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Enhancements in Spray-Dried Powder Functionality,
Using Multistage Fluidized-Bed Drying and a New Templating Process

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

by
Morteza Saffari

Supervisor: Prof. Timothy Langrish

April 2016

The University of Sydney
School of Chemical and Biomolecular Engineering
Declaration

This thesis is a presentation of my original research work. Wherever contributions of others are involved, every effort is made to indicate this clearly, with due reference to the literature, and acknowledgement of collaborative research and discussions. The work was done under the guidance of Professor Timothy Langrish, at the University of Sydney, Australia.

Morteza Saffari
April, 2016.
SUMMARY

Spray drying is a technique that is widely applied to produce dry powders from their liquid or slurry states in the food and pharmaceutical industries. Due to the rapid removal of water in this technique, amorphous solids may be formed. Spray-dried forms of dairy powders may have several advantages, such as greater solubility, dissolution rates and surface areas. However, their molecular structures are relatively disordered, and they are thermodynamically-unstable solids, which may undergo undesirable changes, such as caking after production.

To overcome this problem, a fluidized-bed dryer has been used in this study to improve the degree of lactose crystallinity of sweet whey. Powder was fed at different rates for each fluidization process at different sets of process temperature, humidity, and residence time. It has been found that, with controlling the operating conditions in a continuous multi-stage fluidized bed dryer, whey powders can have different degrees of lactose crystallinity between 10% and 20% with reasonable overall processing times of 30 minutes. Gravimetric moisture sorption tests were performed on the degree of lactose crystallinity for the spray-dried powders and the processed powders and compared with X-ray powder diffraction, Fourier transform infrared spectroscopy, and Raman spectroscopy analyses. Experimental results using all these methods confirm that that there were significant reductions in the amorphicity of lactose at different humidities and temperatures and suggested that the overall extent of lactose crystallinity for processed whey powders has been between 10% and 20% within the processes studied.

However, crystalline powders may have some undesirable properties, such as lower dissolution rates. The creation of highly-porous crystalline powders with better functional (free flowing), and storage (non-caking) properties, would be helpful in the food industry and for pharmaceutical formulations, especially for controlled drug delivery and release applications. Thus, a new templating method has been developed to create spray-dried powders with high porosity and controlled characteristics, while maintaining the high stability of a highly crystalline powder. In this technique, solutions containing core materials such as lactose/mannitol and ethanol-soluble food-grade acids as templating agents were spray dried. The resulting powders were then washed with ethanol to remove the templating agent and produce porous frameworks of lactose/mannitol. There were significant improvements in the surface areas, from $0.3 \pm 0.2 \text{ m}^2 \text{ g}^{-1}$ (for conventional spray-dried
lactose) to 21.5 ± 0.5 m² g⁻¹. The typical specific surface areas of mannitol powders have been reported to be 0.3 m² g⁻¹ (Babu and Nangia, 2011; Ho et al., 2012) and this templating method resulted in a mannitol network with significant porosity and a high surface area of 10.5 ± 0.5 m² g⁻¹.

It has been found that altering the concentration of templating acids was very effective in changing the degrees of lactose crystallinity in the spray-dried products and the Brunauer, Emmett and Teller (BET) surface areas of the resultant porous materials. Therefore, the effect of different acids with various acidity indices, such as boric acid, ascorbic acid, and lactic acid, has been studied on the crystallinity of the spray-dried powder, on the process yield, and the templating performance of these acids in the production of high-porosity lactose particles. The results of present study suggested that there was a link between the extent of lactose crystallization in the spray-dried powders and the BET surface areas for the ethanol-washed particles. Increasing the degree of crystallinity for the spray-dried powders at high acid concentrations decreased the amounts of acid molecules incorporated in the lactose structure, leading to lower BET surface areas.

It was found that increasing the templating-acid concentrations significantly increased the degrees of crystallinity for lactose in spray-dried powders. Textural properties, such as the surface area of the resultant lactose, decreased considerably by increasing the concentrations of different templating acids, due to increase in the lactose crystallinity for the final spray-dried products. The yields from spray drying were also decreased significantly at higher concentrations of templating acids. For instance, when using lactic acid as a templating acid a change in lactic acid concentration from 1 w/w % to 3 w/w % showed a reduction in the surface areas from 14.9 ± 0.9 m² g⁻¹ to about 9.5 ± 0.8 m² g⁻¹ and the yield of the spray-drying process altered from 71% ± 2% to about 44% ± 1%. Likewise, in the case of using citric acid as a templating acid, it was observed that adding 1% w/w citric acid as a templating material significantly increased the BET surface area of lactose to 20.8 ± 0.9 m² g⁻¹. However, adding further citric acid content (3 w/w%) decreased the BET surface area of lactose to 12.3 ± 0.8 m² g⁻¹ and the yield of the process significantly decreased from 71% ± 2% to 16% ± 4%. The results suggested that using templating acids, with lower glass-transition temperatures than that for lactose, decreased the overall glass-transition temperature of the spray-dried mixture according to the Gordon–Taylor equation. Lower glass-transition temperatures increase the temperature difference (\(T-T_g\)), which in turn decreases the crystallization time as suggested
by the Williams–Landel–Ferry equation, leading to higher degrees of lactose crystallinity for
the spray-dried particles. Therefore, the porosities and the BET surface areas of the powders
decreased as the amorphous content decreased, which is connected with the decrease in the
amount of incorporated templating-acid molecules, due to the increase in the degree of
crystallinity for the spray-dried lactose powders. However, the main reason for this yield
behavior is due to having lower glass-transition temperatures in the powders and also greater
product moisture contents at higher templating-acid concentrations, which make the particles
stickier. The optimum concentration of lactic acid, citric acid, and ascorbic acid were found
to be 1 w/w % with the BET surface area of 14.9 ± 0.9 m² g⁻¹, 20.8 ± 0.9 m² g⁻¹, and 10.5 ±
0.6 m² g⁻¹, respectively while that for the spray-dried lactose with boric acid as a templating
agent was 3 w/w % with the BET surface area of 18.5 ± 0.8 m² g⁻¹.

These engineered particles were then used as porous excipients in an adsorption technique to
evaluate the potential of this technique for improvement of the dissolution characteristics of
poorly water-soluble drugs and for content uniformity enhancement by incorporating the drug
molecules onto this porous structure. Indomethacin, nifedipine, and acetaminophen as model
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<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>BET</td>
<td>Brunauer, Emmett and Teller</td>
</tr>
<tr>
<td>BJH</td>
<td>Barrett-Joyner-Halenda</td>
</tr>
<tr>
<td>DIAL</td>
<td>Dairy Innovation Australia Limited</td>
</tr>
<tr>
<td>DSC</td>
<td>Differential Scanning Calorimetry</td>
</tr>
<tr>
<td>FB</td>
<td>Fluidized Bed</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier Transform Infrared spectroscopy</td>
</tr>
<tr>
<td>LSD</td>
<td>Least Significant Difference</td>
</tr>
<tr>
<td>MDSC</td>
<td>Modulated Differential Scanning Calorimetry</td>
</tr>
<tr>
<td>RSD</td>
<td>Relative Standard Deviation</td>
</tr>
<tr>
<td>SGF</td>
<td>Simulated Gastric Fluid</td>
</tr>
<tr>
<td>STD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>WLF</td>
<td>Williams–Landel–Ferry</td>
</tr>
<tr>
<td>WP</td>
<td>Whey Powder</td>
</tr>
<tr>
<td>WPI</td>
<td>Whey Protein Isolate</td>
</tr>
<tr>
<td>XRD</td>
<td>X-Ray Diffraction</td>
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LIST OF PUBLICATIONS

The following publications and conference papers were published from content of the work presented in this thesis at the time of submission of this thesis.

From work described in Chapter 4:

Significant results from chapter 4 were presented in the *5th Annual Student Research Conference*: Implementation of Crystallization in Fluidized Bed Processing. Faculty of Engineering and IT, The University of Sydney. October, 2013 (Poster presentation).

From work described in Chapter 5:


From work described in Chapter 6:


From work described in Chapter 7:

From work described in Chapter 8:


From work described in Chapter 9:

CHAPTER 1  INTRODUCTION

1.1  Spray Drying

Spray drying is a low-cost and high-throughput continuous drying technique. It is among a wide variety of drying operations that are applied to produce stable low moisture-content products, which reduce costs for storage and transportation from their liquid or slurry states in the food and pharmaceutical industries (Morgan and Vesey, 2009; Sollohub and Cal, 2010). The rapid removal of water from solutions by this technique, during drying, does not allow sufficient time for full crystallization to occur for most materials and causes the formation of amorphous, thermodynamically-unstable solids (Roos and Karel, 1991; Hogan and O'Callaghan, 2010). This situation may lead to an increased rate of physicochemical changes in dried products, such as sticking, collapse, caking, agglomeration and crystallization (Bhandari and Howes, 1999). The stickiness phenomenon in spray drying, and the caking phenomenon in storage, are associated with the presence of high sugar and food acid concentrations in the product (Bhandari et al., 1997b), which can cause problems for food powders and related substances.

1.2  Enhancements in Spray-Dried Powder Functionality

Processing of spray-dried powder into marketable attractive final products faces major economical obstacles. The main constituents of dairy powders are carbohydrates, proteins, water, and fat. Among the different ingredients of milk powders, amorphous lactose is one of the most hygroscopic and unstable materials. Different operating conditions can be used to obtain different extents of crystallinity in various processes to reduce the hygroscopic nature of lactose in dairy powders by converting a portion of the lactose to the more stable crystalline components, such as pre-crystallization and “in-process” crystallization steps before and within spray drying, respectively and post process crystallization in fluidized-bed drying, which is a controlled process to transform amorphous-lactose fraction to a crystalline form rapidly as compared with the rate in storage (Bhandari et al., 1997b; Nijdam et al., 2008; Hogan and O'Callaghan, 2010; Islam et al., 2010; Yazdanpanah and Langrish, 2011a).
Due to this controlled process, more stable powder products can be produced, but crystalline powders may have some undesirable properties, such as lower dissolution rates.

The creation of highly-porous crystalline powder with better functional (free flowing), and storage (non-caking) properties would be helpful in the food industry and pharmaceutical applications. Thus, a new spray-drying process has been developed with post-drying treatment to create powder structures with significant porosities and high surface areas, while maintaining the high stability of a highly crystalline powder.

1.3 Application of New Engineered Particles with High Porosities and Controlled Characteristics

Pharmaceutical dosage forms that include tablets and capsules are some of the most popular and commonly-employed methods of drug delivery, which currently account for over two-thirds of the total number of medicines produced in the world (Zheng, 2009; Sahoo, 2012). Their final formulation contains both active pharmaceutical ingredient (API) and excipients added to aid the formulation and manufacture of the subsequent dosage form for administration to patients (Rowe et al., 2003). Different types of sugars such as lactose, mannitol, sorbitol, and dextrin and inorganic compounds, such as silica and calcium carbonate are commonly used as excipients to provide inert or inactive ingredients (Rowe et al., 2003; Millqvist-Fureby et al., 2014). However, this reason for using excipients has undergone changes due to the needs for controlled properties of the final dosage form such as bioavailability and stability and growth of novel forms of delivery (Rowe et al., 2009).

For instance, major challenges facing the design of oral dosage forms are their poor bioavailability and uniformity of drug dosage (Garcia and Prescott, 2008; Huang and Sherry Ku, 2010; Grigorov et al., 2013) and poor solubility is one of the main causes of low bioavailability (Schreiner et al., 2005; Savjani et al., 2012). More than 40% of newly developed drugs in the pharmaceutical industry are poorly water-soluble, which may cause a range of medication control problems, such as insufficient dosing (Liu, 2008; Jain et al., 2012). Formulation and dosage-form design problems of poorly water soluble drugs must be addressed to better meet the needs of users and the targeted product requirements, such as clinically acceptable performance.
One potential approach to solve the abovementioned challenges for better control of the drug release characteristics is loading or nano-confinement of drugs into porous excipients as hosts (Salonen et al., 2005a; Qu et al., 2006; Xia and Chang, 2006; Prestidge et al., 2007). Mesoporous silica is of specific interest as excipients for these drug-loading methods due to its high specific area and large pore volume (Millqvist-Fureby et al., 2014).

Mesoporous silica is expensive and has low water solubility (Millqvist-Fureby et al., 2014) and therefore other porous excipients, such as mannitol with its high water solubility (216 g/l; Ohrem et al., 2014), may be potential carriers for controlled-release systems of poorly water-soluble drugs despite the lower specific area and smaller pore volume compared with those of mesoporous silica. It can be expected that preparing an excipient with higher surface areas and larger pore volumes, such as mesoporous silica, would result in a higher drug loading, as it provides more available pore volume in order to host the drug molecules. However, high drug loadings are not always needed and, in the formulation and manufacture of low-dose drug products, the amount of API in the solid-dosage form can be as low as 0.1 w/w % (Zheng, 2009; Grigorov et al., 2013). Moreover, major challenges facing the design of the oral dosage form, such as poor bioavailability and uniformity of drug dosage, are more pronounced for low-dose drug products, which may result in undesirable variations in dosage and (Cartilier and Moes, 1989; Garcia and Prescott, 2008; Zheng, 2009; Huang and Sherry Ku, 2010). Therefore, providing porous carriers with enough specific surface area and reasonable pore volumes for the targeted drug-loadings seems to be desirable. However, most current techniques involve producing porous inorganic particles through templating process and the key challenge is to extend this understanding of the process from inorganic materials to organic ones.

There are several drug loading methods, such as incipient wetness impregnation (Mellaerts et al., 2008; Van Speybroeck et al., 2009; Verraedt et al., 2010) and adsorption methods, in which carrier particles are immersed in drug solution and drugs can be dispersed and deposited at the surface and into the pore spaces of porous carriers (Qu et al., 2006; Xia and Chang, 2006; Heikkilä et al., 2007; Hillerström et al., 2009).

This improvement can be ascribed to several factors. First, dissolution rate improvement due to nanoconfinement of the drug molecules inside the internal void structures of nanoporous excipients. This situation results in an increase in the solubility with a reduction in the particle size of the drug, which maximizes the surface area of the compound that comes into
contact with the dissolution medium as the carrier dissolves, often resulting in significant increases in bioavailability. Second, excipients with high porosity can improve the drug release rate into the dissolution medium by enabling faster release of the drug as a result of better drug-excipient matrix permeability and penetration of solvent into the drug-excipient matrix. Moreover, greater porosity of excipients facilitates the diffusion of the API components and increases the rate of drug adsorption. Last but not least, the adsorption method is independent of the control strategy for both the particle size of the drug and excipients in the finished dosage units, so the particle size of the final formulation does not appear to have any effect on drug uniformity. The variability for the content uniformity and delivered dose may then be low. Therefore, experimental design is necessary to create new engineered frameworks with high porosity and controlled characteristics. These drug-loading processes are gaining acceptance, as shown by the rapid expansion of this field in pharmaceutical formulations, especially for controlled delivery and release applications (Salonen et al., 2005a; Xia and Chang, 2006; Heikkilä et al., 2007; Mellaerts et al., 2007; Prestidge et al., 2007; Mellaerts et al., 2008; Hillerström et al., 2009; Van Speybroeck et al., 2009; Millqvist-Fureby et al., 2014).

1.4 Thesis Structure
Chapter 2 provides some background to the solid-state crystallization process for the spray-dried form of dairy powders and also considers a controlled process using fluidized-bed dryers for crystallization of dairy powders. This chapter also reviews the previous works on templating techniques that have been applied to improve the porosity of spray-dried particles.

Chapter 3 reviews the applicable features regarding the characterization of products, such as the particle size and shape, the moisture content, the glass-transition behavior and amorphous/crystalline states, and other known issues concerning templating and drug-loading processes, such as BET surface area analysis, tablet crushing tests, UV-spectrophotometry, and in-vitro dissolution studies.

The effects of operating conditions on the crystallization properties of sweet whey powder in a continuous multi-stage fluidized bed dryer to achieve the maximum degree of crystallinity with reasonable overall processing times are described in Chapter 4. Powder was fed at
different rates for each fluidization process at various sets of process temperatures, humidities, and residence times. Gravimetric moisture sorption tests were performed on the processed powders and compared with X-ray Powder Diffraction, FTIR, and Raman spectroscopy analyses. The results show significant improvements in the crystallinity of the lactose. Experimental results showed that there were significant changes on the degree of lactose crystallinity between samples that were processed (crystallized) at different humidities and temperatures. Increasing the rate of powder feeding did not have a significant effect on the degrees of lactose crystallinity for the processed powders. The results of this study are useful for guiding the processing conditions to produce and control crystallization in carbohydrate-containing dairy powders during spray and fluidized-bed processing.

In Chapter 5, the effect of acidity on the final product properties from the spray drying of lactose solutions has been investigated. Moreover, the crystallization kinetics of lactose/protein solutions have been studied regarding their in-process crystallization characteristics during spray drying, especially when lactic acid is added to the solution to imitate the composition of a typical acid whey solution. Gravimetric moisture sorption tests have been performed on the spray-dried powders processed under these conditions and compared with X-ray powder diffraction and modulated differential scanning calorimetry (MDSC) analyses to measure the degree of lactose crystallinity. It has been found that very large changes in the degrees of lactose crystallinity for the final spray-dried product have occurred when increasing the lactic acid concentration. The yields (or solids recoveries) from spray drying have also been significantly decreased at higher concentrations of lactic acid. The results of this study have implications in choosing the processing conditions to produce and control crystallization in carbohydrate-containing dairy powders and also powders of acid-rich foods, such as fruit juices, during spray and fluidized-bed processing.

A new production process has been designed to produce highly-porous powder, and this process has been discussed in Chapters 6 and 7. This new templating process has been successfully developed to create highly-porous lactose particles with high surface areas through the spray drying of lactose solutions containing ethanol-soluble food-grade acids, such as lactic acid, citric acid, boric acid, and ascorbic acid, as templating agents, and then removing these acids by ethanol washing of the spray-dried powders. Chapter 6 also reports the effect of using different concentrations for various food-grade acids, such as lactic acid, citric acid, boric acid, and ascorbic acid, on the degree of crystallinity for spray-dried lactose
powders and the porosity of the ethanol-washed powders. One innovative aspect of this approach, which uses the insolubility of lactose in ethanol and the solubility of templating acids in ethanol as a basis, is the potential to create highly-porous templates or frameworks of lactose using relatively benign and non-toxic materials, such as food-grade acids. Another novel contribution of this work is the use of the low-cost and high-throughput spray-drying process, which is an improvement on the batch and semi-batch processes described so far. Recently, the use of mannitol as an alternative to lactose in food products and pharmaceutical formulations has significantly increased. Lactose is a reducing sugar, which is incompatible with some active pharmaceutical ingredients, such as peptides and proteins, and also has problems associated with lactose intolerance (Westermarck et al., 1998; Steckel and Bolzen, 2004; Littringer et al., 2012). Therefore, in Chapter 7, this new templating method has been developed to create highly-porous mannitol through spray drying, using citric acid as the templating agent. It has been demonstrated in Chapter 7 that textural properties, such as surface area and pore volume of the resultant mannitol, can be tuned by varying the concentrations of citric acid, whey protein isolate (WPI), and Gum Arabic.

A new adsorption method for solubility and content uniformity enhancements of poorly water-soluble drugs was developed in Chapter 8. Highly-porous excipients with high surface areas that were produced according to the templating method in Chapter 7 have been used in an adsorption method to investigate drug dissolution. This work has been done by applying an adsorption technique and modifying the current templating process described in Chapter 7. Highly-porous mannitol particles with high surface areas have been successfully produced through the spray drying of mannitol solutions containing ethanol-soluble food-grade acids, such as citric acid as a templating agent, and then removing the citric acid by ethanol washing of the spray-dried powders to create porous powders. Production of highly-porous frameworks of mannitol having unique properties, such as a significant surface area of $9.1 \pm 0.9 \text{ m}^2 \text{g}^{-1}$, and a total pore volume of $0.11 \pm 0.03 \text{ ml g}^{-1}$, which can be tuned by varying the concentrations of citric acid and WPI. These features make this material suitable as a carrier for adsorption method. However, this chapter has also investigated the possibility of using carbohydrate sugars, such as sucrose, as non-acidic templates that are commonly used as excipients in drug delivery for pharmaceutical applications. After ethanol washing, the
resultant porous particles have been transferred to ethanol solutions to dissolve and carry acetaminophen as a sample drug into the pores of porous mannitol.
CHAPTER 2   LITERATURE REVIEW

2.1  Amorphous and Crystalline Powders

The rapid removal of water from solutions in spray drying does not allow sufficient time for crystallization to occur for most materials and causes the formation of amorphous, thermodynamically-unstable solids (Roos and Karel, 1991; Hogan and O'Callaghan, 2010). Above the glass-transition temperature, an amorphous solid exists in a "rubbery" state, and the molecular mobility of the matrix and the reactants are increased. This situation may lead to an increased rate of physicochemical changes in dried products, such as sticking, collapse, caking, agglomeration and crystallization (Bhandari and Howes, 1999), which are time, temperature and moisture-dependent phenomena. The stickiness phenomenon in spray drying, and the caking phenomenon in storage, are associated with the presence of high concentrations of sugar in the product (Bhandari et al., 1997b).

2.2  Sticking and Caking Mechanism of Amorphous Lactose

Spray-dried milk powders, which are normally in amorphous states, have several advantages compared with crystalline powders, such as greater dissolution rates and surface area (Hancock and Parks, 2000; Salonen et al., 2005b; Babu and Nangia, 2011). However, they are thermodynamically-unstable solids (Roos and Karel, 1991; Hogan et al., 2009; Hogan and O'Callaghan, 2010), which can decrease the physical and chemical stability of the products (Buckton and Darcy, 1995, 1996). They have a tendency to sorb moisture and form caked powders that are not free flowing.

Stickiness and caking tendencies of hygroscopic, amorphous powders can be problems for food powders and related substances. Stickiness has been defined as the situation when particles stick to each other (cohesion) or to other surfaces (adhesion). A symptom is that particles stick to one another or to the walls of the drying apparatus (Downton et al., 1982; Wallack and King, 1988; Paterson et al., 2005). When the surface temperature of a sugar-based powder particle exceeds $T_g$, a decrease in viscosity of the amorphous material from a ‘glassy’ to a ‘rubbery’ state allows the formation of liquid bridges between particles in contact with each other or with equipment surfaces (Hogan and O'Callaghan, 2010). These
liquid bridges may be of molten fat, amorphous sugar or a concentrated sugar solution material. This situation can lead to various issues, such as lower product yield or recoveries, and powder-handling difficulties and caking during storage. Over time, these liquid bridges can crystallize, leading to the irreversible consolidation of the liquid bridges. Caking is defined as the stage where crystallization has occurred and hence solid bridges form (Foster et al., 2004, 2006). Caking may also occur as a result of recrystallization, either after fat melting or after solubilization at crystal surfaces; surface wetting followed by moisture equilibration or cooling; or electrostatic attraction between particles (Aguilera et al., 1995) (Figure 2.1).

![Figure 2.1 Sticking and caking mechanism of amorphous lactose.](image)

Paterson et al. (2005) demonstrated that the sticking behaviour of amorphous lactose can be characterised by the magnitude of the difference between the actual particle temperature and the glass-transition temperature of the particle \((T - T_g)\), regardless of which combination of water activity and temperature are used to achieve this critical \(T - T_g\) level. They stated that amorphous lactose, at the same value of \(T - T_g\) but at different temperatures and water activities, showed similar relationships between the levels of cohesiveness for the powders with time, and amorphous lactose became stickier much faster at higher values of \(T - T_g\).
Above the glass-transition temperature, the molecular mobility increases, as shown by a decrease in viscosity (Burnett et al., 2004). Water (moisture content) acts as a plasticizing, or softening agent, in amorphous food materials, significantly lowering the overall glass-transition temperature (Roos, 1995). The extent of $T_g$ depression depends on the concentration of the plasticizer and its interaction with the amorphous material (Roos, 1995). Above the glass-transition point, amorphous materials of low molecular weight will crystallize after a given time, and the water sorption capacity decreases, resulting in mass loss since excess water is desorbed during crystallization (Roos and Karel, 1991; Burnett et al., 2004).

The glass-transition temperature is affected by various factors, of which the composition of the material, molecular weight and water (moisture) content are the most important. For the calculation of the glass-transition temperature of the mixture, Gordon and Taylor (1952) originally proposed an equation for binary polymer mixtures. Later, Roos (1993) found that the Gordon–Taylor Equation (2.1) can be used to estimate the glass-transition temperature ($T_g$) of carbohydrates at various water (moisture) contents:

$$T_g = \frac{w_1T_{g1} + kw_2T_{g2}}{w_1 + kw_2}$$

where $w_1$ and $w_2$ are the weight fractions of the solute and water, respectively, $T_{g1}$ is the glass-transition temperature of the solute, $T_{g2}$ is the glass-transition temperature of water ($K$), and $k$ is a curvature constant, which can be determined empirically. The weight fraction of water, $w_2$, is related to the moisture content, $X$, expressed on a dry basis, through the equation $w_2 = X/(1+X)$.

### 2.3 Crystallization Kinetics

Crystallization from amorphous materials in the solid state occurs when molecules of the amorphous solids rearrange themselves into an orderly structure (Jouppila and Roos, 1994a). The transformation from solid amorphous to solid crystalline products has been investigated by several researchers. They suggested that the crystallization rate of various amorphous sugars can be estimated by using one of the following approaches: the Williams–Landel–Ferry (WLF) equation (Williams et al., 1955), the Avrami equation or the activated-state model (Das and Langrish, 2012). The difference between the glass-transition temperature ($T_g$)
of the materials and the process temperature ($T$) has been widely accepted as a best indicator to avoid this stickiness during drying (Bhandari et al., 1997b; Islam et al., 2010). According to the Williams–Landel–Ferry (WLF) equation, a higher particle temperature and lower particle glass-transition temperature increase the crystallization rate of the particles during the spray-drying process.

### 2.3.1 Modelling the Kinetics of Solid-Phase Crystallization with the Williams–Landel–Ferry Equation

The ratio ($r$) of the time for crystallization ($\theta_{cr}$) at any temperature ($T$) to the time for crystallization ($\theta_g$) at the glass-transition temperature ($T_g$) can be correlated by the Williams–Landel–Ferry (WLF) equation, Equation 2.2 (Williams et al., 1955). The WLF equation can be expressed as a rate equation (Equation 2.3) for the crystallization process, and the crystallization rate may be assumed to be inversely proportional to the crystallization time:

$$
log_{10} r = \log_{10} \left( \frac{\theta_{cr}}{\theta_g} \right) = -17.44 \frac{(T - T_g)}{51.6 + (T - T_g)}
$$

$$
k_{cr} = 10^\left( -17.44 \frac{(T - T_g)}{51.6 + (T - T_g)} \right) k_g
$$

where, $\theta_{cr}$ is the time for crystallization (s), $\theta_g$ is the time for crystallization at the glass-transition temperature (s), $k_{cr}$ is the rate of crystallization (s$^{-1}$) at the particular local conditions ($T-T_g$), and $k_g$ is the rate of crystallization at the glass-transition temperature ($T_g$). The glass-transition temperature can be estimated from the Gordon–Taylor equation (1952).

The WLF equation suggests that the rate of crystallization is related to the difference between the material temperature ($T$) and its glass-transition temperature ($T-T_g$), where the glass-transition temperature depends on the moisture contents. The WLF equation is only valid for temperatures up to 100°C greater than the glass-transition temperature (Williams et al., 1955), and the validity of the universal constants (17.44 and 51.6) in this equation has been debated (Roos and Karel, 1991; Peleg, 1992). Roos and Karel (1991) found that these fixed constants can be applied for the crystallization times of sucrose and lactose. However, Peleg (1992) suggested that these constants depend on the substance investigated and the difference
between $T$ and $T_g$, particularly 20-30 K above the $T_g$. These constants are most likely to be product specific (Langrish, 2008).

Another limitation of the WLF approach was reported by Roos and Karel (1992). They showed that the kinetics for the crystallization process have been expressed in an integrated form rather than as a function of reactant concentration. Therefore, this approach makes the reaction appear to be a zero-order reaction regarding the concentration. Das and Langrish (2012) reported that the WLF equation was inconsistent in predicting the rates of crystallization at the glass-transition temperature and found that, since the WLF equation is a temperature-shift equation, it does not take into account the fundamental effect of moisture content on the crystallization rate. Therefore, with the above limitations, the WLF equation is unlikely to predict high-temperature crystallization accurately in a quantitative manner.

### 2.3.2 Modelling the Kinetics of Solid-Phase Crystallization with the Avrami Equation

Another approach to modeling solid-phase crystallization is the Avrami equation (Avrami, 1940), which gives the degree of crystallinity as a function of time and not of reactant concentration. Ibach and Kind (2007) determined the Avrami exponent (reaction order) over a range of temperatures and humidities for lactose, whey, and whey-permeate powders.

The Avrami equation can be written in the form of Equation 2.4 to calculate the degree of crystallinity from the XRD data, based on the extent of completion ($I_f - I_t$) compared with the total change ($I_f - I_0$) in XRD peak intensity.

\[
\theta = 1 - \frac{I_f - I_t}{I_f - I_0} = 1 - e^{-kt^n}
\]

where $\theta$ is the degree of crystallinity, $t$ is time, $k$ is the rate constant, $n$ is the Avrami exponent, $I_f$ is the maximum value of the intensity of the peaks or the maximum value of the peak areas occurring at the maximum extent of sample crystallization, $I_t$ is the intensity of the peaks or the peak areas at time $t$, and $I_0$ is the intensity of the peak or the peak areas for a noncrystalline, amorphous sample. This approach can also be used with the moisture content instead of the peak intensity (XRD), for water/moisture sorption data (Langrish, 2008).

