International Journal of Pharmaceutics, 72 (1991) 97–110

ADONIS 037851739100211P

IJP 02409

Atmospheric spray-freeze drying: a suitable alternative in freeze-drying technology

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(Received 17 December 1990)
(Modified version received 21 January 1991)
(Accepted 29 January 1991)

Key words: Vacuum freeze drying; Atmospheric freeze drying; Kinetic analysis; Instant product; Free-flowing powder; α-Interferon; Coffee extract; Flavor retention

Summary

The freeze-drying technique is one of the most useful processes for drying thermosensitive substances that are unstable in aqueous solutions. Because of the rapid evolution of biotechnologically obtained materials, increased attention has been focused on this process, especially in pharmaceutical technology, during recent years. Actually, freeze-drying techniques are used to dry many kinds of mainly biological materials. Food products, in particular, are processed on a large scale with considerable success. As an alternative to the classical freeze-drying process in a vacuum, the feasibility of dehydrating frozen pharmaceutical solutions and liquid foods at atmospheric pressure was investigated. An apparatus and a technique for spray-freezing aqueous solutions in situ at very low temperatures ($\approx -90°C$) and for subsequent dehydration of the resulting frozen particles in a stream of cold, desiccated air was developed. The influence of various process variables and of certain product characteristics on the drying kinetics as well as on the quality properties of the respective lyophilizates is discussed. Compared to the classical freeze-drying process the following differences can be pointed out: (1) improved heat and mass transfer between the circulating drying medium and the frozen sample; (2) high and homogeneous quality properties of the dry product with an increased retention of volatile aromatic compounds in foods; (3) instead of a cake, a fine, free-flowing powder with a large inner surface area and good instant, i.e. wetting and solubility, properties was obtained.

Introduction

Although lyophilization (freeze drying, sublimation drying) has been a common practice in the pharmaceutical industry for many years, the process has recently attained, partially because of the rapid evolution of the biotechnology area, a new and increasing importance in pharmaceutical drying technology. The major reasons for freeze-drying pharmaceuticals are primarily the same as 40 years ago – high product stability and quality. In fact, this technique produces the highest quality product when compared with other evaporative drying processes, especially in the case of heat-sensitive compounds and/or materials, which un-

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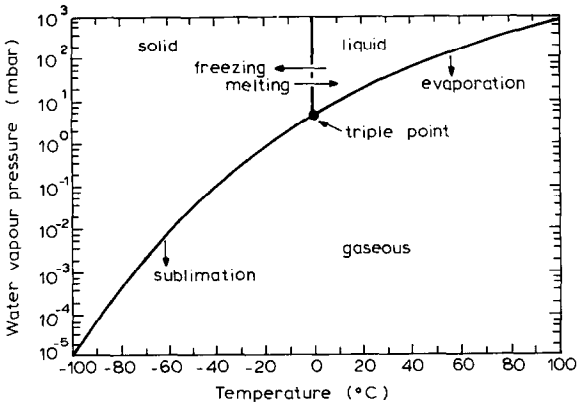

Fig. 1. Phase diagram for water and representation of the corresponding phase-transition processes.

dergo rapid decomposition in aqueous solutions, such as biotechnologically manufactured proteins, antibodies, enzymes, or peptides.

Freeze drying is a two-step preservation and dehydration process, in which the product is first frozen and the water then removed as vapour from the frozen state. As the water passes from the solid phase directly into the vapour phase, it is necessary that the vapour pressure and the temperature of the sublimation zone are held below those of the triple point on the phase diagram for water (Fig. 1).

However, the same low temperatures ($\ll 0°C$) and the maintenance of the frozen state lead to very low driving forces for heat and mass transfer and therefore, often to very low drying rates and thus, very long drying times. Thus, despite its capability of providing a very high-quality dehydrated product, freeze drying has been and remains a considerably energy intensive and consequently, a very expensive dehydration process. In order to reduce costs and drying times very extensive research and development work are still underway and suggestions for improved, more economic freeze-drying processes are continuously appearing in the literature.

Conventionally, freeze drying occurs under vacuum conditions. The presence of a vacuum is, however, not an indispensable prerequisite for sublimation to occur, as shown in Fig. 1. In fact, freeze drying is in principle thermodynamically possible even at higher pressures. The only absolute requirement is that the partial pressure of water vapour in the drying medium must be kept low enough to provide a mass transfer driving force for water vapour removal from the frozen sample. The use of cold gas (air, nitrogen, helium) as a water removal and heating medium to cause sublimation of moisture from a frozen material at or near atmospheric pressure is commonly known as 'atmospheric freeze drying'. While the application of atmospheric freeze drying in food technology is quite extensively studied and reported in the literature, no publication has been found, which deals with the application of this drying operation in pharmaceutical technology. In fact, it has generally been assumed that the rate of atmospheric freeze drying is too slow to be economically feasible. The rate-controlling parameter is molecular diffusion of water vapour (mass transfer) in free air as well as in air within the dry porous product structure, as compared to vacuum freeze drying, which is generally heat transfer limited. Nevertheless, the interest in freeze drying at atmospheric pressure has increased in recent times, the process being one possible technique for reducing costs of the drying operation, since expensive vacuum-associated components could be eliminated.

The potential for atmospheric freeze drying was first demonstrated by Meryman in 1959. He showed that the drying rate of a material undergoing freeze drying is a function of ice temperature and the vapour pressure gradient between the site of water vapour formation and the drying media, rather than the total pressure in the drying chamber. He therefore proposed that it should be possible to freeze-dry successfully at atmospheric pressure if the partial pressure of water in the drying chamber is held at a very low value and he suggested that such a process should be based on the principle of convective freeze drying, i.e. a cold air stream, kept dry by a molecular sieve desiccant or by a refrigerated condenser, should be circulated. Results obtained by Dunoyer and Larousse (1961) as well as the economic analysis of the energy costs for moisture removal of Woodward (1963) indicated furthermore that atmospheric freeze-drying rates of small particles can be equivalent to vacuum freeze drying. Heldman and Hohner

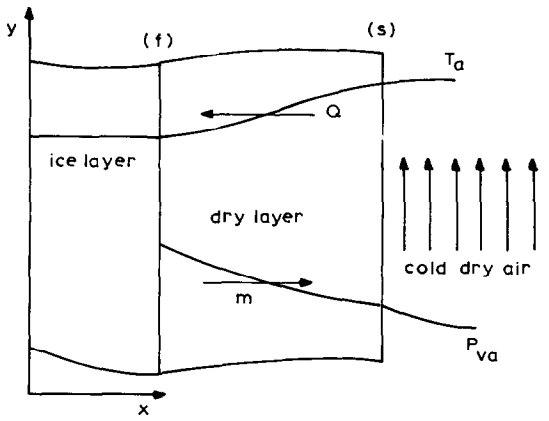

Fig. 2. Schematic diagram of atmospheric freeze drying (f, interface; s, surface; Q, heat transfer; m, mass transfer; T_a, temperature gradient; P_{va}, partial pressure gradient).

