Pharmaceutical Nanocomposites

Structure–Mobility–Functionality Relationships in the Amorphous State

JOEL HELLRUP
Amorphous materials are found in pharmaceutical formulations both as excipients and active ingredients. Indeed, these formulations are becoming an essential strategy for incorporating drugs into well-performing solid dosage forms. However, there is an unmet need of better understanding of the microstructure and component interactions in amorphous formulations to be able to design materials with improved functionalities. The aim of this thesis is to give deepened knowledge about structure-mobility-functionality relationships in amorphous formulations by studying composites produced from sugars and filler particles. The structure, the mobility, and physical stability of the composite materials were studied using calorimetry, X-ray diffraction, microscopy, spectroscopy, and molecular dynamics simulations. Further, the moisture sorption of the composites was determined with dynamic vapor sorption. The compression mechanics of the composites was evaluated with compression analysis.

It was demonstrated that fillers change the overall properties of the amorphous material. Specifically, the physical stability of the composite was by far improved compared to the amorphous sugar alone. This effect was pronounced for formulations with 60 wt% filler content or more. Amorphous lactose that normally recrystallizes within a few minutes upon humidity exposure, could withstand recrystallization for several months at 60% RH in composites with 80 wt% cellulose nanocrystals (CNC) or sodium montmorillonite (Na-MMT). The increased physical stability of the amorphous sugars was related to intra-particle confinement in extra-particle voids formed by the fillers and to immobilization of the amorphous phase at the surface of the fillers. Also, the composite formation led to increased particle hardness for the lactose/CNC and the lactose/Na-MMT nanocomposites. The largest effect on particle hardness was seen with 40-60 wt% nanofiller and could be related to skeleton formation of the nanofillers within the composite particles. The hygroscopicity for the lactose/Na-MMT nanocomposites decreased as much as 47% compared to ideal simple mixtures of the neat components. The nanofillers did not influence the water sorption capacity in the amorphous domains; however, lactose (intercalated into Na-MMT) interacted with the sodium ions in the interlayer space which led to the lowered hygroscopicity of this phase.

The thesis advanced the knowledge of the microstructure of amorphous pharmaceutical composites and its relationship with pharmaceutical functionalities. It also presented new approaches for stabilizing the amorphous state by using fillers. The concept illustrated here might be used to understand similar phenomena of stabilization of amorphous formulations.

Keywords: amorphous, pharmaceutical composites, solid state, structure, molecular mobility, spray-drying, freeze-drying, moisture sorption, physical stability, compression

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urn:nbn:se:uu:diva-300159 (http://urn.kb.se/resolve?urn=nbn:se:uu:diva-300159)
To my family
Hallelujah!

I will give thanks to the LORD with all my heart
in the company of decent people and in the congregation.

The LORD’s deeds are spectacular.
They should be studied by all who enjoy them.

[...] 

The fear of the LORD is the beginning of wisdom.
Good sense is shown by everyone who follows God’s guiding principles.
His praise continues forever.

Psalm 111 (God’s Word Translation)
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV  Hellrup, J; Mahlin, D., Confinement of Amorphous Lactose in Pores formed upon Co-Spray-Drying with Nanoparticles. *Submitted*.