The Avrami equation can be rearranged as follows when fitting experimental data:
\[ \ln[-\ln(1 - \theta)] = \ln k + n \ln t \]

A plot of \( \ln[-\ln(1 - \theta)] \) versus \( t \) gives a straight line with a slope of \( n \) and an intercept of \( \ln k \). Values of \( k \) and \( n \) vary for different materials and conditions.

The applicability of the Avrami equation has been debated. It has been used as a correlation for fitting data from isothermal crystallization experiments, and the equation does not explicitly account for the effect of temperature (Langrish, 2008). Roos and Karel (1992) tested the applicability of the Avrami equation by measuring the crystallization rate for amorphous lactose using water-induced crystallization (crystallization at constant relative humidity) and found that the equation did not fit the results well.

The physical process of crystallization consists of two main steps, which are nucleation and crystal growth. Both the WLF and Avrami equations do not distinguish between the two processes and instead lump them together (Das and Langrish, 2012). Langrish (2008) also suggested that, due to the parameters in the Avrami equation being less universal compared with those in the Williams–Landel–Ferry equation, the approach using the Avrami equation currently appears to have less generality than using the Williams–Landel–Ferry equation.

### 2.4 The Controlled Crystallization Processes

The main constituents of dairy powders are carbohydrates, proteins, water, and fat. Among the different ingredients of milk powders, amorphous lactose is a very hygroscopic and unstable material. Stickiness and caking tendencies of hygroscopic, amorphous powders can be problems for food powders and related substances. Stickiness occurs when the surface temperature of the powder particle exceeds \( T_g \), and a decrease in the viscosity of the amorphous material from a ‘glassy’ to a ‘rubbery’ state allows the formation of liquid bridges between particles that are in contact with each other or with equipment surfaces (Hogan and O'Callaghan, 2010). Reducing stickiness in materials can be achieved through partial or complete crystallization of the sticky components.

Due to the hygroscopic nature of amorphous lactose, lactose-containing materials become sticky when exposed to humid environments. Different operating conditions can be used to obtain different extents of lactose crystallinity in various processes to reduce the hygroscopic
nature of lactose in dairy powder by converting a portion of the lactose to the more stable crystalline state. Examples include pre-crystallization and “in-process” crystallization steps before and within spray drying, respectively, and post process crystallization in fluidized-bed drying. The pre-crystallization process involves seeding a supersaturated solution with fine lactose crystals to nucleate crystallization (Nijdam et al., 2008). The difference between the glass-transition temperature \( T_g \) of the materials and the process temperature \( T \) has been widely accepted as a good indicator to avoid this stickiness and to give specific advantages in various processes, such as spray drying (Bhandari et al., 1997b; Islam et al., 2010) and post processing in fluidized-bed units (Nijdam et al., 2008; Hogan and O'Callaghan, 2010; Yazdanpanah and Langrish, 2011a).

### 2.4.1 Modified Spray-Drying Technique

Islam et al. (2010) proposed a modified spray-drying technique called “Humid Loop” to spray dry lactose, which uses highly humid hot air to obtain highly crystalline lactose from spray dryers. They suggested that, according to Williams–Landel–Ferry kinetics (WLF), a higher particle temperature and lower glass-transition temperature should increase the crystallization rate of the particles during the spray-drying process while still giving dry powders (Figure 2.2). The results of their work showed that they could reach higher degrees of lactose crystallinity compared with typical spray-dried lactose particles. Although the effects of other components, such as proteins, on the crystallization rate, kinetics, crystal shapes, and distributions have not been fully explained yet, this technique could also possibly apply to other lactose-containing powders (Yazdanpanah and Langrish, 2011a).
2.4.2 Crystallization in Fluidised-Bed Dryers/Crystallizers

Fluidized beds have found widespread applications for drying, mixing, granulation, coating, heating and cooling due to their excellent mixing capabilities, which cause good heat transfer, temperature uniformity and ease of process control (Rhodes, 2007). A very important application of the fluidized bed is to the drying of solids. Fluidized-bed dryers can be used to improve dairy powder crystallinity in food-processing industries (Cruz et al., 2005; Nijdam et al., 2008; Yazdanpanah and Langrish, 2011a; 2011b; 2011c).

Nijdam et al. (2008) investigated the fluidization of partially- and fully-crystallized whey powders at different relative humidities and air temperatures (Figure 2.3). They stated that partially-crystallized whey powder can be fluidized in a vibrated bed at temperatures of 25°C to 40°C above the glass-transition point of lactose, depending on the relative humidity of the air, before the powder becomes too sticky to fluidize, while this temperature difference can be increased up to 80°C by fluidizing the fully-crystallized whey powder. They suggested that, for partially-crystallized whey powder, the relative humidity can be increased by a further 15% above the glass-transition curve found by Vuataz (2002). Fully-crystallized whey powder can be fluidized up to a relative humidity of approximately two times that of partially-crystallized whey powder. They also tried to fluidize a mixture of partially- and fully-crystallized whey powders, with the aim of coating the sticky partially-crystallized whey particles by non-sticky crystallized whey particles. They also assessed whether or not an industrial whey-powder crystallization process is achievable, in which a portion of the...
whey powder already fully crystallized in a fluidized bed is recycled and mixed with fresh partially-crystallized whey powder being fed into the fluidized bed. The result of this process showed the highly agglomerated whey particles were formed during fluidization. In addition, they could not reduce the time required to fully crystallize the amorphous-lactose fraction in partially-crystallized whey powder sufficiently to be feasible in an industrial crystallization process.

Figure 2.3 The upper limit on the relative humidity at which partially- and fully-crystallized whey powders can be fluidized. In this figure, Vuataz [10] corresponds to the glass-transition curve found by Vuataz (2002) for milk-based powders.

Hogan and O'Callaghan (2010) determined the relative stickiness behaviour for a range of powders with different lactose/protein ratios, as a function of temperature and relative humidity, using a fluidized bed. They found that increasing the proportion of protein decreased the susceptibility of powders to sticking due to the combined influence of both $T_g$ and $T- T_g$. Their work also showed that the rate of transition of amorphous lactose from the free-flowing, though the thermodynamically unstable, ‘glassy’ form, to the unstable, ‘rubbery’ (sticky) condition and subsequently to the stable crystalline state, was delayed by proteins, due possibly to a competitive sorption mechanism.

Yazdanpanah and Langrish (2011a; c) advanced the above knowledge of stickiness by using fluidized-bed dryers to crystallize lactose and milk powders with multiple stages of processing at different temperatures and humidities to achieve different degrees of powder crystallinity. They showed that the upper limit of fluidization depends on the percentage of
crystallinity in the powders. The worst fluidization corresponds to the highest amorphicity in the powders, and fully crystalline milk powder has very smooth fluidization at high temperatures and humidities (Figure 2.4) (Yazdanpanah and Langrish, 2011c). Therefore in their later study (Yazdanpanah and Langrish, 2011a), they showed that different fluidization abilities may occur for different amounts of crystallinity in the powders. Hence in the fluidization-crystallization process, the humidity and temperature can be increased as a function of time while the crystallinity of powders is developing. In other words, the processing time was suggested to be split into different modules to maximize the crystallization rate by maintaining an adequately high differential temperature ($T-T_g$) in different stages corresponding to different amounts of amorphicity in the powders (Figure 2.5). They found that, with proper spray-drying conditions followed by similar strategic processes in fluidized-bed dryers, the overall processing time to reach the maximum degree of lactose crystallinity could be decreased.

![Figure 2.4](image)

**Figure 2.4** The upper limit of fluidization as related to the relative humidity of process air, for different lactose base materials (Yazdanpanah and Langrish, 2011b).
Figure 2.5 The upper limit on the relative humidity for which different degrees of crystallinity in skim milk powder can be fluidized and the process pathways between different stages of crystallization-drying. A) Fluidization of conventional spray-dried powders in three stages, B) Fluidization of Humid Loop spray-dried powders in two stages (Yazdanpanah and Langrish, 2011a).

Processed milk powders show less moisture sorption and more lactose crystals, leading to an improvement in the degree of amorphismity for spray-dried milk powders by post processing in a series of laboratory-scale fluidized bed dryers.

Chapter 4 involves using continuous multistage fluidized beds, with the aim of reducing the time required to crystallize the amorphous-lactose fraction sufficiently in sweet whey to be feasible in an industrial-crystallization process, where each stage will have particular temperatures and relative humidities. Based on the above findings, it is expected that the process conditions (temperature and relative humidity) for each stage will depend on the feed powder properties (glass-transition temperature, composition, degree of amorphicity) in terms of the carbohydrate content for that stage. Multi-stage fluidized bed processing has been developed to achieve greater control of lactose crystallinity than the control achievable through operating a single-stage fluidized-bed dryer on its own.

2.5 Types and Composition of Whey

The main constituents of dairy powders are carbohydrates, proteins, water, and fat. Whey is a multicomponent solution of various water-soluble milk constituents in water, which is the by-
product remaining after the production of cheese or the removal of fat and casein (80% of the proteins) from milk (De Wit, 2001; Jelen, 2009). There are two basic types of whey: sweet and acid whey, where the acid whey is usually achieved by acidification to below pH 5.0.

Table 2.1. While the main components of both sweet and acid wheys, after water, are lactose (approximately 70–72% of the total solids), whey proteins (approximately 8–10%) and minerals (approximately 12–15%), the main difference is found in the calcium and lactic acid contents (Panesar et al., 2007; Jelen, 2009).

Table 2.1 The typical compositions of sweet and acid whey.

<table>
<thead>
<tr>
<th>Components</th>
<th>Sweet whey (g l⁻¹)</th>
<th>Acid whey (g l⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total solids</td>
<td>63-70</td>
<td>63-70</td>
</tr>
<tr>
<td>Lactose</td>
<td>46-52</td>
<td>44-46</td>
</tr>
<tr>
<td>Protein</td>
<td>6-10</td>
<td>6-8</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.4-0.6</td>
<td>1.2-1.6</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1-3</td>
<td>2-4.5</td>
</tr>
<tr>
<td>Lactate</td>
<td>2</td>
<td>6.4</td>
</tr>
<tr>
<td>Chloride</td>
<td>1.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

(Source: Jelen, 2009; Panesar et al., 2007)

2.6 Effect of Acidity on Lactose Crystallinity

Many milk plants do not have a fully-developed strategy to recycle whey, and around half the global production of whey is treated as a waste product (Salameh and Taylor, 2006). Due to the presence of economically-important components, such as lactose and the whey proteins, the disposal of whey solutions to drain is no longer acceptable. Whey and whey products, as functional ingredients in food and pharmaceutical applications, and as nutrients in dietetic and health foods, have received considerable attention (De Wit, 2001). Different types of whey products contain some of the most valuable milk nutrients, but the processing of whey into marketable and attractive final products faces major economical obstacles (Jelen, 2009).

It has been found that the spray drying of acid whey is not an easy task because powder sticks to the dryer and cyclone walls due to the high content of lactic acid and the low pH (Modler and Emmons, 1978; Salameh and Taylor, 2006; Bhandari, 2008). If the drying conditions and the degree of lactose crystallization are similar, then differences in drying properties can be linked to the lactic acid-lactate content of these products (Modler and Emmons, 1978). Therefore, the rationale of this study has been to investigate the effects of lactic acid
concentration on the degrees of powder crystallinity during the spray drying of lactose solutions with various acid concentrations.

The main ingredients of acid whey are lactose, protein, and lactic acid. Due to the importance of lactose in the food and pharmaceutical industries, there have been extensive studies on the crystallization behavior of lactose (Roos and Karel, 1992; Jouppila et al., 1998). The effect of lactic acid on the crystal growth of lactose needs to be studied due to its fundamental and commercial importance in food processing. However, there is little known about the crystallization behavior of lactose in the presence of lactic acid (Bhandari, 2008), and it has been found that presence of protein at low concentrations (< 5 w/w %) significantly affects the product yield and crystallinity (Haque and Roos, 2004). The crystallization kinetics of lactose/protein solutions, especially when lactic acid is added to the solutions, for example acid whey, have not been studied in terms of in-process crystallization during spray drying. It is difficult to predict the crystallization behaviour of commercial acid whey due to the presence of other impurities. Therefore, in Chapter 5, in one series of experiments, only solid-phase crystallization of lactic acid and lactose was carried out. Then further experimentation has been done on the crystallization behavior of powders produced during spray drying using solutions of lactose/protein/lactic acid to imitate the composition of typical acid whey solutions. Different methods have been used to assess the degree of crystallinity of the spray-dried products for different concentrations of lactic acid.

### 2.7 Disadvantages of Crystalline Powders

As mentioned earlier, the spray-dried forms of dairy powders are normally amorphous and hence relatively disordered in their molecular structures, which may have several advantages, such as greater solubility and dissolution rates and surface areas (Hancock and Parks, 2000; Salonen et al., 2005b; Babu and Nangia, 2011). However, they are thermodynamically-unstable solids (Roos and Karel, 1991; Hogan and O'Callaghan, 2010), which may lead to an increased rate of physicochemical changes in dried products, such as sticking, collapse, caking, agglomeration and crystallization. To overcome these problems, a controlled process, here a multistage fluidized bed, has been used where the transformation from the amorphous state to the crystalline form has been done relatively rapidly compared with the rate in storage, to reduce the time required to crystallize the components of amorphous lactose. Due to the multistage fluidized-bed controlled process, more stable powder products can be
produced, but crystalline powders may have some undesirable properties, such as lower dissolution rates.

The creation of highly-porous crystalline powders with better functional (free flowing) and storage (non-caking) properties, would be helpful for the food industry and pharmaceutical applications. Thus, a new spray-drying process has been developed with post-drying treatment to create powder structures with significant porosities and high surface areas, while maintaining the high stability of a highly crystalline powder.

2.8 A New Templating Method to Produce Highly Crystalline Powder with Significant Porosity and High Surface Area

The most common application of lactose in the pharmaceutical industry is its use as a diluent in tablet processing with both direct compression and wet-granulation methods (Kibbe, 2000). In general, the compressibility of excipient powders, such as lactose and mannitol, has been reported to depend on the powder properties, such as specific surface area, crystallinity, polymorphism, particle size, and crystal habit (York, 1983).

Increasing the particle surface roughness increases the tablet crushing strength by promoting the bonding mechanisms between solid surfaces in the compact agglomerate (Karehill et al., 1990; Riepma et al., 1990). It has been suggested that the dissolution rates of particles with large surface areas and porosities are relatively high, which results in fast tablet disintegration and dissolution (Simões et al., 1996; Danesh et al., 2001; Parikh, 2011; Yamasaki et al., 2011). It has been found that different crystal forms and polymorphs of theophylline have different physicochemical properties, which influences their tableting behaviour (Suihko et al., 2001). The same result has been reported for different polymorphs of mannitol (Debord et al., 1987; Burger et al., 2000). McKenna and McCafferty (1982) reported that decreasing the particle size of spray-dried lactose increases the tablet tensile strength and results in stronger compactions. The effect of crystal habit on compressibility of powders has also been extensively reviewed (Marshall and York, 1991; Garekani et al., 1999). Staniforth et al. (1981) changed the crystal habit and porosity of mannitol and obtained a highly porous mannitol for direct compression by using a special crystallization technique.
Different techniques can be used to obtain porous spray-dried particles, but the dominant method for producing porous inorganic particles by spray drying appears to be the use of aqueous solutions containing the main (core) material with a templating agent that is removed by heat treatment, including calcination (Lee et al., 2010; Nandiyanto et al., 2010; Oveisi et al., 2010; Zhang et al., 2010; Balgis et al., 2011; Balgis et al., 2012; Majano et al., 2012; Sachse et al., 2012; Emmanuelawati et al., 2013; Fiorilli et al., 2013; Jang et al., 2013; Melo et al., 2013; Nandiyanto et al., 2013). The key challenge is to extend this understanding of the powder-templating process from inorganic materials to organic ones, thereby generalizing this understanding.

Nandiyanto et al. (2013) designed a template-driven self-assembly technique to prepare a porous material with multisized pores. In this technique a spray-drying process was used for solutions obtained by mixing silica (an inorganic material) and polystyrene spheres (organic templates) with different sizes to produce porous silica with a range of pore sizes. In materials with controllable pore sizes, an improvement in the material properties, compared with a single-sized pore structure, was achievable. This material may also be very effective for either selective adsorption or catalytic activity (Nandiyanto et al., 2010).

Zhang et al. (2010) reported a simple approach, using spray drying, to prepare macroporous pure CoFe₂O₄ spinel microspheres. In this approach, the precursor slurry containing CoFeFe-LDH, with or without sulfonated polystyrene microspheres as templates for constructing macropores, was spray dried. Then the prepared CoFeFe-LDH microspheres were calcined in air at 700 °C. They found that CoFe₂O₄ spinel microspheres maintain the original spherical morphology of the precursor LDH microspheres during thermal decomposition. Layered double hydroxides (LDHs), as excellent anion exchange materials, are also called anionic clays. These materials have a wide variety of applications in catalysis, separation technology, optics, medical science and nanocomposite material engineering (Khan et al., 2001; Nalawade et al., 2009).

The use of polystyrene particles with various zeta potentials as templates to produce highly-ordered porous agglomerates from inorganic colloids has been demonstrated by Lee et al. (2010). Nanoparticles are important as the building blocks for the construction of periodic and quasiperiodic crystal structures (Chen and Ozin, 2009). In this method, a suspension of silica colloidal nanoparticles and polystyrene as organic template nanoparticles was spray dried and then the template particles were removed by calcination at high temperatures of
over 450°C from the product. It has been reported that the final structures of the particles were highly-ordered porous and hollow nanostructures, the quality of which depends on the initial concentration of particles, the particle size and the zeta potentials of the silica and polystyrene particles.

Spray-dried mesoporous titania particles were prepared with a triblock copolymer as a template by Oveisi et al. (2010). During the process, a suspension of precursor solution, consisting of titanium tetraisopropoxide dissolved in hydrochloric acid with an ethanol solution containing Pluronic F127 as a templating agent, was spray dried and then the products were calcined to remove the surfactants and create the mesoporous particles. The effect of various calcination temperatures on the mesostructures was also studied, and the template was removed by calcination at different temperatures of 350°C, 400°C and 500°C. It was found that the surface areas and the pore volumes were reduced by increasing the calcination temperatures because of the distortion of the mesostructures, due to the grain growth of the anatase phase and the transformation to the rutile phase during the calcination process.

Porous NiO–ZrO₂ powders were made by Balgis et al. (2011) using spray drying, with polystyrene latex (PSL: 400 nm) as a template and the main materials being NiO powders (7 nm) and ZrO₂ sols (1.2 nm). They made porous particles that had an average diameter of 4.5 mm, a surface area of 27 m² g⁻¹ and pore sizes of around 300 nm at a pH of 3.7 in the sprayed solutions. They also found that, by adjusting the solution pH and the size of the template particles, powders with a controlled morphology and pore sizes could be produced. The particles were calcined at 900°C and 1200°C, and the particles shrank by under 36%.

Majano et al. (2012) presented a one-step synthesis method for the formation of a mesoporous matrix by spray drying a slurry consisting of a high mesoporosity surfactant-templated silica matrix and a mesoporous zeolite. The mesoporous silica matrix produced by the evaporation-induced assembly of the silica nanoparticles was combined, together with the non-ionic surfactant from spray drying and the mesoporous zeolite obtained by alkaline treatment, into an attrition-resistant containing sodium hydroxide and tetrapropylammonium bromide. They reported that the final materials were multimodal and highly interconnected porous networks, and they also found that the properties of the matrix could be tuned by changing the spray-drying conditions and the slurry mixture.
Balgis et al. (2012) designed a way to produce carbon-supported platinum (Pt/C) catalysts with controlled morphologies (dense and hollow-porous) for high-performance PEM fuel cell (PEMFCs) applications. Spray drying has been used to produce microspherical carbons (modified catalyst support). The morphological control of carbon microspheres was done by adding the polystyrene latex (PSL) as template particles prior to spray drying. PSL was removed by heating the spray-dried particles to obtain hollow-porous microspheres. Pt/C catalysts were obtained by impregnation of Pt nanoparticles on the surface of the carbon particles. They found that the electrocatalytic activity of the modified Pt/C catalyst particles was improved by comparison with a commercial Pt/C catalyst.

Silica-based microspheres were produced by Yurchenko et al. (2012) using [(C2H5O)3Si]2C2H4 and (C2H5O)3Si(CH2)2P(O)(OC2H5)2 as functionalizing agents and Pluronic 123 as a template through spray drying. The template was removed by boiling in methanol. Silica microspheres produced by this templating method had a large specific surface area of 747 m² g⁻¹.

Mesoporous silica–titania catalysts were made by Sachse et al. (2012) by spray drying an aqueous solution containing an ethanolic suspension of siloxane oligomers with titanium monomer precursor Ti(O'Pr)2(acac)₂ and α-chitin-nanorods as templating agents, then calcining the obtained powders. They demonstrated that textural properties (surface area, pore volume) of the synthesized materials could be tailored by varying the chitin volume fraction during the synthesis and also by adjusting the Si/Ti molar ratios. Mesoporous silica–titania catalyst may be applied to the oxidation of a variety of organic compounds, such as sulfur-containing materials (Huybrechts et al., 1990; Reddy et al., 1992).

Melo et al. (2013) proposed a new approach to produce microbial-imprinted microspheres of silica nanoparticles through the spray drying of mixed colloidal dispersions containing silica and Escherichia coli as the templating agent, and then removing the templating materials by calcination of the spray-dried powders at 300°C for 10 h in a muffle furnace. A high surface area and a three-dimensional matrix were prepared by microbial imprinting, which can be used to treat drinking water. The resulted materials showed effective filtration performance in terms of filtering out microbial cells from aqueous media.

Nanoporous silica particles with controlled morphology, large pore size, and high pore volume were made by Emmanuelawati et al. (2013) using spray drying, with commercial
silica, Aerosil 200, as a precursor and lanthanum nitrate as a templating agent. The particles were calcined in air at 550°C for 5 h. The resulted lanthanum oxide-functionalised microspheres of silica showed high phosphate adsorption capacities of up to 2.317 mmol g⁻¹.

In general, templating techniques have been extensively used to produce highly-porous particles with multi-component mixtures of inorganic and colloidal materials (Lee et al., 2010; Nandiyanto et al., 2010; Zhang et al., 2010; Balgis et al., 2011; Balgis et al., 2012; Nandiyanto et al., 2013). The key challenge is to extend this understanding of the powder-templating process from inorganic materials to organic ones, thereby generalizing this understanding. In Chapter 6, a method has been developed to create highly-porous templates or frameworks of lactose through the spray drying of lactose using food-grade acid as the templating agent (both water soluble). Then the templating material has been removed by ethanol washing of the spray-dried powders, simultaneously crystallizing the powders, giving stable porous and crystalline powder particles. Novel contributions of the new process reported in this work include the use of a food-grade, non-toxic and benign templating material, citric acid, in a process involving spray drying, which is a low-cost continuous drying technique relative to many other drying operations, such as freeze drying.

The effect of glass-transition temperature and strength of the acid (pH of the solution) on the degree of crystallinity for lactose in spray-dried powders is critical, with implications for the performance of the templating approach using acidic templates. Therefore, in this chapter the effect of using different concentrations for various food-grade acids, such as lactic acid, citric acid, boric acid, and ascorbic acid, on the degree of crystallinity for spray-dried lactose powders and the porosity of the ethanol-washed powders has been investigated.

### 2.9 Mannitol as an Alternative to Lactose

Recently, the use of mannitol as an alternative to lactose in food products and pharmaceutical formulations has significantly increased. Lactose is a reducing sugar, which is incompatible with some active pharmaceutical ingredients, such as peptides and proteins, and also has problems associated with lactose intolerance (Dangaran and Krochta, 2006; Dangaran et al., 2006; Babu and Nangia, 2011; Littringer et al., 2012). The non-hygroscopic nature of mannitol, and consequently its low moisture content, make it a desirable additive and
excipient for moisture-sensitive ingredients (Babu and Nangia, 2011). Mannitol has also been used as a primary material for protein stabilization in dried protein formulations (Bhandari et al., 1997a; Bakaltcheva et al., 2007; Hulse et al., 2009).

Jayasundera et al. (2010) improved the tableting properties of mannitol by decreasing the crystallinity of the particles through rapid solidification of the melted mannitol in a spray dryer. However, the produced amorphous fused mannitol was rather unstable, and its compressibility decreased as the crystallinity gradually increased during storage. Maas et al. (2011) produced spray-dried mannitol particles with different surface roughnesses by spray drying at different outlet temperatures. They found that increasing the outlet temperature of the spray dryer increased the crystal size and particle surface roughness, which was attributed to different crystallization mechanisms. In an attempt to increase the mannitol surface area, Modler and Emmons (1978) found that exposing the mannitol to a high relative humidity after spray drying significantly changed the morphology of the particles and increased their surface area from 0.4 to 2.3 m$^2$ g$^{-1}$, which was associated with the moisture-induced polymorphic transition of mannitol from the $\delta$ to the $\beta$ form. The high surface-area mannitol produced with this method has been shown to possess excellent compaction behaviour (Drapier-Beche et al., 1997). Typical specific surface areas of mannitol powder have been reported to be between 0.3 to 0.6 m$^2$ g$^{-1}$ (Babu and Nangia, 2011; Ho et al., 2012).

A templating approach has been applied here according to the method described in Chapter 6 to obtain highly-porous templates or frameworks of mannitol through the use of the low-cost and high-throughput spray-drying process for mannitol using citric acid as the templating agent. Then, the template material (citric acid) has been removed by ethanol washing of the spray-dried powders. The core materials (mannitol), and the citric acid as the templating agent (both water soluble), have been mixed and spray dried. The resulting powders have been washed with ethanol to create porous powder particles by removing the citric acid. The effects of surface active compounds, such as whey protein isolate (WPI) and Gum Arabic, on the surface area and the pore volume of the resultant mannitol have also been investigated in Chapter 7.
2.10 Highly Porous Excipients as a Solution for Poor Solubility and Poor Content Uniformity in Solid Dosage Form

Solid-dosage form drugs that include tablets and capsules are some of the most popular and commonly-employed methods of drug delivery, which currently account for over two-thirds of the total number of medicines produced in the world (Zheng, 2009; Sahoo, 2012). Their final formulation contains an active pharmaceutical ingredient (API), its excipients and also additives, which may be included in the formulations to enhance the physical appearance, improve stability, and aid in disintegration after administration. However, major challenges facing the design of the oral dosage form are poor bioavailability and uniformity of drug dosage, especially in low-dose solid-drug products (Garcia and Prescott, 2008; Huang and Sherry Ku, 2010; Grigorov et al., 2013). Among other essential qualities of a well-made pharmacopeia, uniformity of drug dosage is a very important. The problems associated with the mixing of an active pharmaceutical ingredient (API) with excipients are many and complex, especially for low-dose (<100μg) drugs during the manufacturing of solid dosage forms, which may result in undesirable variations in dosage (Cartilier and Moes, 1989; Garcia and Prescott, 2008; Zheng, 2009; Huang and Sherry Ku, 2010; Grigorov et al., 2013).

Therefore, it is critical that the drug be uniformly distributed in the final product. The potential problems associated with the control of dose uniformity need to be addressed carefully to ensure that the proper dosage of the drug is delivered to the patient. The content-uniformity requirements are regulated throughout the world to ensure that the mixture of the drug and its excipients is adequately uniform in the finished products (Garcia and Prescott, 2008). The Food and Drug Administration (FDA), in setting standards for the content uniformity of pharmaceutical products, requires that the relative standard deviation (RSD) is less than or equal to 6%, while the maximum acceptable deviation in the active substance content of the finished products must not exceed ± 5% at the time of manufacture, according to European Pharmacopoeia requirements (FDA, 2003; Directive, 2003/63/EC).

Particle size control of the API can enhance the uniformity of solid dosage forms; however, this approach for drugs may not be able to maintain the level of homogeneity throughout processing due to the possibility of blend desegregation, and consequently poor blending uniformity as a result of differences in particle size, shape, or density of the materials being blended (Garcia and Prescott, 2008; Zheng, 2009; Huang and Sherry Ku, 2010). In addition
to blending uniformity, bioavailability, as one of the important quality parameters of drug formulations, refers to the extent and rate at which an active drug reaches systemic circulation. Poor solubility is one of the main causes of low bioavailability (Schreiner et al., 2005; Savjani et al., 2012). More than 90% of small molecular-weight drugs are delivered to the human body in crystalline form; however, 90% of crystalline drugs have low solubility in water (Variankaval et al., 2008). Low aqueous solubility is the major problem encountered with formulation development, and poorly soluble drugs often require high doses in order to reach the desired bioavailability after oral administration, which may lead to increased side effects. Formulation and dosage-form design must ensure that solubility requirements are met for manufacturing as well as clinical applications.

There are various solubilization techniques to enhance the solubility of poorly water-soluble drugs, such as solid dispersion, particle size reduction, complexation, the use of surfactants, and novel excipients (Savjani et al., 2012; Ojha and Prabhakar, 2013; Dhillon et al., 2014). Common strategies to increase the dissolution rate and hence the bioavailability of such drugs include reduction of particle size (Leuner and Dressman, 2000) to generate effective surface areas. As a particle becomes smaller, the surface area to volume ratio increases, and the larger surface area allows greater interaction with the solvent, which causes an increase in solubility (Savjani et al., 2012). Particle size reduction may also enhance the possibility of API uniformity for solid dosage forms (Huang and Sherry Ku, 2010). Another potential approach to solve the abovementioned challenges for better controllable release characteristics of a drug is deposition or nano-confinement of drugs into porous excipients as hosts, in which a precise amount of highly-concentrated drug solution can be dispersed in the pore spaces of a porous carrier (Charnay et al., 2004; Beiner et al., 2007; Mellaerts et al., 2007; Mellaerts et al., 2008; Rengarajan et al., 2008; Van Speybroeck et al., 2009; Ji et al., 2010; Verraedt et al., 2010; Grigorov et al., 2013).