(1974) analysed the kinetics of the freeze-drying operation with a mathematical model and determined the influence of various operating variables on the sublimation rates. Using a one-dimensional model the sample under atmospheric freeze drying can be represented schematically as shown in Fig. 2. An ice-vapour interface (f) recedes toward the centerline (y, $x = 0$) as heat of sublimation (Q) is transported from the surface (s) to the interface in response to a temperature gradient (T_a). Simultaneously, water vapour flows through the porous dry layer to the surface (s) in response to the partial pressure driving force (P_{va}) From the experimental results, Heldman and Hohner concluded that a reduction of particle size and an increase in surface mass transfer coefficient, expressed as the ratio of external to internal mass transfer in the sample, appear to be the most effective ways to increase atmospheric freeze-drying rates.

Finally, kinetic studies of sublimation drying at atmospheric pressure of Boeh-Ocansey (1983–1984) demonstrated as well that, for product pieces with a large surface area and limited thickness, sublimation time is far shorter using the atmospheric technique than drying under vacuum.

As an alternative to the classical freeze-drying process, an apparatus and technique for freezing pharmaceutical solutions and/or liquid foods in situ as very small spheres for subsequent freeze drying at atmospheric pressure was therefore developed. The objective of this study was to investigate the influence of various operating variables on the drying kinetics as well as on the quality properties of the resulting products (Mumenthaler and Leuenberger, 1988; Mumenthaler, 1990).

Materials and Methods

Apparatus

Preliminary experiments were carried out with the apparatus shown in Fig. 3. Depending on the process to be carried out, the cold air stream can be passed either through the drying chamber or through the bypass system. The drying medium therefore always circulates in a closed cycle and is continuously regenerated by condensation of the humidity on the refrigerated surface of the cooling systems. At the same time, the bypass position allows one to carry out manipulations at the drying chamber, like taking periodical samples for moisture determination, without the simultaneous loss of conditionated, cold, and dry air. The airflow rate can be adjusted to the desired value by varying the position of different air flaps, while the temperature of the circulating gas can be raised to the desired value (i.e. below or above the eutectic temperature of the sample) by means of an internal heater.

Control of the drying process

During the freeze-drying process the following parameters were periodically recorded: (a) temperature of the circulating medium (inlet air and outlet air) as well as of the frozen sample (Testovent 4000, Quarz AG, Switzerland); (b) flow rate (inlet air and outlet air) of the circulating medium (Testovent 4000-Anemometer, Quarz AG, Switzerland); and (c) dew-point temperature (inlet air and outlet air) of the circulating medium (Condensation Dew-Point Hygrometer System 1100 DP, Bakrona AG, Switzerland).

At the same time, the progress of sublimation was recorded either after interrupting the drying process by gravimetric determination of the moisture loss (Mettler IR-Dryer LP15, Mettler AG,

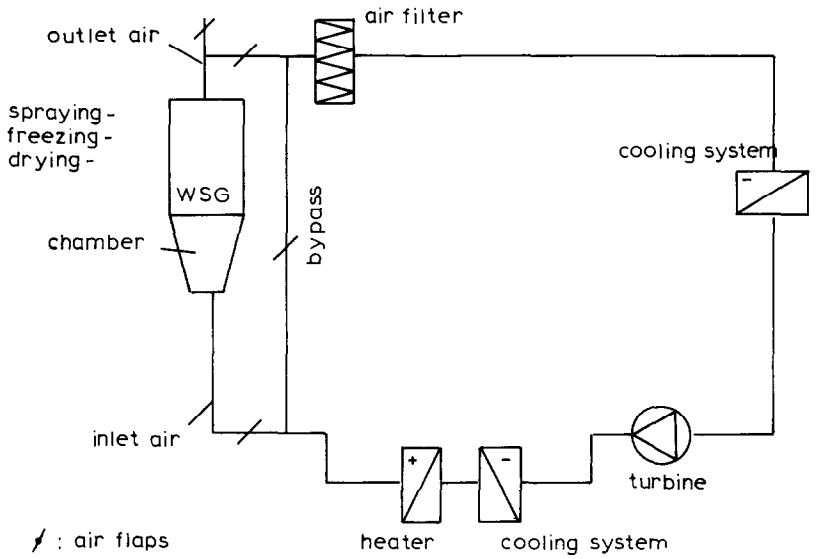

Fig. 3. Schematic diagram of the experimental apparatus (Glatt AG, 1986).

Switzerland) of periodically removed samples, or under continuous drying conditions indirectly by numerical evaluation of the dew-point curve of the circulating drying medium. In the latter case, changes in moisture content per time unit of the product to be dried can be mathematically expressed with the following equation:

$$\frac{dm}{dt} = \delta_T \cdot V_T \cdot (x_{AO} - x_{AI}) \quad (1)$$

where dm/dt denotes the loss of moisture content per time unit (kg H_2O/s), δ_T is the density (kg/m^3) of the circulating medium at the drying temperature T, V_T represents the volume of the circulating medium (Nm^3 dry gas/s) at the drying temperature T, and $x_{AO} - x_{AI} = \Delta x_A$ is the difference in humidity content (g H_2O/kg dry gas) between inlet air (x_{AI}) and outlet air (x_{AO}), determined with the corresponding dew-point values and with the help of the Mollier h,x diagram.

