 and 3 sec.

Three questions seemed to require investigation.

The first was this. If a protozoon would not survive freezing, was it possible to dry it at a temperature above freezing? Was this why Annear's technique was successful with *S. oncopelti*? And, was Annear's technique really not freeze-drying?

The second question followed from the first. Was residual moisture content critical with higher forms of life? By analogy with the viruses ought we to leave much more than the 1 per cent residual moisture necessary for bacteria when drying higher forms of life?

The third question was: could other critical freezing curves, similar to Meryman's curve for spermatozoa be found for higher forms of life?

In an attempt to answer these questions, I reproduced Meryman's apparatus at Cambridge and, with the help of Dr. Polge, tried to repeat his results with sperm, but with no success. My experience is not unique for, though several other workers have also tried, no one except Tokio Nei (Nei and Nagase, 1961), on one occasion, has been successful. Indeed Meryman himself cannot now get any success. The reason for this is a mystery, as yet unsolved.

I was, however, able to repeat his success in drying red blood corpuscles which remained intact if they were resuspended after drying in a 40 per cent solution of polyvinylpyrrolidone.

I have also done many experiments to try to dry *Euglena gracilis* and *Strigomonas oncopelti*, and see whether a critical freezing curve could be obtained for them. These experiments were very frustrating. Occasionally some success resulted, but could never be repeated with certainty.

However, using this apparatus, I was able to make the temperature measurements that Annear had failed to do, and was able to show that his drying was probably at a temperature below 0° in a supercooled state. It was very easy to supercool Annear's foams to −9° and, under these circumstances, the method gave good survival of *S. oncopelti*, but not *E. gracilis*. If freezing occurred, *S. oncopelti* was killed.

In an attempt to discover when *E. gracilis* was dying during the drying process, counts were done at 2 min. intervals. These showed a continuous slow loss of viability until 80 per cent of the water was removed, at which point total loss of viability occurred. Similarly, counts of *E. gracilis* were made after the various stages of the Meryman freeze-drying curve, which showed clearly that *E. gracilis* could not be successfully frozen in the absence of some protective agent.

Looking at the series, virus, bacteria, protozoa, it seems that as the organism becomes more complex so more water must be left if viability is to remain. But if a high water content is necessary for a good survival, is this likely to be compatable with long term preservation?

I was feeling rather pessimistic as a result of these experiences when, at this time I was given a sample of dried Nigerian mud. This mud contained the desiccated forms of small nematode worms. When water was added to this dried mud, the worms swelled and swam away.

Nature has succeeded where man has failed. But this experience must be accepted as a challenge for the future.

Heat Transfer in Freeze-Drying Systems

The most common criticism of the freeze-drying process is made on the grounds of slowness of drying. The necessary apparatus for freeze-drying is costly, and if the throughput is small, drying costs are high. This does not greatly matter if the cost of the product is high, as it usually is with medical products, but it becomes decisive if cheap products, such as foods, are to be dried.

The rate of drying depends directly on the rate of application of that amount of heat which is required to supply the latent heat of sublimation of the ice. Much of the recent research on the freeze-drying process has, therefore, been directed into investigating methods of heat transfer and identifying the factors which limit the rate of heat transfer.

In my 1946 review (Greaves, 1946) I pointed out that in a freeze-drying system one had a water vapour pressure difference between the water vapour pressure of the drying material and the condenser, a resistance to the flow of vapour and a rate of flow. This may be expressed thus:

$$\frac{\text{Vapour pressure difference}}{\text{Resistance to flow}} = \text{Rate of flow.}$$

As the vapour pressure of ice is a function of temperature, the formula may be rewritten:

$$\frac{\text{VP. } T_1 \text{ (drying material)} - \text{VP. } T_2 \text{ (condenser)}}{\text{Resistance to flow}} = \text{Rate of flow} = \text{Constant K} \times \text{watts.}$$

If you wish to dry at a low temperature, then VP $(T_1 - T_2)$ must be kept small so that the drying temperature approximates to the condenser temperature, and if drying is to be fast, the heat input must be high. This, in turn, means that we must keep all obstruction to the flow of vapour as low as possible.