For successful adsorption of drugs, highly-porous excipients are needed, with high surface areas being the most important property (Grigorov et al., 2013). However, it is unclear how the effects of porous excipients are related to the solubility of final drug formulations. Carriers with high porosity can improve the solubility by enabling faster release of the drug as a result of better penetration of solvent into the drug-excipient matrix. Presenting a suitable drug-loaded particle, which consists of dispersing APIs in the host pore space of highly-porous excipients, results in particle size reduction of the drug powders to the size range of...
nanometres. Nanconfinement breaks up the intermolecular interactions of the API molecules and separates them inside the internal void structures of nanoporous excipients. This situation combines the benefits of an increase in the solubility with a reduction in the particle size of the API and maximizes the surface area of the compound that comes into contact with the dissolution medium as the carrier dissolves.

The reduction in the particle size of an active pharmaceutical ingredient (API) to the nanocrystal size range may cause a significant increase in the dissolution rate of the API, often resulting in significant increases in bioavailability. Greater porosity of excipients facilitates the diffusion of the API components and increases the rate of drug adsorption.

For this purpose, a method of adsorption has been developed using highly-porous excipients with high surface areas produced according to the templating method described in Chapter 7. These new engineered particles, furthermore, have been used as the key part of an adsorption method to investigate drug dissolution. This work has been done by applying an adsorption technique and modifying our current templating process, as described in the following chapters (Chapters 8 and 9). Highly-porous mannitol particles with high surface areas have been successfully produced through the spray drying of mannitol solutions containing ethanol-soluble food-grade acids, such as citric acid as a templating agent, and then removing the citric acid by ethanol washing of the spray-dried powders to create porous powders. The resultant porous particles, after ethanol washing, have been transferred to ethanol solutions to dissolve and carry acetaminophen as a sample drug into the pores of porous mannitol (Chapter 8).

Chapter 9 has reported on the evaluation of the potential for this new adsorption technique to improve the dissolution characteristics and bioavailability of poorly aqueous-soluble drugs, such as indomethacin and nifedipine, using porous mannitol as the carrier.
CHAPTER 3 MATERIALS, EQUIPMENT AND METHODS

This chapter reviews the most appropriate techniques regarding characterization of products, such as the particle size and shape, the moisture content, the glass-transition behaviour and amorphous/crystalline states, and other issues concerning templating and drug-loading processes, such as BET surface area analysis, tablet crushing tests, UV-spectrophotometry, and in-vitro dissolution studies.

3.1 Materials

The following materials have been used in the experiments, as shown in Table 3.1.

Table 3.1 List of materials used in the experiments.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Formula</th>
<th>Reagent Grade</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>pure α-lactose monohydrate</td>
<td>C₁₂H₂₂O₁₁.H₂O</td>
<td>analytical reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
<tr>
<td>crystals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sucrose</td>
<td>C₁₂H₂₂O₁₁</td>
<td>laboratory-grade reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
<tr>
<td>lactic acid</td>
<td>C₃H₆O₃</td>
<td>88% w/w, laboratory reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
<tr>
<td>D-Mannitol</td>
<td>C₆H₁₄O₆</td>
<td>analytical reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
<tr>
<td>citric acid as monohydrate</td>
<td>C₆H₈O₇.H₂O</td>
<td>analytical reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
<tr>
<td>Gum Arabic from acacia trees</td>
<td></td>
<td>analytical reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
<tr>
<td>ascorbic acid</td>
<td>C₆H₈O₆</td>
<td>analytical reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
<tr>
<td>boric acid</td>
<td>H₃BO₃</td>
<td>laboratory reagent</td>
<td>Ajax Finechem, Australia</td>
</tr>
<tr>
<td>sweet whey powder</td>
<td></td>
<td>-</td>
<td>Dairy Innovation Australia Limited (DIAL)</td>
</tr>
<tr>
<td>potassium phosphate monobasic</td>
<td>KH₂PO₄</td>
<td>ACS reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
<tr>
<td>sodium hydroxide</td>
<td>NaOH</td>
<td>ACS reagent</td>
<td>Chem-Supply, Australia</td>
</tr>
</tbody>
</table>
### Compound | Chemical Formula | Reagent Grade | Supplier
--- | --- | --- | ---
absolute ethanol 100% denatured | C$_2$H$_5$OH | laboratory reagent | Chem-Supply, Australia
methanol | CH$_4$O | ACS spectrophotometric grade, ≥99.9% | Sigma-Aldrich
acetaminophen | C$_8$H$_9$NO$_2$ | BioXtra, ≥99.0% | Sigma-Aldrich
acetone | C$_3$H$_6$O | laboratory-grade reagent | Chem-Supply, Australia
indomethacin | C$_{19}$H$_{16}$CINO$_4$ | ≥99% | Baoji Guokang Biotechnology Co., China
nifedipine | C$_{17}$H$_{18}$N$_2$O$_6$ | ≥99% | Baoji Guokang Biotechnology Co., China
sodium lauryl ether sulfate | (CH$_3$(CH$_2$)$_{11}$(OCH$_2$CH$_2$)$_n$OSO$_3$Na) | analytical reagent | Chem-Supply, Australia
hydrochloric acid | HCl | 32 %, laboratory-grade reagent | Chem-Supply, Australia
sodium chloride | NaCl | laboratory-grade reagent | Chem-Supply, Australia
pepsin |  | laboratory-grade reagent | Chem-Supply, Australia
whey protein isolate | consisting of 92 g protein, 0.4 g fat (total) including 0.2 g saturated fat, 0.5 g carbohydrate, and sodium 0.6 g per 100 g | - | Balance, Vitaco Health Ltd, Auckland, New Zealand

### 3.2 Equipment

#### 3.2.1 Spray Dryer

A mini spray dryer B-290, (Büchi AG, Switzerland) was used to dry the solutions at wide ranges of inlet air temperatures (°C), a full air flow rate (38 m$^3$ h$^{-1}$), and different liquid pump rates (mL min$^{-1}$), nozzle air flow rate (L h$^{-1}$) and feed concentrations (w/w) % for all the experiments. A basic schematic diagram of the spray dryer is shown in Figure 3.1.
3.2.2 Fluidized-Bed Dryer

A three-stage fluidized-bed drying (F.B.) system has been used for the experiments (Figure 3.1). The consecutive stages have been partially separated by fixed partitions. This arrangement has given different sets of air temperatures and relative humidities for each stage. Therefore, for continuous flow of solids through the stages, the particles have been exposed to different process conditions to reach different levels of crystallinity. A pneumatic linear vibrator (piston type, maximum pressure 6 bar) has been attached to the inlet side of the bed to vibrate the fluidized bed and keep the solids well fluidized. The whole bed sits on four springs located at the four corners of the bed. The springs and the supporting bed-frame are securely attached to the base frame/structure of the unit. Each process stage has an air blower (170 m³ h⁻¹) and an air heater (containing customized heating coils, each coil 240 V and 2500 W). The first stage-heater (warm-up zone) has two coils, the second stage-heater (main processing zone) has three coils, and the third stage-heater (finishing zone) has a coil in the heater. A ‘Humidifier’ is connected to the second stage. The humidifier has two inlets—one for the hot air and the other for the steam, and two outlets—one for the humidified hot gas and
the other for draining any condensate. This cylindrical column type unit has stainless steel wool distributed on a support frame just below the inlets at the top of the column and a similar distributor at the bottom of the column and just above the outlets. These arrangements have been made to ensure better mixing of the hot gas and the steam without excessive pressure drop. There is a ‘hood’, split into three sections by partitions, which are aligned with the bed separators. At the top of the hood, three exit ducts are connected, to direct the gas to the cyclones/exhaust duct. There are arrangements of perforated plates above the ‘Wind Box’ to ensure good distribution of air across the bed. The wind box is also partly filled with stainless steel wool to distribute the gas within the confined space.

A set of dry- and wet-bulb temperature probes (RTD PT100) are placed just below (2~3 cm) the fluid bed for each stage. The dry-bulb temperature can be set to a particular level using the heater control system. Dry- and wet-bulb temperatures also give a relative humidity measurement at these particular points. There are also three temperature probes on the ‘Hood’, close to the exit of each stage, to record the final/exit gas temperature of the each stage. The air blowers can be adjusted for different flow rates using the variable speed drives (Figures 3.2 and 3.3).
Figure 3.2 Schematic diagram of the Pilot-Scale Fluidized Bed Dryer.
Determining the degree of crystallinity for lactose is important in understanding if the product experiences changes during different processing or storage conditions. Different methods have been utilized for the detection and qualification of the amorphous fractions or components in lactose within dairy powders, including: Moisture sorption measurement, X-ray diffraction (XRD), conventional differential scanning calorimetry (DSC), modulated differential scanning calorimetry (MDSC), Infrared and Raman spectroscopy and microscopy (Sperling, 1986; Miao and Roos, 2005; Lehto et al., 2006).

Most methods used in the characterization of the solid state are based on the detection of its structural properties, such as the crystalline structure, which may be derived from X-ray diffraction studies (XRD). XRD is a practical technique for identifying crystal forms and following or characterizing rates of crystallization for components, especially when the systems are complicated, such as systems with several crystallizing components (Miao and Roos, 2005).

The amorphous states have disordered structures, and the physical state of amorphous materials is related to molecular mobility (Roos, 1995). Molecular mobility is affected by the
temperature and phase transitions. Various spectroscopic methods are available for the examination of molecular mobility. Spectroscopic methods that have been used in the determination of molecular mobility in food materials include Raman spectroscopy (Sperling, 1986) and Fourier transform infrared (FTIR) spectroscopy (Slade and Levine, 1995).

The analysis of increasing intensities and areas of the peaks in X-ray diffraction (XRD) patterns using X-ray diffractometry is an important technique in observing the properties of crystalline solid materials, polymers, and food materials (Roos, 1995), which can be used to obtain qualitative and quantitative information about the crystalline structure (Marsh and Blanshard, 1988; Drapier-Beche et al., 1997; Jouppila et al., 1997; Corrigan et al., 2004; Langrish and Wang, 2009; Islam et al., 2010; Yazdanpanah and Langrish, 2011b). In food applications, X-ray diffraction patterns are extremely useful in the characterization of crystalline states and crystal structure in such materials as starch and sugars, and in the detection of crystallinity in partially amorphous food components. In this technique, the powdered sample is exposed to a source of X-rays from a series of angles in a scanning manner. The diffracted radiation can be detected using photographic film or an electronic counter. True crystalline states will demonstrate a sharp peak of reflection from the lattice structure, while amorphous food materials have no characteristic X-ray diffraction patterns (Roos, 1995).

Water sorption in amorphous food polymers is known to be a time-dependent phenomenon (Jouppila and Roos, 1994b). Amorphicity can be investigated by detecting the mass change profile during the absorption of moisture and the subsequent desorption due to crystallization taking place in the sample (changes in moisture content, percent (100× kg.kg$^{-1}$ dry basis)). The end of the crystallization process can be determined by the point where the sorption curve reaches a plateau region (Lai and Schmidt, 1990; Jouppila and Roos, 1994b; Jouppila et al., 1998). Amorphous materials absorb moisture more than their corresponding crystalline counterparts, and after the moisture-induced recrystallization, the desorption of excess water after crystallization of the amorphous components is observed (Lehto et al., 2006).

Changes in the physical state are observed from changes in the thermodynamic quantities, which can be measured with a number of techniques, such as calorimetric ones (Roos, 1995). Differential scanning calorimetry (DSC) is probably the most common technique for the determination of phase transitions in inorganic, organic, polymeric and also food materials (Roos and Karel, 1992; Arvanitoyannis and Blanshard, 1994; Roos, 1995; Kedward et al.,
This technique can be used to observe phase transitions and to determine glass-transition temperatures and the degree of crystallinity, for which the observations of the melting and crystallization peaks are required. In the DSC method, the samples are usually placed in pans that can be hermetically sealed, and the temperature difference between the sample and the reference is recorded to derive the difference in the energy supplied. Therefore, the method can be used to observe phase transitions and to determine glass-transition temperatures (Roos, 1995). This technique also can be used to determine the degree of crystallinity, for which the observations of the $T_{\text{melting}}$ and $T_{\text{crystallization}}$ peaks are required. The ratio of the heights or the areas under the peaks for the melting and crystallization peaks give a value for the crystallinity of the sample.

Modulated differential scanning calorimetry (MDSC) allows separation of the total heat flow signal into its thermodynamic (heat capacity) and kinetic components. MDSC offers simultaneous improvements in sensitivity and resolution, and can separate overlapping events that are difficult or impossible to do by standard DSC.

Microscopy and Infrared and Raman spectroscopy may also be applied to obtain information on the crystallinity of amorphous systems (Akao et al., 2001; Mazzobre et al., 2003; Murphy et al., 2005; Yazdanpanah and Langrish, 2013b). Microscopic methods, including optical microscopy and electron microscopy, are particularly useful in the observation of changes that may occur in the crystal size and crystallinity in foods during storage (Roos, 1995).

### 3.4 Measurements of Degree of Crystallization and Thermal Transitions

#### 3.4.1 Moisture Sorption Tests

Time-dependent moisture sorption tests have been carried out for the powders from each experiment. It has been suggested by Lehto et al. (2006) that the moisture adsorption peak heights (changes in moisture content, percent ($100 \times \text{kg.kg}^{-1}$ dry basis)) from the moisture-sorption experiments can be used to assess the extent of lactose amorphicity by detecting the mass change profile during the absorption of moisture and the subsequent desorption due to the crystallization taking place in the sample. The end of the crystallization process can be determined by the point where the sorption curve reaches a plateau region (Lai and Schmidt, 1990; Jouppila and Roos, 1994b; Jouppila et al., 1998). Amorphous materials absorb moisture more than their corresponding crystalline counterparts, and after the moisture-
induced recrystallization, the desorption of excess water after crystallization of the amorphous components is observed (Lehto et al., 2006).

A mass of 1–2 g of the powder product (obtained just after spray drying the sample solution) was placed on a Petri dish (borosilicate glass) of 10-cm-diameter. The dish was placed on an analytical balance (± 0.0001 g, Mettler Toledo, AB 204-S, Switzerland), and the dish and the balance were placed in a sealed container. In this container, electric light bulbs and a sodium-chloride saturated-salt solution were used to control the temperature (24.5-25ºC) and the relative humidity (70-75% RH), respectively, and the mass change as a function of storage time was recorded by a computer once per minute over a period of 1–2 days until the mass of the sample and dish stayed constant for more than six hours. The crystallization process has been considered to be virtually complete when the moisture content remained constant for a long time at a low level (Lehto et al., 2006). However, in the present study, the moisture sorption curves have been normalized for the amount of lactose in the final spray-dried powders (containing lactose and food-grade acids) since during the moisture sorption tests only lactose crystallizes. Hence, the corresponding peak heights should be corrected on the basis of the dry mass of lactose not the whole spray-dried powder (only for sample that the lactose portions have been changed the final spray-dried powder).

3.4.2 X-Ray Diffraction (XRD)

A Siemens D5000 diffractometer with Cu target and maximum power of 2200 W has been used to measure the overall powder crystallinity. Samples have been loaded into standard plastic plates for measurements according to standard sample preparation procedure. The operating conditions have included a range for scanning of 5–30º, 1 step/s was taken with a 0.02º step size, and the current and voltage have been 30 mA and 40 kV, respectively. An analysis program, DIFFRAC Plus, Bruker analytical X-ray system, GmbH, has been used to search for relevant peaks and to calculate the areas under the peaks when assessing the relative degrees of lactose crystallinity for different samples.

3.4.3 Modulated Differential Scanning Calorimetry (MDSC)

The glass-transition and crystallization temperatures and also the heats of crystallization for the powders have been determined by modulated differential scanning calorimetry (MDSC).
Samples for MDSC measurements have been prepared according to standard procedures using hermetically-sealed pans. Four to six milligrams of sample have been used in each analysis. The samples have been heated from 5ºC to 250ºC using a ramp rate of 5ºC min⁻¹ with a 1ºC modulated signal every 60 seconds using a modulated differential scanning calorimeter (TA Instruments Q1000).

3.4.4 Raman Spectroscopy

Raman spectra were measured to assess the degree of surface crystallinity for the powders using a Raman Station 400F (PerkinElmer, CA, USA). The samples were analysed using a power level of 100% with a 785 nm laser and a five second exposure time, with five exposures over a wavelengths range from 200 cm⁻¹ to 1500 cm⁻¹. The spectra were baseline corrected using the software Spectrum v6.3.4.0164 and further analysed using Microsoft Excel. Two spectral bands were chosen for the determination, one centred at 440 cm⁻¹ for amorphous lactose and another centred at 470 cm⁻¹ for crystalline lactose. The band areas were integrated between the spectral regions of 410 cm⁻¹ to 490 cm⁻¹ and 450 cm⁻¹ to 490 cm⁻¹. This spectra region has been chosen since this region has been used to estimate the crystallinity of lactose by Niemelä et al. (2005) and Katainen et al. (2005).

3.4.5 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR absorbance spectra were used to distinguish the degree of surface crystallinity for the lactose using a single bounce diamond ATR (Universal ATR) in a Nicolet 6700 FTIR spectrometer (Thermo Fisher Scientific Inc.) controlled by OMNIC 8.2.387. The FTIR spectra were collected at a resolution of 4 cm⁻¹ with 32 scans over a wavelengths range from 600 cm⁻¹ to 2000 cm⁻¹. The graphs were base line corrected using the OMNIC 8.2.387 software and were further analysed using Microsoft Excel. Peaks have been analysed at 875 cm⁻¹, 900 cm⁻¹ and 1260 cm⁻¹, since they have been reported to distinguish amorphous from crystalline lactose (Listiohadi et al., 2009). The FT-IR absorbance spectra were also used to measure the extent of citric acid removal. The spectrum of the pure citric acid solution has a stretching band at 1,625 cm⁻¹, attributed to the C=O in the dissociated carboxylic acid, while it is 1,730 cm⁻¹ when not dissociated (Socrates, 2001; Masoudpanah and Seyyed Ebrahimi, 2011).
3.5 Characterization of Drug-Loaded Powders

3.5.1 Determination of Drug Loading and Blend Uniformity

An UV-spectrophotometric method has been developed according to an approach described by Behera et al. (2012) using a solvent consisting of methanol and water (15:85, v/v) as a diluent to determine the drug content in the final formulations. Six standard solutions of acetaminophen in the range of 0–150 μg mL\(^{-1}\) were prepared using diluents, and UV spectroscopic scanning (200–500 nm) was carried out by a UV Spectrophotometer (Cary 50, Varian, USA) to obtain a calibration curve. At the maximum-absorption wavelength (\(\lambda_{\text{max}}\)) of 275 nm, a linear response for acetaminophen was found with a correlation coefficient of \(R^2 = 0.999\). However, in the case of poorly water soluble drugs, indomethacin and nifedipine, five standard solutions of drugs in the range of 0–50 μg mL\(^{-1}\) were prepared using a solvent consisting of ethanol and water (50:50, v/v) as a diluent, and UV spectroscopic scanning (200–500 nm) was carried out by a UV Spectrophotometer to obtain a calibration curve. At the maximum absorbance wavelengths (\(\lambda_{\text{max}}\)) of 335 nm and 320 nm, linear responses with a correlation coefficient of \(R^2 = 0.999\) were found for nifedipine and indomethacin, respectively.

These calibration curves have been used to quantify the drug content in the final formulation. The drug content of the drug-loaded mannitol was measured using the predetermined standard curve. 50–150 mg samples of drug-loaded mannitol were carefully weighed, dissolved in dilute solution and agitated, at which time the solutions were visually transparent. From these solutions, 2 mL was taken and diluted again with diluents depending on the estimated loading. The percentage relative standard deviation (\% RSD) for the drug content of drug-loaded mannitol has been calculated by taking at least five samples for each drug concentration in each experiment, as the important acceptance criteria for the content-uniformity dosage requirements of the pharmaceutical industry must be less than a 6\% RSD (FDA, 2003; Directive, 2003/63/EC).

3.5.2 Dissolution Experiments

\textit{In-vitro} dissolution rate studies of drug-loaded mannitol in the form of capsules were performed by Apparatus 2 (paddle assembly) according to the United States Pharmacopeia (Dressman and Krämer, 2005) in a 1-L vessel with a paddle speed of 50 rpm.
Size 0 gelatin capsules (Nutritional Health Supplements, Australia) were filled with each sample using a capsule filling machine. At least three 300 mg samples of acetaminophen-loaded mannitol were tested, while the temperature of the phosphate (900 mL) buffer at pH 5.8 (as the media) was maintained at 37°C by a water bath. During the test, samples were taken to calculate the drug content of final formulation by a UV spectrophotometer at the main absorbance wavelength of the corresponding drugs. The result was compared with the release rate for the physical mixture of non-porous mannitol and drug powder in which the ratios of drug to mannitol were similar to the weight ratios in the final formulation of drug-loaded mannitol.

However, in the case of poorly water-soluble drugs, dissolution experiments were conducted in a medium of simulated gastric fluid (SGF) with 0.5% SLS for indomethacin and release medium of SGF with 0.35% SLS for nifedipine (Van Speybroeck et al., 2009). The temperature of the release media (900 mL) was maintained at 37 ± 0.5 °C by a water bath. In order to estimate the solubility of indomethacin and nifedipine in their release medium, saturated solutions of both drugs were prepared. Excess amount of the drugs were added to the release medium and then mixed using a magnetic stirrer for 48 h at the room temperature of 25°C. The solutions were then filtered and analyzed by a UV Spectrophotometer to obtain the absorbance wavelengths representing the fully-dissolved level of both drugs.

Drug release from the drug-loaded samples was compared to that of their corresponding physical mixture of non-porous mannitol (as the carrier) and drug. The constant non-sink condition of 0.01 mg drug/mL of release medium has been applied. Generally, sink conditions for most dissolution studies are recommended (Liu et al., 2013). Sink conditions normally require that the drug solubility be ten times the total concentration of drug in the dissolution medium. However, such an approach may be inappropriate in dissolution studies for a poorly water-soluble drug since it is not desirable to have incomplete drug dissolution or over-saturated condition in the dissolution evaluation (Tang et al., 2001; Sirisuth et al., 2002; Petralito et al., 2012). In addition, sink conditions or high amount of available drug increase the dissolution rate and lead to rapid dissolution rates for crystalline drugs with different particle sizes, causing difficulties in discriminating dissolution profiles between different formulations (Liu et al., 2013). Since this study focused on the comparison of dissolution profiles for nanometre size drug crystals in the formulation with physical mixture of non-porous mannitol and crystalline drug (bulk drug), the non-sink condition for the dissolution
study allow discriminating dissolution profiles with different drug particle size. This condition was suggested by Van Speybroeck et al. (2009) in order to give better differentiation of various formulations and physical mixtures. Size 0 gelatin capsules (Nutritional Health Supplements, Australia) were filled by different amounts of samples to provide 0.01 mg drug/mL of release medium using the capsule filling machine. During the test, 5 mL samples were taken, filtered over a 0.45 µm PTFE syringe filter, and analyzed by a UV Spectrophotometer at the corresponding absorbance wavelengths of both nifedipine and indomethacin. The absorption results at the appropriate wavelengths were then compared with those of standard solutions (the absorbance wavelengths representing the fully-dissolved level of drugs) to obtain the percentage of dissolved drugs.

### 3.5.3 Tableting Properties

Drug-loaded mannitol powders and physical mixtures of the non-porous mannitol with drug powders were used for measuring the tableting properties. Tablets with an identical weight of 150 mg were prepared by manually introducing powders into a flat-faced punch of a hydraulic press at different compaction loads in the range of 100 MPa to 400 MPa. Tablet dimensions were measured using a caliper with an accuracy of 0.001 mm, and the tablet thicknesses were plotted as a function of the applied compaction load. An Instron hardness tester 5943 (Instron, Germany) with a strain rate of 0.2 mm/min and a load capacity of 100 N was also used to determine the tablet hardness.

### 3.6 Particle Sizing and Morphology Studies

#### 3.6.1 Scanning Electron Microscope (SEM)

The powders have been observed using a scanning electron microscope, to show the structures of both the surface and the bulk material. Sample preparation has included placing a small amount of the sample onto a carbon tape on an aluminium sample stab. A standard thickness of 30 nm gold coating has been given for each sample to produce the conductive surface (Emitech, K550X, Quorum Technologies, UK). A Hitachi S4500 FEG- scanning electron microscope with an operating voltage of 5 kV has been used. A wide range of magnifications has been used in the images, and the images have been captured using the software ImageSlave v2.11.
3.6.2 Particle Size Analysis

The particle size distribution was measured by the laser diffraction technique using a Malvern Mastersizer 3000 (Malvern Instruments, UK) with a dry powder feeder unit (Aero S).

3.6.3 BET Surface Area Analysis

Surface area and pore volumes (or pore size distribution) were determined from nitrogen adsorption and desorption isotherms, measured at the temperature of liquid N₂ (77 K) using a surface area analyzer (Quantachrome Autosorb-1). The surface area was calculated from the Brunauer-Emmet-Teller (BET) equations, and the total pore volume was calculated according to the Barrett-Joyner-Halenda (BJH) method. Outgassing at room temperature overnight has been performed for all samples prior to all experiments.

3.7 Other Items of Methods and Equipments

3.7.1 Moisture Content Measurement

The free moisture content (MC, dry basis) has been measured by weighing the sample before and after drying in a fan circulated oven (Labec, Australia) at 85°C for 24 hours.

3.7.2 pH of Aqueous Solution

The pH of the solutions was measured with a pH electrode, InPro 3250 series (Mettler Toledo, M 300, Switzerland).

3.7.3 Statistics

Data in this study have been presented as means ± STD (standard deviation) and were obtained from at least three independent experiments. For statistical analysis, least significant difference (LSD) tests have been performed first for comparisons between different groups, and then one-way ANOVA tests have been performed to determine the overall significance.
of variations. The statistics program IBM SPSS Statistics 22 was employed for all statistical analyses, and differences were considered significant at $P < 0.05$. 
CHAPTER 4  COMBINED DRYING AND CRYSTALLIZATION IN A CONTINUOUS MULTI-STAGE FLUIDIZED-BED DRYER

This chapter reports the investigation of the effects that operating conditions have on the crystallization properties of whey powder in a continuous multi-stage fluidized-bed dryer to achieve the maximum degree of lactose crystallinity within a reasonable overall processing time. Powder was fed at different rates for each fluidization process at different sets of process temperatures, humidities, and residence times using a continuous multistage fluidized bed. The aim was to reduce the time required to crystallize the amorphous-lactose fraction sufficiently to be feasible in an industrial-crystallization process, where each stage will have particular temperatures and relative humidities (Figure 4.1). Based on the earlier findings in dairy powder crystallization using fluidized-bed dryers (Cruz et al., 2005; Nijdam et al., 2008; Yazdanpanah and Langrish, 2011a; 2011b; 2011c), it is expected that the process conditions (temperature and relative humidity) for each stage should depend on the feed powder properties (glass-transition temperature, composition, extent of amorphicity for the lactose) for that stage. A multi-stage fluidized bed processing scheme has been developed to achieve greater control of lactose crystallinity than the control achievable through operating a single stage fluidized-bed dryer on its own.
4.1 Sample Preparation

4.1.1 Fresh Spray-Dried Whey Powder

Aqueous solutions of sweet whey powder (as supplied by Dairy Innovation Australia Limited, DIAL) (35% w/w) were prepared. The solutions were spray dried using a Buchi-B290 Mini Spray Dryer with an inlet temperature of 150°C, an aspirator setting of 100% (38 m³ h⁻¹), a pump rate of 25% (8 mL min⁻¹), and a nozzle air flow rate of 470 L h⁻¹ (40 on the nozzle rotameter scale). These operating conditions caused the outlet temperature to be 90 ± 2°C. Freshly spray-dried milk powder was collected from a vessel at the bottom of a cyclone and instantly fed to the fluidized bed.

4.1.2 Crystalline Whey Powders

In order to create highly-crystalline whey powders (WP), 100 g of fresh spray-dried whey powder was placed in a Petri dish and stored in a sorption box with a saturated NaCl solution (25°C and 75% relative humidity) for two weeks. Every day, the bulk material was gently agitated to break up the caked materials and to mix the powders, exposing all particles to the moisture in the air. Jouppila and Roos (1994b) and Langrish and Wang (2006) showed that the amorphous lactose in milk powder is mostly crystallized under such conditions in two weeks.

Figure 4.1 Multi-stage processing scheme for the fluidized-bed dryer.
4.2 Process Conditions

Table 4.1 represents all the experiments performed for this study. Amorphous powders were produced by spray drying, and then the fluidized-bed dryer was used to process the powders further. Many researchers have studied the sticky behavior of food powders. Yazdanpanah and Langrish (2011a) found the upper limit of fluidization depends on the percentage of lactose crystallinity in the powder (Figure 2.4). Preliminary trials were initially performed to identify the combinations of temperatures, humidities, and residence times to achieve maximum crystallinity of lactose in whey powders with reasonable processing time. It has been found that processing condition of 45°C and 35% relative humidity in the first stage, 55°C and 45% relative humidity in the second stage, and 40°C and 40% relative humidity in the third, allow fluidization to occur through minimizing the chances of bed collapse. These process conditions also allow to maximize the crystallization rate by maintaining an adequately high differential temperature \((T–T_g)\) in different stages and to achieve a greater degree of crystallinity in less time.

