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ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 68 (2008) 781–794
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Supercritical fluid drying of carbohydrates: Selection of suitable excipients and process conditions

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Received 9 March 2007; accepted in revised form 29 June 2007
Available online 6 July 2007

Abstract

The processibility of 15 carbohydrates, more or less commonly used, was investigated as excipients in supercritical fluid drying. The focus was on the ability to produce amorphous powder, the stability of the powders towards crystallisation, and the residual water and ethanol content. The aqueous solutions were sprayed into a pressurised carbon dioxide–ethanol mixture flowing cocurrently through a coaxial two-fluid nozzle. The powder characteristics appeared to be influenced by the supersaturation level reached during the SCF-drying process and by the properties of the sugar species, such as water solubility and glass transition temperature, or the solution viscosities. The stability and the residual solvent content of a selected set of sugars and some mixtures were further analysed. The stability of amorphous powders was investigated at 4 °C, room temperature, 40 and 50 °C. Lactose, maltose, trehalose, raffinose, cyclodextrin, low-molecular-weight dextran and inulin could form free-flowing powders that remained amorphous during the 3-month stability study. Sucrose had to be mixed with other sugars to form a stable amorphous powder. Ethanol could be entrapped in supercritical fluid dried low-molecular-weight sugars, whereas polysaccharide powders were free of ethanol. Measures to prevent or overcome the presence of ethanol are discussed.

Keywords: Aqueous solution; Amorphous powder; Carbohydrates; Excipients; Supercritical carbon dioxide; Crystallisation; Ethanol

1. Introduction

Supercritical fluid (SCF)-drying methods are attractive for the production of pharmaceutical formulations in dry powder form as these technologies can be adapted to the production of free-flowing microparticulates in a single step. Among others, SCF techniques have been investigated for stabilising pure and formulated dried proteins [1–6], and could be an alternative for other drying methods. SCF-drying has the advantage of avoiding drying stresses such as freeze damage – as in freeze-drying – or denaturation by heat – as in spray-drying. However, other stresses, such as low pH or organic solvents, might be caused by the SCF-drying process. Even though dry protein formulations are generally composed of a large fraction of amorphous sugars, polyols or polysaccharides for in-process as well as long-term stabilisation [7], only limited effort has been put towards the comprehension of the precipitation behaviour of sugars in SCF processes.

In freeze-drying of pharmaceutical proteins, sucrose and trehalose are commonly used stabilisers [7]. The high viscosity of these carbohydrate solutions at low temperature is a major factor in the inhibition of the crystallisation of

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doi:10.1016/j.ejpb.2007.06.019

the sugar during the freeze-drying process. Besides stabilisation, sugars, polyols and polysaccharides are also added as bulking agent. Mannitol, for instance, is often used to facilitate the drying. This excipient crystallises rapidly forming a porous structure improving the drying rate of the cake [7].

Unlike freeze-drying, the SCF-drying process from aqueous solutions involves a spraying step and higher temperatures; consequently affecting the kinetics of the system and the sugar selection. In this respect, SCF-drying is more closely related to spray-drying. This technique is commonly used for the production of lactose [8] and mannitol particles used for pharmaceutical applications such as inhalation and tablet production [9–11]. Spray-drying is also considered for the direct preparation of formulations for inhalation containing peptides [12], hormones [13], enzymes [14], DNA [15], etc. Numerous challenges are inherent to the spraying of carbohydrate solutions for drying purposes. First of all, the solubility of many sugars is very high, compared to other compounds (e.g., proteins), which causes them to precipitate late in the drying process. Second, the metastable zone (i.e., solute concentration above the solubility but below unstable supersaturation condition where spontaneous crystallisation is probable) of sugars is normally wide and high levels of supersaturation can be reached before precipitation occurs [16,17]. Third, the higher viscosity of the solution (i.e., compared to other solutions generally spray-dried) is detrimental to the atomisation process as the break-down of the jet of solution into drops is limited or can even be inhibited. This causes a reduction of the surface area of the droplet available for mass transfer (e.g., evaporation of the water from the droplet). Fourth, the sticky drops of sugar solution have the tendency to accumulate on surfaces, even at very low residual water content. Finally, sugar particles are prone to remain soft, and therefore easily deform and agglomerate, because of the low glass transition temperature (T_g) of the particles caused by the residual solvent content [18].

Challenges with sugars also persist with the powder form, especially with amorphous products. The amorphous state is thermodynamically metastable and measures must be taken to preserve that physical state to avoid degradation of the product. Furthermore, the hygroscopicity of the powder is an important factor to consider as it might complicate the handling of the product, its packaging and its stability.

Most studies on the drying of pure sugars using supercritical carbon dioxide (SC-CO_2) have been done with lactose, but maltose, sucrose and trehalose have also been occasionally investigated [1,19–25]. In all these studies, SC-CO_2 was used together with a modifier to increase the water-solubility in the SCF phase, and the solution was injected simultaneously into a pressurised vessel through a multiple fluid nozzle. Mixing of the liquid and SCF-drying medium occurred at the nozzle, causing precipitation of the solute, similar to the process used in this study. However, a direct comparison between the precipitation characteristics of these sugars is difficult as the process conditions – nozzle, solvent, modifier, pressure and temperature – were all different. Only a few general trends can be depicted from the studies. Temperature and pressure seemed to have insignificant effects on the particle size, morphology and residual water content [23]. Illustrative to the importance of the choice of sugar is that amorphous spongy spheres were formed with maltose and trehalose, whereas crystals were produced with sucrose and lactose under the same conditions [20]. Unfortunately, no explanations for these different behaviours were given.

A number of the physicochemical properties of the solute or solution, such as solubility, T_g, nucleation and crystallisation rates and viscosity, are expected to influence its behaviour during processing. The effect of the solubility is such that the time required to achieve saturation of either sucrose and lactose solutions from a 10% (w/w) solution will be significantly affected by their respective solubilities [26–28].

To get an overview of the phenomena happening during traditional drying processes, the drying paths expected in freeze and spray-drying are illustrated in a typical water–sugar phase diagram (Fig. 1). While increasing the concentration of a sugar solution, the viscosity increases towards infinity when approaching the T_g. Similarly, the diffusion rate of sugar decreases. The diffusion rate of water decreases as well as but to a lesser extent [29]. In freeze-drying, a solution is rapidly cooled at least until its T_g to

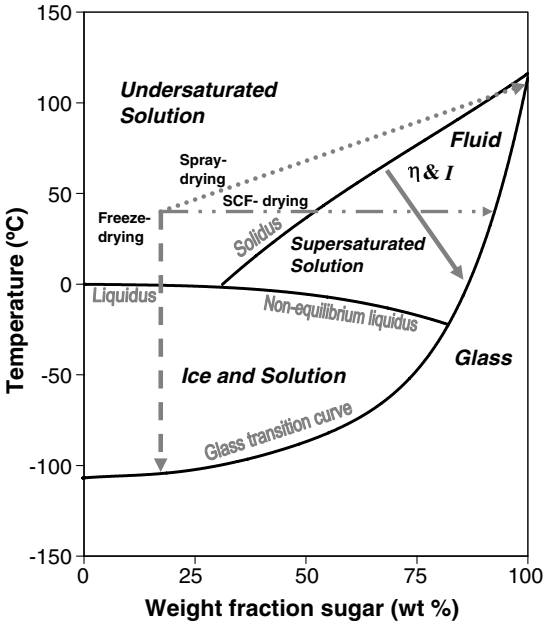

Fig. 1. Typical phase diagram of a system water + sugar showing the equilibrium liquidus and solidus lines and the non-equilibrium extension of the liquidus line and the glass transition curve. The solid arrow indicates the direction of increase of viscosity (η) and induction time to crystallisation (I), the dashed arrow the path followed during freeze-drying, the dotted arrow the path followed during spray-drying and the dashed double-dotted arrow the path followed during SCF-drying.

increase its viscosity and therefore avoid the formation of crystals. In spray-drying, the T_g is reached by rapidly evaporating the water using hot air. The time required to reach the T_g at the processing temperature should then be shorter than the induction time to crystallisation if an amorphous product is desired.