The Importance of Design

In a freeze-drying system, factors which lead to high degrees of obstruction are poor design, such as restricted vapour paths, or poor construction causing leakage and so producing a high partial pressure of non-condensable gases. But in any well designed plant, these factors are of small magnitude compared with the obstruction to the flow of water vapour caused by the dried material as the drying boundary receeds from the surface. Thus, the very nature of the dried material places a limiting factor on the speed of drying and, since this limitation is a function of the density of the dried product, it does not necessarily follow that an advantage in speed of drying will result from concentrating the liquid before freeze-drying. An extreme example of obstructive resistance to vapour flow is caused by the intact membranes of cells and, as everybody knows who has used the freeze-drying technique for preparing histological preparations of tissues, drying becomes very slow indeed.

Methods of Applying Heat

Heat may be applied by conduction, radiation or convection or by dielectric heating or by a combination of any of these methods.

An analysis of the problem as to the most suitable method of applying heat is best made by considering the simple case of subliming distilled water ice.

Assuming a condenser temperature of −40°, the temperature at the surface of the drying ice will be around −35° in a well designed apparatus. Supposing we have a block of ice, 2 in. thick, frozen on a metallic heating plate. As melting will not occur till the temperature of the heating plate has risen to 0°, it is safe to raise the temperature to −5°. This will give a gradient of 30° through the ice to the drying surface. As drying proceeds, the thickness of the ice will decrease; if the heat input is kept constant, the heater temperature will fall. Alternatively, the heater temperature could be kept constant at −5°, in which case the heat input would constantly increase, and with it the drying rate.

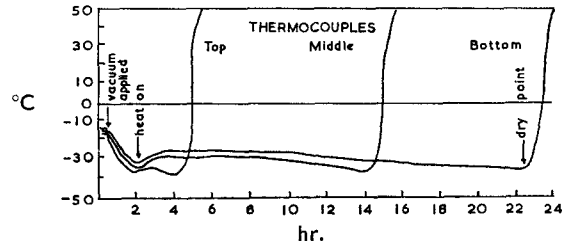

FIG. 6. Drying curves for 2 litres of distilled water ice prefrozen in a rectangular tin giving a depth of 3 in. Heating was by radiant heat from above. Heat input 100 W. Vacuum 0·05 mm./Hg. Condenser temperature −50°.

If heating was by radiation, the conditions would be very different. There would be no gradient through the ice, and provided the obstructive resistance of the system was low, vast amounts of heat could be applied without significantly raising the drying temperature (Fig. 6). Alternatively, as it would be quite safe to dry at −5°, it would be possible to raise the condenser temperature to say −10° with a big increase in the economic efficiency of the process.

An additional advantage of radiant heating would be that since one side of the block no longer needed to be in contact with the heater plate, drying could take place from both sides of the block, thereby effectively halving its depth.

With distilled water ice, there is a very obvious advantage for radiant as opposed to conductive heating. However, the advantages when drying a biological solution are not as great due to the limitation imposed by the danger of overheating and even burning the dried material on the surface of the block.

Suppose we wish to dry a protein solution which has shown eutectic melting at −21·6° on previous thermal analysis. With conductive heating

it will not be safe to raise the heater temperature above −25°, so that the maximum permissible gradient across the frozen block will be 10°. This means that either we must dry slowly with a thick block or faster with a thin block, and the calculation of the optimal thickness for a maximum efficiency of operation becomes difficult.

As drying proceeds, the increasing layer of dried material causes increasing resistance to the flow of vapour, and if the heat input remains constant, the drying temperature will rise and the temperature at the point of contact with the heater may rise above the eutectic temperature causing local melting. This will completely upset the uniformity of heating and wet patches will probably be found in the dry product.

