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*Technology and applications*

# Spray freeze-drying – the process of choice for low water soluble drugs?

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## Abstract

Most of the novel highly potent drugs, developed on the basis of modern molecular medicine, taking into account cell surface recognition techniques, show poor water solubility. A chemical modification of the drug substance enhancing the solubility often decreases the pharmacological activity. Thus, as an alternative an increase of the solubility can be obtained by the reduction of the size of the drug particles. Unfortunately, it is often difficult to obtain micro or nanosized drug particles by classical or more advanced crystallization using supercritical gases or by milling techniques. In addition, nanosized particles are often not physically stable and need to be stabilized in an appropriate matrix. Thus, it may be of interest to manufacture directly nanosized drug particles stabilized in an inert hydrophilic matrix, i.e. nanostructured and nanocomposite systems. Solid solutions and solid dispersions represent nanostructured and nanocomposite systems. In this context, the use of the vacuum-fluidized-bed technique for the spray-drying of a low water soluble drug cosolubilized with a hydrophilic excipient in a polar organic solvent is discussed. In order to avoid the use of organic solvents, a special spray-freeze-drying technique working at atmospheric pressure is presented. This process is very suitable for temperature and otherwise sensitive drugs such as pharmaproteins.

## Introduction

Most of the novel highly potent drugs, developed on the basis of modern molecular medicine, taking into account cell surface recognition techniques, show very low water solubility. This fact is an important problem as solid-dosage forms are the first choice of any manufacturer. Solid-dosage forms with a low water soluble drug substance are prone to have a reduced bioavailability. For this reason, it is important to find solutions to overcome this problem. Nanoscience and Nanotechnology offer opportunities to improve the solubility of such drugs and to increase the bioavailability. Drug particles in the nanometer range (5–50 nm) show a substantial increase in (water) solubility that should lead to an improved bioavailability. Early findings revealed that an important improvement in bioavailability could already be obtained with a reduction of the initial mean particle size from 22 to 3.7 μm in case of Digoxine (Shaw & Careless, 1974), a low water soluble drug. A higher specific surface area of a drug leads in general to a higher dissolution rate and as a consequence to a higher bioavailability of a drug (Lindenbaum et al., 1973). Particles in the μm and nm range need in many cases to be chemically or physically stabilized. For this reason, the production of nanocomposites, i.e. solid dispersions of nanoparticles in an appropriate matrix or solid solutions, i.e. a molecularly dispersed active substance in a matrix can offer important advantages. It is known for a long time that solid solutions and solid dispersions of Griseofulvin (Chiou & Riegelmann, 1969, 1971; Chiou & Niazi, 1976; Frömming et al., 1981)

improve the solubility and bioavailability of the low water soluble drug.

In a first approximation, the higher solubility of a small particle with the size $r$ (in the range of μm and less) is governed by the Kelvin equation.

$$\ln\left(\frac{S}{S_b}\right) = \frac{2\gamma v}{r}, \quad (1)$$

where $S$ is the solubility of fine particles (with radius $r < 10\,\mu m$), $S_b$ the solubility of coarse particles ($r \gg 100\,\mu m$), $\gamma$ the interfacial tension and $v$ the molar volume.

It is evident that the preparation of a solution with very fine drug particles can lead to a supersaturation of the system. During the subsequent precipitation of the drug substance coarse crystals can be formed. Thus, it is important to consider stability problems. It is well known that the drug absorption by passive diffusion through the intestinal membrane is facilitated if the drug is available in a molecularly dispersed form. Recent findings show that it is not only the size of the drug particle or its solubility that can influence drug absorption, but also the formulation, i.e. the matrix substance such as polyethyleneglycol may enhance the absorption of the drug. This type of findings is related to the existence of P-glycoprotein or the cytochrome P450 3A subfamily, in particular CYP3A4 and CYP3A5 in the intestinal membrane, working as an active efflux transporting system for the drug substance. If this transport system can be blocked or saturated by an excipient, food or another drug the bioavailability of the specifically investigated drug such as a new chemical entity may be enhanced (Benet et al., 1996; Soldner et al., 1999).