In SCF-drying, the path followed in the process is similar to that of a spray-drying process. However, the temperature of the drying medium is significantly lower (i.e., 35–40 °C instead of above 100 °C) meaning that if only evaporation is considered, a larger amount of water needs to be evaporated at a higher rate to reach T_g before crystallisation occurs. A significant difference between spray-drying and SCF-drying is that in the SCF-drying process it is possible to add modifiers to the drying medium (SCF phase) which also act as an anti-solvent on the solute, accelerating its amorphous precipitation and perhaps kinetically preventing crystallisation.

The present study contains two distinct parts. The first section focuses on the selection of 15 carbohydrates (Table 1) suitable for use as stabilisers in SCF-drying in relation to the physical properties of the product. The effect of the physicochemical properties of these sugars and their solutions is considered in an analysis of the limiting factors of the application of the SCF-drying technology. The second section is a detailed investigation of a selected set of sugars to address more specifically two aspects: the stability of the amorphous powder towards crystallisation and the residual solvent content. Issues related to the stability of the amorphous powder were tackled by considering the process conditions and the use of sugar mixtures. The process conditions, the utilisation of ethanol and the post-treatment of the powder were considered to reduce the residual solvent content of the powder.

Table 1
Evaluation of sugar, polyol and polysaccharides for processing by SCF-drying

Sugar/polyol/polysaccharide	T_g (°C)		Product	Crystallinity
	Measured[a]	Literature		
Glucose	n/a	36 [40]	Paste	n/a
Lactose	118	108 [30]	Powder	Amorphous
Leucrose	n/a	89.5 [41]	Powder	Amorphous
Maltose	98	100 [42]	Powder	Amorphous
Raffinose	118	102 [30]	Powder	Amorphous
Sucrose	71	74 [30]	Powder	Crystalline
Trehalose	117	115 [30]	Powder	Amorphous
Maltitol	n/a	39 [43]	Syrup	n/a
Mannitol	n/a	15 [44]	Powder	Crystalline
Sorbitol	n/a	−1 [44]	Syrup	n/a
Xylitol	n/a	−29 [43]	Syrup	n/a
Cyclodextrin	250	n/a	Powder	Amorphous
Dextran, LMW	208	n/a	Powder	Amorphous
Dextran, HMW	225	n/a	Syrup	n/a
Inulin	129–134	n/a	Powder	Amorphous

n/a, not available.
[a] The measured values of T_g (°C) are for amorphous freeze-dried products.

2. Materials and methods

2.1. Materials

D-Saccharose (sucrose; EP), and D-(+)-maltose monohydrate were purchased from Riedel-de Haen (Steinheim, Germany). D-Trehalose dihydrate (crystalline), glucose anhydrous (USP), maltitol (+98%), xylitol (+99%) and dextran from *Leuconostoc mesenteroides*, Strain No. B-512 (HMW dextran; $M_r \sim 68800$, clinical grade) were purchased from Sigma (Steinheim, Germany). D-Lactose anhydrous (EP), D-mannitol (EP), D-leucrose (+98%), D-(+)-raffinose pentahydrate (+99%), (2-hydroxypropyl)-β-cyclodextrin (cyclodextrin; $M_r \sim 1380$), and dextran from *Leuconostoc* spp. (LMW dextran; $M_r \sim 6000$) were purchased from Fluka (Steinheim, Germany). D-Sorbitol (+98%) was purchased from Aldrich (Steinheim, Germany). Short chain inulin (90–95%, 8–12 monomers, Frutafit®IQ) was supplied by Sensus (Rosendaal, The Netherlands). Technical grade ethanol (100%, Chemproha, Dordrecht, The Netherlands) was used and CO_2 (grade 3.5) was purchased from Hoek Loos (Schiedam, The Netherlands).

2.2. Amorphous sugars

Amorphous sugars were prepared by freeze-drying (ZIRBUS sublimator 400, ZIRBUS Technology, Bad Grund, Germany) with conditions similar to those suggested by Saleki-Gerhardt and Zografi [30]. Lactose, maltose and sucrose solutions (10% w/v) were placed on shelves pre-cooled at −45 °C for 72 h, −30 °C for 48 h and finally at 0 °C for another 48 h and 60 °C for 48 h. Trehalose and raffinose (10% w/v) were placed on shelves pre-cooled at −45 °C for 12 h, −30 °C for 48 h, 0 °C for 48 h and 60 °C for another 48 h. Mixtures of sugars were processed like sucrose when freeze-dried.

2.3. Supercritical fluid drying

In the experimental set-up (Fig. 2) (type SFP4, Separex, Champigneulles, France), the SC-CO_2 was supplied by a diaphragm pump. The ethanol added from a piston pump was mixed with the SC-CO_2 in a T-mixer. This fluid was then directly fed through the outer outlet of a coaxial nozzle (inner and outer diameter of, respectively, 0.15 and 1.1 mm). The sugar solution was simultaneously added through the inner outlet of the nozzle using a syringe pump. The pressure in the cylindrical 4-l precipitation vessel (10 cm inner diameter) was controlled using the exit valves of the vessel. Aqueous solutions were sprayed into a pressurised precipitation vessel together with SC-CO_2 enriched with ethanol through a coaxial nozzle. Once the desired temperature (37 °C) and pressure (100 bar) in the particle formation vessel and incoming SC-CO_2 and ethanol streams were achieved, the pressurised aqueous solution was sprayed into the vessel. After completion of the spraying process, the vessel was flushed with sufficient

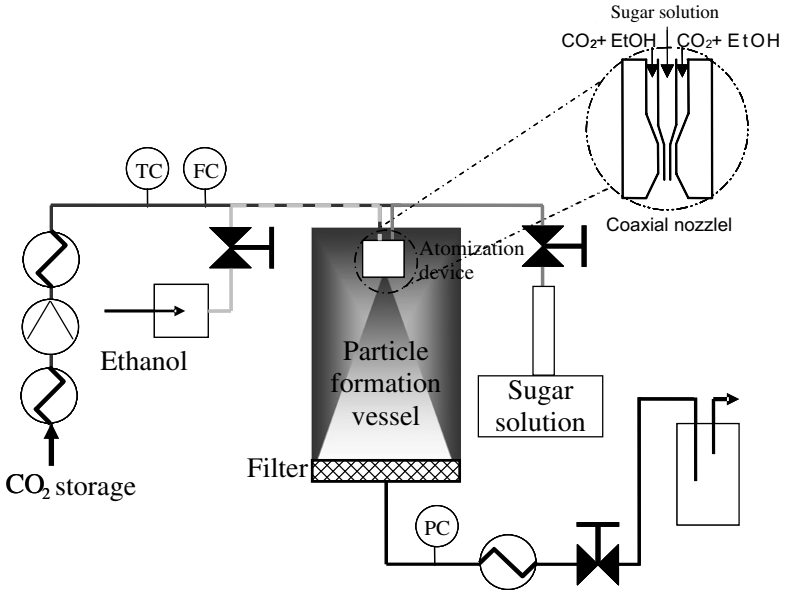

Fig. 2. Basic scheme of the experimental set up.

SC-CO_2 (more than twice the volume of the vessel) to remove the residual ethanol from the vessel. Following depressurisation, the powder was collected from the filter of the precipitation vessel.

2.4. Stability studies

The powders were recovered into ~100 mg samples and stored individually in 1-ml vials. The hermetically closed vials were exposed to different temperature conditions: 3 months at 4 °C, 3 months at room temperature, 10 days at 40 °C and 5 days at 50 °C. A new vial was open for each analysis.