Practical procedure

The apparatus was allowed to run for about 1 h to reach thermal equilibrium. Aqueous solutions (the batch size varying between 140 and 300 g) of the substances to be dried were then spray-frozen in situ at very low temperatures (-70°C down to -90°C). Because of the fact that the geometrical dimensions of the drying chamber were not ideal for spraying against the cooling medium in the void space and that the efficiency of the cooling systems was not high enough to reach such low temperatures, the spray-freezing process gas accomplished by atomizing the solutions against a fluidized bed of pulverized dry ice (top spraying). As the dry ice sublimates quite easily, it must be added continuously into the drying chamber in order to maintain a fluidized bed during the whole spray-freezing procedure. Subsequently, the frozen particles were dried in a stream of cold desiccated air at or below the respective eutectic temperature (T_e) of the frozen solution. The eutectic temperatures (T_e) were taken from the literature and verified by our own resistivity measurements (Mumenthaler, 1990).

Materials

Among others, atmospheric freeze-drying experiments were conducted with the following substances:

Carrier materials commonly used in classical lyophilization, such as (a) mannitol USPXX (Hefti

AG, Switzerland), (b) glycine USPXX, (c) urea Ph.H.VII, and (d) glucose Ph.H.VII (all Siegfried AG, Switzerland);

Biologically active substances, such as (a) the glycoprotein α_I1-bovine interferon (Genentech Inc., U.S.A.), generously supplied as a lyophilizate (solid matter content 425 mg/vial) by Ciba-Geigy AG, Switzerland; (b) the undecapeptide cyclosporin A, generously supplied by Sandoz AG, Switzerland; (c) the hepatic enzyme *S*-adenosyl-L-methionine, generously supplied as sulphate-*p*-toluolsulphonate salt ($\approx 50\%$ $SAMe^+$) by Bioresearch Netherlands B.V., Switzerland; and (d) the blue alga spiruline (70% proteins, 20% carbohydrates and vitamins, 10% lipids), generously supplied by Flamant Vert, Switzerland;

Commercial liquid foods with different characteristics, like (a) milk products with a high amount of lipids, and therefore leading to freeze-dried samples with poor instant properties; (b) orange juice (11% solids) with a very high concentration ($\geq 95\%$) of carbohydrates (mainly sucrose), and therefore leading to end products with often very hygroscopic properties and (c) coffee extract, a real challenge for the freeze-drying process, due to the very high quality requirements (colour, taste, volatile flavour components) claimed for the dehydrated products.

Sample analysis

The freeze-dried products were subjected to the following tests, which are related to the desired product properties: (a) aspect (colour and macroscopic pollutions; taste, flavour and odour; flow properties); (b) residual humidity; (c) particle size analysis (optical microscopy with the semi-automatic Videoplan-Morphometric System Kontron GmbH, Germany, whereby the maximal/minimal diameter of a structure is calculated using 32 projections); (d) instant properties and aspect of the reconstituted solution (time required for complete reconstitution of the dehydrated sample in distilled water at room temperature); (e) biological activity (antiviral activity of α-interferon in vitro against vesicular stomatitis virus [VSV]); (f) denaturation and structural conformation of the α-interferon sample (Phast-System Electrophoresis 250 V/10 mA); (g) chemical decomposition of the *S*-adenosyl-L-methionine sample (quantitative determination of adenine, adenosine and methylthioadenosine); and (h) protein content of the spiruline-alga sample. Tests (e) and (f) were performed by Ciba-Geigy Laboratories; test (g) was performed by Bioresearch Laboratories.

Results and Discussion

The spray-freezing technique

The nature of the freezing conditions before freeze drying, i.e. freezing rate [respectively fast ($> 10°C$/min) then slow ($< 2°C$/min)], freezing temperature (the lowest temperature reached by the sample), and freezing time (the time that the sample is kept at the freezing temperature), is most critical and thus, most important for the success of the drying process. In fact, the resulting sublimation rates as well as the appearance and the properties of the dried product, such as the dissolution rate, colour (Barnett, 1973), survival rate of microorganisms (Moor, 1964), stability of aqueous liposome dispersions (Özer et al., 1988) or of protein solutions (Woog, 1988; Pikal, 1990), are often significantly altered by the method applied for freezing. Generally, the small ice crystals formed during rapid freezing leave a very fine microporous structure in the sample to be dried, thereby affecting the water vapour permeability within the dry layer and thus, the drying rates. The resulting product shows a fast solution rate and a very light colour. On the other hand, slow freezing can lead to the growth of macrosized ice crystals and simultaneously to concentrated solutions, which are kept for longer periods of time in the sample. Consequently, the frozen sample contains a relatively low number of large ice crystals, which on their part may destroy biological membrane structures or may induce degradation of proteins. The appropriate freezing conditions must therefore be adapted to the respective product in the most optimal way.

In the prototype described in the previous section, the freezing procedure could only be varied in a limited way. Nevertheless, by the spray-con-

gealing method used in this study, several advantages could be achieved at the same time:

(1) the freezing of the solution is accomplished in situ, i.e. in the chamber to be employed for drying – the thawing of the frozen samples can be avoided;
(2) fast freezing rates can be achieved – these are in general preferred in freeze drying of pharmaceutics;
(3) very small frozen particles can be obtained – thus faster drying rates can be expected;
(4) the dry ice used as support does not need to be separated from the dry product at the end of the drying process.

The kinetics of freeze drying

With aqueous mannitol solutions as model substance the influence of various process parameters on the atmospheric freeze-drying kinetics – defined as moisture loss of the sample to be dried as a function of drying time – was studied.