The powders were processed at 45°C and 35% relative humidity in the first stage and then 55°C and 45% relative humidity in the second stage and finally 40°C and 40% relative humidity in the third and final stage. These safe process conditions of temperature and humidity were below the upper limits on the relative humidity for which whey powder could be fluidized and avoid cake formation. The residence time in each stage was ten minutes. In the next step, different rates of powder feeding were used for each fluidization process in order to assess the effect of feed rate on the crystallization properties of lactose in the processed whey powder. Therefore, in all experiments, the air temperature, relative humidity, and residence time were kept constant, and the only variable parameter was the feed rate. The degrees of amorphicity for the lactose in the processed powders have been investigated by the techniques described above. Samples were taken after the fluidization process and immediately used for analytical tests (moisture content and gravimetric moisture analysis); otherwise they were kept in sealed bags and in a refrigerator to do X-ray diffraction, FTIR, and Raman spectroscopy on the following day.
4.3 Results and Discussion

Experimental results showed that there were significant improvements in the degree of crystallinity for the lactose in the spray-dried powder by post-processing in the multi-stage fluidized bed at different humidities and temperatures with the same residence time, as shown in Table 4.1. Gravimetric moisture sorption tests were performed on the degree of crystallinity for the lactose in the spray-dried powders and the processed powders and compared with X-ray powder diffraction, Fourier transform infrared spectroscopy, and Raman spectroscopy analyses. The degrees of lactose crystallinity measured using all these methods confirm that the lactose crystallinity of the processed powders has been increased. However, there were significant differences in the estimated degree of crystallinity for lactose by different crystallinity measurement techniques (Table 4.1). Fourier transform infrared spectroscopy and Raman spectroscopy analyses have been reported to be able to measure the degree of surface crystallinity of powders, while X-ray diffraction can be used to investigate the bulk crystallinity in the powders. X-ray diffraction has been reported to have a sensitivity range of 5% to 10% (Gombas et al., 2002). Therefore, the results of X-ray diffraction are more precise than other techniques that have been used here, and it measures the bulk crystallinity rather than surface one.

In scoping experiments of this study was on adjusting the process conditions. However, in the next stage, project aimed to assess the feasibility of increasing the feed rate. Different rates of powder feedings from 0.3 kg h\(^{-1}\) to 2.6 kg h\(^{-1}\) were investigated on the crystallization properties of processed whey powder. The results showed that increasing the rate of powder feeding did not have a significant and specific effect on the degrees of lactose crystallinity for the processed powders (according to their moisture sorption peak heights). The heights of powder bed prior to fluidization were varied from approximately 0.1 cm to 1 cm for 0.3 kg h\(^{-1}\) to 2.6 kg h\(^{-1}\) powder feeding, respectively. The higher bed height may decrease the amount of particle vibration and movement during fluidization and therefore higher chance of agglomeration and subsequent bed de-fluidization. However, the lower bed depth increases the possibility of fine particles being elutriated from the fluidized bed. Thus, the processed powders fed with different rates of powder feeding are not expected to have different degrees of lactose crystallinity since the residence time did not change during the fluidizations. The results show that processed powder with higher degree of lactose crystallinity was achievable for different throughputs at these sets of conditions in the fluidized-bed dryer, although no
clear trend was found between the different rates of powder feeding and the degrees of lactose crystallinity for the processed powders.
Table 4.1 Summary of the experimental results for whey powder processed in the fluidized-bed dryer.

<table>
<thead>
<tr>
<th>Run</th>
<th>Feed rate</th>
<th>Sample</th>
<th>Moisture sorption</th>
<th>Crystallinity measurement (%)</th>
<th>FTIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peak height,</td>
<td>Bulk Crystallinity</td>
<td>875 cm⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(moisture content change, %, kg.kg⁻¹ dry basis)</td>
<td>Surface crystallinity</td>
<td>900 cm⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peak height change, %</td>
<td>XRD</td>
<td>Raman</td>
</tr>
<tr>
<td>Run1</td>
<td>50 g/10 min (0.3 kg h⁻¹)</td>
<td>Spray Dried (35 w/w %)</td>
<td>4.4</td>
<td>50% ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -1st stage</td>
<td></td>
<td>FB -2nd stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -3rd stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run2</td>
<td>80 g/10 min (0.5 kg h⁻¹)</td>
<td>Spray Dried (35 w/w %)</td>
<td>3.5</td>
<td>20% ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -1st stage</td>
<td></td>
<td>FB -2nd stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -3rd stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run3</td>
<td>160 g/10 min (1 kg h⁻¹)</td>
<td>Spray Dried (35 w/w %)</td>
<td>3.3</td>
<td>20% ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -1st stage</td>
<td></td>
<td>FB -2nd stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -3rd stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run4</td>
<td>250 g/10 min (1.5 kg h⁻¹)</td>
<td>Spray Dried (35 w/w %)</td>
<td>3.5</td>
<td>15% ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -1st stage</td>
<td></td>
<td>FB -2nd stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -3rd stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run5</td>
<td>440 g/10 min (2.6 kg h⁻¹)</td>
<td>Spray Dried (35 w/w %)</td>
<td>3.4</td>
<td>18% ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -1st stage</td>
<td></td>
<td>FB -2nd stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -3rd stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run6</td>
<td>440 g/10 min (2.6 kg h⁻¹) Repeat of Run 5</td>
<td>Spray Dried (35 w/w %)</td>
<td>2.5</td>
<td>40% ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -1st stage</td>
<td></td>
<td>FB -2nd stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FB -3rd stage</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.3.1 Moisture Sorption Tests

Processed milk powders showed less moisture sorption and more lactose crystals, leading to a reduction in the degree of lactose amorphicity for spray-dried milk powder by post-processing in a series of laboratory-scale fluidized bed dryers. The net percentage changes in mass (dry basis) as a function of time for whey powder, which has been processed in both spray- and fluidized beds, have been displayed in Figure 4.2. The peak height (the distance between the peak and the plateau of the crystallization process) for each powder characterised the degree of lactose amorphicity for that material. Figure 4.2 has demonstrated the significant decrease in amorphicity (less sorption) of lactose after processing the powders at different temperatures and humidities.

The peak height analysis (Table 4.1) showed that the peak heights for spray-dried whey powders at different runs were 2.5-4.4%. The peak height columns in Table 4.1 showed progressive decreases in amorphicity of lactose and the lower amount of sorption for all runs that were caused by different humidities, temperatures, and residence time within different stages in the fluidized bed, as shown in Figure 4.2 and Table 4.1. By increasing the process temperature and/or increasing the water activity by sorbing more moisture at a higher relative humidity in the first two stages, $T-T_g$ increased and the crystallization time decreased, according to the Gordon–Taylor and Williams–Landel–Ferry equations (Gordon and Taylor, 1952, equation 2.1; Williams et al., 1955, equation 2.3). Therefore, as the results show, by increasing the temperatures and relative humidities in different stages, the sorption peak height decreased, suggesting that less amorphous lactose (the most hygroscopic component) remained in the whey powder.
4.3.2 X-Ray Diffraction (XRD)

In this study, XRD analysis has been used to evaluate the formation of lactose crystals and the improvement in the extent of crystallinity for different powders. The locations of the peaks in the reference data from previous studies have been used to identify various types of lactose crystals. The peaks for lactose are likely to be found at the following angles: \(2\theta = 12.5^\circ, 16.4^\circ, 20.0^\circ, \) and \(20.1^\circ\) for \(\alpha\)-lactose monohydrate; \(10.5^\circ, 20.9^\circ, \) and \(21.0^\circ\) for anhydrous \(\beta\)-lactose; \(19.1^\circ, 20.0^\circ,\) and \(20.1^\circ\) for the mixture of anhydrous \(\alpha:\beta\) with a molar ratio of 5:3; and \(19.5^\circ\) for the mixture of anhydrous \(\alpha:\beta\) with a molar ratio of 4:1 (Jouppila et al., 1997; Haque and Roos, 2005).

To define the quantitative determination of crystallinity for whey powder, X-ray diffractograms of the samples with different amorphous content were recorded. There are two acceptable methods of X-ray diffraction analysis for quantitative studies; peak height (intensities) measurement and measurement of the area under the peak. It has been suggested by Gavish and Friedman (1973) that peak height analysis of X-ray diffraction data is

Figure 4.2 Results of the moisture sorption behaviour of the spray-dried whey powder compared with whey powder that was processed after being exposed to different conditions in the fluidized bed (sorption test at 25°C and 75% relative humidity) (Run 1).
preferable to peak area analysis since both showed a similar level of reproducibility, and the peak height analysis is easier to perform especially when the curves are symmetrical.

On the diffractogram of the mixture, the intensity of the diffraction (counts/second) for the individual components is proportional to the quantity of the components in the mixture. Hence quantification is possible provided that the total amount of sample (and its preparation) are kept constant from experiment to experiment (Gombas et al., 2002). In this investigation, spray-dried powder was considered to be 0% crystalline, and physical mixtures of amorphous and crystalline whey powders were prepared to give different crystalline contents by mass.

The curves here have been observed to be symmetrical, so the heights of the curves can also describe the intensity. Based on these references, the peak at $2\theta = 20^\circ$ was taken as the characteristic peak to measure the intensity when crystalline lactose for assessing the relative crystallinity of different whey powders (Table 4.2). The intensity of the characteristic peak at $2\theta = 20.0^\circ$ for $\alpha$-lactose monohydrate with FB processed whey powder (Run 3) was found to be 196 cps (Figure 4.3), while the peak height for spray-dried powder (considered to be 0% crystalline), and powder mixtures of 10% crystallinity and 20% crystallinity were 88 cps, 151 cps, and 413 cps, respectively. Comparing the intensity values of the characteristic peak at $2\theta = 20.0^\circ$ for different runs with those for the 10% and 20% crystallinity mixtures of whey powders suggested that the overall extent of crystallinity for processed whey powders has been between 10% and 20% within the processes studied here (Run 3) (Figure 4.3).

In order to quantitatively determine the degree of lactose crystallinity for whey powder, the intensities of the characteristic peaks at $2\theta = 20.0^\circ$ for 0% crystalline powder and mixtures with 10%, and 20% lactose crystallinity have been fitted to a polynomial equation. A second-order polynomial trendline ($Y = 0.995x^2 - 3.65x + 88$) at $2\theta = 20.0^\circ$ appeared to fit the data points closely (Figure 4.3). This function was then applied to estimate the degree of lactose crystallinity for the spray-dried whey powders and the FB processed powders (Table 4.2).
Table 4.2 XRD intensity values and the estimated degree of crystallinity at chosen 2θ values for the whey powders used here.

<table>
<thead>
<tr>
<th>Sample (degree of crystallinity)</th>
<th>Peak at 2θ = 12° intensity, cps</th>
<th>Peak at 2θ = 20° intensity, cps</th>
<th>Degree of crystallinity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray dried whey powder (0% Crystallinity)</td>
<td>55</td>
<td>88</td>
<td>0</td>
</tr>
<tr>
<td>Whey Powder with 10% Crystallinity</td>
<td>116</td>
<td>151</td>
<td>10</td>
</tr>
<tr>
<td>Whey Powder with 20% Crystallinity</td>
<td>179</td>
<td>413</td>
<td>20</td>
</tr>
<tr>
<td>FB-Processed whey powder Run 3</td>
<td>73</td>
<td>196</td>
<td>12.4</td>
</tr>
<tr>
<td>FB-Processed whey powder Run 4</td>
<td>59</td>
<td>159</td>
<td>10.5</td>
</tr>
<tr>
<td>FB-Processed whey powder Run 5</td>
<td>94</td>
<td>209</td>
<td>13.0</td>
</tr>
<tr>
<td>FB-Processed whey powder Run 6</td>
<td>176</td>
<td>318</td>
<td>17.1</td>
</tr>
</tbody>
</table>
Figure 4.3 X-ray diffraction patterns for spray dried whey powder compared with FB processed whey powder (Run 3), 10%, and 20% crystalline whey powders.

4.3.3 Estimating the Degree of Surface Crystallinity Using Raman and FTIR

Raman and Fourier Transform Infrared spectroscopy (FTIR) has been reported to be able to distinguish between amorphous and crystalline lactose (Katainen et al., 2005; Niemelä et al., 2005; Listiohadi et al., 2009; Islam et al., 2010; Yazdanpanah and Langrish, 2013a). Whey powder consists mainly of lactose, and therefore Raman and FTIR were used to distinguish the degree of crystallinity for the spray-dried and fluidized-bed whey powders.

Physical mixtures of whey powders, with an amorphous lactose content of 0-100% (w/w) (0%, 10%, 20%, 30%, 40%, 50%, and 100%), were prepared to estimate the Raman band ratio and the FTIR peak heights at 875 cm\(^{-1}\), 900 cm\(^{-1}\), and 915 cm\(^{-1}\) as a function of the amorphous/crystalline lactose contents. The Raman measurements of the physical mixed samples are shown in Figure 4.4. It can be seen that, with increasing lactose crystallinity, the peak height at 476 cm\(^{-1}\) increases as well. The Raman band ratio as a function of the amorphous content was estimated, and a polynomial second order trendline appeared to fit the data points with a correlation of determination \(R^2 = 0.99\), as shown in Figure 4.5. The function was then used to estimate the degree of lactose crystallinity for the spray-dried whey
powders and the fluidized powders, as shown in Table 4.1. The lactose in the spray-dried whey powders have a lower degree of lactose crystallinity compared with the fluidized-bed powders, which indicates that the fluidized-bed process increased the surface crystallinity of lactose.

![Raman spectra of whey powder with varying degrees of lactose crystallinity.](image)

**Figure 4.4** Raman spectra of whey powder with varying degrees of lactose crystallinity. The intensity increases at 476 cm\(^{-1}\) with increasing lactose crystallinity. The band areas used for the calculations are shown in Figure 4.5.
Figure 4.5 Ratio of the Raman band areas as a function of the amorphous lactose content for the physical mixtures. The correlation was based on the average values of the amorphous lactose content.

The FTIR results for the physical mixtures show an increase in peak height with increasing lactose crystallinity in the region from 860 cm\(^{-1}\) to 930 cm\(^{-1}\) and at a wavelength of 1260 cm\(^{-1}\), as indicated in Figure 4.6, which seems to agree with Listiohadi et al. (2009). Further, the region between 860 cm\(^{-1}\) and 930 cm\(^{-1}\) has been normalized for better comparison and further analysis, as shown in Figure 4.6. The peak at 1260 cm\(^{-1}\) was not further considered, since it corresponds to the vibration of the three amide groups in proteins, as indicated by Cai and Singh (2000). This research focuses on the lactose crystallisation and the characteristic bands in the region between 860 cm\(^{-1}\) and 930 cm\(^{-1}\) are probably due to configurational and conformational transformations of the carbohydrate molecules, as mentioned by Listiohadi et al. (2009).

The FTIR measurements of the physically mixed samples were used to find the peak heights at wave numbers of 875 cm\(^{-1}\), 900 cm\(^{-1}\), and 915 cm\(^{-1}\), which were plotted as a function of the amorphous lactose content, as shown in Figure 4.7. The equations of the trendlines fitted through the data points of Figure 4.8, as well as the \(R^2\) values, have been summarised in Table 4.3. A second order polynomial trendline fitted all the data points for all the different peak heights well, with an \(R^2\) above 0.98.
Figure 4.6 FTIR spectra of whey powders with varying degrees of lactose crystallinity. The absorbance increases at 875 cm$^{-1}$ and 900 cm$^{-1}$ with increasing lactose crystallinity. The region in the square was used to determine the areas underneath the peaks, as shown in Figure 4.7.
Figure 4.7 FTIR spectra of whey powders normalized at 928 cm\(^{-1}\), with varying degrees of lactose crystallinity in the region from 860 cm\(^{-1}\) to 930 cm\(^{-1}\).
Figure 4.8 The peak heights at 875 cm\(^{-1}\), 900 cm\(^{-1}\) and 915 cm\(^{-1}\) as function of the amorphous lactose content. A second order polynomial trendline has been fitted through the data points. The data points are the averages of five measurements.

Table 4.3 Summary of the trendline equations fitted through the data points of Figure 4.8.

<table>
<thead>
<tr>
<th>Peak</th>
<th>Trendline equation</th>
<th>(R^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>875</td>
<td>3E-06x(^2) - 0.0005x + 0.0292</td>
<td>0.99</td>
</tr>
<tr>
<td>900</td>
<td>4E-07x(^2) - 0.0001x + 0.0132</td>
<td>0.98</td>
</tr>
<tr>
<td>915</td>
<td>3E-07x(^2) - 9E-05x + 0.0068</td>
<td>0.99</td>
</tr>
</tbody>
</table>

The degrees of lactose crystallinity in the samples (as measured by FTIR) were estimated using the peak heights at 875 cm\(^{-1}\), 900 cm\(^{-1}\), and 915 cm\(^{-1}\), since those peaks corresponded to the characteristic bands for monosaccharides, due to conformational transformations of the carbohydrate molecules as indicated by Listiohadi et al. (2009). In addition, the results have been compared with the Raman method (Table 4.1). The results show that the degrees of lactose crystallinity estimated at the peak height 915 cm\(^{-1}\) are similar to the degrees of lactose crystallinity estimated with the Raman method. On the other hand, the degrees of lactose
crystallinity estimated at the peaks of 875 cm\(^{-1}\) and 900 cm\(^{-1}\) are approximately three times larger compared with Raman and the degree of lactose crystallinity estimated at the peak 915 cm\(^{-1}\). Overall, the Raman and FTIR results indicated that the fluidized-bed process increased the surface lactose crystallinity of the whey powders, since the spray-dried powders (0% lactose crystallinity) appeared to have a lower degree of lactose crystallinity compared with the fluidized-bed powders.

The spray-dried powders showed a larger sorption peak height compared with the fluidized-bed processed powders, which indicates that the spray-dried lactose in the powders are more amorphous lactose compared with the fluidized-bed powders. The trend from the moisture sorption test appears to have been confirmed by the FTIR and Raman results, where the spray-dried whey powders have a lower surface lactose crystallinity compared with the fluidized-bed powders.

### 4.3.4 Particle Size Analysis

The particle size distribution was measured for spray-dried and processed whey powders. Each test was carried out two or three times, and the average mean particle size was reported. Particle size analysis of processed materials has shown some particle agglomeration for the processed powders compared with the spray-dried whey powders. The agglomeration and size enlargement was observed for all types of processed powders due to processing at high humidity conditions that caused particles to stick together during the process. The particles have been enlarged from the size of 7 ± 1 \(\mu\)m (\(D[3,2]\), Sauter mean diameter (SMD) for amorphous whey powder) to 59 ± 14 \(\mu\)m (\(D[3,2]\) for a processed powder). The agglomeration and particle enlargement was not necessarily the result of crystallization of lactose in powders; however agglomeration was not avoidable in this technique due to processing by high-humidity air and at a temperature above the glass-transition temperature of the powders. The agglomerated powders might result in better dissolution than the spray-dried powder since they could sink and disperse easier in water despite the higher degree of lactose crystallinity compared with that of spray-dried powders. The bulk densities (\(\rho_b\)) of the powders, which was the mass of the powders divided by the total volumes they occupied for the spray-dried and processed whey powders, were 665 ± 5 kg m\(^{-3}\) and 620 ± 10 kg m\(^{-3}\), respectively.
4.3.5 Surface Morphology

Microscopy has also been applied to obtain information on the lactose crystallinity of powders. SEM micrographs show some morphological changes for whey powders after processing in the fluidized beds at different humidities and temperatures. Crystals appeared to be formed on the surface and inside the particles. Figure 4.9 shows the whey powder before and after processing (crystallization) in a fluidized-bed dryer. The surface of the spray-dried whey powder (produced by conventional spray drying) appeared to be amorphous (Figure 4.9 A), while the processed whey powder had a heavily textured appearances, suggesting that part of the particle (the lactose) is crystalline (Figure 4.9 B:D).

The processed powders remained free-flowing at room temperature and humidity for at least three days (Figure 4.10 C, D), while the raw powder has created a solid cake and become stuck in the Petri dish (Figure 4.10 A, B). The room conditions during the three-day test were 19–25°C and 55–65% relative humidity. Cake formation and agglomeration are other physical properties that are strongly affected by the surface structure of the particles, so the crystalline surfaces developed by this experiment prevented bridge formation between particles due to more hygroscopic amorphous lactose. The crystal texture on the surface appeared to preserve the particle core from deteriorative changes and also appeared to enhance the powder's physical properties.
Figure 4.9 A) Surface of spray-dried whey powder (amorphous) produced in a conventional spray-drying process at a high magnification. B:D) Morphological structure of processed whey powder in the fluidized bed.
4.4 Conclusions

This chapter has reported the effects of operating conditions on the crystallization behaviour of whey powders. Powder was fed at different rates to the continuous multistage fluidized bed, where each stage had particular temperatures and relative humidities. Gravimetric moisture sorption tests were performed on the processed powders to assess the degree of lactose crystallinity and compared using X-ray Powder Diffraction, FTIR, and Raman spectroscopy analyses. The results showed significant improvements in the degree of lactose crystallinity for the powders. Experimental results showed that there were significant changes in lactose crystallinity between samples that were processed (crystallized) at different humidities and
temperatures, and increasing the rate of powder feeding did not have a significant effect on the degrees of lactose crystallinity for the processed powders. The results of this study help when choosing the processing conditions to produce and control lactose crystallization in carbohydrate-containing dairy powders during spray and fluidized-bed processing.
CHAPTER 5 EFFECT OF ACIDITY ON IN-PROCESS CRYSTALLIZATION OF LACTOSE DURING SPRAY DRYING

Spray drying of acid whey is a significant problem for the dairy industry due to its high content of lactic acid. The main ingredients of acid whey are lactose, protein, and lactic acid. Due to the importance of lactose in the food and pharmaceutical industries, there have been extensive studies on the crystallization behavior of lactose (Roos and Karel, 1992; Jouppila et al., 1998). Studying the effect of lactic acid on the crystal growth of lactose is necessary due to its fundamental and commercial importance in food processing. However, there is little known about the lactose crystallization behavior of lactose in the presence of lactic acid. Bhandari (2008) found that lactic acid significantly influenced the crystallization of lactose during drying by decreasing glass-transition temperature of lactose and the depression of the crystallization temperature. He also found that adding lactic acid to the lactose solutions decreased the yield the spray-drying process. It has been found that the presence of proteins at low concentrations (< 5 w/w %) significantly affects the product yield and crystallinity (Haque and Roos, 2004). The crystallization kinetics of lactose/protein solutions, especially when lactic acid is added to the solution, for example acid whey, have not been studied in terms of in-process crystallization during spray drying. It is difficult to predict the performance of the crystallization for commercial acid whey due to the presence of other impurities. Therefore in one series of experiments in this paper, only solid-phase crystallization of lactic acid and lactose was carried out. Then further experimentation has been done on the crystallization behavior of powders produced during spray drying using solutions of lactose/protein/lactic acid to imitate the composition of typical acid whey solutions. Different methods have been used to assess the degree of crystallinity for the spray-dried products produced with different concentrations of lactic acid.

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1 The content of this chapter has been published as the following paper:
5.1 Materials and Methods

5.1.1 Sample Preparation

One series of experiments was carried out by varying the composition of the solution with additions of whey protein isolate from 1 to 10% (w/w), whilst maintaining the level of lactose concentration in solution at 10% (w/w). Further experimentation has been done by adding lactose and whey protein isolate to create solutions with 15% (w/w) lactose and 5% (w/w) WPI (lactose lactose/WPI ratios of 75:25 (w/w)), and then varying the composition of the solution with additions of lactic acid from 1% to 20% (w/w). Each solution was made up to a total weight of 100 g. The composition of the solution was used at that ratio, in order to imitate the typical composition of whey solution(s) regarding the amounts of sugar and protein (Panesar et al., 2007; Jelen, 2009). All solutions were magnetically stirred at the room temperature of 25°C for at least 30 minutes, so a clear solution was obtained without any visible crystals being present. The clear solutions were then spray dried. The pH of the solutions was measured with a pH electrode, InPro 3250 series (Mettler Toledo, M 300, Switzerland).

5.1.2 Operating Conditions for Spray Drying

The solutions were spray dried using a Buchi-B290 Mini Spray Dryer with an inlet gas temperature of 180°C, an aspirator setting of 100% (38 m³ h⁻¹), a pump rate of 25% (8 mL min⁻¹), and a nozzle air flow rate of 470 L h⁻¹ (40 on the nozzle rotameter scale). These operating conditions caused the outlet gas temperatures to be 108 ± 3°C and 112 ± 4°C for lactose and lactose/WPI solutions, respectively. All experiments were performed in triplicate. Freshly spray-dried powder was collected from a collection vessel at the bottom of a cyclone and was immediately used for analytical tests (moisture content, MDSC analysis and gravimetric moisture analysis); otherwise the powders were kept in sealed bags and in a refrigerator for X-ray diffraction tests on the following day.
5.2 Results and Discussion

5.2.1 Yield from Spray Drying

It can be seen, in Tables 5.1 and 5.2 and Figure 5.1, that adding lactic acid to the lactose and to the lactose/WPI solutions decreased the yield (or recovery) of the spray-drying process, which agreed well with the result of Bhandari (2008). This decrease in the yield can be attributed to stickiness during the spray-drying process. A key explanation for the steady downward trend in the yield can be seen in the work of Hanus and Langrish (2007). In their study, it was found that direct deposition of very wet particles on the dryer walls is a very significant phenomenon in small-scale spray dryers, which may be linked with the limited drying time that is possible in the equipment and corresponding increase in moisture content of product when increasing the lactic acid concentration (Figure 5.2). Another reason (not mutually exclusive) for this yield behavior might also be due to the powders having lower glass-transition temperatures (Jouppila and Roos, 1994a; Roos, 1995; Bhandari and Howes, 1999). This situation means that, as the lactic acid concentrations increase, the glass-transition temperatures decrease, making the particles stickier (Table 5.1). The statistical analysis of the yield data showed that even adding 1% (w/w) of lactic acid to the lactose solution significantly decreased the yield of the process to 60%. However, with increasing the lactic acid content to more than 5% (w/w), producing dry powder was impossible (Table 5.1). However, adding 2% (w/w) lactic acid to the lactose/WPI solution did not have a significant effect on the yield of the process, whereas increasing the amount of lactic acid concentration to 15% (w/w) significantly decreased the yield of the process to 26% (Table 5.2). The higher yield of the spray-drying process for lactose/WPI solutions than lactose solutions with the same concentration of lactic acid can be explained by the decrease in wall deposition during spray drying due to the surface coverage of proteins, which remain non-sticky due to their higher glass-transition temperatures (Adhikari et al., 2009; Wang and Langrish, 2010).
Figure 5.1 Effect of the lactic acid concentration on the yield of the spray-dried products.