2.5. Scanning electron microscopy

Scanning electron microscopy (Jeol JSM-5400, Peabody, USA) images were used to examine the morphology of particles. Conductive double-sided tape was used to fix the particles to the specimen holder before sputtering them with a thin layer of gold. In some instances, cryogenic conditions were used to prepare (i.e., carbon coating) and scan the samples.

2.6. X-ray powder diffraction (XRPD)

XRPD was performed using a D8Discover X-ray diffractometer with general area detector diffraction system (Bruker AXS, Madison, USA). The sample was set at 6 cm of the diffractometer possessing a two-dimensional (1024×1024 channels) detector. The incident Cu radiation of 1.54 Å was used with a beam of 0.5 cm cross section. The powders were prepared in a 0.5 mm thick sample holder. Data were integrated along the χ angle to obtain the intensity as a function of the scattering angle (2θ). Diffraction profiles were used to confirm the amorphous or crystalline state of the powders.

Powder was recovered from most compounds. Syrup of maltitol, sorbitol, xylitol and HMW dextran was obtained. The recovered glucose was a foamy paste similar to marshmallow candy. A similar product was recovered from the precipitation of sucrose, but in that case the paste could be recovered as a powder upon cooling of the product from process to room temperature. All powders were soluble and dissolved within seconds.

2.7. Differential scanning calorimetry (DSC)

Modulated DSC was performed on a Q-1000 calorimeter, TA instruments (New Castle, Delaware, USA) to distinguish between reversible events, such as T_g, and non-reversible events (e.g., crystallisation). Five to ten milligram of dry powder was sealed hermetically in an aluminium pan. The T_g was determined by heating the samples at a rate of 1 °C/min and a modulation of ±1 °C/min.

2.8. Residual water, ethanol and carbon dioxide analysis

The residual water content of dried powders was measured with the Karl–Fischer method (KF) using a coulometer (Metrohm, 756 KF, Herisau, Switzerland) as per manufacturer instructions. Methanol (1 ml) was added to ~10 mg of powder, mixed, and left to extract for at least 30 min before analysis by injecting 50 µl of the methanol into the coulometer. The water content of every sample is given as the average of the measured residual water contents of three repeated analyses, the standard deviation being always smaller than 0.1% residual water content.

A thermogravimetric analysis (TGA) balance (TA Instruments, SDT 2960, New Castle, Delaware, USA; Software Thermal Advantage version 1.1A and Universal Analysis 2000 version 4.1D) was coupled to a Fourier

Transform Infrared (FTIR) spectrometer (Thermo Nicolet Corporation, Nexus with TGA interface; Software OMNIC version 7.18) to probe for residual ethanol, CO_2 and water in the powder. Approximately 5 mg of powder was placed into an open alumina crucible. Samples were then heated at a rate of 5 °C/min from 30 to 200 °C. The balance was purged by a constant flow of helium (100 ml/min) to transport the gases released during heating to the FTIR. The gas phase was then analysed on-line by FTIR to detect ethanol, CO_2 and water vapour.

Quantification of the residual ethanol in the powder was performed by gas chromatography (GC) (Chromopack CP9002, Bergen op Zoom, The Netherlands). Approximately 20 mg of powder and 1 ml of water were placed into a 2-ml GC vial before capping it. A volume of 0.1–0.5 μl of solution was then injected directly into the column (Varian, CP SIL 5CB, 25 m, 0.53 mm, film thickness 5 μm) at a 120 °C isotherm for analysis (Software Galaxie Chromatographie Workstation, version 1.8.501.1, Varian Inc.). The calibration was achieved by preparing an aqueous solution containing 2% (w/w) of the previously freeze-dried studied sugar and 0.1% ethanol. Volumes between 0.1 and 0.5 μl of solutions were then injected. The peak area of ethanol was selected to prepare the calibration curve by linear regression (correlation coefficient $r^2 = 0.9852$).

2.9. Powder hygroscopicity

Approximately 10 mg of powder of known residual water content was aliquoted into 1-ml glass vials. These open vials were stored for 2 h in desiccators over saturated salt solutions – NaCl (78% RH) and $MgCl_2$ (32% RH) – which were placed in a temperature controlled incubator at 30 °C. After exposure, the residual water content was measured by KF titration and the water absorption calculated.

3. Results and discussion

3.1. Selection of potential sugar, polyol and polysaccharide excipients

3.1.1. Powder formation

Sugars, polyols and polysaccharides were processed by SCF-drying. For this comparative study, a 10% (w/w) solution concentration was used, and solution, ethanol and SC-CO_2 flow rates were set at 0.5, 25 and 267 g/min, respectively, to evaluate which stabilisers are most appropriate to be included into a sugar-containing protein formulation processed by SCF-drying (Table 1). The first criterion was the capability to form a powder. As a second criterion, the product should keep its powdery properties for at least 15 min, to allow easy handling and sampling (i.e., no caking, melting, or becoming gummy). The third criterion was a sustained amorphicity of the powders over 24 h to perform XRPD analysis. The crystallinity of the powder was verified as the stabilising excipient of a solid protein formulation should be mainly amorphous. The fourth criterion was the complete dissolution of the powders.

3.1.2. Particle morphology

Fig. 3 shows typical morphologies of particles prepared by SCF-drying. Using the screening process conditions, amorphous particles – lactose (not shown), raffinose (Fig. 3A), trehalose (Fig. 3C), cyclodextrin (Fig. 3E), inulin (not shown) and LMW dextran (Fig. 3F) – were spherical with a relatively smooth surface. Comparatively, sucrose particles (Fig. 3B) had a more irregular spheroid shape and edges could be identified on their surface. Their shape suggests that the particles could have been amorphous at one point during drying but recrystallised. The crystallised mannitol (Fig. 3D) had formed into long, thin, single needles (0.5–2 μm wide, 10–100 μm long). Except for sucrose, the particles look well detached from each other.

3.1.3. Effect of physicochemical properties on SCF-drying

Numerous physicochemical properties of the sugars and their solution might affect the SCF-drying process. From the results, the effect and interaction of the T_g, viscosity of the sprayed solution, viscosity of the saturated solution if available, solubility of the sugar in water and water–ethanol mixtures on the powder formation are discussed.

The ability to form a dry free-flowing powder appeared to be closely related with the T_g of the material. Most compounds – glucose, maltitol, sorbitol and xylitol – from which a powder could not be produced have a T_g (Table 1) close or below the process temperature (37 °C). This means that only a small difference in the amount of residual water causes the transition between the amorphous dry product being a viscous liquid state instead of a glass state. The droplets containing these sugars would then be prone to coagulation as they could remain soft and sticky even after complete removal of the water. Furthermore, they would be prone to crystallisation in presence of humidity as their T_g is below the process temperature. For example, the T_g of mannitol is below the process temperature, and its powder was identified as crystalline by XRPD right after SCF-drying. As mannitol precipitated into long needles with sharp edges (Fig. 3D), the polyol has probably directly crystallised following nucleation. With the exception of sucrose, all sugars and polysaccharides were amorphous powders upon formation.