Effect of air-flow rate on the sublimation process

The dependence of the drying rates on the chosen inlet air velocity and thus, on the cold gas volume flowing per time unit through the frozen material, merits further comment. Although frozen mannitol particles fluidized well at −20°C in air having a dew-point of −35°C the resulting drying rate was very slow in agreement with results obtained by Malecki et al. (1970). In fact, despite the increased specific surface area of the droplets suspended in a fluidized bed, neither improved heat nor mass transfer between the circulating medium and the material to be dried could be attained and, on the contrary, a moisture loss of only about 4% per could be recorded. On the other hand, at higher air-flow values the sublimation rate of the same sample could be markedly enhanced, as

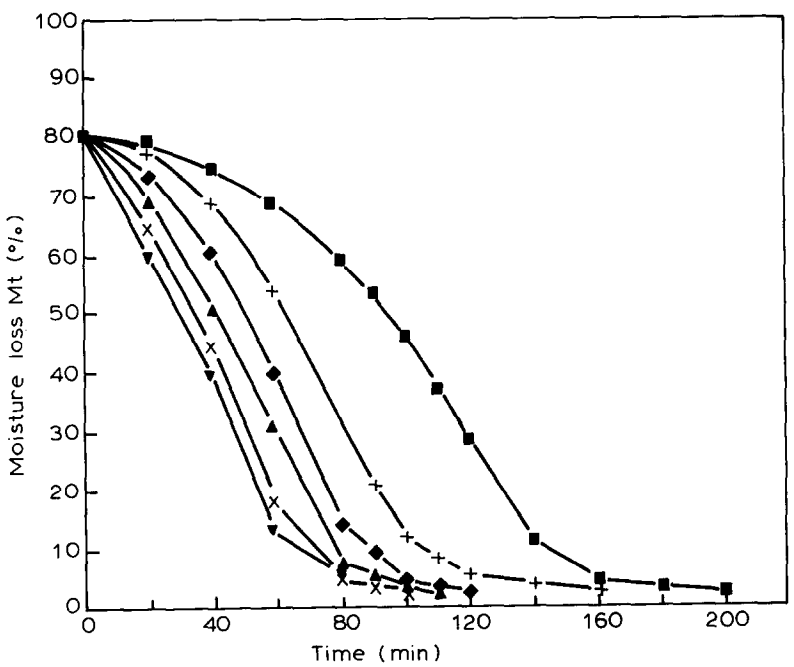

Fig. 4. Effect of air flow-rate on sublimation time (aqueous mannitol solution, 20% solid content, drying temperature −20°C). (■) 0.219 m/s, (+) 0.344 m/s, (◆) 0.469 m/s, (▲) 0.594 m/s, (×) 0.719 m/s, and (▼) 0.844 m/s.

shown in Fig. 4. Thus, at these air velocities a fluidized bed can no longer be maintained and the frozen particles will be dried as a thin static layer at the surface of the filter system.

Effect of inlet air temperature on the sublimation process

Due to the heat transfer necessary to accomplish the sublimation process, theoretically, the inlet air temperature can be kept higher than the eutectic temperature of the respective frozen sample. Thus, the temperature at the ice-water vapour interface can be much lower than the temperature of the inlet air.

Under constant drying conditions the atmospheric freeze-drying curves can be subdivided into three characteristic sections, which depend on the operating variables (air-flow rate and process temperature) more or less defined, as illustrated in Figs. 4 and 5, respectively. The first section, defined as lag time, is recognizable in the drying curves of the samples dehydrated at very low (-30°C up to approx. -15°C) air temperatures (see Fig. 5). The reason for designating the first section as lag time is due to the very poor moisture loss per unit time (< 0.2 g H_2O/min) during this drying phase. The second section, in which the weakly bound surface water, the water of the coarse capillaries, as well as, at least partially, the capillary water out of deeper product layers is removed, is then characterized by a sudden fall in the drying curve. Depending on the air temperature the drying rate increases from 0.5 g H_2O/min (-30°C) up to almost 3 g H_2O/min (-2°C). Finally, the third section of the curve corresponds to the phase, which in drying technology is commonly known as 'tailing', i.e. where the residual adsorbed water is very hard to remove (mean sublimation rate ≤ 0.1 g H_2O/min). However, the total freeze-drying time can be considerably shortened by increasing the temperature of the circulating medium in this final stage of the process even above the respective eutectic temperature of the frozen sample without affecting the characteristics of the freeze-dried product. The residual moisture content at which this rise in temperature is possible must be investigated specifically for each product. According to our experience, this can often be carried out already at a residual moisture content of $\leq 10\%$ (w/w).

Effect of initial water content in the solution to be dried on the sublimation process

Introductory remarks The following comments relate to the freeze-drying process in general, where the heat and mass transfer is limited by the porous network of the sample (see Fig. 2). These remarks are necessary for the presentation of the different results obtained by our atmospheric spray-freeze-drying technique.

According to Raoult's law:

$$p = p^{\circ}(1 - X_2) \tag{2}$$

where p is the is the saturation water vapour pressure of a solution at a given temperature, p° denotes the saturation vapour pressure of pure water or ice at the same temperature and X_2 is the mole fraction of dissolved solutes. The effect of increasing the concentration of a solution to be freeze-dried is a reduction in the vapour pressure difference between the sublimation zone and the product's surface. Consequently, since in freeze drying at higher pressures the Knudsen molecular diffusivity of water vapour (mass transfer) across the porous dry layer is rate-limiting, more concentrated solutions lead to a reduction in the sublimation rates of the atmospheric technique and, therefore, longer processing times should be expected. Furthermore, the porous dry layer left behind at the surface as the ice front recedes offers resistance to the heat transfer from the drying medium to the receding sublimation zone as well as inversely to the water vapour transfer from the ice front to the drying medium. The mass transfer characteristics of the dry region thereby reflect the initial conditions of freezing (freezing rate) and the initial concentration of the solution. A higher initial content of solids usually leads to a denser structure, i.e. to reduced porosity of the dried layer and hence, to a slower rate of freeze drying, which again results from a lower water vapour permeability of the outer dry layer. However, in the case of atmospheric freeze drying based on our investigated principle of spray-freeze drying, the above considerations do not seem to