With radiant heating there will be no gradient across the frozen block so that it will be impossible to cause melting of the eutectic mixture. The limitation of heat input will be set by the highest safe temperature to which the dried material may be raised. This temperature is usually about +80°, and if the radiant heater plates are automatically controlled at this temperature, and if radiant heat is applied to both sides of the block, it is found that a 1½ in. thick block can be dried in 38 hr., whereas a ¾ in. block dried in 11 hr. These figures show the advantage of keeping thickness to a minimum.

The advantages of radiant heat on both sides of the block are very obvious, but this may not always be convenient. Conductive heat from the bottom of the block, coupled with radiant heat from above may be a satisfactory compromise.

When exact experiments are made on the absorption of radiant heat, it is found that more heat is absorbed at a given heater temperature than theoretically it should be. The probable explanation for this discrepancy is that the water vapour being evolved from the drying product becomes superheated, and some of this heat is returned to the drying product by convection. Rey and Rieutord (personal communication) have examined this phenomenon and find that by controlled injection of non-condensable gas into the vacuum they can increase this convection heating and can transfer as much heat from heater plates at +80° as would be possible without convection with plates at +200°. This gives a considerable increase in the rate of drying without running into danger of burning the dried product. The only disadvantage is that the increase in non-condensable gases increases the resistance to flow of the water vapour. This, as I have already shown, will cause a rise of the drying temperature. Thus, there is an upper limit to the amount of injection which can be used for a particular product.

In the Accelerated Freeze-Drying (A.F.D.) method of food preservation (Hanson, 1961) the food is placed between heater plates and is separated from them on both sides by expanded aluminium sheets. This gives a combination of radiant and conductive heating but because it causes considerable obstruction to vapour flow the drying temperature is high, but the drying rate is fast. Presumably much of the vapour is superheated and returns part of this heat in the form of additional convection heating.

Continuous Removal of the Dried Product

Another approach to avoiding the danger of burning the dried product with radiant heating occurred to me, namely, to remove the dried product continuously by scraping so that the radiant heat contacted only a frozen surface. Theoretically, it should be possible to dry at an extremely fast rate, and to test this theory I built the apparatus shown in Figs. 7 and 8.

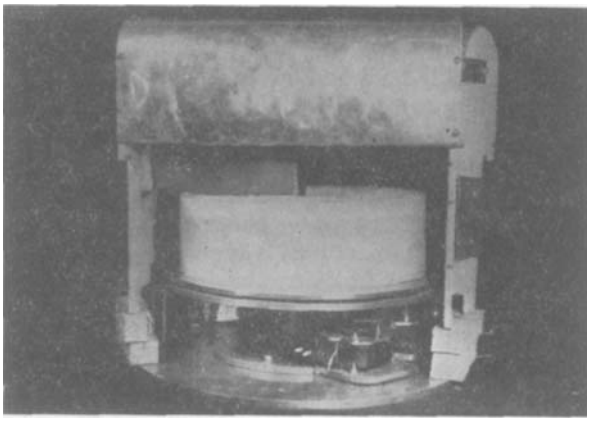

FIG. 7. Apparatus for the continuous scraping and removal of the dried surface.

This apparatus proved that the theory was correct. The limitations which I met with were firstly when I burnt out the heating elements and, secondly, at very high rates of drying, the dried particles were carried away in the vapour stream to the condenser. Nevertheless, drying rates 200 times as fast as conventional drying rates were achieved.

Dielectric Heating

Finally, dielectric heating. The dielectric constants of frozen and dried material differ considerably, and it should be possible to put heat into the the frozen material without any danger of heating the dried material. There are certain technical difficulties in applying this type of heat, mostly concerned with ionisation and flash-over in the vacuum chamber. These difficulties have been largely overcome now that it is possible to develop considerable power at a frequency around 1,000 mcs./sec. But, unfortunately, the ice block is heated fairly uniformly and gradients develop much as with conductive heating. Moreover, there is a tendency for heating not to be uniform, leading to melting at a point. At once considerable positive feedback occurs and the whole block of ice explodes. Possibly as still higher frequencies become available a skin effect may result so that all the energy is absorbed at the drying surface when enormous drying speeds should be achieved without the danger of burning the dried product.