Besides T_g, the anti-solvent effect of the ethanol during precipitation and the solubility of the solute in water and water–ethanol may also affect the powder formation process. For example, for solutions containing the same percentage of solid per weight, the amount of water that needs to be removed to reach saturation depends on the solubility of the solute. The solubilities of sugars, polyols and polysaccharides in water, and in 50, 95 and 100% (w/w) ethanol at 37 °C were investigated in a separate paper [31]. The difference in solubility of the sugars was extreme: from about 0.133 to 0.769 g/g solution in water, and 0.002 to 0.693 g/g solution in 50% ethanol. Overall,

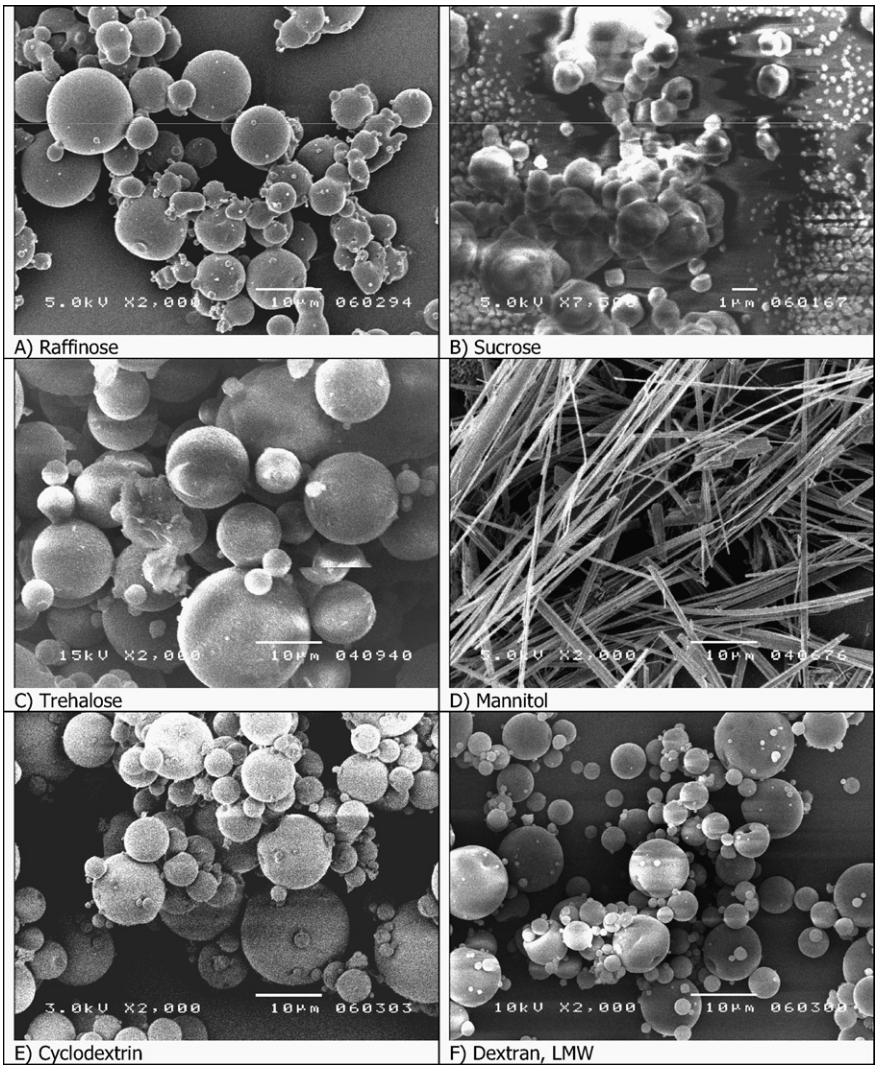

Fig. 3. SEM pictures of various SCF-dried carbohydrates.

no clear correlation could be identified between the solubility and the ability to form powder in SCF-drying. However, when considering only sugars (mono-, di- and trisaccharides), glucose is the only one which has both a high solubility and low T_g, suggesting that the combination of both high solubility in water–ethanol and low T_g is problematic in the production of SCF-dried powders. Polysaccharides do not show this uniformity in their behaviour. The solubility is highly polysaccharide dependent and can vary from very low to very high, even in ethanol. The saturated solution of cyclodextrin was so viscous that it could not be stirred, while the viscosity of saturated solution of the other polysaccharides was comparable to that of saturated solutions of other sugars. However, all studied polysaccharides have a very high T_g. Macromolecules generally have a higher T_g (Table 1), so their solidification can occur already at a higher residual water content as the T_g rapidly reaches a value above the process temperature which will facilitate the recovery of powder.

Another aspect to be considered is the supersaturation, which may occur during cooling of the sugar solutions. It was also previously shown that the width of the metastable zone (i.e., the level of supersaturation that can be achieved) measured during anti-solvent precipitation with ethanol is wider for sugars than for mannitol [31]. This might in part explain why mannitol is crystalline while the sugar powders are usually amorphous: once the ethanol fraction in the droplet gets high enough, the solubility drops and the mixture precipitates so rapidly that crystallites cannot get organised into crystals.

The viscosity of aqueous 10% sugar, polyol and polysaccharide solutions, and saturated water–ethanol sugar and polyol solutions was also previously investigated [31]. The viscosity of a 10% HMW dextran solution was 4- to 5-fold higher than the viscosities of the other sugar solutions (~5 mPa s versus 1–1.25 mPa s). This high viscosity affected the spraying process by hindering the jet break-up into droplets. The poor atomisation results in a longer drying time because of the smaller ratio between the surface and the volume of the drop.

The viscosity of saturated solutions also gives important indications about the drying process, especially about the

evaporation of the liquid phase from the droplet as the viscosity and the diffusion are inversely correlated. The viscosities of the sorbitol (≫100 mPa s) and sucrose (92 mPa s) solutions are much higher than the viscosity of trehalose (9.5 mPa s), maltose (9.0 mPa s), lactose (2.1 mPa s), raffinose (3.0 mPa s) and mannitol (1.9 mPa s) [31]. Therefore, it is expected that particles of sucrose and sorbitol will be more difficult to dry.

To establish the main factors involved in the successful recovery of powders from the SCF-drying process, a comparative table considering the T_g, viscosity of the sprayed solution, viscosity of the saturated solution (if available), and the solubility in water and 50% ethanol was created (Table 2). Based on the physicochemical properties, the compounds were rated for the possibility of forming powder, and assuming that powder is produced, if it is expected to be amorphous. The rating for the production of powder was based on the viscosity, the solubility and the width of the metastable zone (Table 2, prediction of SCF-dried product characteristics, powder), and the amorphicity was based on the T_g and the width of the metastable zone (amorphous). Because of the lack of specifications on the processibility of chemicals by SCF-drying, all properties were assumed to have an equivalent effect on the product formation. This table suggests, for instance, that the production of mannitol powder is extremely easy, but that the powder should be crystalline, whereas the production of HMW dextran powder is delicate, but the powder should be amorphous.

The physicochemical characteristics used in Table 2 correlate quite well to the experimental data (Table 1). The only two major deviations are cyclodextrin and leucrose. In the case of cyclodextrin, the recovery of powder is possible as the saturated solution forms a very stiff porous gel that can be dried by the SC-CO_2. Leucrose is very similar to glucose and maltitol in solubility, but the T_g of leucrose is significantly higher than those of glucose and maltitol. The viscosity of the starting solution seems to have a strong influence on the spraying process (HMW dextran), and should be sufficiently low to ensure proper atomisation. Diluting the solution might be a way to counteract the effect of the high initial solution viscosity.

3.2. Particle properties of selected amorphous powders

Selected compounds that could be processed into amorphous powder were further assessed for the stability of their amorphous character. Two strategies were adopted to increase the stability of amorphous powders: the first one is the modification of the process conditions – process

Table 2
Predicted powder formation and amorphicity of the powder produced by SCF-drying based on the physicochemical properties of the solute and solution[a]

Compound	T_g[b]	Viscosity at 37 °C		Solubility at 37 °C		Width metastable zone		Prediction of SCF-dried product characteristics[i]	
		10%[c]	Saturated[d]	Water[e]	50% ethanol[f]	Powder[g]	Amorphous[h]	Powder	Amorphous
Glucose	−−−	+++	+	−−	−	n/a	n/a	+/−	−−−
Lactose	++	+++	+++	+++	+++	++	−	+++	+
Leucrose	++	+++	+	−−	−−	n/a	n/a	+/−	++
Maltose	++	+++	+	+	++	+	++	++	++
Raffinose	++	+++	+++	+++	+++	n/a	n/a	+++	++
Sucrose	+	+++	−	−−−	−−	−	+++	−	++
Trehalose	++	+++	+	+	++	n/a	n/a	++	++
Maltitol	−−−	+++	+	−−	−	n/a	n/a	+/−	−−−
Mannitol	−−−	+++	+++	+++	+++	+++	−−−	+++	−−−
Sorbitol	−−−	+++	−−−	−−−	−−−	n/a	n/a	−−	−−−
Xylitol	−−−	+++	+	−−−	−−−	n/a	n/a	−	−−−
Cyclodextrin	+++	+++	−−−	−	−−−	n/a	n/a	−−	+++
Dextran, LMW	+++	+	−	+++	+++	n/a	n/a	++	+++
Dextran, HMW	+++	−−	−	++	+++	n/a	n/a	−	+++
Inulin	+++	+++	+++	+++	++	n/a	n/a	+++	+++