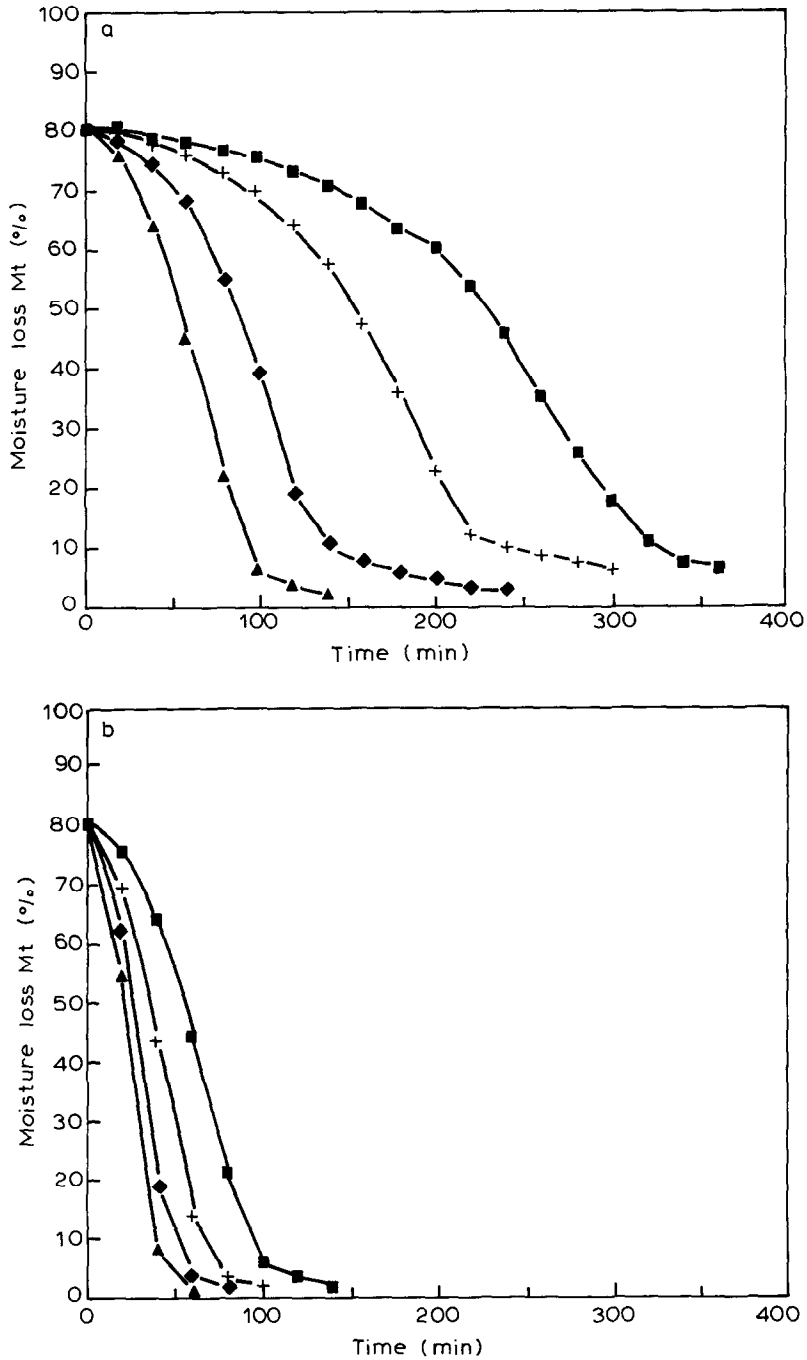

Fig. 5. Effect of drying temperature on sublimation time (aqueous mannitol solution, 20% solid content, air-flow rate 0.375 m/s). (A) (■) −30°C, (+) −25°C, (◆) −20°C, and (▲) −15°C; (B) (■) −15°C, (+) −10°C, (◆) −5°C, and (▲) −2°C.

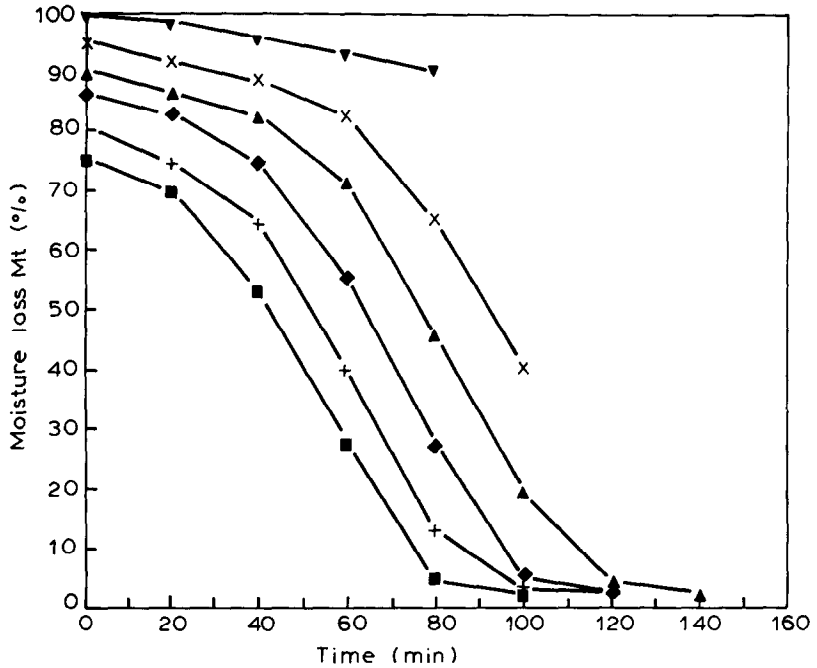

Fig. 6. Effect of dry matter content on sublimation time (aqueous mannitol solution {saturation solubility of mannitol in water ≈ 20%}, drying temperature −15°C, air-flow rate 0.375 m/s). (■) 25%, (+) 20%, (◆) 15%, (▲) 10%, (×) 5%, and (▼) 1%.

hold, as shown in Fig. 6. As is evident (Fig. 6), the higher the initial solids content of the solution, the faster are the resulting freeze-drying rates. The total operating time therefore seems to be directly dependent on the overall amount of sublimable water and thus does not appear to be affected by the microporous structure of the frozen sample resulting from the freezing conditions and/or from the initial concentration of the solutions to be dried.

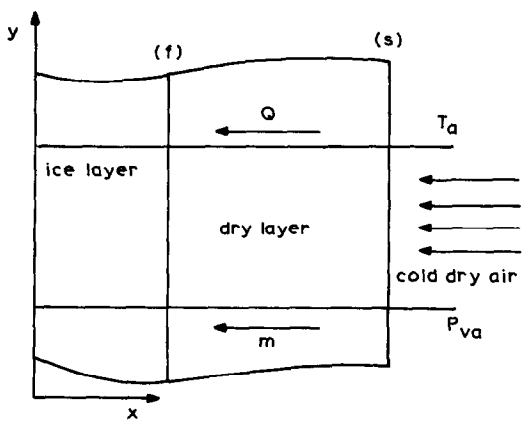

Fig. 7. Modified schematic diagram of atmospheric freeze drying (f, interface; s, surface; Q, heat transfer; m, mass transfer; T_a, temperature gradient; P_{va}, partial pressure gradient).