## Process technologies used for the size reduction of drug particles

### *Pyrolysis, milling, classical crystallization and the use of supercritical gases*

Many processes to manufacture nanoparticles need high temperatures (e.g. pyrolysis) and thus, are not suitable for manufacturing small sized drug particles. Such processes are specially used for inorganic materials, e.g. for the production of $SiO_2$, $TiO_2$ (Komiyama et al., 1990) or of Carbon Black.

The classical milling of drug substances often did not lead to particles less than 10 μm size. Even for inorganic substances, it is not easy to obtain submicron particles (Tanaka, 1995). In addition, it has to be kept in mind that during the milling process hydrophobic surfaces are created as the polycrystalline material preferably breaks at interfaces with the weaker, hydrophobic bond (Bongartz, 2001). Grinding or milling is a top–down technique. An alternative is the bottom–up approach by chemical synthesis, which is often used for the preparation of nanoparticles for drug targeting and/or for a systemic administration of such a drug delivery system with a prolonged residence time in the systemic circulation (Stella et al., 2000). This type of approach will not be discussed further in this paper.

Recently, a lot of investments were done in the research and development of techniques based on the use of supercritical gases as solvents for drugs and/or for a subsequent manufacturing of fine particles, e.g. by rapid expansion of the supercritical fluids (Robertson et al., 1998; Weber et al., 1998). These techniques have advantages and disadvantages. The main disadvantage is the fact, that it is difficult to control the particle size and the 'instant property' of the particles (ideal wettability for water, etc.) for a fast dissolution in water. Similar problems are encountered as in the case of a classical crystallization of drugs, where solvent mixtures of a good and a less good solvent for the drug is used for the precipitation of the drug substance. This effect is related to the fact that supercritical carbondioxide, the most widely used supercritical fluid, usually has to be modified by adding an organic solvent such as methanol to become a solvent with the desired properties for the drug substance.

An alternative approach consists in the manufacturing of nanocomposite systems, i.e. nanoparticles embedded in a well water soluble matrix. Such a powder can be obtained by novel process technologies such as vacuum-fluidized-bed systems using hydrophilic organic solvents or atmospheric spray freeze-drying of appropriate hydrophilic drug solutions or for the preparation of solid dispersions or solid solutions.

### *The Glatt vacuum-fluidized-bed system*

#### *Introduction and rationale*

This new equipment was designed as a closed-loop system with a solvent recovery facility (see Figure 1). Thus, the advantages of the vacuum drying and of the fluidized-bed process could be combined in a unique