[a] The scale goes from very high, +++, to very low, −−−.
[b] T_g: +++ > 120 °C, ++ > 90 °C, + > 70 °C, −−− < 40 °C.
[c] Viscosity of 10% solution: +++ < 1.3 mPa s, + < 2 mPa s, −− > 4 mPa s.
[d] Viscosity of saturated solution: +++ < 3.5 mPa s, + < 10 mPa s, − < 100 mPa s, −−− > 100 mPa s or gel.
[e] Solubility in water: +++ < 0.4 g/g solution, ++ > 0.4 g/g solution, + > 0.5 g/g solution (°C), − > 0.55 g/g solution, −− > 0.6 g/g solution, −−− > 0.7 g/g solution.
[f] Solubility in 50% ethanol: +++ < 0.1 g/g solution, ++ > 0.1 g/g solution, + > 0.2 g/g solution, − > 0.3 g/g solution, −− > 0.4 g/g solution, −−− > 0.5 g/g solution.
[g] A narrow metastable zone signifies that only a low supersaturation has to be achieved before precipitation occurs. Grading was assigned based on comparison of the few available data: +++ = narrowest, ++ = very narrow, + = relatively narrow, − = relatively wide.
[h] A wide metastable zone signifies that high supersaturation might be achieved before simultaneous precipitation occurs, encouraging the production of an amorphous product. Grading was assigned based on comparison of the few available data: +++ = widest, ++ = quite wide, − = relatively narrow, −−− = narrowest.
[i] Powder: the product could be a powder, but a sticky paste or even syrup could be recovered. Amorphous: if a powder is produced it is expected to be amorphous or crystalline.

Table 3
Details of the process conditions used to prepare samples used in the determination of the stability and residual water content of amorphous sugars processed by SCF-drying

Conditions	Solute concentration % (w/w)	Flow rates (g/min)		
		CO_2	Ethanol	Solution
Standard	10	420	20	0.50
Low CO_2	10	250	20	0.50
Low solution	10	420	20	0.25
No ethanol	10	420	0	0.25
High ethanol	10	420	40	0.50
High concentration	35	420	20	0.25

flow rates and solution concentration – and the second one involves the mixing of different sugars.

3.2.1. Effect of process conditions on the powder properties

The results of the investigation on the effect of the solution concentration and process flow rates (Table 3) – CO_2, ethanol and solution – are summarised in Table 4. Conditions that led to the production of protein microspheres – standard conditions (420 g/min CO_2, 20 g/min ethanol and 0.5 g/min solution) – in a previous study [32] were selected as standard conditions for comparison purposes. Powders of lactose, maltose, trehalose and raffinose were produced from these conditions, but a paste of sucrose was recovered. Crystalline or partially amorphous sucrose powders could however be produced when increasing the ethanol flow rate, decreasing the CO_2 flow rate, lowering the solution flow rate or increasing the solute concentration. Contrary to sucrose, trehalose powders could be produced even when no ethanol was added to the SC-CO_2. Powders of sugars other than sucrose had characteristics similar to those of trehalose powders (i.e., handling properties, appearance, etc.), irrespective of the process conditions.

XRPD profiles of amorphous trehalose powders produced by SCF-drying and freeze-drying are given in

Table 4
Stability and residual water content of amorphous sugars processed by SCF-drying

Sugar	Process conditions	Aging stability[a]		Residual water content (%)	Hygroscopicity[b]		T_g (°C)[c] (measured)
		Temperature (°C): 4-room-40-50	Appearance at 50 °C		Sorption	Appearance at 78% RH	
Lactose	Standard	AAAA	Powder	5.5	+/−	Paste	43
	Low CO_2	AAAA	Powder	1.8	+/−	Paste	44
	Low solution	AAAA	Powder	2.2	+	Paste	51
Maltose	Standard	AAAA	Powder	3.9	+/−	Paste	32
	Low CO_2	AAAA	Melt	1.6	+	Melt	47
	Low solution	AAAA	Powder	2.3	+	Cake	47
	High concentration	AAAA	Powder	1.6	+	Melt	54
Sucrose	Standard	—-	n/a	n/a	n/a	n/a	n/a
	Low CO_2	C—	n/a	3.4	n/a	n/a	n/a
	High ethanol	C–C	Powder	0.1	n/a	n/a	n/a
	Low solution	A+C–C	Powder	3.0	n/a	n/a	15
	High concentration	A+C–C	Powder	1.5	n/a	n/a	13
Trehalose	Standard	AAAA	Powder	5.9	−	Cake	38
	Low CO_2	AAAA	Powder	2.5	+/−	Paste	42
	High ethanol	AAAC	Powder	0.6	+++	Paste	27
	Low solution	AAAA	Powder	3.8	+/−	Paste	66
	High concentration	AAAC	~Cake	1.5	+	Cake	40
	No ethanol	A—	n/a	3.3	n/a	n/a	41
Raffinose	Standard	AAAA	Powder	3.7	+/−	Melt	31
	Low CO_2	AAAA	Powder	2.4	+	Paste	30
	High ethanol	AAAA	Powder	0.4	+++	Melt	24
	Low solution	AAAA	Powder	2.6	+/−	Melt	43
Cyclodextrin	Low CO_2	AAAA	Powder	2.0	+	~Cake	262
Dextran, LMW	Low CO_2	AAAA	Powder	4.8	+/−	~Cake	120
Inulin	Low CO_2	AAAA	Powder	7.0	−	Paste	128

[a] The stability of the powder was verified by its crystallinity after aging for 12 weeks at 4 °C, 12 weeks at room temperature, 10 days at 40 °C and 5 days at 50 °C. A, amorphous; C, crystalline; A+C, amorphous–crystalline mixture; -, not measured. The appearance of the product after aging at 50 °C for 5 days is noted.

[b] The hygroscopicity is indicatively expressed as a − to +++ scale. −, around 2-fold increase of residual water content; +/−, 2- to 3-fold increase; +, 4- to 10-fold increase; +++, more than 10-fold increase; n/a, not available. The appearance of the product after 2 h of exposition to 78% RH is also given. ~Cake, slight caking; cake, caked product could be broken down to powder during handling; paste, spongy and sticky cake; melt, powder turned into a single drop-like mass.

[c] n/a, not applicable.

Fig. 4. Comparable characteristic amorphous profiles were also obtained with the other compounds studied (not shown). The similarity between the XRPD patterns of amorphous powders produced by different techniques indicates that a similar amorphous phase was produced by different ways. The slight distortion of the scans could not be explained by some degree of crystallinity. However, the presence of residual compounds or nano-pores could cause deviations in the shape of the XRPD profiles.

Whereas sucrose was crystalline, all other sugars and polysaccharides remained amorphous for at least 12 weeks of storage at 4 °C or at room temperature, or for 10 days at 40 °C. Also, most remained amorphous when exposed to 50 °C for 5 days, except two sets of process conditions used with trehalose (Table 4).

Table 4 shows that the residual water content in the powder was reduced when increasing the ethanol ratio in the SCF phase. The ethanol ratio in the SCF phase was increased by either increasing the ethanol flow rate or decreasing the CO_2 flow rate (Table 3). These manipulations of the process parameters favour a higher solubility of the water in the SCF phase, and consequently result in a lower residual water content in the powder. Reducing the CO_2 flow rate to increase the ethanol fraction in the SCF phase could however affect the quality of the spray resulting in the production of larger droplets, and at the limit hinder the production of powder because of the unfavourable surface area of the droplets limiting the mass transfer.