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I was highly involved in the planning, study design, experimental work, data analysis, and writing of all papers listed above. However, I did not perform the electron microscopy, thermogravimetric analysis, solid state nuclear magnetic resonance, or molecular dynamic simulations.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Δα</td>
<td>change in thermal expansion at the glass transition temperature</td>
</tr>
<tr>
<td>δ</td>
<td>number of dimensions</td>
</tr>
<tr>
<td>Φ</td>
<td>decay function describing the relaxation</td>
</tr>
<tr>
<td>λ</td>
<td>wavelength</td>
</tr>
<tr>
<td>θ</td>
<td>diffraction angle</td>
</tr>
<tr>
<td>ρ</td>
<td>true density</td>
</tr>
<tr>
<td>τ</td>
<td>relaxation time</td>
</tr>
<tr>
<td>A200</td>
<td>Fumed silica, Aerosil® 200 Pharma</td>
</tr>
<tr>
<td>ASD</td>
<td>amorphous solid dispersion</td>
</tr>
<tr>
<td>BET</td>
<td>Brunauer, Emmett, and Teller</td>
</tr>
<tr>
<td>C</td>
<td>engineering strain</td>
</tr>
<tr>
<td>CaCO₃</td>
<td>calcium carbonate</td>
</tr>
<tr>
<td>CNC</td>
<td>cellulose nanocrystals</td>
</tr>
<tr>
<td>ΔCₚₜg</td>
<td>change in heat capacity at the glass transition temperature</td>
</tr>
<tr>
<td>d</td>
<td>distance between the planes in the crystal</td>
</tr>
<tr>
<td>d₀₀₁</td>
<td>basal spacing</td>
</tr>
<tr>
<td>d₀₀₁,Ave</td>
<td>average basal spacing</td>
</tr>
<tr>
<td>DoE</td>
<td>design of experiments</td>
</tr>
<tr>
<td>DSC</td>
<td>differential scanning calorimetry</td>
</tr>
<tr>
<td>DVS</td>
<td>dynamic vapor sorption</td>
</tr>
<tr>
<td>E</td>
<td>porosity of compact</td>
</tr>
<tr>
<td>f</td>
<td>Shapiro compression parameter</td>
</tr>
<tr>
<td>f₉ₜₜ</td>
<td>fraction of crystallized material</td>
</tr>
<tr>
<td>ΔG</td>
<td>Gibbs free energy change</td>
</tr>
<tr>
<td>ΔGₛ</td>
<td>Gibbs free energy change at formation of surface</td>
</tr>
<tr>
<td>ΔGᵥ</td>
<td>Gibbs free energy change of the transformation per unit volume</td>
</tr>
<tr>
<td>ΔGᵥ</td>
<td>Gibbs free energy change at formation of new bonds</td>
</tr>
<tr>
<td>ΔHₐ</td>
<td>enthalpy recovery after annealing</td>
</tr>
<tr>
<td>ΔHₘ</td>
<td>melting enthalpy</td>
</tr>
<tr>
<td>JMAK</td>
<td>Johnson–Mehl–Avrami–Kolmogorov</td>
</tr>
<tr>
<td>k</td>
<td>recrystallization rate constant</td>
</tr>
<tr>
<td>m</td>
<td>Johnson–Mehl–Avrami-Kolmogorov exponent</td>
</tr>
<tr>
<td>KWW</td>
<td>Kohlrausch–Williams–Watts</td>
</tr>
<tr>
<td>MC</td>
<td>microcalorimetry</td>
</tr>
<tr>
<td>MCC</td>
<td>microcrystalline cellulose</td>
</tr>
</tbody>
</table>
MD  molecular dynamic
mDSC  modulated differential scanning calorimetry
MMT  montmorillonite
$M_w$  molecular weight
$n$  order of reflection
Na-MMT  sodium montmorillonite
NMR  nuclear magnetic resonance spectroscopy
$P$  heat power
$P_c$  compression pressure
$P_y$  Heckel yield pressure
PVP  poly(vinylpyrrolidone)
$r$  radius
$r_c$  critical nucleus size
RH  relative humidity
SEM  scanning electron microscopy
SKH  Shapiro–Konopicky–Heckel
t  time
$T_a$  annealing temperature
$T_{cr}$  crystallization temperature
$T_g$  glass transition temperature
$T_{g,\text{mix}}$  glass transition temperature of mixture
$\Delta T_g$  width of the glass transition temperature
$T_m$  melting temperature
TEM  transmission electron microscopy
TGA  thermogravimetric analysis
$V$  volume of the powder column at pressure $P_c$
$V_0$  initial powder volume at compression
$w$  weight fraction
XRD  X-ray diffraction
Amorphous Pharmaceutical Solids

The amorphous state plays an increasingly important role in drug formulation and product development due to the low solubility of modern drug compounds. This low solubility problem can be dealt with by amorphization. The increasing importance is apparent by the number of publications in this area and the number of marketed formulations with amorphous components. The last twenty years, the number of publications per year in this area has grown more than tenfold. Furthermore, the number of marketed amorphous solid dispersions has tripled in the same time span.