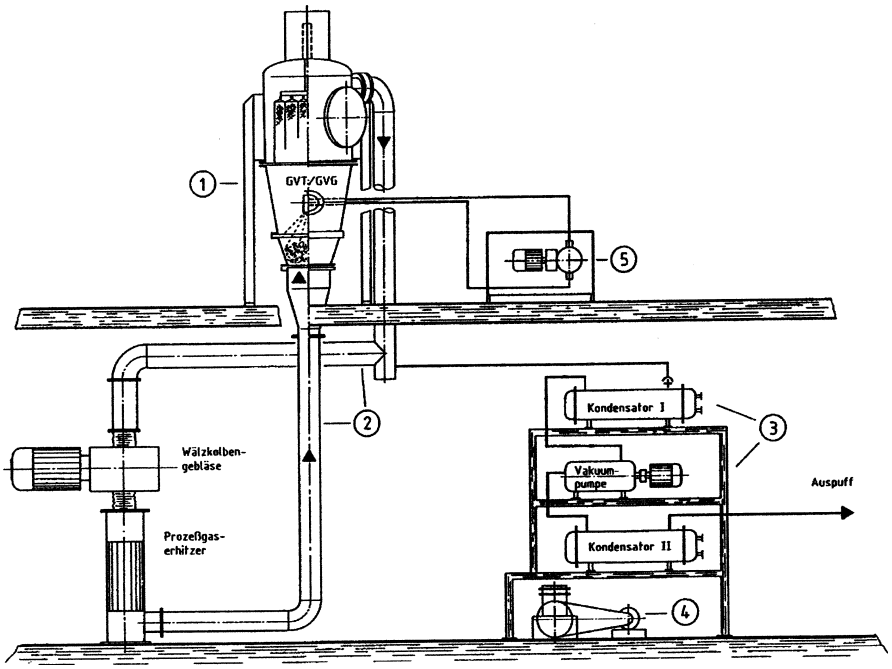


*Figure 1.* Diagram of the vacuum-fluidized-bed system. 1 = operating tower; 2 = closed-loop system; 3 = solvent recovery; 4 = chiller unit; 5 = high-pressure spray system.

way. In addition, the superposition of both principles leads to new product properties and consequently to a high potential for innovative and optimized solid-dosage forms (Luy et al., 1989a,b; Leuenberger et al., 1990).

In the case of organic solvents, vacuum drying is a fast process. It is important that the organic solvents are removed to an acceptable extent concerning the toxicity of the residual amount. This process is also advantageous for oxygen and temperature-sensitive materials.

*Explosion hazards*

The use of organic solvents in a conventional spray-drying tower is absolutely forbidden, as at atmospheric pressure extremely explosive air – organic solvent vapor – mixtures can be formed.

Due to the lowering of the system pressure in the vacuum-fluidized-bed system below the ignition pressure of organic solvents, the use of an inert gas carrier can be in general avoided. However, it has to be taken into account that the ignition pressure of a hybrid system (organic solvent vapor, residual air and powder) may be different from the minimum ignition pressure of the pure organic solvent.

*Use of the fluidization process*

A fluidized bed has the advantage of an excellent heat and mass transfer. Geldart (Geldart et al., 1983) classifies different types of powder material, as a function of its fluidization ability. Thus, an extremely wet powder, which is very cohesive, cannot be fluidized. In such a case, a pretreatment by vacuum drying of the material on the bottom plate of the product chamber would be the method of choice and emphasizes again the combination of the vacuum drying with a fluidized-bed-drying process.

It is important to realize that a fluidized bed can be established also at rather low pressures, such as, e.g. 100 mbar as the gas velocity can be adjusted to maintain a fluidized bed. In the equation that describes the conditions of the fluidized bed the gas velocity shows a quadratic dependence (see Eq. (2)), whereas the density $q$ decreases linearly with the system pressure $p$ assuming in a first approximation that the ideal gas equation can be applied (see Eq. (3)).

$$Dp = \frac{h\,(1-e)\,qu^2gc}{d}, \tag{2}$$

$$p = q\frac{RT}{M}, \tag{3}$$

where $Dp$ is the differential pressure across fluidized bed, $p$ the system pressure, $q$ the gas density, $R$ the gas constant and $T$ the absolute temperature. Further, $M$ is the molecular weight of the gas, $h$ the height of fluidized bed, $e$ the porosity of the fluidized bed, $c$ the constant and $d$ the particle diameter.

*The vacuum-fluidized-bed system*

The equipment is described in detail in Figure 1 and permits to operate the fluidized bed in a closed-loop system. The residual air and/or the residual vapor of the organic solvent is used at rather high gas velocities to maintain the fluidized bed of the powder. The gas is heated up by the process gas heater. The pressure difference $Dp$ to maintain the fluidized bed is achieved with the Roots molecular pump. The solvent vapor is partially removed from the closed-loop system by the solvent recovery unit. This unit consists of two condensers and permits recovery rates from 90% to 95% on the low-pressure (vacuum) side, where the recovered solvents show a high purity, due to the efficient filter system, which prevents particulate contamination. On the high-pressure side, an additional amount of solvent is condensated leading to a total of up to 99% recovery rates. It is evident that the additional amount of solvent recovered which passed through the oil vacuum pump can be contaminated by traces of oil. Thus, the exhausted air should be filtered by active carbon to meet all requirements for an optimal environmental protection. As the closed-loop system operates normally under vacuum conditions, no inert gas carrier is present which has to be cooled down for solvent recovery purposes and recycled, i.e. heated up again to maintain the classical fluidized bed at atmospheric pressure.