Figure 5.2 Effect of the lactic acid concentration on the moisture contents of the spray-dried products.
Table 5.1 Summary of the experimental conditions used in spray drying for lactose-lactic acid solutions (lactose 10% w/w), inlet gas temperature of 180°C and outlet gas temperature of 108 ± 3°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Lactic acid concentration (% w/w)</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray-dried powder</td>
<td>Yield (% w/w)</td>
<td>71±2a</td>
<td>60±2b</td>
<td>44±1c</td>
<td>22±3d</td>
<td>*NA</td>
</tr>
<tr>
<td></td>
<td>Moisture content, % (dry basis)</td>
<td>1.3±0.1a</td>
<td>2.7±0.5b</td>
<td>7.4±0.8c</td>
<td>8.1±0.5c</td>
<td>*NA</td>
</tr>
<tr>
<td>Solution</td>
<td>pH</td>
<td>6.7±0.1a</td>
<td>2.53±0.01b</td>
<td>2.24±0.01c</td>
<td>2.11±0.03d</td>
<td>1.91±0.01c</td>
</tr>
<tr>
<td>Sorption test</td>
<td>Peak height, (% moisture content change, % kg.kg⁻¹ dry basis of lactose)</td>
<td>6±1a</td>
<td>5.5±0.4a</td>
<td>4±1b</td>
<td>0.7±0.3c</td>
<td>*NA</td>
</tr>
<tr>
<td>Modulated differential scanning calorimetry</td>
<td>Glass transition temperature (°C)</td>
<td>82±8a</td>
<td>64±2b</td>
<td>40±10c</td>
<td>20±10d</td>
<td>*NA</td>
</tr>
<tr>
<td></td>
<td>Crystallization temperature (°C)</td>
<td>153±9a</td>
<td>142±7a</td>
<td>90±10b</td>
<td>69±6c</td>
<td>*NA</td>
</tr>
<tr>
<td></td>
<td>Latent energy of Crystallization (J/g)</td>
<td>89±2a</td>
<td>60±10b</td>
<td>46±4b</td>
<td>30±4c</td>
<td>*NA</td>
</tr>
<tr>
<td>X-ray diffraction</td>
<td>Intensity (cps)</td>
<td>140±10a</td>
<td>270±20b</td>
<td>440±20c</td>
<td>570±50d</td>
<td>*NA</td>
</tr>
</tbody>
</table>

All values are mean ±standard deviation of at least two replicate analyses. For each property, means in a row followed by different letters (a-e) are significantly different at p = 0.05. *NA: not available.
Table 5.2 Summary of the experimental conditions used in spray drying for lactose-WPI-lactic acid solutions (lactose 15% w/w) + (WPI 5% w/w), inlet gas temperature of 180°C and outlet gas temperature of 112 ± 4°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Lactic acid concentration (%, w/w)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>7</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray-dried powder</td>
<td>Yield (%, w/w)</td>
<td>81±5a</td>
<td>77±3a</td>
<td>75±6a</td>
<td>58±3b</td>
<td>42±1c</td>
<td>26±7d</td>
<td>*NA</td>
</tr>
<tr>
<td></td>
<td>Moisture content,% (dry basis)</td>
<td>1.2±0.2a</td>
<td>1.2±0.3a</td>
<td>3.5±0.2b</td>
<td>5.1±0.3c</td>
<td>5.9±0.6d</td>
<td>6.5±0.1e</td>
<td>*NA</td>
</tr>
<tr>
<td>Solution</td>
<td>pH</td>
<td>6.7±0.1a</td>
<td>3.7±0.3b</td>
<td>3.2±0.2c</td>
<td>2.5±0.1d</td>
<td>2.3±0.1c</td>
<td>2.1±0.1f</td>
<td>1.98±0.08g</td>
</tr>
<tr>
<td>Sorption test</td>
<td>Peak height, (moisture content change, %, kg.kg⁻¹ dry basis of lactose)</td>
<td>6±1a</td>
<td>5.6±0.4b</td>
<td>4.8±0.3b</td>
<td>4.4±0.6b</td>
<td>4.5±0.5b</td>
<td>4.3±0.4b</td>
<td>*NA</td>
</tr>
<tr>
<td>X-ray diffraction</td>
<td>Intensity (cps)</td>
<td>80±10a</td>
<td>94±4a</td>
<td>150±20b</td>
<td>160±20b</td>
<td>300±20c</td>
<td>380±70d</td>
<td>*NA</td>
</tr>
</tbody>
</table>

All values are mean ±standard deviation of at least two replicate analyses. For each property, means in a row followed by different letters (a-g) are significantly different at p= 0.05. *NA: not available
5.2.2 Assessment of the Particle Crystallinity by Moisture Sorption Tests

Figure 5.3 illustrates the moisture sorption behavior (moisture content change, %, kg.kg$^{-1}$ dry basis of lactose) for spray-dried products of lactose solutions at different lactic acid concentrations, which shows a gradual improvement in lactose crystallinity through less moisture sorption, representing lower degrees of lactose amorphicity in the powders. There were significant changes between different spray-dried lactose powders with different lactic acid concentrations. The first curve (highest peak) is the moisture sorption by powders from the spray drying of pure lactose solutions (0%, w/w), which were mostly amorphous. The highest peak shows the greatest amorphicity of lactose compared with the other spray-dried powders. The other curves (for example, Figure 5.3, curve 4) show a significant reduction in moisture sorption by spray-dried powder from lactose solutions with 5% (w/w) lactic acid.

Increasing the lactic acid concentration in the lactose solutions significantly decreases the degree of lactose amorphicity in the spray-dried powders, which leads to lower peak heights. The sorption peak heights for lactose can be altered from 6% ± 1 % to about 0.7% ± 0.3%. The statistical analysis of the peak height data showed that increasing the lactic acid concentration from 1% to 5% (w/w) significantly decreased the peak heights for spray-dried powder (Figure 5.4).
Figure 5.3 Moisture sorption behaviour of the spray-dried products from lactose for different lactic acid concentrations (the sorption test environment was at a temperature of 25°C and 75% relative humidity).

The net percentage changes in mass (dry basis) as a function of time for spray-dried lactose/WPI mixtures with different concentrations of lactic acids are displayed in Figure 5.5, which demonstrates the significant decrease in lactose amorphicity (less sorption) when increasing the lactic acid concentrations in the lactose/WPI solutions. The statistical analysis of the moisture sorption behaviour also showed that adding lactic acid to the lactose/WPI solution had a significant effect on the peak heights of the spray-dried powders, where increasing the amount of lactic acid concentration from 1% to 15% (w/w) significantly decreased the peak heights from 4.6% ± 0.3% to 2.9% ± 0.6% (Table 5.2).

The sorption peak heights for lactose can be altered from 6% ± 1% to about 0.7% ± 0.3%, compared with 6% ± 1% to 4.3% ± 0.4% for the spray-dried lactose/WPI mixtures. The presence of proteins during the spray drying of the lactose/WPI mixtures is likely to reduce the extent of crystallization for lactose during spray drying.
5.2.3 Further Assessment of the Particle Crystallinity by MDSC

The MDSC results of spray-dried powders from lactose solutions with different lactic acid concentrations showed very clear phase transitions during the thermal analysis, while those for lactose/WPI solutions were complicated to analyze due to multiple components being present in
the particles (Figure 5.6). The presence of protein, fat, additives, and mineral contents in whey isolate powder made it difficult to distinguish each transition in the thermogram separately (Vuataz, 2002), because the transitions of each component may have overlapped with those of lactose.

The MDSC results (Figure 5.7) suggest that increasing the lactic acid concentration in the lactose solutions decreased the glass transition and crystallization temperatures of the spray-dried powders. There is a downward trend in the latent energy of crystallization for the spray-dried products with increasing acid concentrations, which indicates a decrease in the amorphous content of the spray-dried powders. The downward trends of glass-transition temperatures with increasing lactic acid concentrations are similar to the results of Bhandari (2008). The glass-transition temperature of pure lactose was 82 ± 8°C, and the crystallization peak appeared at 153 ± 9°C, with the exothermic heat of crystallization being 89 ±2 J/g. The corresponding figures for spray-dried powders from lactose solutions with 5% (w/w) lactic acid concentrations significantly decreased to 20 ± 10°C, 30 ± 4°C, and 69 ± 6 J/g, respectively (Table 5.1).

The statistical analysis of the MDSC results showed that increasing the lactic acid concentration from 1% to 5% (w/w) significantly decreased all of these values (Table 5.1) (the glass-transition temperature, the crystallization temperature, and the latent heat of crystallization).
Figure 5.6 Thermal transitions during MDSC scans of the spray-dried products from lactose solutions for different lactic acid concentrations.

The results from all these methods agree well with the results from the moisture sorption tests and suggest that the crystallinity of the lactose powders increased with greater lactic acid concentrations. The results suggested that, when the lactic acid concentrations increased, less amorphous lactose (the most hygroscopic component) remained in the spray-dried powder, which could be due to the greater temperature difference (\(T-T_g\)) and consequently the decrease in the crystallization time, according to the Gordon–Taylor and Williams–Landel–Ferry equations (2.1, Gordon and Taylor, 1952; equation 2.3, Williams et al., 1955).
Figure 5.7 Effect of lactic acid concentration on the glass-transition temperatures, the crystallization temperatures, and the latent energies of crystallization for the spray-dried products from lactose solutions.

5.2.4 X-Ray Diffraction (XRD)

In this study, XRD analysis has been used to evaluate the formation of lactose crystals and the improvement in the extent of crystallinity for different powders. The different types of lactose crystals were identified by the location of peaks in the reference data of previous studies. The most noted representative peaks for crystalline carbohydrates have been assigned at 2θ= 12.5°, 16.4°, 20.0°, and 20.1° for α-lactose monohydrate; 10.5°, 20.9°, and 21.0° for anhydrous β-lactose; 19.1°, and 21.1° for the mixture of anhydrous α:β with a molar ratio of 5:3; and 19.5° for mixture of anhydrous α:β with a molar ratio of 4:1 (Simpson et al., 1982; Drapier-Beche et al., 1997; Jouppila et al., 1997; Haque and Roos, 2005). When the curves are symmetrical, the height of the curves can also describe the intensity. In this investigation, based on these references, the peak at 2θ= 20.1° was taken as the characteristic peak to measure its intensity for finding the relative crystallinity of different powders (Tables 5.1 and 5.2). The diffraction patterns for spray-dried lactose with different lactic acid concentrations show clear sharp peaks associated with α-lactose monohydrate at high intensities (2θ= 12.5°, 20.0°, and 20.1°). There is no distinguishable peak for anhydrous β-Lactose, and the peak intensities for the mixture of anhydrous α:β lactose...
with different molar ratios at 19.1° and 19.5° are relatively low. Table 5.1 and Figure 5.8 show some improvement in the degree of crystallinity for lactose powders with increasing lactic acid concentrations. The intensity of the characteristic peak at 2θ = 20.1° for the spray-dried lactose without lactic acid was found to be 140±10 cps while those for the spray-dried lactose with 1% (w/w), 3% (w/w), and 5% (w/w) lactic acid concentrations were 270 ± 20 cps, 440 ± 20 cps, and 570 ± 50 cps, respectively. Simply comparing the intensity values of the characteristic peak at 2θ= 20.1° for different lactic acid concentrations suggests that the crystallinity of the lactose increased by increasing the lactic acid concentrations in lactose solutions. The statistical analysis of the XRD results showed that adding lactic acid to the lactose solutions had a significant effect by increasing the crystallinity of lactose (Table 5.1).

For lactose/WPI feed-solutions, Table 5.2 and Figure 5.9 show that adding lactic acid increased the crystallinity of lactose powders to some extent. This increase was considerable when more than 5% (w/w) lactic acid was added to the solution. The diffraction patterns are similar to those of spray-dried lactose, which show clear sharp peaks associated with α-lactose monohydrate at high intensity (2θ= 20.0° and 20.1°) and indicate that most of the lactose crystals are in the α-monohydrate form. There is no distinguishable peak for anhydrous β-lactose, and the peak intensities for the mixture of anhydrous α:β anomers with different molar ratios at 19.1° and 19.5° are relatively low. The statistical analysis of the XRD results also showed that adding lactic acid to the lactose/WPI solution had a considerable effect on increasing the intensity values of spray-dried powder, where increasing the lactic acid concentration from 1% to 15% (w/w) significantly increased the intensity values from 80 ± 10 cps to 380 ± 70 cps (Table 5.2).
Figure 5.8 X-ray diffraction patterns of the spray-dried products from lactose solutions for different lactic acid concentrations.
Figure 5.9 X-ray diffraction patterns of the spray-dried products from lactose-WPI solutions for different lactic acid concentrations.

5.3 Conclusions

This chapter describes experiments in which lactic acid, in various proportions, was added to lactose and lactose/WPI solutions to investigate the effect of acidity on lactose crystallization. Higher concentrations of acid appear to increase the extent of lactose crystallization during spray drying. The sorption peak heights for lactose were altered from 6% ± 1% to about 0.7% ± 0.3% for lactose/lactic acid mixtures and from 6% ± 1% to 4.3% ± 0.4% for spray-dried lactose/WPI/lactic acid mixtures. However, the yield from spray drying lactose/lactic acid was significantly decreased at higher concentrations of acid, and the yield for lactose/WPI/lactic acid solutions was higher than lactose solutions with the same concentration of lactic acid, as expected, due to the surface coverage of proteins when using WPI. The degrees of crystallinity measured using MDSC and XRD methods agreed well with the results of the moisture sorption tests and confirm that the crystallinity of the lactose increased with increasing lactic acid
concentration. This increase in crystallinity may be due to increasing the \( T-T_g \) difference (with the low \( T_g \) of lactic acid) and consequently decreasing the crystallization time, according to the Gordon–Taylor and Williams–Landel–Ferry equations (2.1 and 2.3, respectively). The results of this study have implications for choosing processing conditions to control crystallization in carbohydrate-containing dairy powders and also powders of acid-rich foods, such as fruit juices, during spray and fluidized-bed processing.
CHAPTER 6  A NEW TEMPLATING APPROACH FOR HIGH-POROSITY SPRAY-DRIED PARTICLE PRODUCTION²

In this chapter, a new production process is used to create highly-porous powder templates through the spray drying of lactose solutions containing ethanol-soluble food-grade acids, such as lactic acid, citric acid, boric acid, and ascorbic acid, as templating agents and then removing these acids by ethanol washing of the spray-dried powders. This chapter has also investigated the effect of different concentrations for various templating acids on the porosity of the final products from a new templating approach, and the extents of in-process crystallization for the lactose/templating acids powders have been studied during spray drying.

It has been found in Chapter 5 that significant increases in the degrees of crystallinity for the final spray-dried products of lactose solutions have occurred at increasing lactic acid concentrations, and the yields from spray drying have also been significantly decreased at higher concentrations of lactic acid. This increase in crystallinity may be due to increasing the $T-T_g$ difference (with the low $T_g$ of lactic acid) and consequently decreasing the crystallization time, according to the Gordon–Taylor and Williams–Landel–Ferry equations. The increase in the rate of lactose crystallization at low pH may also be connected with the increase in the mutarotation rate and the rate of orientation of lactose molecules into the crystals (Twieg and Nickerson, 1968; Nickerson and Moore, 1974; Jenness, 1988; Singh et al., 1991).

The effect of glass-transition temperature and strength of the acid (pH of the solution) on the degree of crystallinity for lactose in spray-dried powders is critical, with implications for the performance of the templating approach using acidic templates. Therefore, the aim of this research is to investigate the effect of using different concentrations for various food-grade acids, such as lactic acid, citric acid, boric acid, and ascorbic acid, on the degree of crystallinity for spray-dried lactose powders and the porosity of the ethanol-washed powders. The results of this

² The content of this chapter has been published as the following paper:  
study have implications in choosing the best processing conditions to control the extent of lactose crystallization for producing spray-dried powders with high concentrations of surface asperities and large specific surface areas in order to increase the dissolution rates of food products, such as food infusions, and also in flavoring or encapsulating processes.

6.1 Materials and Methods

6.1.1 Sample Preparation

In order to investigate and report the effects of different templating acid concentrations on the BET surface areas of lactose, experiments were carried out by varying the composition of the solutions with different amounts of templating acids (citric acid, ascorbic acid, boric acid, and lactic acid), whilst maintaining the level of lactose concentration in solution at 10% (w/w). Each solution was made up to a total weight of 100 g. A magnetic stirrer was used to enhance the dissolution rate of lactose at the room temperature of 25°C for at least 30 minutes, so that clear solutions were obtained without any visible crystals being present. The clear solutions were then spray dried. The pH of the solutions was measured with a pH electrode. Further experimentation has been done by adding whey protein isolate (0.2%, w/w) to 10% (w/w) lactose solutions to increase the yield of the process (Islam et al., 2013) and also by controlling the degree of crystallinity and varying the compositions of the solutions with different additions of templating acids.

6.1.2 Operating Conditions for Spray Drying

A BüchiB-290 spray dryer has been used in the experiments. The inlet air temperature has been 180°C, the main air flow rate through the dryer has been 38 m³ h⁻¹ (aspirator setting of 100%), the pump rate has been 8 mL min⁻¹ (25% of the maximum rate), and the nozzle air flow rate has been 470 L h⁻¹ (40 on the nozzle rotamer scale). Freshly spray-dried powder was collected from a collection vessel at the bottom of a cyclone and was immediately used for analytical tests (moisture content, modulated differential scanning calorimetry (MDSC), and gravimetric moisture analysis); otherwise, the powders were kept in sealed bags and in a refrigerator for X-
ray diffraction and scanning electron microscope (SEM) tests on the following day. Part of the powder collected from the vessel at the bottom of the cyclone has been washed with ethanol for 24 h at the room temperature of 25°C to remove the templating acid, filtered under vacuum, and dried for one hour in a laboratory oven at 60°C. Crushing, grinding, and sieving the dried powder mass was used to produce the final powders. For each concentration, experiments have been done three times, and at least two replicate analyses have been done on samples. Data in this study have been presented as means ± STD (standard deviation) and were obtained from at least three independent experiments. Figure 6.1 illustrates the overall process.

Figure 6.1 Schematic diagram of the experimental setup and an illustration of the templating process.
6.2 Results and Discussion

6.2.1 Yield from Spray Drying

Experimental results showed that the addition of templating acids to the lactose solutions decreased the yield (or solids recovery) from the spray-drying process. At higher concentrations of templating acids, it has also been found that the moisture contents of the particles are higher, as shown in Tables 6.1-6.5. These trends in yield and moisture content have also been observed in Chapter 5. The main reason for this yield behavior is likely to be due to having lower glass-transition temperatures in the powders and also greater product moisture contents at higher templating-acid concentrations (Jouppila and Roos, 1994a; Roos, 1995; Bhandari and Howes, 1999). This situation means that, as both the templating-acid concentration and the product moisture contents increase, the glass-transition temperatures decrease, making the particles stickier (Tables 6.1-6.5). Another reason for the steady downward trend in the yield can be attributed to direct deposition of very wet particles on the dryer walls, which is a very significant phenomenon in small-scale spray dryers (Hanus and Langrish, 2007).

It can be seen in Tables 6.1-6.5 that even adding 1% (w/w) of lactic acid to the lactose solution significantly decreased the yield of the process from 71% ± 2% to 60% ± 2%, and the yield was reduced to 51% ± 2% by adding only 1% (w/w) citric acid to the lactose solution. Likewise, in the case of using ascorbic acid as a templating acid, increasing the ascorbic acid concentration to 1% (w/w) significantly decreased the yield of the process to 35% ± 4%. By increasing the ascorbic acid content to more than 2% (w/w), producing dry powder was impossible (Table 6.3). The use of boric acid at concentrations of about 3% (w/w) did not have a significant effect on the yield of the process, suggesting that boric acid is the best templating material for powder recovery. However, increasing the boric acid concentration to 7% (w/w) decreased the yield of the process to 56% ± 5% (Table 6.5).

In order to increase the yield of the spray-drying process, 0.2% (w/w) whey protein isolate has been added to 10% (w/w) lactose with different concentrations of ascorbic acid. The yield of the spray-drying process can be increased from 35% ± 4% to about 87% ± 2% for the spray-dried lactose/WPI mixture with 1% (w/w) ascorbic acid (Table 6.4). The effect of WPI in creating high yields with potentially stickier core materials (with more citric acid) may be due to the reduction
in wall deposition caused by the WPI coating the particle surfaces, with the WPI having higher
glass-transition temperatures and hence being less sticky than lactose, ascorbic acid, or their
mixtures (Adhikari et al., 2004; Wang and Langrish, 2010; Islam et al., 2013).

Table 6.1 Summary of the experimental conditions used in spray drying for lactose- lactic acid solutions
(lactose 10% w/w), inlet gas temperature of 180°C and outlet gas temperature of 108 ± 3°C (The data
were mainly presented earlier in Table 5.1).

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Lactic acid concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Spray-dried powder</td>
<td></td>
</tr>
<tr>
<td>Yield (% w/w)</td>
<td>71±2</td>
</tr>
<tr>
<td>Moisture content (% dry basis)</td>
<td>1.3±0.1</td>
</tr>
<tr>
<td>Solution</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>6.69±0.09</td>
</tr>
<tr>
<td>Sorption test</td>
<td></td>
</tr>
<tr>
<td>Peak height (moisture content change, %, kg.kg⁻¹ dry basis of lactose)</td>
<td>6±1</td>
</tr>
<tr>
<td>Modulated differential scanning calorimetry</td>
<td></td>
</tr>
<tr>
<td>Glass-transition temperature (°C)</td>
<td>82±8</td>
</tr>
<tr>
<td>Crystallization temperature (°C)</td>
<td>153±9</td>
</tr>
<tr>
<td>Latent energy of crystallization (J/g)</td>
<td>89±2</td>
</tr>
<tr>
<td>X-ray diffraction</td>
<td></td>
</tr>
<tr>
<td>Intensity (cps)</td>
<td>140±10</td>
</tr>
<tr>
<td>BET of ethanol-washed powder</td>
<td></td>
</tr>
<tr>
<td>Surface area (m² g⁻¹)</td>
<td>0.3±0.2</td>
</tr>
</tbody>
</table>

All values are means ±standard deviations of at least three replicate analyses.
Table 6.2 Summary of the experimental conditions used in spray drying for lactose-citric acid solutions (lactose 10% w/w), inlet gas temperature of 180°C and outlet gas temperature of 113 ± 2°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Citric acid concentration (% , w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Spray-dried powder</td>
<td>Yield (% , w/w)</td>
</tr>
<tr>
<td></td>
<td>Moisture content (% dry basis)</td>
</tr>
<tr>
<td>Solution</td>
<td>pH</td>
</tr>
<tr>
<td>Sorption test</td>
<td>Peak height (moisture content change, %, kg.kg⁻¹ dry basis of lactose)</td>
</tr>
<tr>
<td>X-ray diffraction</td>
<td>Intensity (cps)</td>
</tr>
<tr>
<td>BET of ethanol-washed powder</td>
<td>Surface area (m² g⁻¹)</td>
</tr>
</tbody>
</table>

All values are means ±standard deviations of at least three replicate analyses.
Table 6.3 Summary of the experimental conditions used in spray drying for lactose-ascorbic acid solutions (lactose 10% w/w), inlet gas temperature of 180°C and outlet gas temperature 112 ± 2°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Ascorbic acid concentration (%, w/w)</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray-dried powder</td>
<td>Yield (%, w/w)</td>
<td>35±4</td>
<td>10±2</td>
</tr>
<tr>
<td></td>
<td>Moisture content (% dry basis)</td>
<td>1.8±0.2</td>
<td>1.9±0.1</td>
</tr>
<tr>
<td>Solution</td>
<td>pH</td>
<td>2.83±0.04</td>
<td>2.62±0.01</td>
</tr>
<tr>
<td>Sorption test</td>
<td>Peak height (moisture content change, %, kg.kg⁻¹ dry basis of lactose)</td>
<td>5.9±0.9</td>
<td>4.8±0.5</td>
</tr>
<tr>
<td>Modulated differential scanning calorimetry</td>
<td>Glass-transition temperature (°C)</td>
<td>54±4</td>
<td>45±2</td>
</tr>
<tr>
<td></td>
<td>Crystallization temperature (°C)</td>
<td>100±6</td>
<td>90±3</td>
</tr>
<tr>
<td></td>
<td>Latent energy of crystallization (J/g)</td>
<td>39±5</td>
<td>33±3</td>
</tr>
<tr>
<td>X-ray diffraction</td>
<td>Intensity (cps)</td>
<td>240±20</td>
<td>470±30</td>
</tr>
<tr>
<td>BET of ethanol-washed powder</td>
<td>Surface area (m² g⁻¹)</td>
<td>10.5±0.6</td>
<td>8.3±0.4</td>
</tr>
</tbody>
</table>

All values are means ± standard deviations of at least three replicate analyses.
Table 6.4 Summary of the experimental conditions used in spray drying for lactose (10% w/w) – WPI (0.2% w/w) - ascorbic acid solutions, inlet gas temperature of 180°C and outlet gas temperature 112 ± 3°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Ascorbic acid concentration (%, w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Spray-dried powder</td>
<td>Yield (%, w/w)</td>
</tr>
<tr>
<td></td>
<td>Moisture content (% dry basis)</td>
</tr>
<tr>
<td>Solution</td>
<td>pH</td>
</tr>
<tr>
<td>Sorption test</td>
<td>Peak height (moisture content change, %, kg.kg⁻¹ dry basis of lactose)</td>
</tr>
<tr>
<td>BET of ethanol-washed powder</td>
<td>Surface area (m² g⁻¹)</td>
</tr>
</tbody>
</table>

All values are means ± standard deviations of at least three replicate analyses.

Table 6.5 Summary of the experimental conditions used in spray drying for lactose (10 % w/w) - boric acid solutions, inlet gas temperature of 180°C and outlet gas temperature of 98 ± 4°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Boric acid concentration (%, w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Spray-dried powder</td>
<td>Yield (%, w/w)</td>
</tr>
<tr>
<td></td>
<td>Moisture content (% dry basis)</td>
</tr>
<tr>
<td>Solution</td>
<td>pH</td>
</tr>
<tr>
<td>Sorption test</td>
<td>Peak height (moisture content change, %, kg.kg⁻¹ dry basis of lactose)</td>
</tr>
<tr>
<td>BET</td>
<td>Surface area (m² g⁻¹)</td>
</tr>
</tbody>
</table>

All values are means ± standard deviations of at least three replicate analyses.
6.2.2 Assessment of the Degree of Crystallinity for the Lactose in Spray-Dried Powders

6.2.2.1 Moisture Sorption Characteristics

Time-dependent moisture sorption tests (moisture content change, %, kg kg\(^{-1}\) dry basis of lactose) showed significant changes in the crystallinity of lactose in the spray-dried products from lactose solutions with different templating-acid concentrations. The moisture sorption behavior of spray-dried powders demonstrated a gradual increase in the apparent degree of lactose crystallinity through less moisture sorption, when the acid concentration was increased.

Adding 1% (w/w) lactic acid to the lactose solution decreased the degree of lactose amorphicity for the spray-dried powders, by lowering the sorption peak heights from 6% ± 1% to about 5.5% ± 0.4% (Table 6.1). Further increasing the lactic acid concentrations to about 3% (w/w) decreased the sorption peak height to around 4% ± 1%, suggesting higher degrees of lactose crystallinity in the spray-dried powders. Similarly, when using citric acid and ascorbic acid as the templating acid, a steady increase in the degree of lactose crystallinity through less moisture sorption (lower peak heights) has been observed. Table 6.2 shows that spray drying of lactose solution with 3% (w/w) citric acid resulted in a significant reduction in peak height to about 2.9% ± 0.6%. The highest ascorbic acid concentration used in this study was 2% (w/w). This concentration decreased the peak heights from 6% ± 1% to about 4.8% ± 0.5% (Table 6.3).

However, the addition of ascorbic acid to the lactose/WPI solutions did not significantly change the degrees of lactose crystallinity in the spray-dried powders. Using ascorbic acid at concentrations ranging from 1% to 3% (w/w) gave almost the same peak heights, of about 14%. The higher peak heights for lactose/WPI solutions (compared with lactose solutions at the same concentration of ascorbic acid) were expected, as it has been found that the presence of proteins at low concentrations significantly decreases the lactose product crystallinity (Jouppila and Roos, 1994a).

Increasing the boric acid concentrations from 1% to 7% (w/w) also did not have a significant effect on lactose crystallinity, as the peak heights only changed from 7% ± 1% to about 6% ± 1% (Table 6.5). Lower degrees of lactose crystallinity for the spray-dried powders from the lactose/boric acid solutions may be explained by the lower acidity of boric acid, as suggested by the greater pHs of the solutions. An explanation for the greater lactose crystallinity at higher
templating-acid concentrations may be connected with the increase in mutarotation rate and the rate of orientation of lactose molecules into the crystals at lower pHs (Twieg and Nickerson, 1968; Nickerson and Moore, 1974; Jenness, 1988; Singh et al., 1991).

6.2.2.2 Modulated Differential Scanning Calorimetry

Modulated Differential scanning calorimetry (MDSC) has been used to observe phase transitions and to determine glass-transition temperatures and the degree of lactose crystallinity for spray-dried powders from lactose solutions with different templating-acid concentrations. The MDSC results for spray-dried powders with different ascorbic acid concentrations showed very clear phase transitions during the thermal analysis (Figure 6.2), while those for lactose/WPI solutions were complicated to analyse due to multiple components being present in the particles. The presence of protein, fat, additives, and mineral contents in whey isolate powder made it difficult to distinguish each transition in the thermogram separately (Vuataz, 2002), because the transitions of each component may have overlapped with those of lactose.

The MDSC results presented in Figure 6.2 suggested that increasing the ascorbic acid concentrations in the lactose solutions decreased the glass-transition and crystallization temperatures for the lactose-ascorbic acid mixtures in the spray-dried powders. There was a downward trend in the latent energy of crystallization for the spray-dried products, which indicated a decrease in the amorphous content of the spray-dried powders as the acid concentration increased. The glass-transition temperature of pure lactose was $82 \pm 8^\circ C$, and the crystallization peak appeared at $153 \pm 9^\circ C$ with an exothermic heat of crystallization of $89 \pm 2$ J/g. The corresponding figures for spray-dried powders from lactose solutions with 2% (w/w) ascorbic acid concentrations significantly decreased to $45 \pm 2^\circ C$, $90 \pm 3^\circ C$, and $33 \pm 3$ J/g, respectively (Tables 6.1 and 6.2).

The MDSC results of spray-dried powder of lactose solutions with different lactic acid concentrations also showed clear phase transitions during the thermal analysis. The glass-transition temperature, the crystallization temperature, and the exothermic heat of crystallization for the spray-dried lactose with 1% (w/w) lactic acid concentrations were found to be $64 \pm 2^\circ C$, respectively.
142 ± 7°C, and 57 ± 13 J/g, respectively while those for the spray-dried lactose with 3% (w/w) lactic acid concentrations decreased to 40 ± 10°C, 90 ± 10°C, and 46 ± 4 J/g, respectively (Table 6.1).

The results from the MDSC technique agreed well with the results from the moisture sorption tests and confirmed that the crystallinity of the lactose powders increased with greater ascorbic/lactic acids contents. During the spray-drying process, several phase transformations may occur within the material. Depending on the process intensity and material physical properties, the dispersed liquid turns into a solid with some crystalline regions and many amorphous ones (governed by drying kinetics and liquid-phase crystallization) due to the evaporation of the solvent, and the predominantly amorphous regions may also transform to crystalline ones (governed by Williams–Landel–Ferry kinetics) (Bhandari et al., 1997b; Islam et al., 2010). The results suggested that using ascorbic/lactic acids, with lower glass-transition temperatures than that for lactose, decreased the glass-transition temperature of the spray-dried mixture according to the Gordon–Taylor equation (2.1). Lower glass-transition temperatures increase the temperature difference \((T-T_g)\), which in turn decreases the crystallization time as suggested by the Williams–Landel–Ferry equation (2.3), leading to higher degrees of crystallinity for the spray-dried particles.
Figure 6.2 Effect of the ascorbic acid concentration on the glass-transition temperatures, the crystallization temperatures, and the latent energies of crystallization for the spray-dried products from lactose solutions.