We believe that these results may be attributed to the particular conduction of the circulating drying medium in the process described. In fact, the cold dry air is not only passed across the frozen sample, as illustrated in Fig. 2, but also the gas flows mainly through the frozen sample, as shown in Fig. 7. With the resulting unidirectional and more intensive heat and mass transfer between the drying medium and the frozen material, a more equal drying without local temperature or concentration gradients in different product layers can therefore be achieved.

Dew-point measurements

Fig. 8 presents the results of the dew-point measurements of the circulating drying medium before entering the sublimation chamber (dew-p. inlet) and after passing through the frozen material

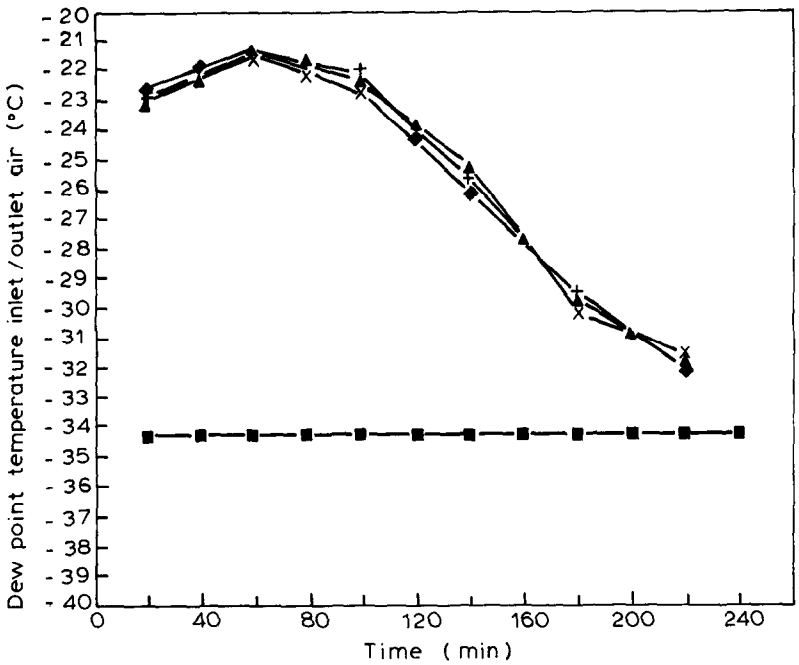

Fig. 8. Dew-point temperatures of inlet air and outlet air (aqueous mannitol solution, 20% solid content, air-flow rate 0.375 m/s, 4 trials) as a function of time. (■) Dew-point inlet air 1–4, (+) dew-point outlet air 1, (◆) dew-point outlet air 2, (▲) dew-point outlet air 3, and (×) dew-point outlet air 4.

(dew-p. outlet). Besides the good reproducibility of drying trials run under constant operating conditions (constant air-flow rate and drying temperature), it becomes evident from the curves that the dew-point temperatures of the outlet air suddenly fall as sublimation occurs – the steepness of the drop being of course strongly dependent on the process parameters – until reaching the value of the inlet air, which is more or less constant. Therefore, it can be assumed that the drying process is completed as soon as the dew-point temperatures of the outlet air and the inlet air show the same value. Recording of the course of the dew-point curve is, however, very useful for the in-process control of the drying experiment. In fact, it allows one to calculate changes in the moisture content of the sample (dm) per time unit (dt), as described in a previous section and thus, it permits the continuous supervision of the process without interruption for sample removal and moisture content determination. Thus, this dependence (Eqn 1) permits the optimization of the drying procedure as a function of time, inlet air temperature, end-point detection, and product quality.

Product qualities

The desired properties of a freeze-dried sample include: (1) a dry, stable, and intact cake, showing the same shape and size as the original frozen mass; (2) sufficient strength to prevent cracking, powdering, or collapse; (3) uniform colour and consistency; and (4) rapid solubility upon reconstitution in water – increased inner surface area and suitable (mostly amorphous) crystal structure of the active substance. However, the drug alone often does not provide the characteristics appropriate for the dry lyophilizate and inert carrier substances, such as mannitol, glycine, urea, and glucose, must be added prior to the freeze drying in order to achieve the desired product qualities. Unlike the above-mentioned 'cake-shaped' appearance of the dry samples resulting from classical lyophilization under vacuum, the atmospheric