*Applications of the vacuum-fluidized-bed system*

*Experiences with drying.* In Figures 2 and 3, the decrease in moisture content is plotted as a function of process time. It is evident that an initial high content of organic solvent can be removed very fast with this drying technique. To avoid 'tailing effects' in case of polar solvents (see Figure 3), it is possible to shorten the drying time by purging the system with nitrogen gas.

*The use of inert gas carriers to purge the system.* It is of course possible to use an inert gas carrier, e.g. nitrogen, to purge the system. Thus, an additional reduction in the residual content of organic solvent in the final product can be achieved. In special cases, the equipment can also be used as an open-loop system in the final drying stage. As the residual content of organic solvent is already low, the requirements of environmental protection can be met easily again. An exhaust air-active charcoal filter may be used in addition if desired.

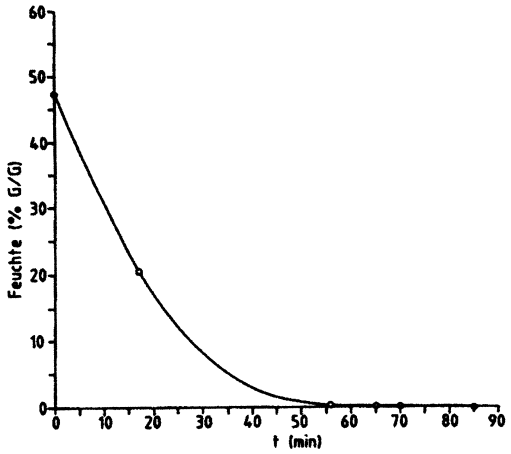


*Figure 2.* Drying of an enol-ester compound in vacuum-fluid bed; solvent: ethyl acetate.

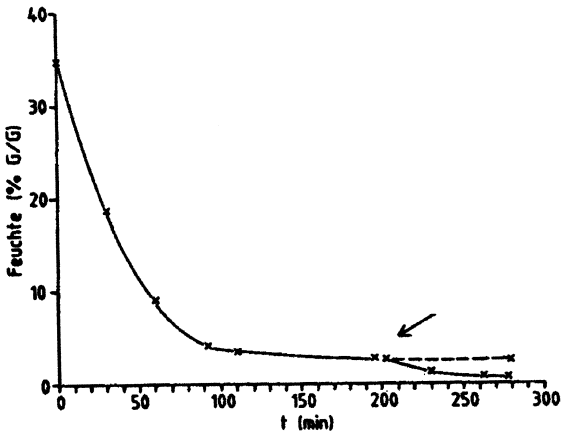


*Figure 3.* Drying of a cephalosporin antibiotic containing water in vacuum-fluid bed.

*Spray agglomeration, spray-drying and product optimization*

It is evident that for the spray solutions a special high-pressure nozzle is needed, as no air should be injected into the product chamber (see Figure 1). Due to the fact that organic solvents can be used as granulating liquid, a lot of applications in the field of controlled release of active substances and of highly water-sensitive materials become feasible. As mentioned earlier, many