However, these high drying rates could only be achieved with very thin layers as the obstructive resistance of the dried material would cause melting of the frozen product.

Microwave heating might, however, prove very useful in the period of desorption, when the removal of the last traces of water from the dried material proves a slow process using conventional methods of heating.

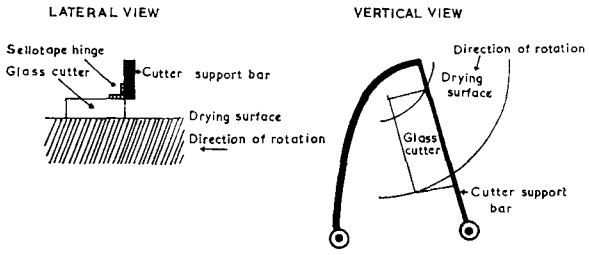

FIG. 8. Schematic diagram of surface scraping mechanism.

HIGH VACUUM SPRAY FREEZE-DRYING

The most successful method for drying foods has been spray drying of liquids in a current of hot air at atmospheric pressure. Owing to the large surface for evaporation from the small particles, drying is very rapid at a temperature well below that of the hot air stream. Such spray drying plants being continuous in their operation and constant in their energy requirements, have proved to be economical to operate. But there is usually a loss of flavour and solubility of the products dried by this process. A lowering of the air temperature leads to an improvement in quality of the dried product but at the expense of an increase in drying time and an increase in the size of the apparatus.

Improved products can be obtained by drying at lower temperatures by reducing the pressure. Such plants usually distribute the liquid as a thin layer on a belt in a vacuum chamber. If the pressure is low enough, the liquid may froth or foam but this, by increasing the drying surface, may be an advantage. Usually the lower the drying temperature the better the dried product, but a lower limit in temperature is set by the temperature at which the product freezes, for if this occurs the feed mechanism also freezes.

A continuous batch process for the freeze-drying of solid foods has been devised. In this process a batch of prefrozen material is introduced through a lock into a vacuum tunnel through which it progresses, the dried material being removed from time to time by way of a vacuum lock at the far end of the tunnel. Liquid foods prefrozen in blocks could also be dried in such a tunnel.

Nevertheless, a process for freeze-drying liquids, in which the liquid could be continuously introduced, the dried powder being removed by way of a vacuum lock from time to time as required for packaging, would offer great attractions to the food industry and also in the pharmaceutical

industry when freeze-drying is necessary as a step in manufacture, as in the production of streptomycin.

The problems of spraying liquids into a freeze-drying chamber are associated with the extremely rapid evaporative freeze which occurs and which leads to the freezing and complete occlusion of the jet.

My early attempts to overcome this problem (Greaves, 1946), led me to conclude that a very high velocity of the liquid as it left the jet orifice was essential. Some success was achieved by making a jet from a minute hole in a piece of brass foil. Such jets could be made so fine that they discharged only about 100 ml./hr., but were very apt to be blocked by particulate matter, and the frozen particles were very variable in size.

After the war, the American Chain Belt Co. patented a process for continuous freeze drying in which the liquid was continuously introduced t hrough a jet and fell as liquid onto a moving belt on which it froze.

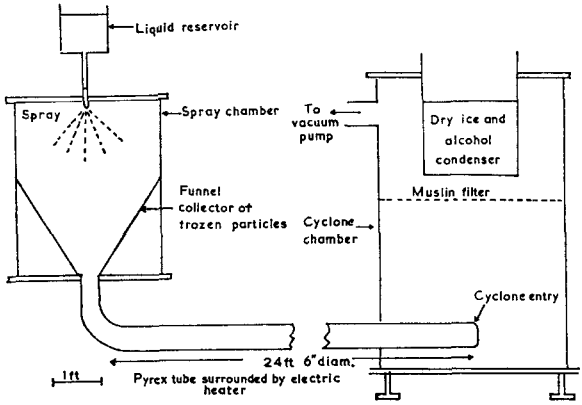

FIG. 9. Schematic diagram of experimental apparatus for vacuum spray drying.