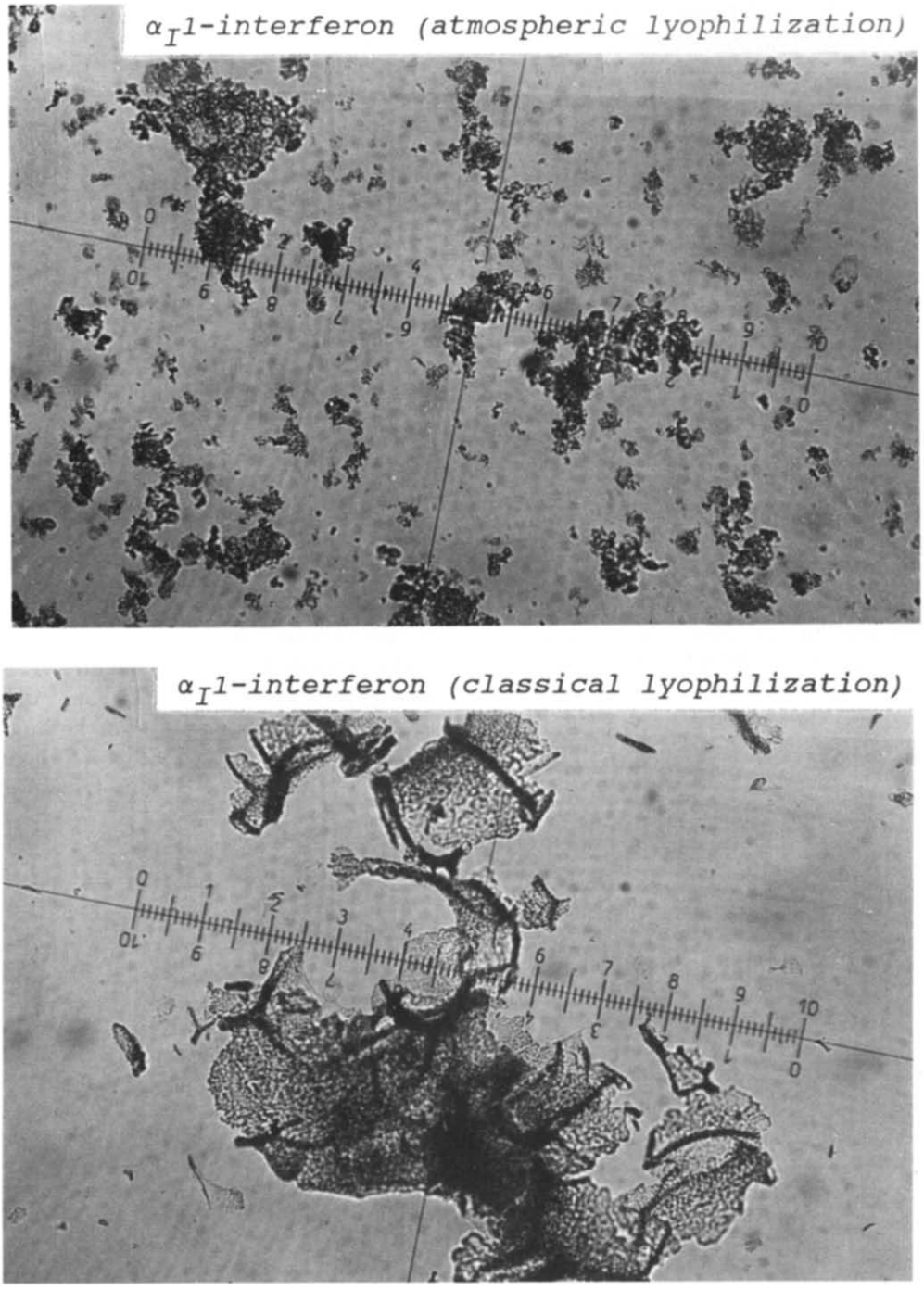

Fig. 9. Photomicrographs of freeze-dried samples suspended in paraffin oil (magnification 31 ×).

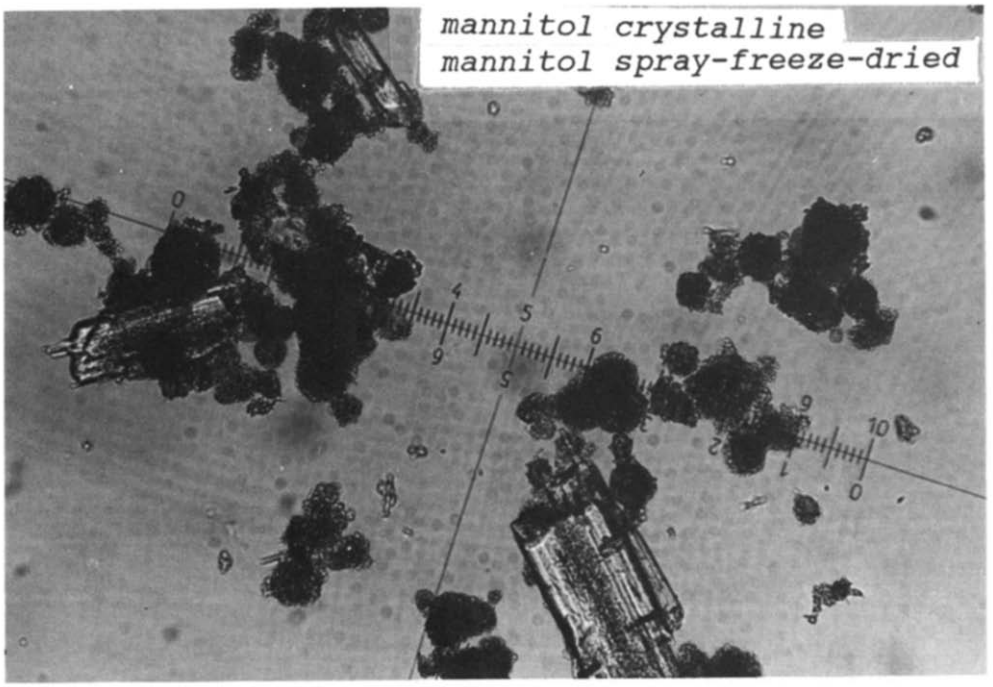

Fig. 9 (continued; graduation: 10 = 74 μm identical in all micrographs).

spray-freeze-dried products were mostly obtained in the form of dry (residual moisture content < 1.5%), very fine, and voluminous but still free-flowing powders, showing a uniform colour and consistency as well as good instant (wetting and solubility) properties. As was demonstrated by microscopic analysis of the respective specimens, the good flow and instant qualities are due to the existence of fine (mean diameter $\approx 18 \pm 8.97$ μm, after suspension in paraffin oil for microscopic inspection), quite porous spherical secondary agglomerates (see Fig. 9), which are formed during the drying process, but which then redisintegrate quite easily into the primary particles (diameter < 3 μm) when redissolved in water. On the other hand, with highly hygroscopic materials, for example, sucrose, lactose, *S*-adenosyl-L-methionine (SAMe), or orange juice, a satisfactory product can only be obtained after adding a suitable excipient to the solution to be dried.