biologically very active substances show a low water solubility (e.g. <0.01% w/v). Thus, the dissolution of the active drug from a solid-dosage form leads to problems and subsequently *in vivo* to a poor bioavailability that is not acceptable. In order to improve the dissolution properties of a poor-soluble drug, drug-solid solutions may be prepared, e.g. by spray-drying where the drug is embedded into a hydrophilic matrix which can be easily dissolved in water. Polyvinylpyrrolidone (PVP) or polyethylene glycol (PEG) is often used as hydrophilic matrix and acetone as a solvent if the active substance is soluble in acetone. It is evident that such a preparation needs special attention. For this purpose, the vacuum-fluidized-bed equipment was used to optimize the product properties and to study the performance of this system used for a spray agglomeration process. Thus, an acetone solution containing PVP and the active substance was sprayed on a powder consisting of microcrystalline cellulose, corn starch and polyplasdone XL.

*Special issues related to the above vacuum-fluidized-bed process*

It is important to notice that the granules, which can be obtained, show a high porosity and a high specific surface. Due to the aspects of the granules, it can be concluded that the spray agglomeration process prevailed. However, if the system pressure is lowered to ca. 100 mbar, part of the PVP drug solution is spray-dried leading to typical spherical hollow shells. The samples analyzed in an X-ray diffractometer showed that the active substance was present in an amorphous state. Thus, the long-term physical stability and possible crystallization effects need to be monitored. Due to the high porosity of the final tablets, it is not astonishing that the active substance was released in water within 5 min. Due to the use of organic solvents, it is important to keep the residual content of organic solvents of the product within acceptable limits.

*Spray freeze-drying at atmospheric pressure*

*Introduction and rationale*

Freeze-drying, frequently termed lyophilization, is a process consisting of two steps – the solvent (usually water) is first frozen out and then removed by sublimation usually in a vacuum environment. Furthermore, the drying step may be divided in two stages: Primary drying (ice sublimation) and secondary drying (moisture desorption). It will be shown, later in this paper, that the spray-freeze-drying process at atmospheric pressure leads to interesting and different product qualities than the classical freeze drying technique.

After freeze-drying, a dry porous mass of approximately the same size and shape as the original frozen mass is left. The resulting product is in a stable form and can be redissolved rapidly in water. In general, a product is freeze-dried if the aqueous solution is not stable enough for marketing. In this manner, a compound that is heat sensitive and undergoes rapid decomposition in aqueous solution can be formulated into a stable form, for example injectables. Because freeze-drying takes place at lower temperature than spray-drying, it is normally considered less destructive to protein products (Pikal et al., 1984; 1991; Maung et al., 1989).

Producing the highest product quality compared with other evaporative drying processes, freeze-drying has attained an increasing importance in pharmaceutical technology following the rapid growth of the bioindustries during the past decade.

*The principle of atmospheric freeze drying*

Solutions or dispersions (No. 4, Figure 4) are sprayed against a stream of cold air (−60°C; top spraying) using a two-fluid pneumatic nozzle with heating facilities (Nos 2 and 3, Figure 4).

The frozen droplets formed by this spray-freezing step are dried during the following atmospheric freeze-drying in the cold desiccated air stream by sublimation. A filter (No. 5, Figure 4) holds the fine product back in the drying chamber, while the water vapor is removed by the circulating air in the cooling systems (No. 9, Figure 4), where the humidity condenses on the refrigerated surfaces.

In order to reduce the relative humidity and to deliver the energy necessary for sublimation, the cold air passes through a heater (No. 10, Figure 4) yet keeping the temperature below the respective eutectic temperature or the glass transition temperature of the frozen solution.

At this point, the air is again capable of taking up humidity corresponding to the Mollier-h,x-diagram and passes through the product again.

The apparatus is equipped with two cooling systems (No. 9, Figure 4) working alternately: While one is cooling, the other one is de-icing and vice versa.