6.2.2.3 X-Ray Diffraction (XRD)

In this investigation, based on the references (Jouppila et al., 1997; Haque and Roos, 2005), the peak at $\theta = 20.1^\circ$ was taken as the characteristic peak to measure its intensity for finding the relative lactose crystallinity of different powders (Tables 6.1-6.3). The diffraction patterns for spray-dried lactose with different lactic acid/citric acid concentrations show clear sharp peaks associated with $\alpha$-lactose monohydrate at high intensities ($2\theta = 12.5^\circ$, $20.0^\circ$, and $20.1^\circ$). There is no distinguishable peak for anhydrous $\beta$-lactose, and the peak intensities for the mixture of anhydrous $\alpha:\beta$ with different molar ratios at $19.1^\circ$ and $19.5^\circ$ are relatively low. There were some improvements in the degrees of crystallinity for lactose powders with increasing lactic acid concentrations (Table 6.1). The intensity of the characteristic peak at $\theta = 20.1^\circ$ for the spray-dried pure lactose was found to be $140 \pm 10$ cps, while the intensities for the spray-dried lactose with 1% (w/w) and 3% (w/w) lactic acid concentrations were $270 \pm 20$ cps and $440 \pm 20$ cps, respectively. Simply comparing the intensity values of the characteristic peak at $\theta = 20.1^\circ$ for...
different lactic acid concentrations suggests that the lactose crystallinity of the powders increased by raising the lactic acid concentrations in lactose solutions.

Likewise, XRD analyses have shown distinct peaks associated with α-lactose monohydrate at high intensities by increasing the citric acid concentrations in lactose solutions. These results support the results of MDSC and sorption tests in confirming the increase in the degree of lactose crystallinity when the lactic/citric acids contents were raised (Table 6.1). The intensities of the characteristic peak at $2\theta = 20.1^\circ$ for the lactose in the spray-dried powders with 1% (w/w) and 3% (w/w) citric acid concentrations were 290 ± 20 cps and 410 ± 20 cps, respectively. Similarly, in the case of using ascorbic acid as a templating acid, there were distinct peaks associated with α-lactose monohydrate at high intensities by increasing the ascorbic acid concentrations in lactose solutions. The intensity of the characteristic peak at $2\theta = 20.1^\circ$ for the spray-dried lactose with 1% (w/w) ascorbic acid was found to be 240 ± 20 cps, while that for the spray-dried lactose with 2% (w/w) ascorbic acid concentrations was 470 ± 30 cps. However, addition of ascorbic acid to the lactose/WPI solutions did not significantly change the degrees of lactose crystallinity in the spray-dried powders, as there were no distinguishable peaks associated with different types of lactose crystals. These results agreed well with the results of the moisture sorption tests and suggested that the resulted spray-dried powders from lactose/WPI solutions with different concentrations of ascorbic acid were amorphous. These results are also consistent with the effect of adding WPI on the product crystallinity, since it has been found that the presence of proteins at low concentrations significantly affects the product crystallinity (Jouppila and Roos, 1994a; Haque and Roos, 2006) (Table 6.3). There were also no significant changes in peak intensities for different types of lactose crystals in the spray-dried powders from lactose solutions with different boric acid concentrations, which means that the relative lactose crystallinity of different powders has not been changed by increasing the boric acid content. The evidence supports this suggestion, with the sorption peak heights being almost the same when the concentration of boric acid was increased (Table 6.3).

The degrees of crystallinity measured using MDSC and XRD methods have agreed well with the results of the moisture sorption tests and confirm that the crystallinity of the lactose increased when the templating-acid concentration was raised. The results of the crystallinity tests and the moisture contents of the final products support the suggestion that the crystallization rate is
related to the difference between the material temperature and the glass-transition temperature, which has been observed by other researchers (Bhandari and Howes, 1999; Islam et al., 2010). This situation means that, as the templating-acid concentrations and the product moisture contents increase, the glass-transition temperatures decrease. Therefore, the difference between the glass-transition temperatures ($T_g$) of the materials and the process temperatures ($T$) increases, thereby enhancing the crystallization rate, according to the Williams–Landel–Ferry equation (Eq. 2.2).

The acidity or the pH of the lactose solutions also had a significant impact on the lactose crystallinity. The pHs of the lactose solutions containing lactic acid, citric acid, and ascorbic acid (almost constant under different acid concentrations) were much lower than the ones for lactose/boric acid solutions (Tables 6.1-6.3). Hence, the higher degrees of lactose crystallinity for the spray-dried powders with lactic/citric/ascorbic acids, as suggested by the moisture sorption, MDSC, and XRD techniques, were expected. Higher acidic strengths of lactic acid, citric acid, and ascorbic acid compared with boric acid decreased the pH of the solution, which increased the mutarotation rate and then the crystallization rate of lactose (Twieg and Nickerson, 1968; Nickerson and Moore, 1974; Jenness, 1988; Singh et al., 1991).

### 6.2.2.4 BET Specific Surface Area

The BET surface areas of the processed lactose particles using templating methods with different concentrations of templating acids have been shown in Tables 6.1-6.3. There has been a significant improvement in the surface area by using lactic acid as a templating material, from $0.3 \pm 0.2 \text{ m}^2 \text{ g}^{-1}$ (for conventional spray-dried lactose) to $14.9 \pm 0.9 \text{ m}^2 \text{ g}^{-1}$ at a lactic acid concentration of 1 w/w %. Above this concentration, there was a considerable reduction in the surface area to $9.5 \pm 0.8 \text{ m}^2 \text{ g}^{-1}$ (3 w/w %). It can also be observed, in Table 6.1, that adding 1% w/w citric acid as a templating material significantly increased the BET surface area of lactose to $20.8 \pm 0.9 \text{ m}^2 \text{ g}^{-1}$. However, adding further citric acid content (3 w/w %) decreased the BET surface area of lactose to $12.3 \pm 0.8 \text{ m}^2 \text{ g}^{-1}$.
The BET surface areas of the lactose particles, using ascorbic acid as a templating acid, have been given in Table 6.3. The highly-porous lactose powders with surface areas of 10.5 ± 0.6 m² g⁻¹, a total pore volume of 0.096 ± 0.008 m² g⁻¹ and a mean pore diameter of 31.4 ± 0.2 Å have been achieved using 1% w/w ascorbic acid, and adding more ascorbic acid (2% w/w) decreased the BET surface area to 8.3 ± 0.4 m² g⁻¹. However, when increasing the ascorbic acid content to more than 2% (w/w), producing dry powder was impossible. As mentioned earlier, in order to increase the yield of the spray-drying process and also reducing the degree of crystallinity, 0.2% (w/w) whey protein isolate (WPI) has been added to 10% (w/w) lactose with different concentrations of ascorbic acid. WPI addition significantly improved the BET surface area of the ethanol-washed particles from 10.5 ± 0.6 m² g⁻¹ to 21.5 ± 0.5 m² g⁻¹ using 1% w/w ascorbic acid. The BET surface area of lactose (0.2% w/w WPI) decreased from 21.5 ± 0.5 m² g⁻¹ for 1% w/w ascorbic acid to about 18.2 ± 0.7 m² g⁻¹ with 3% w/w ascorbic acid. The total pore volumes and mean pore diameters were also affected at different ascorbic acid concentrations, such that the templated lactose particles (after ascorbic acid removal) showed a reduction in pore volume from 0.32 ± 0.05 ml g⁻¹ to 0.27 ± 0.04 ml g⁻¹ (with a change in ascorbic acid concentration from 1% to 3 % w/w) and the mean pore diameters decreased from 14.8 ± 0.5 Å to 28.3 ± 0.9 Å.

It can also be observed, in Table 6.5, that the BET surface area of lactose can be altered from 17.2 ± 0.5 m² g⁻¹ for the spray-dried lactose with 1% w/w boric acid as a templating material to about 9.9±0.6 m² g⁻¹ for 7% w/w boric acid. It can be seen that adding more than 2% w/w boric acid did not have a significant effect on the surface area of the ethanol-washed powders. Again, with increasing the templating-acid concentration, the porosity of lactose significantly decreased, with the particle BET surface area decreasing from 18.5 ± 0.8 m² g⁻¹ for 3% w/w boric acid to 9.9 ± 0.6 m² g⁻¹ for 7% w/w boric acid.

These results have supported the link between the extent of lactose crystallization in the spray-dried powders, concentrations of the templating acids, and the BET surface areas of the processed powder, as will now be explained. Crystalline solids are known to have distinctive and organized internal structures, called crystal lattices, while the atoms and molecules in amorphous solids are arranged randomly with no regular patterns (Averill and Eldredge, 2007). During the crystallization process, molecules of each component are more likely to join their own crystal structure (Jones and Mirkin, 2013), and the impurities (templating materials) tend to be rejected.
during crystal growth (Bhandari and Howes, 1999; Lorenz and Beckmann, 2013). Therefore, each growing crystal tends to consist of only one type of molecule.

Lower degrees of crystallinity for spray-dried lactose powders mean that the lactose crystal structures have become less regular, which in turn means that the number of templating-acid molecules incorporated in the whole lactose structure (amorphous and crystal) has increased. Washing with ethanol removes the templating-acid molecules, either scattered in the amorphous portion of the lactose particles or accumulated on the surface of the crystals, rather than inside the crystal lattice. Therefore, the porosities and the BET surface areas of the powders increased as the amorphous lactose content increased, which may be connected with the increase in the amount of incorporated templating-acid molecules, due to the decrease in the degree of lactose crystallinity for the spray-dried powders. This explanation implies lower surface areas at higher templating-acid concentrations, as seen experimentally here (Table 6.1-6.3).

The presence of proteins during the spray drying of the lactose/WPI mixtures is likely to reduce the rate and extent of crystallization for lactose during spray drying. The presence of WPI increased the glass-transition temperatures of the surfaces for the particles, making it difficult for the lactose in the particles to crystallize completely in the process and resulting in higher levels of amorphyicity in the particles (Jouppila and Roos, 1994a; Haque and Roos, 2006). However, this work aimed to produce pure porous lactose, which means that using less surfactant to reach this goal has been preferred. Hence higher concentrations of WPI have not been desired or tested for this product development, since increasing the WPI amounts have had detrimental effects on the product properties.

### 6.2.2.5 SEM Micrographs

Scanning electron microscopy has also been used to study the morphology of the powders. Figure 6.3 shows the SEM micrographs of the spray-dried powders from lactose/0.2% (w/w) WPI solutions with 1% w/w ascorbic acid before and after ethanol washing, where the surfaces of the spray dried powder appeared to be non-porous and amorphous (Figure 6.3A), while ethanol-washed powders show porosity on the surface (Figure 6.3B) and also inside the particles (Figure 6.3C and D). The final processed particles are highly-interconnected porous networks...
showing porosity in the bulk as well as on their surfaces, suggesting the relatively uniform
distribution of the pores throughout the particles. However, the SEM images of the ethanol-
washed particles from lactose solution with 1 w/w % ascorbic acid (Figure 6.4) show some dense
and non-porous block crystal areas, suggesting low porosities, as also indicated by the BET
measurements. Overall, the results are consistent with the measurements of the BET surface
areas for the samples.

The morphologies of the particles support the critical role of amorphicity in the spray-dried
powders for achieving a well-dispersed lactose/template mixture to reach high and uniform
porosities in the processed lactose particles. Adding WPI to the lactose/templating acid solutions
decreased the degree of lactose crystallinity in the spray-dried particles, leading to homogenous
dispersion of the templating acid into the lactose structure to produce highly porous particles
upon removal of acid through ethanol washing (Figure 6.3A and B).

The measurements of the particles size gave a mean particle size of about 19 ± 2 μm (D[3,2]) for
the final processed powder, while that for the spray-dried powder prior to ethanol washing was 5
± 1 μm (D[3,2]). The D[4,3] values for these two powders were 122 ± 7 μm and 43 ± 3 μm,
respectively. The large processed particles have been produced by grinding the dried
agglomerate/filtrate obtained after ethanol washing, which consists of small ethanol-
washed/porous particles, suggesting that the high porosity and relatively large processed particles
are actually agglomerates of smaller porous particles.
Figure 6.3 Scanning electron micrographs of spray-dried powders from lactose/0.2% (w/w) WPI solutions with 1% w/w ascorbic acid, before (A) and after ethanol washing (B:D).
Figure 6.4 Scanning electron micrographs of spray-dried powders from lactose solutions with 1% w/w ascorbic acid, after ethanol washing.
6.3 Conclusions

This chapter has investigated the effects of different types of templating acids at various concentrations on the porosity of lactose through doing experiments in which templating acids, in various proportions, were added to lactose solutions and then spray dried. The optimum concentrations of templating acids have been found. The optimum concentration of lactic acid, citric acid, and ascorbic acid were found to be 1 w/w % with the BET surface area of $14.9 \pm 0.9 \text{ m}^2 \text{ g}^{-1}$, $20.8 \pm 0.9 \text{ m}^2 \text{ g}^{-1}$, and $10.5 \pm 0.6 \text{ m}^2 \text{ g}^{-1}$, respectively while that for the spray-dried lactose with boric acid as a templating agent was 3 w/w % with the BET surface area of $18.5 \pm 0.8 \text{ m}^2 \text{ g}^{-1}$. Higher concentrations of different templating acids appear to decrease the surface area of the ethanol-washed lactose particles due to the increase in the extent of lactose crystallinity as the acid concentrations increased. The results of moisture sorption tests, MDSC, and XRD tests confirmed that the crystallinity of the lactose in the spray-dried powders increased with higher templating-acid concentrations. This increase in lactose crystallinity may be due to increasing the $T-T_g$ difference, consequently decreasing the crystallization time, according to the Williams–Landel–Ferry equation, or increasing the acidity of the solution, which increases the mutarotation rate and then the crystallization rate of lactose. It has also been found that the increasing templating acid concentration decreases the yield of the spray-drying process due to stickiness. The decrease in yields is associated with the decrease in the glass-transition temperatures for the amorphous spray-dried intermediate products, since the templating agent has a very low glass-transition temperature. The results of this study can be of specific interest for controlled drug deliveries and release applications (Millqvist-Fureby et al., 2014) by choosing the processing conditions to control the extent of crystallization to produce highly-porous particles with the wide range of porosities.
CHAPTER 7 FORMATION OF HIGH POROSITY MANNITOL PARTICLES BY A NEW TEMPLATING PROCESS

In the previous chapter (Chapter 6), a new method has been successfully developed to create highly-porous powder templates through spray drying, using food-grade acid as the templating agent and then removing the template material by ethanol washing of the spray-dried powders. As mentioned earlier, the use of mannitol as an alternative to lactose in food products and pharmaceutical formulations has significantly increased. The non-hygroscopic nature of mannitol, and consequently its low moisture content, make it a desirable additive and excipient for moisture sensitive ingredients (Babu and Nangia, 2011). In this chapter, a templating approach has been applied according to the method described in Chapter 6, to create highly-porous templates or frameworks of mannitol through the spray drying of mannitol using citric acid as the templating agent and then removing the template material (citric acid) by ethanol washing of the spray-dried powders. It is also demonstrated that textural properties, such as the surface area and the pore volume of the resultant mannitol, can be altered by varying the concentrations of citric acid, WPI, and Gum Arabic.

7.1 Materials and Methods

7.1.1 Sample Preparation

In order to investigate and report the effects of citric acid, WPI, and Gum Arabic concentrations on the BET surface areas of mannitol, experiments were carried out by varying the composition of the solutions with additions of citric acid, WPI, and Gum Arabic, whilst maintaining the level of mannitol concentration in solution at 10% (w/w). Each solution was made up to a total weight of 100 g. All solutions were magnetically stirred at room temperature of 25°C for at least 30

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3 The content of this chapter has been published as the following paper:
minutes, so a clear solution was obtained without any visible crystals being present. The clear solutions were then spray dried. The pH of the solutions was measured with a pH electrode.

7.1.2 Operating Conditions for Spray Drying

The solutions have been spray dried using a Buchi-B290 Mini Spray Dryer with an inlet gas temperature of 150°C, an aspirator setting of 100% (38 m³ h⁻¹), a pump rate of 25% (8 mL min⁻¹), and a nozzle air flow rate of 470 L h⁻¹ (40 on the nozzle rotameter scale). Freshly spray-dried powder has been collected from a collection vessel at the bottom of a cyclone, and a portion of that powder has been treated with ethanol for 24 h to remove the citric acid, vacuum filtered, and oven dried at 60°C for one hour, as shown in Figure 6.1. The final powders have been produced by crushing and grinding the dried cake. The freshly spray-dried and ethanol washed powders were immediately used for analytical tests (moisture content, gravimetric moisture analysis, Fourier transform infrared spectroscopy (FTIR), and BET); otherwise the powders were kept in sealed bags and in a refrigerator for scanning electron microscope (SEM) tests on the following day. The free moisture content (dry basis) was measured by weighing the sample before and after drying in a fan circulated oven (Labec, Australia) at 85°C for 24 hours.

7.2 Results and Discussion

7.2.1 Yield from Spray Drying

It can be seen in Table 7.1 that adding citric acid to the mannitol decreased the yield (or recovery) of the spray-drying process, which can be attributed to greater stickiness during the spray-drying process. The yield for mannitol was decreased from 70% ± 2% to about 8% ± 1% by increasing the citric acid concentration to 2% (w/w). Likewise, in the case of using 0.5% (w/w) Gum Arabic as an additive, increasing the citric acid concentration to 2% (w/w) significantly decreased the yield of the process down to 15% (Table 7.3). A key explanation for the steady downward trend in the yield can be seen in the work of Bhandari et al. (1997b), due to stickiness. There is a significant increase in the moisture content of the product when increasing the citric acid concentration (Table 7.1). The increase in moisture content means an increase in
stickiness due to the effect of moisture content in depressing the glass-transition and sticky-point
temperatures (Bhandari et al., 1997b). The presence of citric acid must also decrease the glass-
transition temperature and hence increase stickiness at any moisture content. In order to increase
the yield of spray-drying process, 0.2% (w/w) whey protein isolate has been added to 10% (w/w)
mannitol with different concentrations of citric acid. The yield of the spray-drying process can be
altered from 19% ± 5% to about 84% ± 3% for the spray-dried mannitol/WPI mixture with 1%
(w/w) citric acid, compared with 8% ± 1% to 33% ± 8% with 1% (w/w) citric acid (Table 7.1).
The higher yields of the spray-drying process for mannitol with WPI solutions compared with
mannitol solutions at the same concentrations of citric acid can be explained by the decrease in
wall deposition during spray drying due to the effective encapsulating properties of proteins,
which remain non-sticky due to their higher glass-transition temperatures (Adhikari et al., 2004;

Further experimentation has been done to investigate the effect of WPI and Gum Arabic on both
BET surface area and the yield of the process by adding whey protein isolate and Gum Arabic to
10% (w/w) mannitol, and then varying the composition of the solution with additions of citric
acid. The results suggest that only 0.5% (w/w) WPI concentration was enough to give high
spray-drying yields and that further increases in the WPI content in the mannitol/WPI mixtures
did not change the process yield significantly (Table 7.2). In the case of using Gum Arabic as a
surfactant, increasing the concentration of Gum Arabic did not improve the yield of the process;
increasing the amount of Gum Arabic concentration to 3% (w/w) decreased the yield of the
process down to 8%. However, the lower yields of the spray-drying process for mannitol with
Gum Arabic solutions than mannitol/WPI solutions with the same concentration of citric acid
can be attributed to the lower surface activity of Gum Arabic than WPI. This result suggests that
more Gum Arabic stays in the particle structure as an incorporated material (Table 7.3).
Table 7.1 Summary of the experimental conditions used in spray drying for mannitol-citric acid-WPI solutions (mannitol 10% w/w), inlet gas temperature of 150°C and outlet gas temperature of 90 ± 4°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Citric acid: WPI concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0:0</td>
</tr>
<tr>
<td>Yield (% w/w)</td>
<td>70±2</td>
</tr>
<tr>
<td>Moisture content,%</td>
<td>0.15±0.1</td>
</tr>
<tr>
<td>(dry basis)</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.3±0.1</td>
</tr>
<tr>
<td>BET Surface area (m² g⁻¹)</td>
<td>0.71±0.05</td>
</tr>
</tbody>
</table>

All values are mean ± standard deviation of at least two replicate analyses.
Table 7.2 Summary of the experimental conditions used in spray drying for mannitol (10% w/w) - citric acid (2% w/w)- WPI solutions (% w/w), inlet gas temperature of 150°C and outlet gas temperature of 90 ± 3°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>WPI concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Spray-dried powder</td>
<td>8±1</td>
</tr>
<tr>
<td>Moisture content, % (dry basis)</td>
<td>3.4±0.5</td>
</tr>
<tr>
<td>Solution pH</td>
<td>2.23±0.03</td>
</tr>
<tr>
<td>BET Surface area (m² g⁻¹)</td>
<td>1.6±0.1</td>
</tr>
</tbody>
</table>

All values are mean ± standard deviation of at least two replicate analyses.

Table 7.3 Summary of the experimental conditions used in spray drying for mannitol- citric acid –Gum Arabic solutions (mannitol 10% w/w), inlet gas temperature of 150°C and outlet gas temperature of 89 ± 3°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Citric acid: Gum Arabic concentrations (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5:0.5</td>
</tr>
<tr>
<td>Spray-dried powder</td>
<td>51±3</td>
</tr>
<tr>
<td>Moisture content, % (dry basis)</td>
<td>0.8±0.1</td>
</tr>
<tr>
<td>Solution pH</td>
<td>2.65±0.09</td>
</tr>
<tr>
<td>BET Surface area (m² g⁻¹)</td>
<td>1.8±0.1</td>
</tr>
</tbody>
</table>

All values are mean ± standard deviation of at least two replicate analyses.
*NA: not available
7.2.2 BET Specific Surface Area

It can be observed from Table 7.1 that adding 1% w/w citric acid as a templating material significantly increased the BET surface area of mannitol from $0.71 \pm 0.05 \text{ m}^2 \text{ g}^{-1}$ to $1.91 \pm 0.04 \text{ m}^2 \text{ g}^{-1}$. Increasing the citric acid content (2% w/w) did not have a significant effect on the surface area of the ethanol-washed powders. However, adding 0.2% (w/w) WPI significantly increased the particle porosity. The BET surface area of mannitol can be altered from $1.91 \pm 0.04 \text{ m}^2 \text{ g}^{-1}$ to about $3.20 \pm 0.90 \text{ m}^2 \text{ g}^{-1}$ for 1% w/w citric acid, compared with $1.60 \pm 0.09 \text{ m}^2 \text{ g}^{-1}$ to $5.60 \pm 0.60 \text{ m}^2 \text{ g}^{-1}$ for the spray-dried mannitol/WPI mixture with 2% w/w citric acid.

This result suggested that there is a link between the spray-dried powder’s mannitol crystallinity and the porosity of the ethanol-washed powders, as explained in Section 6.2.2.4. The results are similar to those of spray-dried mannitol with 0.5% w/w Gum Arabic, which showed that adding 2% w/w citric acid significantly increased the BET surface area of mannitol to $5.1 \pm 0.2 \text{ m}^2 \text{ g}^{-1}$ compared with $1.8 \pm 0.1 \text{ m}^2 \text{ g}^{-1}$ for the spray-dried mannitol/Gum Arabic mixture with 0.5% w/w citric acid (Table 7.3).

The effects of WPI and Gum Arabic concentration on the porosity and BET surface area of the mannitol particles have been shown in Tables 7.2 and 7.3. Due to the higher BET surface area of the mannitol/0.2% (w/w) WPI mixture with 2% w/w citric acid, this concentration of templating material was kept fixed in subsequent experiments. It can be observed that increasing the WPI and Gum Arabic concentrations changed the surface area of mannitol. It can also be seen in Table 7.2 and Figure 7.1 that adding WPI to the mannitol/citric acid solutions significantly increased the BET surface of mannitol up to $8.0 \pm 0.4 \text{ m}^2 \text{ g}^{-1}$. However, higher concentrations of WPI, more than 0.5% w/w, have a detrimental effect on the particle porosity. The results also suggest that only 0.5% (w/w) WPI concentration was enough to give high spray-drying yields and that further increases in the WPI content in the mannitol/WPI mixtures did not change the process yield significantly (Figure 7.1). When using Gum Arabic as a surfactant, increasing the Gum Arabic content to 1% (w/w) made it possible to produce mannitol with a BET surface area of $7.3 \pm 0.3 \text{ m}^2 \text{ g}^{-1}$, while increasing the amount of Gum Arabic concentration to 2% (w/w) significantly decreased the particle porosity down to $2.1 \pm 0.3 \text{ m}^2 \text{ g}^{-1}$ (Table 7.3). These decreases in the BET surface areas with increasing WPI or Gum Arabic concentrations can be explained by the results of FTIR spectra in Section 7.2.4.
7.2.3 SEM Micrographs

Scanning electron microscopy has also been used to study the morphology of the powders. The SEM micrographs of the spray-dried pure mannitol and spray-dried powders from mannitol with WPI/Gum Arabic solutions having different concentrations of citric acid are shown in Figures 7.2 and 7.2. These micrographs show some morphological changes for the mannitol powders, before and after citric acid removal (ethanol washing). More porosity appeared to be present on the surface and inside of the particles after citric acid removal. Figures 7.2 A and B show the spray-dried pure mannitol, where the surfaces of the spray dried powder appeared to be non-porous and amorphous, while the ethanol-washed powders have a more porous structure, suggesting the formation of a porous network (Figures 7.2 C and D and 7.3). The results are consistent with the measurements of the BET surface areas for the samples.

Particle size analysis of powders has shown that the particle size of the processed powder after grinding is about $6.8 \pm 0.5 \mu m$ (D[3,2]), while the particle size of the spray-dried lactose/WPI powder before ethanol washing was in the range of $6.6 \pm 0.3 \mu m$ (D[3,2]). The D[4,3] values for these two powders are $12.8\pm 0.2$ and $108\pm 6 \mu m$, respectively. The large processed particles have been produced by grinding the dried agglomerate/filtrate obtained.
after ethanol washing, which consists of small ethanol-washed/porous particles. Hence, it is not unreasonable to assume that the high porosity and relatively large processed particles are actually agglomerates of smaller porous particles.

![Figure 7.2 A and B) Scanning electron micrographs of spray-dried pure mannitol powder. C and D) spray-dried powder from mannitol with 0.5% (w/w) WPI and 2% (w/w) citric acid solution after ethanol washing.](image)
Figure 7.3 Spray-dried powder from mannitol with 1% (w/w) Gum Arabic and 2% (w/w) citric acid solution after ethanol washing.
7.2.4 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra for the spray-dried powders from solutions with 2% (w/w) citric acid, at different WPI and Gum Arabic concentrations, are presented in Figure 7.4, before and after ethanol washing. The citric acid absorbance peaks at 1730 cm\(^{-1}\) for the powders with 0.5% w/w of WPI before and after ethanol washing show almost complete citric acid removal from the mannitol structure. However, the difference between the absorbance peaks before and after ethanol washing decreases as the WPI concentration increases, suggesting that full citric acid removal has not been achieved for higher contents of WPI. The decrease in the BET surface area from 8.0 ± 0.4 m\(^2\) g\(^{-1}\) (WPI: 0.5% w/w) to 3.4 ± 0.1 m\(^2\) g\(^{-1}\) (WPI: 1% w/w) and 3.5 ± 0.1 m\(^2\) g\(^{-1}\) (WPI: 3% w/w) can be explained by the poor templating removal from the main mannitol structure as a result of an increase in the WPI concentration. This behaviour can be attributed to the accumulation of the WPI on the particle surface during spray drying, as suggested in the literature (Izutsu et al., 2004; Islam et al., 2013). Increasing the WPI concentration increases the thickness of the protein layer covering the particle surface, thereby decreasing the availability of the citric acid molecules for the ethanol molecules to achieve high removal performance. The complete disappearance of the citric acid absorbance peak has also been shown in Figure 7.4 D for the ethanol-washed powder from solutions with 1% of Gum Arabic. A high BET surface area of 7.3 ± 0.3 m\(^2\) g\(^{-1}\) has been measured for this powder, which can be attributed to the high citric acid removal observed by FTIR spectra. Comparing Figure 7.4 B and D, it can be observed that using equal amounts of WPI and Gum Arabic (1% w/w) can lead to different templating removal performances. Gum Arabic is known as an emulsifying agent rather than a surface-active material. The less surface-active properties of Gum Arabic compared with WPI means that Gum Arabic remains incorporated in the particle structure.
Figure 7.4 FT-IR spectra of the spray-dried powder from mannitol (10% w/w) - citric acid (2% w/w) - WPI/Gum Arabic solutions before and after ethanol washing. A) 3% (w/w) WPI. B) 1% (w/w) WPI. C) 0.5% (w/w) WPI. D) 1% (w/w) Gum Arabic. The absorbance peaks at 1730 cm\(^{-1}\) show the citric acid content.
7.3 Conclusions

Highly porous mannitol was prepared through a new production route by the spray drying of solutions containing mannitol and citric acid as the templating agent using a Buchi-B290 mini spray dryer with an inlet temperature of 150°C. It has been demonstrated that textural properties, such as the surface area and the pore volume of the resultant mannitol, can be tuned by varying the concentrations of citric acid, WPI, and Gum Arabic. The resulting powder structure is a mannitol network with significant porosity and a high surface area of $8.0 \pm 0.4 \text{ m}^2\text{ g}^{-1}$ and a total pore volume of $0.066 \text{ ml g}^{-1}$ for mannitol solution with citric acid (2% w/w) and 0.5% (w/w) WPI. This optimum preparation method has been used with the aim of producing the highest possible surface area of the ethanol-washed mannitol particles for drug delivery purpose as discussed in next chapter. The scanning electron microscope micrographs were consistent with the BET surface areas. It has been found that higher concentrations of WPI, more than 0.5% w/w, have a detrimental effect on the porosity of the spray-dried powders from mannitol/WPI solutions with 2% (w/w) citric acid, while the concentration of Gum Arabic causing decreased porosity was 1% (w/w) due to the decrease in the performance of citric acid removal through ethanol washing. The results of this study have implications in the pharmaceutical industry for producing excipient powders with better properties, such as greater specific surface areas.
Poor blending uniformity of drug dosage and the solubility behavior of a drug are key challenges facing the design of solid dosage forms. A new adsorption method has been developed successfully in this chapter, which includes the production of highly-porous mannitol particles with high surface areas according to the method described in Chapter 7, through the spray drying of mannitol solutions containing ethanol-soluble sugar or food-grade acids as templating agents, and then transferring the resulted porous particles after ethanol washing to ethanol solutions containing the drug component.