I was able to experiment with one of the jets, as used by the Chain Belt Co. It is the type which discharges the liquid as a cone, the peripheral edge of the cone breaking up into droplets. The smallest size passed 1·6 gal./hr. The main feature of this type of jet is that the liquid leaves the jet orifice at high velocity. Using this jet to spray into a freeze-drying chamber with a low vacuum, it was possible to produce frozen particles. If the vacuum improved, freezing took place at the edge of the cone, the frozen material looking rather like corn-flakes. Further improvement of the vacuum led to freezing nearer and orifice of the cone and eventually to freezing at the orifice and total blockage of the jet.

Nevertheless, by careful control of the vacuum, it was possible to keep this jet running continuously, and an apparatus was built to study the possibility of continuous freeze-drying using this jet for introducing the liquid (see Fig. 9). The idea was that the difference in pressure between the spraying chamber and the cyclone collecting chamber would drive the particles through the long narrow Pyrex tube, during which period they would be subjected to intense radiant heat. The dry particles should then

be separated from the vapour stream in the cyclone chamber being deposited as a dry powder on its base. But the enormous velocity of the particles through the heater tube had not been anticipated. Nothing could ever be seen, but at the start the tube emitted a musical note which rapidly rose in pitch till it became ultrasonic. It is not surprising that very little heat was absorbed in this very short space of time. Attempts to apply further heat were made by heating the walls of the cyclone, but were not very effective, nor was the cyclone very effective in separating the particles from the vapour stream.

With the jet passing a minimum of 1·6 gal./hr., any experiment was a major engineering project and was costly and time consuming, and it was decided that further experiments must cease until such time as a jet which would pass small quantities could be devised. It is a pity that micro-wave heaters were not available when these experiments were being made, for this apparatus would have been admirably suited for testing its efficiency; but even if it were effective, the problem of removing the particles from the vapour stream would still remain.

It is against this background that I have been working to produce a jet which would allow liquid to be continuously introduced into a freeze-drying chamber. Such a jet should be able to pass very small quantities of about 100 ml./hr. so that small scale apparatus could be used in development, but it should also be able to pass large quantities if required. It should also be possible to vary the particle size over a large range at will.

Principles on Which the Experiments were Based

If the jet was to work with small volumes, high velocity at the orifice could not be obtained with small holes in thin membranes due to the danger of blockage. Speed away from the orifice must therefore be obtained by a moving member.

The rate of flow should be variable and adjustable externally.

The bore of the jet should be reasonably wide and the end should be flat and adjustable so that it is very close to the moving member. This should produce a zone of high vapour pressure so that freezing between the jet and the moving member should be avoided.

Experimental

All the experiments were conducted in a small glass cylinder $6\frac{1}{4}$ in. internal diameter, $10\frac{1}{2}$ in. high, mounted over a hole in the top plate of a small freeze-drying plant, having a condenser mechanically refrigerated to $-40°$ by a quarter h.p. Freon 12-Compressor.

Experiments with High Speed Moving Member

Fig. 10 is a photograph of the apparatus. The moving member is a brass disc of 4 in. in diameter mounted on the spindle of a small motor rotating at a speed of 1,450 rev./min.

The jets which have been used all have an internal bore of $\frac{1}{25}$ in., their ends varying between $\frac{1}{10}$ in. and $\frac{1}{4}$ in., and are of brass, steel or rubber.

The flow rate is controlled externally by rubber pressure tubing squeezed in a differential thread clamp.

In operation, when the vacuum has fallen to 0·1 mm. Hg, the motor for the brass disc is started and the clamp on the liquid line slowly opened. Small particles of ice will be discharged from the jet orifice, and it is important at this stage not to increase the flow too much until the disc has been cooled, when an ice track will form on the disc. The flow may now be increased till the maximum required rate is achieved.