A bypass connecting tube (No. 11, Figure 4) allows one to open the drying chamber, without heating up the conditioned and cold drying air circulating in the closed-loop system. It is possible to use nitrogen as an

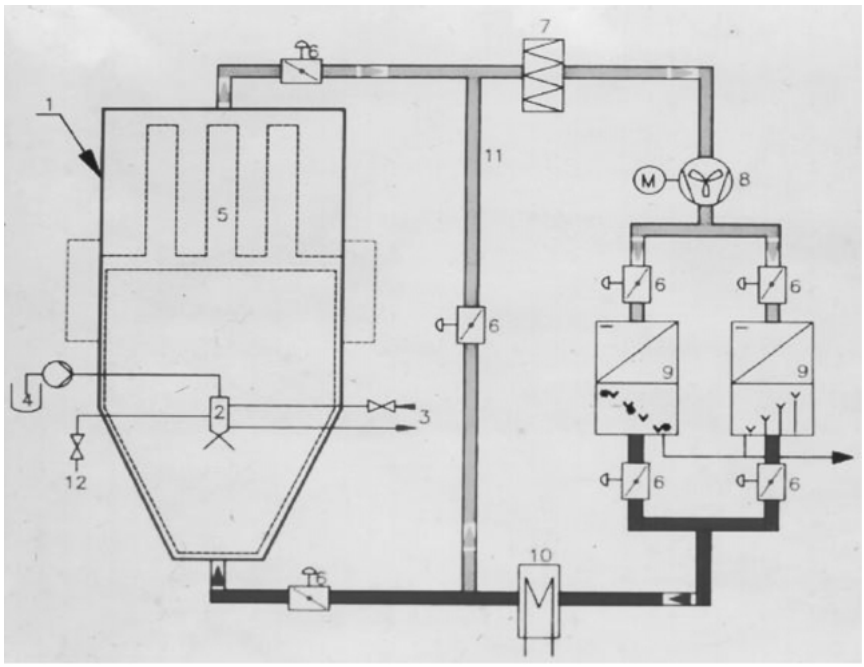


*Figure 4*. Schematic diagram of the atmospheric spray-freeze-drying apparatus: 1. Spray tower, 2. Spray nozzle, 3. Heating device, 4. Spray solution, 5. Filter system, 6. Flap, 7. Airfilter, 8. Fan, 9. Refrigerator and condensors, 10. Heating system, 11. Bypass pipe and 12. Spray air for spray nozzle.

inert drying medium to protect sensitive products from oxidation. This precaution is also necessary for the freeze-drying of liposomal formulations with *t*-butanol.

Figure 5 shows the pilot plant in the process engineering laboratory of Glatt AG in Pratteln, Switzerland.

*Description of the equipment*

*The spray-freezing/drying chamber.* The part of the apparatus containing the product consists of a combined spray-freezing/drying chamber (above named drying chamber (No. 1, Figure 4)). The construction of this part is known from the fluid bed technology: It is composed of a product vessel and an expansion chamber, limited on the top by a shakable filter and on the bottom by a fine sieve. In case of the described pilot plant, the volumes of the product vessel and the expansion chamber are 5 and 15 l, respectively (see Figures 4 and 5).

*The spraying system.* Presently, a two-fluid pneumatic nozzle is used. The pros of such a spraying system are the possibilities of working at low spraying rates and of controlling the droplet size; thus, the particle size in the dried product, independent of the spraying rate by varying the atomizing air pressure. Moreover, this type of nozzle is less susceptible to obstruction than pressure nozzles.

The cons are the relatively high energy consumption and the wide droplet-size distribution. In order to avoid air from outside to be brought into the closed-cycle system, the atomizing air is taken out of the system itself, compressed and given back into the system via the nozzle.

A circulation of hot saltwater prevents the freezing of the aqueous solution inside of the nozzle (No. 3, Figure 4).

*Control of the process.* The measurement of the temperatures in the inlet air, the drying chamber, the outlet air and near to the cooling systems, the measurement of the air flow rate and of the dew-point temperatures before and after passing through the frozen material ensures a continuous supervision of the process (see Figure 6a–c).