The given hygroscopicities of the powders (Table 4) are only qualitative as we determined an order of magnitude of the water uptake by the powder just after production and described its effect on the powder appearance. Therefore, the water content of the powder was not constant before exposure to various humidity levels. It remains that a trend between the process conditions leading to a higher residual ethanol content in the powder and a higher hygroscopicity can be discerned. The exposure of the powders to 32% relative humidity (40 °C) for 2 h left their appearance untouched. However, the only powders that were resistant to the exposure to 78% relative humidity (40 °C) for 2 h were the cyclodextrin and LMW dextran, which were only slightly caked. Inulin, the other polysaccharide investigated, turned into a paste. Lactose samples were paste-like and most raffinose powders deliquesced, even though the water sorption for both of these sugars was comparable. Maltose and trehalose showed various deliquescence levels. Overall, maltose was more sensitive to deliquescence than trehalose, which correlates well with the higher water sorption measured for maltose. No trends were observed between the number of water molecules entering in the formation of the hydrate form and the resistance to deliquescence. If comparing compounds with similar solubility, raffinose which forms into pentahydrate was more sensible than lactose that will form a monohydrate. Conversely, trehalose which can crystallise as dihydrate was less sensitive than the monohydrate forming maltose. No clear trends between deliquescence and the process conditions could be identified, except that the "high ethanol" conditions resulted in the most severe effect on the powder of a specific sugar (i.e., trehalose and raffinose).

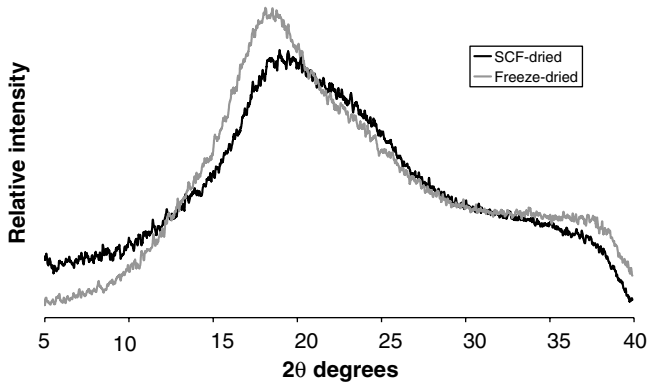

Fig. 4. XRPD profiles of trehalose powders obtained through SCF-drying (black) and freeze-drying (grey).

Depending on the process conditions, a mixture of amorphous and crystalline sucrose was sometimes produced, but crystallisation was completed within a few hours. Possibly an amorphous product was first precipitated, but its T_g was so low that crystallisation started during or soon after processing. Another explanation could be that nuclei were produced during drying initiating the crystallisation. Compared to trehalose aqueous solutions, the self diffusion of water through a sucrose matrix is slower [29]. This, combined with the high viscosity of saturated sucrose solution, could result in a high residual water content during processing, favouring crystallisation.

The appearance of the powders after aging at 50 °C was registered for interpretation of the DSC as the behaviour of SCF and freeze-dried sugars differed during measurements (e.g, freeze-dried trehalose melted in the hermetically closed pan while SCF-dried trehalose foamed, and could even partially seep out of the pan). Furthermore, the simultaneous occurrence of heat flow related processes (e.g., T_g, evaporation of solvents, crystallisation, etc.) might preclude accurate interpretation of the DSC scans. The T_g measured (Table 4) were ~40 °C below the calculated value with Gordon–Taylor equation [33] considering the residual water content [34]. It is also suspected that the measured T_g are underestimated as 7 and 21 samples had T_g's below 40 and 50 °C, respectively, but none of the samples crystallised during these stability studies. Furthermore, the appearance of only two samples changed during aging at 50 °C (Table 4). The stability studies might have been too short to observe crystallisation from an amorphous powder. However, in presence of nuclei, crystallisation would have been expected to occur very rapidly [35]. As the T_g measured did not correlate with the T_g predicted, the potential residual ethanol and CO_2 entrapped in the powder will be further investigated in Section 3.3.

Overall, the characteristics of the powders were only slightly modified by the process conditions; the residual

water content being the main parameter affected. The main effect of the modification of the process conditions was to identify conditions to prepare sucrose in powder form. Such conditions could also be applicable to other compounds that are more difficult to precipitate.

3.2.2. Effect of carbohydrate mixtures on the physical stability of the powders

The investigations of carbohydrate mixtures focused on sucrose, trehalose, raffinose and maltose. Raffinose is known to affect the crystallisation of sucrose from aqueous solution [36]. Furthermore, trehalose and raffinose inhibited the crystallisation of amorphous sucrose [37,38]. Maltose has been investigated solely because it has many similarities with trehalose: hydrate forming, same molecular weight, similar solubility and T_g. Finally, a mannitol–sorbitol mixture was processed to verify if the presence of nuclei could be sufficient to trigger the precipitation of a compound that did not precipitate by itself during SCF-drying.

All sugar mixtures remained amorphous through aging, even sucrose and trehalose mixtures prepared in a ratio of 6:1 (Table 5). It was therefore possible to measure a T_g for sucrose-containing mixtures. These T_g's (14–36 °C) were always below the process temperature (37 °C) and could explain that the pure sucrose was always at least partially crystalline directly after processing. In the case of maltose, two T_g's were measured. This could be the result of a phase separation between the two sugars. The residual water content was usually around 2%.

Powder was retrieved from the mixture of mannitol–sorbitol (Table 5), whereas syrup was recovered when sorbitol was used by itself (Table 1). The powder was partially amorphous and partially crystalline. The rapid crystallisation of mannitol, because of its low solubility and its low supersaturation concentration [31], could have supplied the seeds to encourage the precipitation of sorbitol.

3.3. Residual solvent composition and process improvement

3.3.1. Residual compounds in the powder

Except for polysaccharides, the residual water content was less than 4%, and below 2% in many occasions (Tables 4 and 5). The measured residual water contents seemed too low to solely justify the underestimated 40 °C theoretical T_g of sugars calculated using the Gordon–Taylor equation [33,34]. One potential reason for this discrepancy is that not only water was left in the product, but also ethanol and CO_2.

For analysis of residuals by TGA-FTIR, the powder sample was heated in the TGA where its mass was monitored. The gas released by the heating process was continuously analysed in-line by FTIR. By combining both techniques (Figs. 5–7), the weight loss of the sample could be related to the evaporation of one of the residual compounds (ethanol, CO_2 or water). The TGA scan shows sharp changes in slope (Fig. 5), indicating the release of different residual compounds. The overall intensity of the FTIR signal (Fig. 6) remained low until ~75 °C (11.5 min). Two waves of release were then detected from 11.5 min (~75 °C) to 15.5 min (~95 °C). After 20.5 min (~120 °C) the intensity of the FTIR signal went back down to almost background level. The individual FTIR profiles (Fig. 7) were used to identify the compounds released at each step detected by TGA.