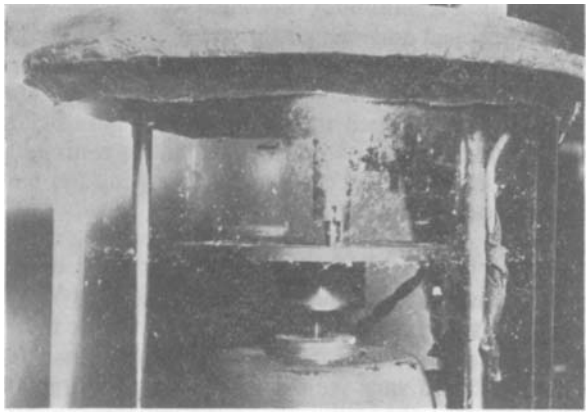

FIG. 10. Electronic flash photograph showing ice track forming on high speed horizontal moving member.

From direct observation, it would appear that most of the liquid leaves the jet as a fine liquid spray which rapidly freezes and drops as frozen particles. This is confirmed by the fact that a proportion of the larger particles reach the glass cylinder which is very close to the jet, and freeze on it. Some of the liquid also freezes on the ice track and is scraped off as it comes round to the back of the jet. This is confirmed by raising the jet when the ice track merely becomes thicker; this is convenient for it ensures that the gap at the orifice of the jet is always kept very small.

As the flow rate is increased, the particle size becomes progressively larger and more and more will freeze on the wall of the glass cylinder. It would be an obvious necessity to work with a much larger cylinder if large volumes were to be processed. The maximum flow of milk, using this small cylinder, was $\frac{1}{2}$ litre/15 min. Beyond this, a large proportion froze on the cylinder wall.

The minimal flow was about 100 ml./hr. Below this rate the flow became intermittent, probably due to intermittent freezing of the jet orifice from direct contact with the ice track as it was no longer being warmed by a sufficient passage of liquid.

The mean particle size is the product of the rate of flow and the speed of the moving member. The slower the speed or the greater the flow the larger the particle.

Drying experiments were carried out with milk. The frozen particles were collected in a metal tin in which was a rotating comb to keep the powder stirred. The tin was heated from below.

If drying was allowed to take place very slowly with no stirring, a very beautiful dried product resulted. But when stirred, large amounts of heat could be absorbed and drying was very rapid, but all the finer particles were carried away in the vapour stream and were lost.

No doubt means could be devised to overcome this difficulty, and it had been intended to experiment along these lines, but further experiments with the jet at slow speeds have shown a much simpler solution of this problem.

Experiments with Slow Speed Moving Member

A second apparatus was constructed with the brass disc on a shaft passing to the exterior so that it could be driven with a reduction gear motor.

At 56 revs./min. the jet operated very much as at high speed but the particle size was very much greater. Less material was thrown off the disc centrifugally; much more freezing on the ice track on the disc which consequently got much colder. It was, therefore, necessary to have a higher rate of flow to prevent the jet freezing than was necessary at high speed.

At 1 rev./min. all the liquid froze on the disc once it became cold and could be removed by a scraper.

At this speed difficulties start to occur. If the disc is too hot the ice does not stick to it and so does not get carried away. It is, therefore, necessary to start the flow very slowly. When the disc is about 5°, the ice gets carried away from the jet satisfactorily, but has separated by the time it arrives at the scraper which merely has to push the ice over the edge of the disc. If the disc gets too cold considerable power is necessary to separate the ice from it. There is also a danger of the jet freezing if the disc gets too cold and, although this may be cured by using a rubber tipped jet, the rate of flow is critical. Suitable thermostatic control of the disc temperature should cure this, but has not been tried.

This continuous extrusion of ice into a freeze-drying chamber does give a product very suitable for drying which has sufficient weight to prevent it being carried away in the vapour stream. But for continuous extrusion the radial drag of a rotating horizontal disc appears incorrect. It was, therefore, decided to construct a drum rotating in a vertical plane. The speed of rotation was 1 rev./min. and the diameter of the drum 4 in.

Fig. 11 shows that if the drum is at the correct temperature no scraping device is necessary to separate the ice from the drum which extrudes as a continuous helix, giving the perfect product for drying.