Most important with regard to the control of the atmospheric freeze-drying process are the dew-point temperature measurements.

The dew point, below 0°C also called frost point, is the temperature to which air must be cooled to achieve water vapor saturation. According to the

*Figure 5.* Atmospheric spray-freeze-drying prototype apparatus.

Mollier-h,x-diagram every dew-point temperature corresponds directly to a certain absolute water content (g water per kg dry air). An optical condensation dew-point hygrometer (chilled mirror sensor) is used to measure these temperatures of water vapor saturation.

The control of the dew-point temperatures of the inlet and the outlet air, correlating directly with certain water content in the respective air stream, persuits to monitor the freeze-drying process. By numerical evaluation of the dew-point curves, it is possible to calculate the changes in moisture content per time unit of the product in the drying chamber without interrupting the process.

*Freeze-drying of food and limitations of the process*

The prototype for the use of the spray-freeze-drying technology was developed in cooperation with Glatt AG, Pratteln, Switzerland and the Institute of Pharmaceutical Technology at the University of Basel (Mumenthaler & Leuenberger, 1991; Mennet, 1994). The size of the actual experimental setup is too large for extremely high-valued pharmaceutical proteins and too small for the freeze-drying of food. In fact the use of this apparatus for a large-scale production of freeze-dried food can be practically ruled out for the following reasons: Without addition of further excipients, a lot of food products show low and not well defined eutectic or glass transition temperatures. For example, in case of high sucrose content, the glass transition temperature can be found at about $-33^{\circ}$C (Mennet, 1994).

As discussed before the costs per kg dry product increase drastically if the atmospheric spray-freeze-drying process has to be carried out at low drying temperatures resulting in long processing times. Therefore, this new drying process can only be profitable if the respective product is characterized by a high market value and a high eutectic or glass transition temperature of its frozen solution.

*Classical freeze-drying and freeze-drying at atmospheric pressure*

Freeze-drying has now become a standard method for the stabilization of labile products, mainly proteins, which are used as therapeutic preparations, biochemical reagents or diagnostic formulations. The classical freeze drying technique has however a number of disadvantages, which is related to the poor heat transfer in vacuum and the preparation of the product to be freeze dried in a vial (Pikal et al., 1984). The novel technique