The residual content of other sugars was also investigated by TGA-FTIR at least 4 months after their preparation to minimise the CO_2 amount left in the powder (Table 6). Only water was detected in sucrose and polysaccharide powders. Similar ethanol and water residual releases were observed for trehalose, lactose, maltose and raffinose. TGA-FTIR results (not shown) showed that the residual water content measured by KF (Table 6) was released from the powder below a temperature of 70–75 °C. The weight loss (Fig. 5) measured during that first stage was 1.5–2.5% which could comprise some CO_2 as slight fluctuations of the characteristic FTIR CO_2 peaks (2340 and

Table 5
Stability and residual water content of amorphous sugar mixtures processed by SCF-drying

Sugar	Concentration % (w/w)	Flow rates (g/min)			Crystalline/amorphous[a] (4-room-40-50)	T_g (°C)[b]	Residual water content % (w/w)
		CO_2	Ethanol	Solution			
Sucrose:Trehalose 1:1	10	250	20	0.5	AAAA	23	2.4
Sucrose:Trehalose 1:1	10	420	20	0.25	AAAA	19–30	2.0–4.1
Sucrose:Trehalose 1:1	35	420	20	0.25	AAAA	19–34	2.3
Sucrose:Trehalose 6:1	10	420	20	0.25	AAAA	14	2.2
Sucrose:Trehalose 1:6	10	420	20	0.25	AAAA	45	2.4
Sucrose:Maltose 1:1	10	420	20	0.25	AAAA	14 & 82	0.6
Trehalose:Maltose 1:1	10	420	20	0.25	AAAA	45 & 87	1.2
Sucrose:Raffinose 6:1	10	420	20	0.25	AAAA	31–36	1.7
Trehalose:Raffinose 6:1	10	420	20	0.25	AAAA	50	2.8
Mannitol:Sorbitol 1:1	10	420	20	0.25	A+C—	n/a	2.0

[a] The stability of the powder was verified by its crystallinity after aging for 12 weeks at 4 °C, 12 weeks at room temperature, 10 days at 40 °C and 5 days at 50 °C. A, amorphous; C, crystalline; A+C, mixture of amorphous and crystalline phases; -, not measured.
[b] &, two T_g's were identified; n/a, not available.

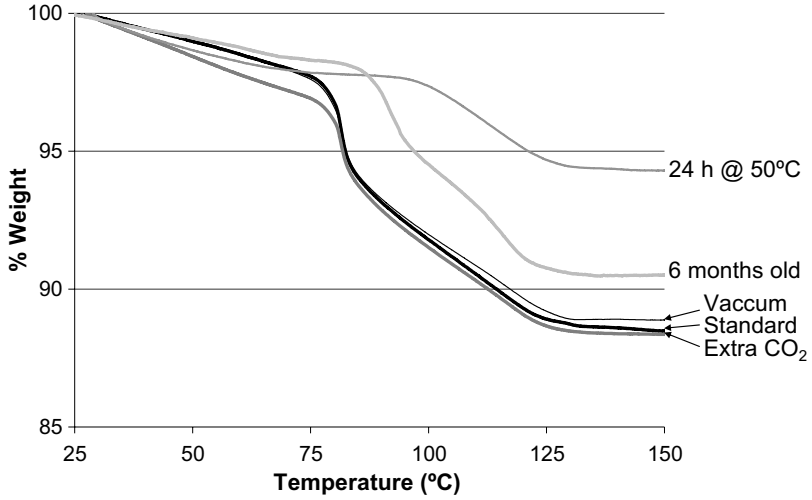

Fig. 5. TGA of trehalose processed by SCF-drying after post-treatment and aging. Standard (thick black line): process conditions used during screening; post-treatments: extra CO_2 (thick dark grey line): the double amount of CO_2 was used to flush the product after precipitation, vacuum (thin black line): the powder was under vacuum at room temperature for 30 min, 24 h @ 50 °C (medium weight medium grey line): the powder was in an oven at 50 °C for 24 h; aging: 6 months (thick light grey line): sample produced the standard process conditions used during screening and aged for 6 months at room temperature.

2370 cm^{-1}) (Fig. 6) were observed. At a temperature of 70–75 °C, ethanol was finally released (peaks at 910, 1030, 1260, 1410, 2930 and 3000 cm^{-1}). Independently of the sample, the ethanol extraction occurred in two waves (Fig. 6, inset). The first wave was completed at 95–120 °C and corresponded to 5–5.5% of the initial weight of powder (2.5% in the case of raffinose). The second wave stretched until 130–135 °C and resulted in another 0.5–2% weight loss (4% in the case of raffinose). The total ethanol content of these powders varied between 6.0% and 7.5%, and no clear sugar specific trend could be identified.

Significant amounts of CO_2 were released in combination with water until 65–70 °C, and with ethanol until 80–85 °C when analysing fresh powders (Fig. 6). The quan-

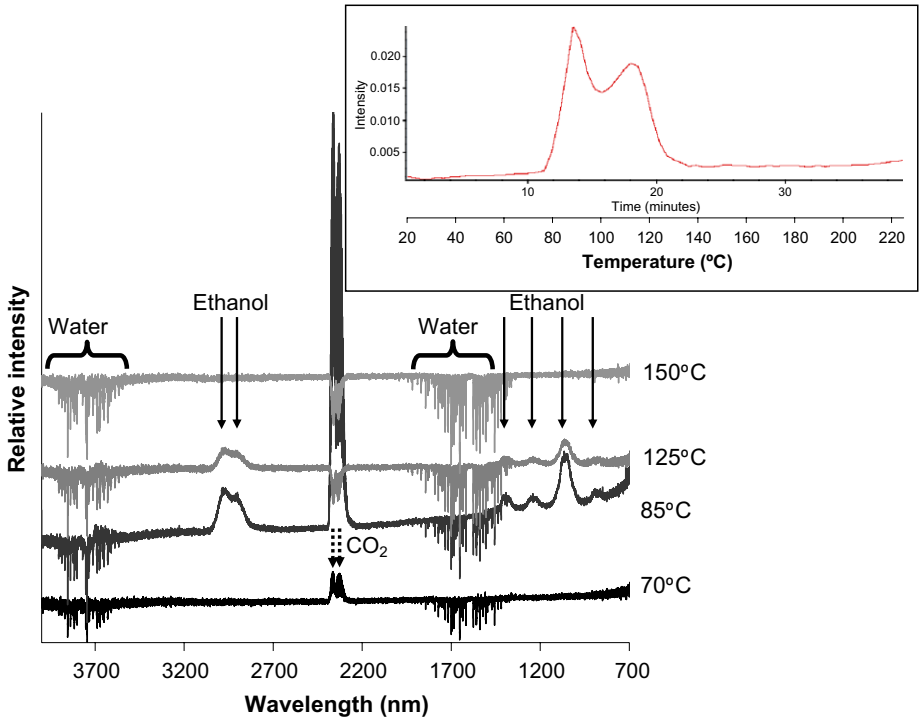

Fig. 6. FTIR of released residual ethanol and CO_2 during TGA analysis of trehalose. The depicted results were (from bottom to top) from measurements at 70 °C: CO_2, 85 °C: CO_2 and ethanol, 125 °C: ethanol and 150 °C: CO_2 and ethanol free. Characteristic peaks are indicated with straight line arrows for ethanol, dotted arrows for CO_2 and braces for water. Inset: total intensity of FTIR signal during TGA of SCF-dried trehalose with the standard process conditions showing the two waves of ethanol release.

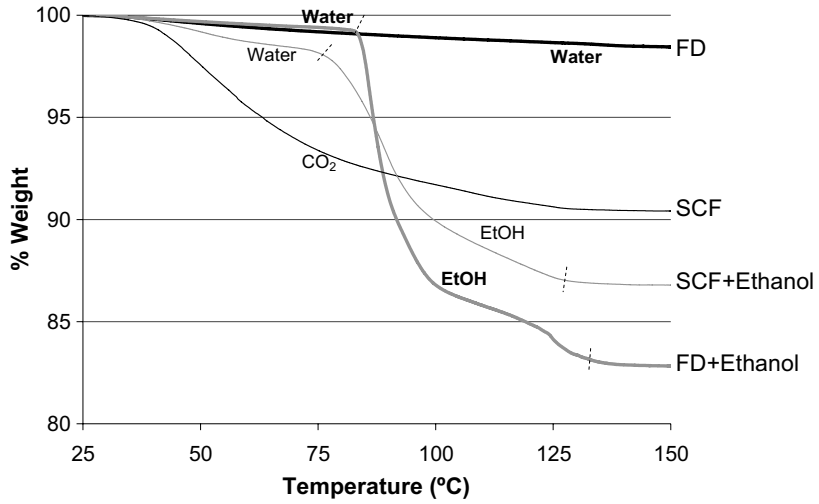

Fig. 7. TGA of freeze-dried (FD) or SCF-dried (SCF) trehalose with or without the use of ethanol. Freeze-drying from aqueous solution: thick black line; freeze-drying from aqueous-ethanol solution: thick grey line; SCF-drying from aqueous solution: thin black line; SCF-drying from aqueous solution using SC-CO_2 enriched with ethanol: thin grey line. The compounds detected by FTIR are noted. The dashed lines indicate the limits of the range of temperatures during which the evaporation of prominently one compound (water, CO_2 or ethanol (EtOH)) occurs.

tity of CO_2 entrapped in powder was estimated ~2% by analysing the total residual content by TGA-FTIR, the ethanol content by GC and water content by KF.