8.1 Materials and Methods

8.1.1 Sample Preparation

Mannitol solutions with citric acid (2% w/w) and WPI (0.5% w/w) were prepared, with the aim being to produce the highest possible surface area of the ethanol-washed mannitol particles, as described in Chapter 7. In order to investigate the effects of sucrose concentrations as a templating sugar on the BET surface areas of ethanol-washed mannitol, experiments were carried out by varying the composition of the solutions with different amounts of sucrose. In order to increase the yield of the spray-drying process, 0.5% (w/w) whey protein isolate has been added to 10% (w/w) mannitol with different concentrations of sucrose.

8.1.2 Porous Mannitol Production and Drug Loading Process

Freshly spray-dried powder has been collected from a collection vessel at the bottom of a cyclone and has been washed with ethanol for 48 h at the room temperature of 25°C to remove the templating agents (citric acid or sucrose) and then filtered under vacuum. The resultant pastes

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4 The content of this chapter has been published as the following paper:
have been immersed in the ethanol solutions with four different concentrations of acetaminophen (0.01 M, 0.05 M, 0.2 M, and 0.5 M) as a model drug in order to load the drug onto highly-porous mannitol for 12 h at the room temperature of 25°C. The final-processed powder has been obtained after vacuum filtering and oven drying at 60°C for one hour to remove any residual ethanol. Sieving has then been carried out on the portion of dried filtrate with a set of sieve sizes ranging between 63 µm and 300 µm, and the final powder has been used for analytical tests. Figure 8.1 illustrates the overall process. In order to investigate the effect of excipient porosity on the efficiency of the adsorption approach, porous mannitol with a range of porosities has been produced through the templating process by varying the concentrations of templating agents and WPI. This material has been used for the adsorption process. In this study, for each drug concentration, an experiment has been repeated three times. Data in this study have been presented as means ± STD (standard deviation). The drug content uniformity of final powder, the percentage relative standard deviation (RSD), has been obtained from one set of independent experiments for different drug concentrations.

Figure 8.1 Schematic illustration of the adsorption process.

8.2 Results and Discussion

8.2.1 Highly-Porous Mannitol Particles Using Sucrose as a Templating Agent

As has been shown in Table 8.1, by adding 0.5% (w/w) WPI, the yield of the spray-drying process could be altered from 50% ± 6% to about 87% ± 5% for the spray-dried mannitol/WPI mixture with 1% (w/w) sucrose, compared with 64% ± 2% to 86% ± 7% with 2% (w/w) sucrose
(Table 8.1). However, when increasing the sucrose content to more than 2% (w/w), producing dry powder was impossible. The higher yields of the spray-drying process for mannitol with WPI solutions than mannitol solutions with the same concentrations of sucrose can be explained by the decrease in wall deposition during spray drying due to the effective encapsulating properties of proteins, which remained non-sticky due to their higher glass-transition temperatures (Adhikari et al., 2004; Islam et al., 2013).

Normally, a higher glass-transition temperature leads to less wall deposition, due to a lower $T_p - T_g$ giving less stickiness. If the temperature difference ($T_p - T_g$) is less than 20°C, then the particles are likely to be non-sticky (Bhandari et al., 1997b), and spray-drying operations would be considered to be “normal” (zone 1, Figure 8.2). Temperature differences of 20°C to 50°C ($T_p - T_g$) are generally considered to cause stickiness and operability problems in spray drying (zone 2, Figure 8.2). This zone has been described as the “Stickiness Barrier” (Imtiaz-Ul-Islam and Langrish, 2009). Imtiaz-Ul-Islam and Langrish (2009) also found that at temperature difference ($T_p - T_g$) above 50°C, the yields increase significantly due to a high enough $T_p - T_g$ to give a sufficient crystallization rate, leading to lower wall deposition (zone 3, Figure 8.2).

The virtually-zero yield with 2% (w/w) sucrose might be due to the higher glass-transition temperature for the mixture of sucrose (62°C; Roos, 1995) and mannitol (10.7°C; Telang et al., 2003) compared with the glass-transition temperature of mannitol with 1% (w/w) sucrose. A lower glass-transition temperature, gives greater crystallization in spray drying, leading to lower wall deposition, due to a high enough $T_p - T_g$ to give a high enough crystallization rate according to the Gordon–Taylor and Williams–Landel–Ferry equations (Figure 8.2, zone 3) (2.1, Gordon and Taylor, 1952; equation 2.3, Williams et al., 1955).
The BET surface areas showed that using sucrose as the templating agent at concentrations up to 2% (w/w) significantly increased the specific surface areas of the mannitol particles. However, adding 0.5% (w/w) WPI caused an increase in the BET surface area of particles compared with mannitol powders having the same concentrations of sucrose (samples 1 and 3 compared with samples 2 and 4, respectively). The presence of WPI increased the glass-transition temperatures of the particle surfaces, making it difficult for the particles to crystallize completely in the process, resulting in higher levels of amorphicity in the particles and consequently higher porosities and BET surface areas for the ethanol-washed particles (Table 8.1).
Table 8.1 Summary of the experimental conditions used in spray drying for mannitol (10% w/w) - sucrose - WPI solutions, inlet gas temperature of 150°C and outlet gas temperature of 80 ± 4°C.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Sucrose: WPI concentration (% w/w)</th>
<th>Citric acid (2% w/w)- WPI (0.5% w/w) Sample5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample 1</td>
<td>Sample 2</td>
</tr>
<tr>
<td>Yield of spray drying (%)</td>
<td>50±6</td>
<td>87±5</td>
</tr>
<tr>
<td>BET surface area (m² g⁻¹)</td>
<td>3.5±0.2</td>
<td>3.9±0.1</td>
</tr>
<tr>
<td>Pore volume (ml g⁻¹)</td>
<td>0.013±0.002</td>
<td>0.021±0.002</td>
</tr>
</tbody>
</table>

All values are means ± standard deviations of at least three independent experiments.

8.2.2 Effect of Porous Mannitol on Drug Loading

There appears to be a relationship between the extent of drug loading in the adsorption process with different concentrations of drug solutions, and the BET surface areas of the processed powders before drug loading, as will now be explained. It can be seen in Table 8.2 that the current adsorption method for the whole range of drug loadings (low to high) has been successful. With increasing the acetaminophen solution concentration, the drug contents for samples 1, 3 and 5 have been increased.

The drug content of sample 1 with the BET surface area of 3.5 ± 0.2 m² g⁻¹ gradually increased from 0.47 ± 0.02 w/w % for 0.01 M acetaminophen solutions to 16.2 ± 0.9 w/w % drug loading for 0.5 M acetaminophen solutions. The results of the drug loading for sample 3 with higher surface areas and pore volumes of 6.1 ± 0.1 m² g⁻¹ and 0.037 ± 0.003 ml g⁻¹, respectively, significantly increased from 0.62 ± 0.03 w/w % to 21.7 ± 0.8 w/w % drug loading when the concentration of acetaminophen was increased from 0.01 M to 0.5 M (Table 8.2).

It can be expected that preparing an excipient with a higher BET surface area, such as lactose, which can be produced according to the method described in Chapter 6, would result in a higher drug loading as it (lactose) provides more available pore volume in order to host the drug molecules. For instance, porous lactose powders produced using ascorbic acid as a templating agent have surface areas of 21.5 ± 0.5 m² g⁻¹, which have a pore volumes of 0.27 ± 0.04 ml g⁻¹. In addition, a probable outcome of using higher concentrations of drug solutions (>0.5 M) might
be higher drug contents, since the driving force for the adsorption process is the drug concentration. Hence for the very low drug loadings (<0.1 w/w %), drug loading of porous mannitol with lower concentrations of drug solutions (<0.01 M) would appear to be achievable.

The question then arises as to why sample 5, even when having a higher surface area and more available pore volume of 10.5 ± 0.5 m² g⁻¹ and 0.11 ± 0.05 ml g⁻¹, respectively, does not have a better performance for the adsorption process. This sample resulted in a final formulation with a lower drug content with the same acetaminophen solution concentrations compared with sample 3, which has a lower BET surface area and pore volume. A similar result has been found for the drug-loaded formulations from samples 2 and 4 compared with samples 1 and 3, where samples 1 and 3 have lower surface areas and pore volumes and have higher drug loadings. However, it has been confirmed that, for all the porous mannitol samples without WPI, higher BET surface areas led to higher drug contents, and the same trend has been found for the porous mannitol containing WPI. WPI has some advantages, such as improving the yield and resulting in lower crystallinity for spray-dried powders, which helps to produce final porous particles with higher surface areas. Nevertheless, WPI accumulates on the particle surfaces during spray drying, as suggested in the literature (Izutsu et al., 2004; Islam et al., 2013). However, the low binding of acetaminophen to protein (Milligan et al., 1994; Zhou et al., 1997) and the barrier properties of WPI for moisture and gas permeation (Cinelli et al., 2014) might be reasons for less sedimentation of drug molecules into the voids of porous mannitol.

The pore size distributions of samples 5 and 3 before and after drug loading in different concentrations of acetaminophen solutions have been presented in Figures 8.3 and 8.4, respectively. The pore size distributions for drug-loaded samples 3 and 5 demonstrated a gradual decrease in the total pore volume through lower pore volumes for the pore diameters between 20-200nm when the drug concentration was increased. The pore size distributions of sample 3 also showed shifting of the pore size distribution to a range of narrower pores at about 4-6 nm as a result of drug sedimentation inside the wider pores.

Comparing the BET surface areas and pore volume values of the porous mannitol before and after drug loading with different acetaminophen concentrations suggests that there is still
significant residual porosity after drug loading, which indicates that acetaminophen molecules have been precipitated onto the voids in the porous mannitol (Grigorov et al., 2013).
Table 8.2 Summary of the experimental results regarding drug loading, BET surface area, and pore volume for different mannitol samples loaded with acetaminophen solutions.

<table>
<thead>
<tr>
<th>Acetaminophen solution concentration (M)</th>
<th>Drug loading, % w (API) /w (mannitol)</th>
<th>Sample 1</th>
<th>Sample 3</th>
<th>Sample 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug content, w/w %</td>
<td>BET (m² g⁻¹) after drug loading</td>
<td>Pore volume after loading (ml g⁻¹)</td>
<td>Drug content, w/w %</td>
</tr>
<tr>
<td>0.01</td>
<td>0.47±0.02</td>
<td>3.5±0.1</td>
<td>0.013±0.001</td>
<td>0.62±0.03</td>
</tr>
<tr>
<td>0.05</td>
<td>1.95±0.08</td>
<td>3.5±0.1</td>
<td>0.013±0.002</td>
<td>3.2±0.07</td>
</tr>
<tr>
<td>0.2</td>
<td>8.1±0.4</td>
<td>3.0±0.2</td>
<td>0.01±0.002</td>
<td>10.4±0.6</td>
</tr>
<tr>
<td>0.5</td>
<td>16.2±0.9</td>
<td>2.5±0.4</td>
<td>0.01±0.0</td>
<td>21.7±0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acetaminophen solution concentration (M)</th>
<th>Sample 2</th>
<th>Sample 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug content, w/w %</td>
<td>BET (m² g⁻¹) after drug loading</td>
</tr>
<tr>
<td>0.5</td>
<td>8.8 ±0.2</td>
<td>3.6±0.2</td>
</tr>
</tbody>
</table>

All values are means ± standard deviations of at least three independent experiments (Sample numbers are the same as in Table 8.1).
Figure 8.3 Pore size distributions for drug-loaded sample 5 in different acetaminophen solutions compared with sample 5 before loading.
8.2.3 Physical State of Loaded Drug

Differential scanning calorimetry provides information about the physical state and the crystalline character of a loaded drug by analyzing corresponding thermal transitions, which are the processes of transitions (for example) between crystalline components and amorphous ones (Westesen and Bunjes, 1995; Jenning et al., 2000; Xue et al., 2001; Feng and Kamal, 2004; Beiner et al., 2007; Doktorovová et al., 2010; de Souza et al., 2012). Physical mixtures of porous mannitol and acetaminophen powder were prepared with a size range of less than 63 µm (22 w/w % drug loading), in which the ratios of drug to mannitol were similar to the weight ratios in the final formulations of drug-loaded mannitol in 0.5 M acetaminophen solutions. These materials were prepared in order to assess the melting point depression and also to evaluate the crystalline character of the loaded drug in the final formulations of sample 3 with 0.5 M and 0.01 M acetaminophen solutions. DSC thermograms suggested that the drug molecules were present in
their crystalline forms in the final formulations since there is no crystallization peak (Figure 8.5). A higher degree of drug crystallinity helps the processing and storage of the drug, such as better physical and chemical stability, resulting in a stable product, so 90% of drug molecules are delivered in the crystalline form (Variankaval et al., 2008).

![DSC thermograms of sample 3 loaded in 0.01 M and 0.5 M acetaminophen solutions compared with a DSC thermogram for a physical mixture of porous mannitol with 22 w/w % acetaminophen powder having a particle size of less than 63 µm.](image)

**Figure 8.5** DSC thermograms of sample 3 loaded in 0.01 M and 0.5 M acetaminophen solutions compared with a DSC thermogram for a physical mixture of porous mannitol with 22 w/w % acetaminophen powder having a particle size of less than 63 µm.

Melting curves from differential scanning calorimetry also can used to compare crystal size distributions (Feng and Kamal, 2004; de Souza et al., 2012). The result of this MDSC analysis suggested that a less ordered arrangement of drug crystals was dispersed in the drug-loaded sample 3 with two different drug loadings concentrations of 0.5 M and 0.01 M, as shown by the onset shifts for melting temperatures. The thermodynamic melting temperature is the temperature where a perfect structure (a large crystal with no defects) would melt. Melting of crystals with smaller sizes (high surface area) and poor quality (large number of defects) is expected to happen
at lower temperatures (Westesen and Bunjes, 1995; Xue et al., 2001), and the depression in the melting point increased with decreasing crystal size. The melting peaks in differential thermograms for sample 3 with two different loadings from 0.5 M and 0.01 M acetaminophen solutions also exhibited a broad melting peak compared with a single sharp endothermic peak for the physical mixture of porous mannitol with 22 w/w % drug loading. The broad peak mainly occurred because of the wide crystal size distribution (Feng and Kamal, 2004; de Souza et al., 2012). The onset shifts of the melting peaks for both sample 3 materials loaded with 0.5 M and 0.01 M acetaminophen solutions were 146.5 ± 0.5°C, with the peak temperatures of 172.2 ± 0.8°C and 167.5 ± 0.3°C, respectively. These peaks should be compared with the thermogram for the physical mixture of porous mannitol with acetaminophen powder (22 w/w % drug loading). This situation indicates that melting commences at 153.5 ± 0.6°C, and goes through a maximum at 172 ± 1°C, following the established phase behavior for acetaminophen (Giordano et al., 2002; Qi et al., 2008). There is an onset shift by almost 7°C for both drug-loaded samples compared with the physical mixture of porous mannitol and acetaminophen powder, which agrees with the observation that acetaminophen confinement into small pores shows different melting behavior than in the bulk (Beiner et al., 2007). The depression of the peak melting point is more marked for sample 3 with 0.01 M acetaminophen solutions. The reasons for the higher shift in the melting peak to lower temperatures can be seen in the work of Beiner et al. (2007). In their study, it was found that, for acetaminophen confined to nanopores with the largest pore diameter of 103 nm, the melting point value was only slightly below the bulk melting point, while shifts to lower values in the melting point increased as the pore diameter decreases.

The X-ray powder diffraction analysis (XRD) was also used to compare the crystal structure of acetaminophen present in the drug-loaded sample 3 having a drug loading concentration of 0.5 M with the sample of porous mannitol and acetaminophen powder (22 w/w % drug loading) prepared by powder mixing and recrystallization methods (Figure 8.6). The XRD pattern for the physical mixture of acetaminophen with mannitol is simply a superposition of each component with the peaks from both drugs and carriers. Figure 8.6 shows the X-ray diffraction pattern of sample 3 loaded with a drug concentration of 0.5 M, compared with the sample of porous mannitol with 22 w/w % acetaminophen powder, which exhibits significant line broadening in all corresponding peak positions for acetaminophen reported in the literature (Jordan, 1993; Nichols and Frampton, 1998). A decrease was found in the areas of the peaks in the X-ray
pattern of the drug-loaded sample, compared with the areas from the physical mixtures of porous mannitol and acetaminophen powder that contained the original crystalline acetaminophen (with a particle size of less than 63 µm).

Less intense and highly-diffused peaks of drug in the diffractograms of the drug-loaded sample indicate that the drug is found in the reduced ordering of the crystal lattice in the final formulation (Ghodke et al., 2010; Jain et al., 2012). In addition, according to the Scherrer equation (Scherrer, 1918), which relates the width of a powder diffraction peak to the average dimensions to estimate the size of the crystallites, the peak width is inversely proportional to the crystallite size. As the crystallite size gets smaller, the peak gets broader. In other words, as the number of lattice repeats increases, the full width becomes narrower at the half maximum height (FWHM), which is the width of the diffraction peak at a height half-way between the background level and the peak maximum in the XRD (Burton et al., 2009). The results from the XRD method agreed well with the results from the MDSC test and confirm that the smaller and less ordered arrangement of drug crystals was dispersed and confined in the pores of mannitol compared with the physical mixture of porous mannitol and acetaminophen powder (Beiner et al., 2007).
Figure 8.6 X-ray pattern for drug-loaded sample 3 in 0.5 M acetaminophen solution compared with the physical mixture of porous mannitol and acetaminophen powder.

8.2.4 Blend Uniformity

In order to evaluate the drug loading efficiency, the relative standard deviation (% RSD) for the drug content of final powder has been calculated by taking at least five samples for each drug loading concentrations of 0.01 M and 0.5 M for one set of experiments, as the important acceptance criteria (must be less than 6% RSD) for the content-uniformity dosage requirements of the pharmaceutical industry. The blend uniformity was around 4% RSD or less, which indicates a highly uniform blend, even for low-dose drug products. A content uniformity test and a BET surface area analysis were also conducted across the particle-size distribution of the final formulation (Table 8.3). Low variability was found for the content uniformity and delivered dose across the particle-size distribution in sample 3 loaded in 0.01 M and 0.5 M acetaminophen.

There were also no significant changes in the BET surface areas for the different size ranges of the drug-loaded sample 3 in 0.5 M acetaminophen, which means that the uniformity of pore sizes
after drug loading over different size ranges was very good. These results suggest that the particle size of the final formulation does not have any significant effect on the drug content and uniformity of pore sizes.

The evidence supports this suggestion, with the MDSC scans of all size fractions for drug-loaded mannitol in 0.5 M and 0.01 M drug solutions being almost the same (Table 8.3). As shown in Figures 8.6 and 8.7 for all size ranges of each drug concentration, there were similar endothermic peaks, representing good drug dispersion throughout the mannitol.

As mentioned earlier, pharmaceutical manufacturers are required to ensure the consistency of dosage units. However, the content uniformity of the finished products, the homogeneity of blend and the poor blending uniformity of finished products, especially for low-dose drug product (high RSD), are typical problems due to a combination of factors. These problems include insufficient blending, segregation, and the large particle size of the drug substance when using blending or mixing unit operations. Control of the particle size for the drug substance may be a solution to ensure the content uniformity of the finished products, but the particle size and size distribution of excipients also have a significant impact on blending homogeneity, powder segregation, and flowability. This situation can result in unacceptable content uniformity and control of excipients for product quality (Zheng, 2009). These results here suggest that the present adsorption method is independent of the control strategy for both the particle size of the drug and excipients in the finished dosage units, so here the particle size of the final formulation does not appear to have any effect on drug uniformity.
Table 8.3 Content uniformity of different size fractions for the drug-loaded sample 3 in 0.01 M and 0.5 M acetaminophen solutions.

<table>
<thead>
<tr>
<th>Acetaminophen solution concentration (M)</th>
<th>Size fraction, µm</th>
<th>Below 63</th>
<th>63-106</th>
<th>106-150</th>
<th>150-212</th>
<th>212-300</th>
<th>Over 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 Drug content, w/w %</td>
<td></td>
<td>0.60±0.02</td>
<td>0.60±0.01</td>
<td>0.59±0.01</td>
<td>0.61±0.01</td>
<td>0.61±0.00</td>
<td>0.60±0.02</td>
</tr>
<tr>
<td>0.5 Drug content, w/w %</td>
<td></td>
<td>20.8±0.2</td>
<td>20.9±0.4</td>
<td>21.0±0.1</td>
<td>21.0±0.3</td>
<td>20.7±0.2</td>
<td>20.9±0.3</td>
</tr>
<tr>
<td></td>
<td>BET(m² g⁻¹) after drug loading</td>
<td>2.9±0.2</td>
<td>2.9±0.1</td>
<td>3.0±0.1</td>
<td>3.2±0.3</td>
<td>3.1±0.2</td>
<td>3.0±0.3</td>
</tr>
</tbody>
</table>

All values are means ± standard deviations of at least two replicate analyses for one set of independent experiment.

Figure 8.7 DSC traces of different size fractions for drug-loaded sample 3 in 0.5 M acetaminophen solutions.
8.2.5 **Morphological Characterization**

Scanning electron microscopy has also been used to study the morphology of the powders. Figure 8.9 shows the SEM micrographs of the spray-dried powders (sample 3) before and after ethanol washing compared with drug-loaded sample 3 that had a drug concentration of 0.5 M. The surfaces of the spray-dried powders appeared to be non-porous and amorphous (Figure 8.9 A), while ethanol-washed powders showed porosity on the surface and also inside the particles (Figure 8.9 B).

The final drug-loaded particles were also highly-interconnected porous networks showing porosity in the bulk as well as on their surfaces, suggesting a relatively uniform distribution of the pores throughout the particles after drug loading (Figures 8.9 C and D) and significant residual porosity after drug loading, as also indicated by the BET measurements. The morphologies of the particles support the measurements of the BET surface areas for the samples and indicate that acetaminophen molecules have been adsorbed onto the voids of porous mannitol, leading to homogenous dispersion of the drug into the mannitol structure. The measurements of the particle sizes showed a mean particle size of about 17 ± 3 μm (D[3,2]) for
the final drug-loaded powder, while the mean size for the spray-dried powder prior to ethanol washing was $7 \pm 1 \mu m$ ($D_{3,2}$), suggesting that the high porosity and relatively large processed particles were actually agglomerates of smaller porous particles. The $D_{4,3}$ values for these two powders were $112 \pm 5 \mu m$ and $46 \pm 2 \mu m$, respectively.

**Figure 8.9** Scanning electron micrographs of spray-dried powders from sample 3, before (A) and after ethanol washing, compared with (B) drug-loaded sample 3 with a drug concentration of 0.5 M (C and D).
8.2.6 Dissolution Profiles

Figure 8.10 shows *in-vitro* dissolution profiles of gelatin capsules filled with drug-loaded sample 3 in 0.5 M acetaminophen compared with the physical mixture of non-porous mannitol and acetaminophen powders. The drug release rate for the drug-loaded sample 3 was slightly faster than the release rate for the physical mixture of non-porous mannitol and acetaminophen powder. The amount of the drug released within the first five minutes of the experiment for the drug-loaded sample 3 was 80%, which meets the USP requirement of 80% release in 20 minutes or less (FDA, 2003; Grigorov et al., 2013). One of the factors that has led to the enhanced dissolution rates of drug-loaded sample 3 is mannitol with high porosity. Porous mannitol may improve the solubility by enabling faster release of the drug as a result of better penetration of solvent into the acetaminophen-mannitol matrix and the large surface area of the compound that comes into contact with the dissolution medium. In addition, deposition of acetaminophen in the pore space of highly-porous mannitol results in particle size reduction of the drug powders to the size range of nanometres, which may cause a significant increase in the dissolution rate of the acetaminophen particles. The *in-vitro* release results agreed well with the results of MDSC, XRD techniques and BET surface areas, and these results suggested that nano-confinement of drugs into the porous excipients has occurred through adsorption method.
Figure 8.10 Dissolution profiles of gelatin capsules filled with both the drug-loaded sample 3 in 0.5 M acetaminophen, and the physical mixture of non-porous mannitol and acetaminophen powder (error bars indicate standard deviations).

8.2.7 Tableting Properties of the Products

The tableting characteristics of drug-loaded sample 3 in 0.5 M acetaminophen solutions were compared with the physical mixture of non-porous mannitol and acetaminophen powder by measuring the thickness and crushing strength of tablets at different compaction loads. The tablet thicknesses as a function of the applied compaction load clearly showed that, when increasing the compression force, the tablet thickness decreased for both the drug-loaded sample 3 in 0.5 M acetaminophen solution and for the physical mixture of non-porous mannitol and acetaminophen powder (Figure 8.11). However, the thickness of the tablet for drug-loaded sample 3 is lower than the tablet thickness for the physical mixture of non-porous mannitol and acetaminophen powder at the same compression forces. This result may be explained by the higher porosity and the lower density of drug-loaded sample 3 compared with the physical mixture of non-porous mannitol and acetaminophen powder, which results in a higher thickness for the final tablets.
Figure 8.11 Comparison of tablet thickness as a function of compression pressure for tablets from the drug-loaded sample 3 in 0.5 M acetaminophen solution compared with the physical mixture of non-porous mannitol and acetaminophen powder (error bars indicate standard deviations).

Figure 8.12 shows the crushing strength of the tablets for the drug-loaded sample 3 in 0.5 M acetaminophen solutions compared with the physical mixture of non-porous mannitol and acetaminophen powder at different compression pressures. It can be seen that, with increasing compaction load, the tablet strength increased significantly. The differences between tablet strengths became less pronounced with increasing the compaction load. This result may be explained by the higher porosity of drug-loaded sample 3 compared with the physical mixture of non-porous mannitol and acetaminophen powder, suggesting that powder-tableting properties and the binding capacities of the powders are related to the particle porosity and surface area. It has been found that particles with higher porosities and surface areas lead to more coherent tablets and a subsequent increase in tablet strength, due to greater fragmentation and a decrease in the initial particle size during compression (Vromans et al., 1987a; Vromans et al., 1987b; Zuurman et al., 1994; Caillard et al., 2012).
8.3 Conclusions

Together with the uniformity of drug dosage, especially in low-dose solid drug products, the solubility behavior of a drug is a key challenge facing the design of solid dosage forms. A new adsorption method was developed to successfully produce highly-porous excipients with nano-confinement drugs dispersed in the pore spaces of a porous carrier. The drug content of porous mannitol with the surface area and pore volume of $6.1 \pm 0.1 \text{ m}^2 \text{ g}^{-1}$ and $0.037 \pm 0.003 \text{ m}^2 \text{ g}^{-1}$, respectively, significantly increased from $0.62 \pm 0.03 \text{ w/w } \%$ to $21.7 \pm 0.8 \text{ w/w } \%$ when the concentration of acetaminophen was increased from $0.01 \text{ M}$ to $0.5 \text{ M}$. This method has increased the dissolution rate of the API due to both the nano-confinement of drugs into porous excipients and the better penetration of the dissolution medium into the pores of the excipients, giving 80% release of the drug within five minutes.
CHAPTER 9  A NOVEL FORMULATION FOR SOLUBILITY AND CONTENT UNIFORMITY OF POORLY WATER-SOLUBLE DRUGS

This chapter investigates the enhancement of the dissolution profile of poorly-water soluble drugs by the adsorption method described in Chapter 8. Indomethacin and nifedipine as model drugs were used in this technique to incorporate the drug molecules onto this porous structure.

9.1  Porous Mannitol Production and Drug Loading Process

Mannitol (10% w/w)-sucrose (2% w/w) solutions were prepared according to the method explained in Chapter 8 and then spray dried using a Büchi mini spray dryer B-290. Freshly spray-dried powder has been collected from a collection vessel at the bottom of a cyclone and two grams of powder has been washed with 80 mL of ethanol for 48 h at the room temperature of 25°C to remove the templating agent (sucrose) and then filtered under vacuum. The resultant pastes were immersed in acetone solutions with two different concentrations of indomethacin and nifedipine (0.08 M and 0.16 M) as model drugs in order to load the drug onto highly-porous mannitol for 12 h at the room temperature of 25°C. The carrier: drug ratios were 1:2 (w/w) and 1:4 (w/w) for 0.08 M and 0.16 M drug solutions, respectively. The final processed powder were obtained after vacuum filtering and oven drying at 60°C for one hour to remove any residual acetone. There was no change in the mass for drug-loaded powder after one hour of oven drying, suggested that no solvent residues were left in the final material. The final powder has been used for analytical tests. In this study, for each drug concentration, an experiment has been done three times, and data have been presented as means ± STD (standard deviation). The drug content uniformity of final powder, % RSD, was obtained from one set of independent experiment for each drug and different drug concentrations.