This continuous extrusion is fascinating to watch. The jet is flat and not shaped to the radius of the drum. It is mounted slightly forward so that the back edge is in contact with the drum. The ice seems to form continuously on the front edge of the jet, and bubbles of gas and liquid can be seen inside the frozen tape immediately on extrusion.

In order to observe this phenomenon more clearly, a $1\frac{1}{2}$ in. diameter drum was constructed so that, with a $\frac{1}{4}$ in. jet, there was considerable discrepancy between the front edge of the jet and the drum. Under these conditions liquid could be seen flowing forward along the surface of the jet then freezing up the front edge and continuously pushing forward only making contact with the surface of the drum about $\frac{1}{10}$ in. in front of the jet. On stopping the drum, ice continued to be extruded for a while. It is possible that working on these lines it might be possible to make a jet which would continuously extrude ice without a moving member.

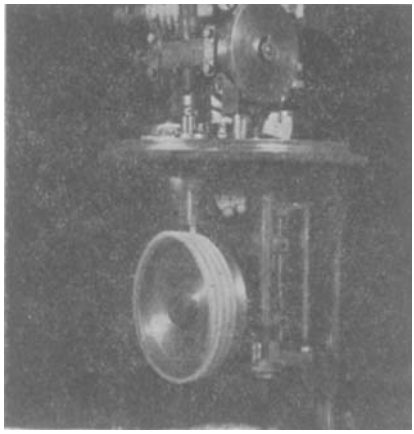

FIG. 11. Ice forming as a continuous helix on slow speed drum.

Using this smaller drum, much greater latitude in operation was obtained by increasing the linear speed from 12 in./min. to 48 in./min. (Fig. 12).

A scraper bar was fitted so that the ice was separated from the drum after three-quarters of a revolution. A radiant heater was focused on the remaining quarter of the drum and adjusted so that the temperature of the drum remained constant at 0° and a small heater placed round the jet to maintain its temperature at +15°.

Under these conditions extrusion could be maintained for a very long period with complete constancy.

CONCLUSION

This review is based on two lectures given at the School of Pharmacy, London University. This explains why my own work figures so largely. I have, however, tried only to describe recent advances in fundamental work and have made no attempt to describe the enormous amount of developmental and applied work which has been done since the war.

In the laboratory and in the pharmaceutical industry, the freeze-drying procedure is widely used for the preservation of very valuable materials.

The cost and time of drying is relatively unimportant provided a perfect product results. Too often freeze-drying is carried out as a purely empirical procedure, and if the result is not satisfactory, the process of freeze-drying is condemned. I would like to see the term freeze-drying reserved for a procedure in which drying takes place below the lowest eutectic temperature of a material which has been treated during pre-freezing so as to ensure that no metastable glassy material is present.

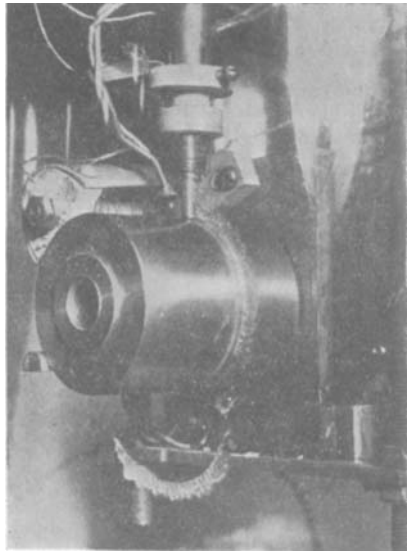

FIG. 12. Final form of apparatus. Linear speed of drum 48 in./min. The ice is removed from the drum after three-quarter revolution. The radiant heaters for the drum and jet can be seen. Electronic flash photograph. Note the section of ice falling from the drum.

A very different problem is posed in the drying of foods. Here we are attempting to preserve, by drying, a relatively cheap commodity, and the cost of achieving the previous criteria would usually be prohibitive. Foods must be dried as rapidly as possible and at the highest temperature consistent with obtaining an acceptable product. Most of the dried foods could not claim to be freeze-dried if my definition is accepted and, for this reason, the freeze-drying of foods has been omitted from this review.

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