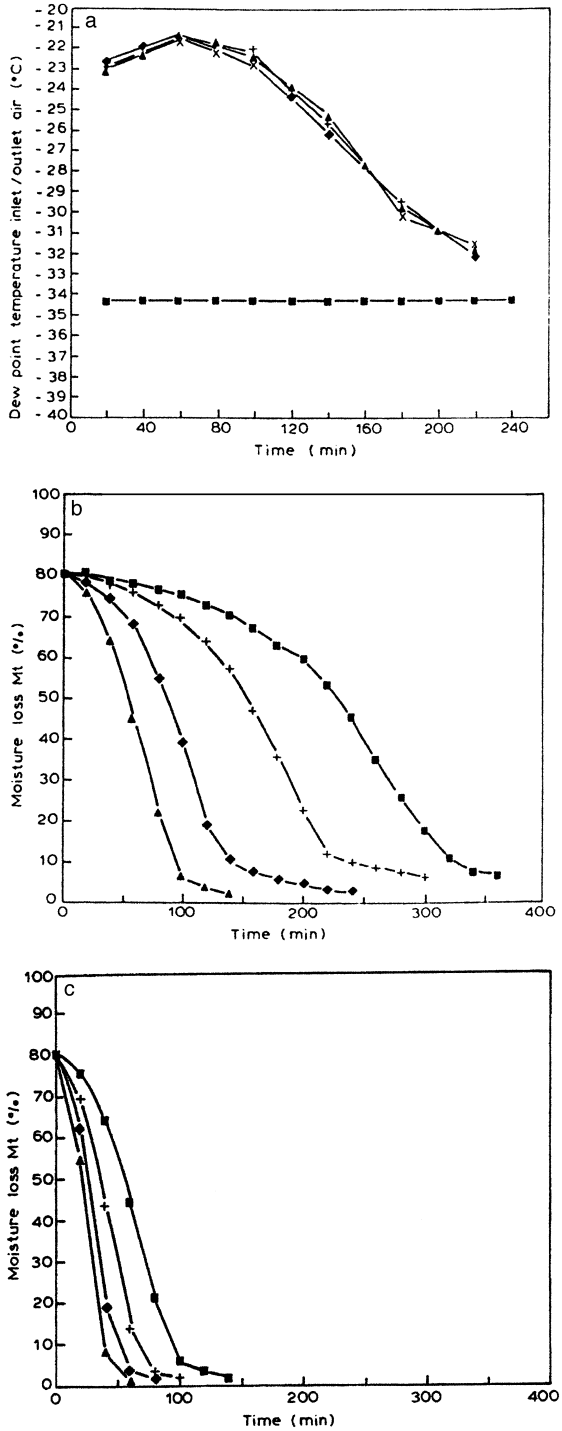


*Figure 6.* (a) Dew-point temperature of inlet and outlet air representing air moisture content. (b) Drying kinetics as a function of inlet air temperature. (c) Drying kinetics as a function of inlet air temperature.

of spray freeze-drying at atmospheric pressure has the following significant advantages:

- The size of the droplets of the solution sprayed can be controlled by the nozzle (with variable range, e.g. 10–30 μm).
- The droplets are immediately frozen in a counter stream of air with a temperature of −60°C. Thus, there is not a phase separation within the droplet between ice of pure water and the frozen eutectic liquid.
- Free flowing powder can be obtained, which contains spherical particles of a similar size like the original droplets. Most of these spherical particles look like a blackberry exhibiting a substructure of finer particles.
- The shape and size of the particles obtained depend on the process parameters of the spray-freeze-drying technique and on the formulation of the drug/excipient material dissolved.
- The technique is especially suitable for drugs with a high potency and low water solubility as well for temperature, pH and salt concentration sensitive drugs such as pharmaceutical proteins or vehicles for gene-transfer (liposomes or other vectors).
- As a pharmaceutical protein formulation, a bovine $\alpha_1$-interferon solution was freeze spray-dried and it could be shown that the initial potency was not changed.
- Nescafé Gold, a classically freeze dried product, was prepared as a solution and spray freeze-dried with varying freeze-drying temperatures. At rather low temperatures ($<-15$°C) the flavors remained in the powder product obtained and the color of the powder changed from a bright yellow at very low drying temperature to a dark brown at an upper drying temperature of −5°C. The change of the color indicates a change in the surface structure of the powder. Thus, the surface of the powder can be influenced by the temperature profile during the drying phase.
- It can be concluded that the spray-freeze-drying technique is the gentlest process of preparing an instant water soluble product of a temperature sensitive drug.
- It could be shown that the process is also suitable for the preparation of enzyme formulations.

## Conclusions

Atmospheric spray freeze-drying appears to be interesting for a variety of applications. The advantages of this new process are especially favorable in drying of

thermosensitive products with a high value added. The spray-freeze-drying technique is the method of choice if the following product properties/intentions are of interest:

- If a porous structure with a high surface area is required (e.g. for instant products, catalyst compounds and pharmaceutical formulations);
- A free-flowing powder for use as intermediate or final product (e.g. for intranasal or pulmonal application, filling of capsules and production of tablets).
- Improvement of the bioavailability of extremely low water soluble drug substances (with low molecular weights, i.e. in general <500) for any type of administration.
- Option to produce solid-dosage forms with a low water soluble drug substance.
- Substitution of Soft Gelatine capsule formulations for low water soluble drug substances by formulations prepared with the spray-freeze-drying technique.
- Option for a special intellectual property protection (combination of drug substance, formulation, unique process technology for a new patent application).

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