Concerning the spray-freeze-dried α-interferon sample, both the bioassay as well as electrophoresis demonstrated that, compared to a standard specimen, structural changes, denaturation, and therefore loss of antiviral bioactivity did not occur in the glycoprotein during the atmospheric freeze-drying process. On the other hand, the extremely hygroscopic *S*-adenosyl-L-methionine (SAMe) could only be processed into a free-flowing, stable product after adding mannitol or glycine in the

TABLE 1

Results of the physico-chemical analysis of the spray-freeze-dried S-adenosyl-L-methionine (SAMe) samples

	Reference (%)	SAMe-mannitol (1:1) (%)	SAMe-glycine (1:1) (%)
Residual humidity	1.05	1.5	2.8
Sulphate ashes	0.107	0.112	0.112
$SAMe^+$ (-ion)	50.894	25.791	24.094
PATES	22.521	11.231	10.899
Sulphuric acid	24.461	12.350	12.012
Adenosine	0.024	0.017	0.035
Methylthio-adenosine (MTA)	0.040	0.043	1.475
DecaSAMe	0.126	0.066	0.066
Iron (ppm)	20	20	–
pH	4.28	6.48	–

ratio of 1 : 1 as inert excipients prior to the freeze drying. While no decomposition of the active compound could be recorded in the mannitol-SAMe specimen, the sample with glycine as support showed an increased amount of the degradation products methylthioadenosine (MTA) and adenosine, as can be seen in Table 1. The resulting loss in activity seems to be due to chemical incompatibility between the drug and the respective excipient.

Finally, the atmospheric freeze-dried food products showed, with regard to their appearance, taste, colour, and reconstitution, high-quality properties and, surprisingly, displayed increased retention of aroma and flavour components, as compared to corresponding samples resulting from classical lyophilization. In the case of coffee extract, the dry products differed, depending on the sublimation temperatures, in colour intensity (dark brown to light brown) as well as in their macroscopic texture; with the highly hygroscopic orange juice, again mannitol as excipient had to be added prior to the freeze drying in order to obtain a satisfactory dry product, while the processing of untreated, i.e. unskimmed milk or cream, generally resulted in dry products with, depending on their initial fat content, more or less poor wetting and thus, instant properties.

Conclusions

The results obtained in this investigation demonstrate the feasibility of freeze drying pharmaceutical solutions and liquid foods at atmospheric pressure. Compared to the classical lyophilization the following differences/ advantages can be pointed out:

(1) true freeze drying – the product is held below its critical (eutectic) temperature for the entire process;
(2) constant drying conditions – the drying medium circulates in a closed cycle and is continuously regenerated by condensation on the surface of the cooling systems;
(3) reduction of the required drying times and thus of the costs of the freeze-drying process – as a consequence of the improved heat and mass transfer between the cold, dry gas and the frozen sample, process energy savings and thus, reduced costs can be expected; however, this point has to be reviewed accurately in further studies with an improved scaled-up pilot plant;
(4) high and homogeneous quality (colour, consistence, moisture content) of the dry product – because of the described particular conduction of the drying medium, more equal drying without local temperature and/or concentration gradients in different product layers can be obtained;
(5) fine powdered, free-flowing product – instead of a cake, a fine powder with a high specific surface area and thus, good instant properties can be achieved;
(6) improved aroma retention – at lower sublimation temperatures and in the absence of a vacuum, the loss of volatile flavours in food products is minimized.

Although further studies concerning the improvement of the spray-freezing procedure, the scaling up and the validation of the process, the possibilities of a further reduction of drying times, as well as the feasibility of working under aseptic conditions still required to be carried out, the authors believe that because of the very promising results obtained in this investigation, the atmospheric freeze-drying technique described can be a suitable alternative in freeze-drying technology.

Acknowledgments

The authors wish to thank Ciba-Geigy AG (Basel, Switzerland) and Bioresearch AG (S. Antonino, Switzerland) for their support in analytical procedures as well as Glatt AG (Pratteln, Switzerland) and KWF (Bern, Switzerland; grant no. 1661) for financial support of this work.

References

Barnett, S., Freezing of coffee extract to produce a darker coloured freeze-dried product. In King, C.J. (Ed.), En-

gineering of food preservation and biochemical processes, *AIChE Symp. Ser. (Food Preservation)* 132, Vol. 69 (1973) 26–32.

Boeh-Ocansey, O., A study of the freeze drying of some liquid foods in vacuo and at atmospheric pressure. *Drying Technol.*, 2 (1983–84) 389–405.

Dunoyer, J.M. and Larousse, J., Expériences nouvelles sur la lyophilisation. *Trans. Eighth Vacuum Symp. Second Int. Congr.*, 2 (1961) 1059–1062.

Glatt Maschinen- und Apparatebau AG, CH-4133 Pratteln/Switzerland, U.S. Patent 4,608,764 (1986) and European Patent PCT/CH/88/00106 (1988).

Heldman, D.R. and Hohner, G.A., An analysis of atmospheric freeze drying. *J. Food Sci.*, 39 (1974) 147–155.

Malecki, G.J., Shinde, P., Morgan, A.I. and Farkas, D.F., Atmospheric fluidized bed freeze drying. *Food Technol.*, 24 (1970) 601–603.

Meryman, H.T., Sublimation freeze drying without vacuum. *Science*, 130 (1959) 628–629.

Moor, H., Die Gefrierfixation lebender Zellen und ihre Anwendung in der Elektronenmikroskopie. *Z. Zellforschung*, 62 (1964) 75–77.

Mumenthaler, M., Sprüh-Gefriertrocknung bei Atmosphärendruck: Möglichkeiten und Grenzen in der pharmazeutischen Technologie und in der Lebensmittel-Technologie. Ph.D. dissertation, Basel (1990).

Mumenthaler, M. and Leuenberger, H., Atmospheric spray-freeze drying of pharmaceutical solutions. *Proc. Int. Symp. Control. Rel. Bioact. Mater.*, 15 (1988) 432–433.

Özer, Y., Talsma, H., Crommelin, D.J.A. and Hincal, A.R., Influence of freezing and freeze drying on the stability of liposomes dispersed in aqueous media. *Acta Pharm. Technol.*, 34 (1988) 129–139.

Pikal, M.J., Freeze drying of proteins. II: Formulation selection. *BioPharm*, 3 (1990) 26–27.

Woodward, H.T., Freeze drying without vacuum. *Food Eng.*, 35 (1963) 96–97.

Woog, H., Galenische Entwicklung von Lyophilisate. In Concept Heidelberg (Ed.), Gefriertrocknung in Entwicklung und Produktion. *J. Pharmatechnol.*, 3 (1989) 14–24.