5 The content of this chapter has been published as the following paper:
9.2 Results and Discussion

9.2.1 Analysis of Drug Loading

The experimental result of drug loading for porous mannitol with a surface area and pore volume of 6.3 ± 0.1 m$^2$ g$^{-1}$ and 0.033 ± 0.002 ml g$^{-1}$, respectively, suggested that increasing the concentrations of drug solution results in higher drug contents for both nifedipine and indomethacin (Table 9.1). Hence different drug loadings with adsorption method of porous mannitol over a range of concentrations for drug solutions seem to be achievable, since the driving force for the adsorption process is the difference between the drug concentration in the porous mannitol and drug solution (Hillerström et al., 2009).

Table 9.1 Summary of the experimental results for drug loading with mannitol samples (BET= 6.3 ± 0.1 m$^2$ g$^{-1}$ and pore volume of 0.033 ± 0.002 ml g$^{-1}$) loaded in drug solutions.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug solution concentration (M)</th>
<th>Drug content, w/w %</th>
<th>BET(m$^2$ g$^{-1}$) after drug loading</th>
<th>Pore volume after loading (ml/g)</th>
<th>Drug content uniformity, % RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>0.08</td>
<td>3.2±0.1</td>
<td>3.8±0.1</td>
<td>0.026±0.002</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td>9.1±0.3</td>
<td>2.5±0.2</td>
<td>0.019±0.006</td>
<td>3.2</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0.08</td>
<td>4.1±0.2</td>
<td>3.6±0.1</td>
<td>0.024±0.004</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td>12.6±0.4</td>
<td>1.9±0.4</td>
<td>0.015±0.006</td>
<td>3.0</td>
</tr>
</tbody>
</table>

All values are means ± standard deviations of at least three independent experiments except the data for drug content uniformity, which was obtained from one independent experiment.

The results suggested that the current adsorption method has been successful for the whole range of drug loadings. The drug content for nifedipine gradually increased from 3.2 ± 0.1 w/w % for 0.08 M drug solution to 4.1 ± 0.2 w/w % drug loading for 0.16 M drug solution. However the final drug content for nifedipine adsorption is slightly lower than the drug content for indomethacin. Indomethacin gave a better performance for the adsorption process and resulted in
a final formulation with higher drug content with the same drug solution concentrations compared with nifedipine, with $4.1 \pm 0.2$ w/w % and $12.6 \pm 0.4$ w/w % for 0.08 M and 0.16 M concentrations of indomethacin, respectively, which might be due to the fact that in adsorption method depending on the chemical nature of the drug, different drug-loading are achieved (Salonen et al., 2005a; Millqvist-Fureby et al., 2014).

The results of drug loading for porous mannitol before and after drug adsorption in different concentrations of drug solutions are presented in Table 9.1 and demonstrated a gradual decrease in the total pore volume as a result of drug sedimentation inside the pores. However, there is still significant residual porosity for drug-loaded mannitol, which indicates that drug molecules have been precipitated onto the voids of porous mannitol. Porous mannitol with the pore volume of $0.033 \pm 0.002$ mL g$^{-1}$ seems not to have enough space to host drug molecules for the resulted drug-loadings. In general, in adsorption method drug molecules are loaded at the surface and in the internal pores of porous carriers (Prestidge et al., 2007). However, the extent of drug loading is more likely to be a function of the degree of surface area available rather than the internal pore volume (Prestidge et al., 2007). In the present work, in addition to the internal pores, porous mannitol provides a large surface area for drug to be deposited on. Besides, the agglomeration of small porous mannitol during the drug-loading stage creates secondary external voids (Boissiere et al., 2011), which provides more available space in order to host the drug molecules.

### 9.2.2 Physical State of the Loaded Drugs

The physical state of the drugs in the final formulations were investigated by DSC thermograms and X-ray patterns of the drug-loaded samples (Westesen and Bunjes, 1995; Jenning et al., 2000; Xue et al., 2001; Feng and Kamal, 2004; Beiner et al., 2007; Doktorovová et al., 2010; de Souza et al., 2012). Physical mixtures of porous mannitol and drug powders (in which the ratios of drug to mannitol were similar to the weight ratios in the final formulation of drug-loaded mannitol) were prepared in order to assess the melting-point depression and also to evaluate the crystalline character of the loaded drug in the final formulation of different samples. DSC thermograms suggested that the drug molecules loaded into the porous mannitol host were in their crystalline forms in the final formulations, since there was no crystallization peak (Figures 9.1 and 9.2).
This might be due to the pore size distributions of porous mannitol, which seems to be large enough to allow the formation of crystalline form of drugs rather than retaining drugs in its amorphous state due to the limited pore sizes (Salonen et al., 2005a). Although the amorphous form of drugs is known to have an advantage of higher dissolution rates than the crystalline form (Hancock and Parks, 2000), but this crystallinity is very important when considering long-term time stability and storage of the drug (Hecq et al., 2005). More than 90% of drug molecules are delivered in the crystalline form due to better physical and chemical stability, which results in a stable final formulation (Variankaval et al., 2008).

![Figure 9.1](image-url)  

**Figure 9.1** DSC thermograms of mannitol drug-loaded in 0.16 M nifedipine compared with a DSC thermogram of a physical mixture of porous mannitol with 9 w/w% nifedipine powder.
The results of the MDSC analysis show that the characteristic endothermic peak, corresponding to drug melting, was broadened and shifted towards the lower temperature, with a reduced intensity in the drug-loaded samples for both drugs, compared with the peaks for the physical mixture of porous mannitol and corresponding drug powder. This result could be attributed to a less ordered arrangement of drug crystals dispersed in the drug-loaded samples (Feng and Kamal, 2004; Modi and Tayade, 2006; de Souza et al., 2012) (Figures 9.3 and 9.4). The depression in the melting point of a perfectly structure drug (a large crystal with no defects) increases with a decrease in the size and the quality of the crystal (Westesen and Bunjes, 1995; Xue et al., 2001). Differential thermograms at the melting peaks for all drug-loaded samples also exhibit a broad melting peak compared with a single sharp endothermic peak for the physical mixture of porous mannitol with the same drug loadings because of the broad crystal size distribution (Feng and Kamal, 2004; de Souza et al., 2012).

The onset shifts of the melting peaks for porous mannitol loaded with 0.16 M nifedipine and indomethacin solutions were 150.5 ± 0.6°C and 148.6 ± 0.4°C, respectively, with the peak
temperatures of 164.8 ± 0.2°C and 164.4 ± 0.3°C, respectively. These results should be compared with the thermogram for the physical mixture of porous mannitol and drug with the same drug contents. This situation indicates that for nifedipine and indomethacin melting commences at 165.1 ± 0.4°C and 157.5 ± 0.4°C, respectively, and goes through the maximum at 167.1 ± 0.3°C and 168.7 ± 0.4°C, respectively.

There are the onset shifts of about 15 and 9°C for drug-loaded mannitol with nifedipine and indomethacin solutions, respectively, compared with the physical mixture of porous mannitol and the corresponding drug powder, which agreed with the observation that drug confinement into small pores shows different melting behavior than in the bulk (Hecq et al., 2005; Beiner et al., 2007).

X-ray powder diffraction analysis (XRD) has also been used to compare the crystal structure of drug present in the drug-loaded samples with a drug loading concentration of 0.16 M with the physically-mixed sample of porous mannitol and drug powder (same drug loading) (Figures 9.3 and 9.4). The X-Ray diffraction pattern for the physical mixture of drugs with mannitol is simply a superposition of each component with the peaks from both drugs. Figures 9.3 and 9.4 show the X-ray diffraction patterns of mannitol loaded with the 0.16 M drug solution for nifedipine and indomethacin, respectively, compared with the sample of porous mannitol having the same drug loading, which showed significant line broadening in all corresponding peak positions for the drugs reported in the literature (Vippagunta et al., 2002; Otsuka et al., 2003; Padrela et al., 2012).

A decrease in the areas of the peaks in the X-ray pattern of the drug-loaded sample, compared with the areas from the physical mixture of porous mannitol and drug powder that contained the original crystalline drug, indicated the presence of significant disorder in the crystalline material present in the final formulation. Less intense and highly-diffused peaks of drug in the diffractograms of solid dispersions indicate that the drug is found in the reduced ordering of the crystal lattice in these dispersions (Ghodke et al., 2010; Jain et al., 2012). The results from the XRD method agreed well with the results from the MDSC test and support the suggestion that the smaller and less ordered arrangement of drug crystals was dispersed and confined in the pores of mannitol (Beiner et al., 2007).
Figure 9.3 X-ray pattern for drug-loaded mannitol in 0.16 M nifedipine solution compared with the physical mixture of porous mannitol and nifedipine powder.
9.2.3 Drug Content Uniformity

In order to evaluate the drug loading efficiency, the relative standard deviation (% RSD) for the drug content of the final powder has been calculated by taking at least five samples for each drug loading concentration of 0.8 M and 0.16 M for one set of experiments. The blend uniformity was less than 4% RSD for drug-loaded mannitol in both nifedipine and indomethacin with two solution concentrations of 0.08 M and 0.16 M. This result indicates highly uniform blends, even for low-dose drug products, as the content uniformity and the homogeneity of blend for pharmaceutical manufacturers, especially for low-dose drug products, are typical problems due to a combination of factors (Zheng, 2009) (Table 9.1). These results also suggest that the present adsorption method is independent of the control strategies for the particle size and shape of both the drug and excipients in the finished dosage units (Wong and Pilpel, 1990; Vikas Anand Saharan, 2008).

Figure 9.4 X-ray pattern for drug-loaded mannitol in 0.16 M indomethacin solution compared with the physical mixture of porous mannitol and indomethacin powder.
9.2.4 Microscopic Characterization

A scanning electron microscope was also used to study the morphology of the powders and to observe the powders in terms of the surface and bulk structures. Figure 9.5 shows the SEM micrographs of the spray-dried mannitol before and after ethanol washing compared with drug-loaded mannitol from a drug concentration of 0.16 M. These micrographs show some morphological changes for the mannitol powders, before (Figure 9.5 A) and after sucrose removal by ethanol washing (Figure 9.5 B). The surfaces of the spray-dried powders appeared to be non-porous, while more porosity appeared to be formed on the surface and also inside the ethanol-washed particles. The final drug-loaded particles were also highly-interconnected porous networks showing porosity in the bulk as well as on their surfaces, suggesting the relatively uniform distribution of the pores throughout the particles even after drug loading (Figures 9.5 C:F). Particle size analysis of the powders has shown that the particle size of the final drug-loaded powder after grinding is about $98 \pm 7 \mu m$ ($D[4,3]$), while the particle size of the spray-dried mannitol/sucrose powder before ethanol washing was $32 \pm 4 \mu m$ ($D[4,3]$), suggesting that the high porosity and relatively large processed particles are actually agglomerates of smaller porous particles. The results are consistent with the measurements of the BET surface areas for the samples, suggesting high residual porosity after drug loading. Therefore, from all the results so far, it can be suggested that drug molecules have been precipitated onto the voids of porous mannitol, leading to homogenous dispersion of the drug into the carrier structure despite the initial differences in particle size and shape of porous mannitol before drug loading.
Figure 9.5 Scanning electron micrographs of spray-dried mannitol, before (A) and after ethanol washing (B) compared with for drug-loaded mannitol in 0.16 M indomethacin (C and D) and nifedipine (E and F) solutions.
9.2.5 Dissolution Profiles

Figures 9.6 and 9.7 the *in vitro* dissolution profiles of gelatin capsules filled with the drug-loaded samples compared with the corresponding physical mixture of non-porous mannitol and drug. Similar drug-release profiles have been found for the drug-loaded samples with different drug loadings. Therefore, dissolution profiles of porous mannitol loaded in different drug concentration of 0.16 M and 0.08 M has been depicted in Figures 9.6 and 9.7 as a single release profile with error bars indicating standard deviations.

The dissolution rate of both drugs was significantly faster for the drug-loaded mannitol than the release rate for the physical mixture of non-porous mannitol and drug powder. More than 80% of the drug was released within the first fifteen minutes of the experiment for the drug-loaded mannitol for both nifedipine and indomethacin, which meets the USP requirement of 80% release in 20 minutes or less (FDA, 2003). This improvement in the drug dissolution rate can be ascribed to several factors. Having a less ordered arrangement of drug crystals that are dispersed and confined into the voids of the carrier, which results in particle size reduction of drug powder to the nanometre size range, compared with the physical mixture of mannitol and drug powder, is one main factor leading to the enhanced dissolution of drug-loaded porous mannitol. Moreover, the concomitant increase in wettability and dispersibility of drug into the drug-excipient matrix (porous mannitol) may be another reason for the solubility improvement and the faster release of the drug. Mannitol with high porosity has given better wettability and penetration of the dissolution medium into the drug-excipient matrix, has maximized the surface area of the compound that comes into contact with the dissolution medium. The *in vitro* release results have agreed well with the results of MDSC, XRD techniques, and BET surface areas and have suggested that nano-confinement of drugs into porous excipients has occurred through adsorption of drug into highly-porous excipients.
Figure 9.6 Dissolution profiles of gelatin capsules filled with drug-loaded mannitol in 0.16 M and 0.08 M nifedipine and the physical mixture of non-porous mannitol powder (error bars indicate standard deviations).
Figure 9.7 Dissolution profiles of gelatin capsules filled with drug-loaded mannitol in 0.16 M and 0.08 M indomethacin solutions and the physical mixture of non-porous mannitol indomethacin powder (error bars indicate standard deviations).

9.3 Conclusions

It was found that indomethacin has a better performance for the adsorption process and resulted in a final formulation with a higher drug content with the same drug solution concentrations, compared with nifedipine. The blend uniformity was less than 4% RSD for drug-loaded mannitol in both nifedipine and indomethacin, which indicates highly uniform blends, even for low-dose drug products. This method significantly enhanced the dissolution rate for both poorly water-soluble drugs due to the nano-confinement of drugs into the porous excipients and the high water solubility of mannitol, where 80% of the drug was released within the first fifteen minutes of the experiment for the drug-loaded samples.
CHAPTER 10 CONCLUSIONS AND RECOMMENDATIONS

10.1 Significant Outcomes of This Study

10.1.1 Crystallization in Fluidized-Bed Dryers/Crystallizer

One of the main foci of the present work was to investigate different processes, such as “in-process” crystallization within spray drying and post-process crystallization in fluidized-bed drying, which is a controlled process to transform the amorphous-lactose fraction to a crystalline one. The experimental work consisted of studying the effects of operating conditions on the crystallization properties of sweet-whey powder in a continuous multi-stage fluidized bed dryer to achieve the maximum degree of lactose crystallinity with a reasonable overall processing time. Powder was fed at different rates for each fluidization process at different sets of process temperatures, humidities, and residence times. Experimental results showed that there were significant reductions in the amorphicity of lactose for the processed (crystallized) powders at different humidities and temperatures. The overall extent of lactose crystallinity for processed whey powders has been found to be between 10% and 20% within the processing time of 30 minutes. Increasing the rate of powder feeding (from 0.3 kg h\(^{-1}\) to 2.6 kg h\(^{-1}\)) did not have a significant effect on the degrees of lactose crystallinity for the processed powders.

10.1.2 Effect of Acidity on Lactose Crystallinity

Experimental studies have also been performed to better understand the choice of processing conditions to produce and control lactose crystallization in acid-rich carbohydrate-powders, such as acid whey, during spray drying. Spray drying of acid whey is a significant problem for the dairy industry due to its high content of lactic acid. It has been found that significant increases in the degrees of lactose crystallinity for the final spray-dried products of lactose solutions have occurred at increasing lactic acid concentrations, and the yields from spray drying have also been significantly decreased at higher concentrations of lactic acid. The sorption peak heights for lactose were altered from 6% ± 1% to about 0.3% ± 0.2% for lactose/lactic acid mixtures with increasing the lactic acid concentration from 1 to 5% (w/w), and adding 5% (w/w) of lactic acid
to the lactose solution significantly decreased the yield of the process by up to 22%. This increase in crystallinity may be due to increasing the $T-T_g$ difference (with the low $T_g$ of lactic acid) and consequently decreasing the crystallization time, according to the Gordon–Taylor and Williams–Landel–Ferry equations. The increase in the rate of lactose crystallization at low pHs may also be connected with the increase in the mutarotation rate and the rate of orientation of lactose molecules into the crystals.

10.1.3 Producing Highly Crystalline Lactose with Significant Porosity and High Surface Area

Although crystalline powders have several advantages compared with spray-dried powders, such as better stability and longer shelf-life, they may have some undesirable properties, such as lower dissolution rates. Therefore, highly-porous crystalline powders with better functional (free flowing), storage (non-caking) properties, have been developed using a new technique.

The experimental work consisted of producing highly-porous powder templates through the spray drying of lactose solutions containing ethanol-soluble food-grade acids, such as lactic acid, citric acid, boric acid, and ascorbic acid, as templating agents and then removing these acids by ethanol washing of the spray-dried powders. The results showed that textural properties, such as the surface area of the resultant lactose, changed considerably by varying the concentrations of different templating acids, due to changes in the degrees of lactose crystallinity for the final spray-dried products. For instance, in the case of using lactic acid as a templating acid, a change in lactic acid concentration from 1 to 3 w/w % showed a reduction in the surface areas from 14.9 ± 0.9 m$^2$ g$^{-1}$ to about 9.5 ± 0.8 m$^2$ g$^{-1}$ since the sorption peak heights decreased from 5.5% ± 0.4% to about 4% ± 1%, suggesting higher degrees of lactose crystallinity in the spray-dried powders.

It has also been found so far that the pH of the feed solution significantly affected the BET surface area and porosity of the processed lactose powder, where these outputs have also been linked to the crystallinity of the spray-dried powder before ethanol washing. For example, increasing the boric acid concentrations from 1 to 3% (w/w) did not have a significant effect on lactose crystallinity compared with lactic acid, as the peak heights remained constant (7% ± 1%). The BET surface area of lactose altered from 17.2 ± 0.5 m$^2$ g$^{-1}$ for the spray-dried lactose with
1% w/w boric acid to about 18.5 ± 0.8 m² g⁻¹ for 3% w/w boric acid. Higher BET surface areas of the lactose particles, using boric acid as a templating acid compared with lactic acid, may be explained by the lower acidity of boric acid, as suggested by the greater pHs of the solutions and therefore lower degrees of lactose crystallinity for the spray-dried powders from the lactose/boric acid solutions. The pH for the lactose/boric acid solutions changed from 5.34 ± 0.08 to 4.47 ± 0.01 with increasing boric concentrations from 1 to 3 w/w %, while pHs measurements for the lactose/lactic acid solutions were 2.53 ± 0.01 and 2.24 ± 0.01, respectively.

Increasing the acid concentration, and consequently decreasing the pH of the solution, increased the crystallinity of the spray-dried lactose/WPI powders, giving a decrease in the BET surface area. Increasing the number of templating molecules incorporated in the main structure is expected to increase the porosity of the templated particle. It has also been stated that acidity can significantly decrease the yield of the spray-drying process due to an increase in stickiness, resulting from a decrease in the glass-transition temperature of the spray-dried powder. For instance, in the case of using lactic acid as a templating acid a change in lactic acid concentration from 1 to 3 w/w % the yield of the spray-drying process altered from 71% ± 2% to about 44% ± 1%. Likewise, increasing citric acid content to 3 w/w% decreased the yield of the process significantly to 16% ± 4%.

10.1.4 Producing Highly Porous Mannitol with High Surface Area

Highly porous mannitol was also prepared through this templating route through the spray drying of solutions containing mannitol and citric acid as the templating agent. It is demonstrated that textural properties, such as surface area and pore volume of the resultant mannitol, can be tuned by varying the concentrations of citric acid, WPI, and Gum Arabic. The resulting powder structure is a mannitol network with significant porosity and high surface area of 8.0 ± 0.4 m² g⁻¹ and total pore volume of 0.075 ml g⁻¹. It has been found that adding 1% w/w citric acid as a templating material significantly increased the BET surface area of mannitol from 0.7 ±0.1 m² g⁻¹ to 1.91 ± 0.01 m² g⁻¹. However, adding WPI 0.2% (w/w) significantly increased the particle surface area to about 3.2 ± 0.9 m² g⁻¹ for 1% w/w citric acid, compared with 5.1 ± 1.1 m² g⁻¹ for the spray-dried mannitol/WPI mixture with 2% w/w citric acid (0.2% w/w WPI). The results
were similar to those of spray-dried mannitol with 0.5% w/w Gum Arabic, which showed that adding 2% w/w citric acid significantly increased the BET surface area of mannitol to 5.1 ± 0.2 m² g⁻¹, compared with 1.8 ± 0.1 m² g⁻¹ for the spray-dried mannitol/Gum Arabic mixture with 0.5% w/w citric acid. It has been found that using emulsifiers such as gum Arabic as an additive could improve the dispersity of the templating agents in the main structure during the solidification step (particle formation) of the spray-drying process.

10.1.5 Effect of acidity on a new templating approach for high-porosity spray-dried particle production

It can be observed in Tables 6.2 and 7.1 that adding 1% w/w citric acid as a templating material significantly increased the BET surface area of lactose to 20.8 ± 0.9 m² g⁻¹. However, adding further citric acid content (3 w/w%) decreased the BET surface area of lactose to 12.3±0.8 m²g⁻¹. The BET surface areas of the mannitol particles, using citric acid as a templating acid, can be altered from 1.91 ± 0.01 m² g⁻¹ for 1% w/w citric acid, compared with 1.6 ± 0.1 m² g⁻¹ for the spray-dried mannitol with 2% w/w citric acid. These results showed that the surface areas both of the resultant lactose and mannitol (core materials), decreased considerably by increasing the concentrations of templating acid. This result suggested that there is a link between crystallinity of core material in the spray-dried powders and the porosity of the ethanol-washed powders, as will now be explained. Crystalline solids are known to have distinctive and organized internal structures, called crystal lattices, while the atoms and molecules in amorphous solids are arranged randomly with no regular patterns (Averill and Eldredge, 2007). During the crystallization process, molecules of each component are more likely to join their own crystal structure (Jones and Mirkin, 2013). Therefore, each growing crystal tends to consist of only one type of molecule.

Lower degrees of core material crystallinity for spray-dried powders mean that the crystal structures have become less developed, which in turn means that the number of citric acid molecules incorporated in the whole core material structure (amorphous and crystal) has increased. Washing with ethanol removes the citric acid molecules, either scattered in the amorphous portion of the core material or accumulated on the surface of the crystals, rather than inside the crystal lattice. Therefore, the porosity and BET surface areas of the powders have
increased as the amorphous content has increased, which may be connected with the increase in the amount of incorporated citric acid molecules due to the decrease in the degree of crystallinity for the spray-dried powders.

The degrees of crystallinity measured using moisture sorption tests and XRD methods confirmed that the crystallinity of the lactose increased when the templating-acid concentration was raised. Spray drying of lactose solution with 3% (w/w) citric acid, resulted in a significant reduction in peak height to about 2.9% ± 0.6% compared with 5.4% ± 0.5% for 1% (w/w) citric acid. The intensities of the characteristic peak at $2\theta = 20.1^\circ$ for the lactose in the spray-dried powders with 1% (w/w) and 3% (w/w) citric acid concentrations were 290 ± 20 cps and 410 ± 20 cps, respectively.

However, these results have shown that increasing the porosity of naturally-crystalline materials, such as mannitol may be much more difficult than lactose. The WLF equation suggests that the rate of crystallization is related to the difference between the material temperature ($T$) and its glass-transition temperature ($T - T_g$) which has been observed by other researchers (Bhandari and Howes, 1999; Islam et al., 2010). This situation means that the lower BET surface area for mannitol compared with lactose might be due to the lower glass-transition temperature for the mixture of mannitol (10.7°C; Telang et al., 2003) with citric acid compared with the glass-transition temperature of lactose (101°C; Roos and Karel, 1991) with the same citric acid concentration. This situation means that, as the glass-transition temperatures decrease, the difference between the glass-transition temperatures ($T_g$) of the materials and the process temperatures ($T$) increases, thereby enhancing the crystallization rate, according to the Williams–Landel–Ferry equation.

The results from experiments on the effects of WPI concentrations on the BET surface areas of mannitol have agreed well with the above-mentioned suggestion, since adding WPI 0.2% (w/w) significantly increased the particle porosity. The BET surface area of mannitol increased from $1.91 \pm 0.01$ to about $3.2 \pm 0.9 \text{ m}^2 \text{ g}^{-1}$ for 1% w/w citric acid, compared with $1.6 \pm 0.1$ to $5.1 \pm 1.1 \text{ m}^2 \text{ g}^{-1}$ for the spray-dried mannitol/WPI mixture with 2% w/w citric acid (0.2% w/w WPI). It also have been found that adding more WPI (0.5% w/w WPI ) to the mannitol/citric acid solutions significantly increased the BET surface of mannitol up to $8.0 \pm 0.4 \text{ m}^2 \text{ g}^{-1}$ (Table 7.2).
This result is also consistent with the effect of adding WPI on the product crystallinity, since it has been found that the presence of proteins at low concentrations significantly affects the product crystallinity (Jouppila and Roos, 1994a; Haque and Roos, 2006).

10.1.6 Solubility and Content Uniformity Enhancement of Poorly Water-Soluble Drugs Using Highly-Porous Excipients

In the next step, a new adsorption method has been developed to investigate enhancement of the dissolution rate of poorly-water soluble drugs and better blending uniformity of drug dosage using mannitol particles with high porosity and high surface area. The engineered particles were used as a porous excipient in an adsorption technique to incorporate the drug molecules onto this porous structure. Indomethacin, nifedipine, and acetaminophen as model drugs were studied. The results of this study showed that adsorption of the drug in the pore-space of highly-porous mannitol resulted in better blending uniformity of drug dosage, as well as faster drug release rate due to the nano-confinement of drugs into the porous excipients and the better penetration of the solvent into the drug-porous mannitol matrix. Porous mannitol particles with a surface area and pore volume of 6.3 ± 0.1 m²g⁻¹ and 0.036 ± 0.002 mlg⁻¹, respectively, were drug loaded with two different concentrations of indomethacin and nifedipine. This adsorption method for the whole range of drug loadings (low to high) was successful and, with increasing the drug solution concentrations, the drug contents for porous mannitol were increased. The results of drug loading for nifedipine showed an increase from 3.2 ± 0.1 w/w % for a 0.08 M drug solution to 9.1±0.3 w/w % drug loading for a 0.16 M drug solution, while indomethacin had slightly better performance for the adsorption process, with 4.1 ± 0.2 w/w % and 12.6 ± 0.4 w/w % for 0.08 M and 0.16 M concentrations of indomethacin, respectively, in the final formulation. Low variability in the drug content of all drug-loaded samples was also found for the finished products, even for low-dose drug products. This result indicated highly-uniform blends with a percentage relative standard deviation of less than 4% for drug-loaded mannitol in both nifedipine and indomethacin. This method gave a significant enhancement in the dissolution rate for both drugs due to nano-confinement of drugs into porous excipients and high solubility of porous mannitol, with 80% drug release within the first fifteen minutes for the drug-loaded samples.
10.2 Recommendations and Future Work

Further areas of interest include studying the possible application of engineered particles with highly-porous structures in food infusions, flavoring, and encapsulating processes. The current wet-adsorption method can be used to enhance the release rate of many other poorly water-soluble drugs using different types of highly-porous excipients. The current templating method might be a potential process for high-porosity particle production of other food and non-food materials, such as calcium and magnesium salts, sodium or potassium chloride, and sodium carbonate. However, the templating research results have shown that increasing the crystallinity of spray-dried powder decreases the porosity of the processed powder. Hence, it can be assumed that increasing the porosity of naturally-crystalline materials, such as sodium carbonate, may be much more difficult. This additional difficulty with materials that crystallize readily during spray drying can be seen in the results here when using mannitol (readily crystallizes during spray drying) and lactose (crystallizes less readily). Controlling the degree of crystallinity and crystal size of these materials by applying different additives might be helpful, which can be investigated.

The micrographs taken in this thesis showed some morphological changes for both the lactose and mannitol powders, before and after citric acid removal (ethanol washing). More porosity appeared to be present on the surface and inside of the particles after removing the templating agent, while the surfaces of the spray-dried powder appeared to be non-porous and amorphous. However, a broad pore size distribution in the range of 2-200 nm has been found for both porous mannitol and lactose particles, suggesting that the templating agents were not evenly distributed within the core materials during the spray-drying process. By contrast, mesoporous silica, as a common carrier for controlled drug delivery, has a narrow pore size distribution (PSD) in the range of mesopores (2-50 nm), resulting from a homogenous distribution of templates during the synthesis procedure (Millqvist-Fureby et al., 2014). In order to achieve desired PSD and to provide a high degree of control over the pore size distributions, different approaches can be taken in future studies. Study of a multicomponent particle-drying model, such as the work by Wang and Langrish (2009), can be developed to describe the component migration during spray drying and distribution of components inside the spray-dried particles. This model takes the diffusion processes of water and dissolved solids, and the effects of the solubilities of the solids
into consideration to simulate the spray-drying process. Another possible study is the use of organic templating agents, such as polyvinylalcohol (PVA) with different particle sizes through a similar template-driven self-assembly technique to produce porous particles with tuneable and narrow pore size distributions.
REFERENCES