From the analysis of the residual solvents in the powders, it appears that both water and CO_2 can diffuse out of the amorphous di/trisaccharide powders more easily than the ethanol. Amorphous powders of polysaccharides were ethanol free.

3.3.2. Comparison with freeze-drying

For comparison, the TGA-FTIR analysis was also performed on freeze-dried trehalose from aqueous solution (Fig. 7). In that case, the water signal was much clearer than the one detected from SCF-dried samples and extended until 160 °C, even though the amount of water measured by KF was only 1.5%. As the energy input required for extracting the water from the freeze-dried powder is higher than the SCF-dried powder, we can suspect that the structure of the amorphous powder is different.

Sucrose, trehalose, raffinose and cyclodextrin were also freeze-dried from aqueous solutions containing 50% ethanol (w/w). This was performed to mimic the variation in solution composition during SCF-drying as ethanol condenses on the aqueous droplet [39]. The XRPD probed crystallinity of the freeze-dried and SCF-dried products was in line: sucrose was crystalline with both techniques, while trehalose, raffinose and cyclodextrin were amorphous. Sucrose has shown to be extremely prone to crystallisation. It is unclear if the cause of the crystallinity is the more rapid crystallisation of sucrose compared to the other sugars or if ethanol has a larger influence on the crystallisation of sucrose. It remains that appropriate conditions must be met to produce stable sucrose in its amorphous state.

Table 6
Residual % (w/w) water (KF) and ethanol (TGA-FTIR) of SCF-dried sugars and polysaccharides measured after >4 months storage

Sugars/polysaccharides	% water	% ethanol		% total ethanol
		1st wave	2nd wave	
Lactose	2.5	5.0	1.0	6.0
Maltose	1.5	5.5	0.5	6.0
Raffinose	2.0	2.5	4.0	6.5
Sucrose	<1.0	0	0	0
Trehalose	2.0	5.5	2.0	7.5
Cyclodextrin	6.0	0	0	0
Dextran, LMW	6.0	0	0	0
Inulin	4.0	0	0	0

The residual ethanol content after freeze-drying was 5.5% for sucrose, 13.6% for trehalose, 9.3% for raffinose and below the detection limit for cyclodextrin. These values of residual ethanol are higher than those of SCF-dried sugars. Thus the presence of ethanol in samples prepared by SCF-drying is not process specific. It is suspected that the sugars might have a certain affinity for the ethanol or that the diffusion of ethanol from the amorphous sugar is constrained by the amorphous matrix. As solidification of amorphous matrices of macromolecules is expected to occur at a higher water content, the porosity of the matrix should be higher allowing water as well as ethanol and CO_2 to diffuse out more easily.

3.3.3. Minimising the residual ethanol content

3.3.3.1. Post-treatment strategy. The force of the release of the residual ethanol from SCF-dried trehalose (9.5% (w/w) ethanol) was attempted by doubling the CO_2 flushing period after the spraying process (9.4% (w/w) ethanol) or putting the powder under vacuum for 30 min (9.0% (w/w) ethanol), but it had no significant effect (Fig. 6). However, exposing the powder to 50 °C for 24 h at atmospheric pres-

sure resulted in the loss of about 50% of the residual ethanol (3.0% (w/w) ethanol). Aging a sample for 6 months at room temperature caused a decrease of 20% of its residual ethanol (i.e., from 9.5% to 7.5% residual ethanol, Fig. 6). From these results, it is clear that once present in the amorphous matrix, ethanol was difficult to remove.

The slow release of CO_2 and especially ethanol can be related to their molecular size. It was shown by Rampp et al. [29] that a deeply supercooled solution (e.g., amorphous phase) of carbohydrates may form a rigid three-dimensional hydrogen-bonded network through which water molecules can still diffuse. Similarly, the pores of rigid hydrogen-bonded network of the SCF-dried sugars might be just large enough to let water diffuse out of the matrix, but small enough to keep the larger ethanol molecules entrapped, whereas the CO_2 molecules slowly diffuse out of the porous structure.

3.3.3.2. Ethanol utilisation strategy. Trehalose was also used in a series of experiments where the modifier, ethanol, was added directly to the aqueous solution instead of the SCF-phase. When adding ethanol to the sugar solution (50% w/w), and not to the SCF-phase, the residual ethanol content of the powder fell below the detection level. However, when ethanol was also added to the SCF-phase, the residual ethanol level was similar to what was measured when no ethanol was added to the aqueous phase. The direction of the mass transfer during SCF-drying and the porosity of the particles could explain the absence of residual ethanol in the product.

3.3.3.3. Recommendations. The residual ethanol is of major concern as it might not be acceptable for some applications like formulations containing labile pharmaceutical proteins. Further investigation is required to understand the affinity of ethanol for the sugar matrices, and to control its release from the powder. Correlations between the crystallisation, the low T_g measured and the ethanol fraction also require closer consideration. Various options could also be assessed to resolve the issue of the residual ethanol content such as the use of other organic solvents with a higher affinity for CO_2 than for water, adjust the process conditions such that the use of an organic modifier is not required, or prepare porous matrices allowing the efficient release of the ethanol.

4. Conclusions and recommendations

The production of relatively stable amorphous sugar matrices is possible by SCF-drying. A wide metastable zone, a solubility of 10–50% (w/w) in water at the process temperature, low viscosity of both the aqueous solution being sprayed and the saturated solution, and high T_g is a combination that is expected to lead to the production of amorphous powder.

Trehalose, maltose, raffinose, lactose, cyclodextrin, LMW dextran and inulin showed good powder formation and stability properties. The combination of carbohydrates was a useful strategy to avoid the crystallisation of amorphous powders, even for easily crystallisable sucrose. Furthermore, the use of mixtures could allow the production of powders of compounds that have shown not to precipitate under standard SCF-drying conditions.

The process conditions should be selected in such a way that the water can be completely extracted by the SCF phase, meaning that the proportion between the streams should at least be within the complete miscibility zone of the CO_2–ethanol–water system. Polysaccharide powders were free of residual ethanol. To produce ethanol free powders of other sugars, ethanol could be added to the aqueous solution instead of the SC-CO_2.

A number of analytical techniques were used to characterise the powder and to determine the stability of the amorphous product. According to these analyses, the production of an amorphous stable product appears possible by SCF-drying. The use of techniques, such as solid nuclear magnetic resonance or differential vapour sorption, could be helpful in the characterisation of the product, but also in gaining a better understanding of the SCF-drying by giving a better insight of the particle formation process. The affinity between the sugars and the ethanol should also be determined to better define the reason of the high residual ethanol content in some powders.

Acknowledgements

The authors thank Paul Durville, Michel van de Brink and Duco Bosma (Process & Energy, Delft University of Technology) for making the SEM pictures and TGA analysis, Mies van Steenbergen (Pharmaceutics, Utrecht University) for the freeze-drying, and Berenguer Batllori Casanovas and Fager Kamalizadeh (Process & Energy, Delft University of Technology) for the SCF-drying. This research was supported by the Technology Foundation STW, applied science division of NWO and the technology programme of the Ministry of Economic Affairs.

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