The formulation scientist can encounter amorphous material in three situations—it may be introduced unintentionally in otherwise crystalline materials, the material may be intrinsically amorphous, or it may be deliberately transformed into the amorphous state.

In the first scenario, it is likely that the amorphous regions are introduced by processing. A good example of such a process is milling, one of the most frequently used unit operations available to reduce the particle size of solids. Tableting and dry mixing are other processes that unintentionally may lead to amorphization. When unintentionally present and uncontrolled, these amorphous regions have unwanted effects on the clinical performance of the formulation. For example, amorphous materials absorb moisture to a much greater extent than their crystalline counterparts. The absorbed water may catalyze chemical degradation in moisture-sensitive compounds. Moisture sorption in amorphous compounds will be covered further in the Moisture sorption chapter. Even when no moisture is sorbed into the amorphous regions in the material, the chemical reactivity increases in the amorphous state which may lead to degradation and therefore loss of activity of the drug.

On the other hand, the amorphous state may be advantageous. Drug discovery methods, such as combinatorial chemistry and high throughput screening often lead to drug candidates that are very lipophilic and subsequently with low aqueous solubility. Nearly 70% of the new chemical entities and 40% of the marketed drugs are poorly soluble in water. The drug molecules needs

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*a Based on the search string “amorphous AND drug” in Scopus.*
to dissolve to perform its action and good formulation strategies are therefore necessary to address low \textit{in vivo} solubility. Amorphization of a substance can improve its biopharmaceutical properties such as enhanced solubility and dissolution rate\textsuperscript{10,11}. Rendering a substance amorphous is an attractive approach to increase the bioavailability of solid state limited, poorly soluble drug compounds.

Biotechnology has led to the development of a broad range of therapies, termed biologics, including vaccines, therapeutics proteins and peptides, and monoclonal antibodies. The development of new biopharmaceuticals constitutes a major trend within the pharmaceutical industry. Indeed, peptides are one of the fastest growing segments in the pharmaceutical industry. Spray- and freeze-drying are used to improve the storage stability of biologics. Amorphous sugars are commonly used as lyoprotectants in freeze- and spray-dried formulations to preserve biologicals by preventing cell or protein damage when the water molecules are removed\textsuperscript{12-14}.

Another potential benefit of the amorphous state is the changed mechanical properties compared to their crystalline counterparts. A good example of intentional introduction of amorphous regions to alter the mechanical properties is commercial spray-dried lactose. Amorphous regions are introduced on \(\alpha\)-lactose monohydrate particles which leads to a product with improved powder flow and compression properties\textsuperscript{15}. Further, quite a few excipients are intrinsically partially or completely amorphous, including microcrystalline cellulose (MCC), starch, and poly(vinylpyrrolidone) (PVP). Mechanical aspects of the amorphous pharmaceutical composites will be covered in the \textit{Compression Mechanics} chapter.

Amorphous substances are not thermodynamically stable and there is the risk of recrystallization from the amorphous state. Recrystallization of the amorphous compound in a drug formulation will dramatically change it and lead to a destroyed formulation. The physical instability needs to be addressed to take advantage of the potential benefits of the amorphous state in a drug formulation. Stabilization of amorphous materials is one of the main themes in this thesis and will be discussed further in the \textit{Physical Stability} chapter.

The fundamentals of the solid state will be gone through in the next chapter to provide a base for the results provided by this thesis work.
The Solid State

Matter has three states—solid, liquid, and gas. Solids consist of molecules that are held in close proximity due to strong intermolecular forces, that is, the forces between the molecules, while liquids and gases have greater molecular mobility and distances of separation between the molecules due to lower intermolecular forces. The strength of the intermolecular bonds is governed by the individual atoms in the material.\(^\text{16}\) For example, only electronegative atoms such as oxygen, nitrogen, and fluorine atoms are able to form hydrogen bonds with hydrogen atoms covalently bonded to an electronegative atom (for example, O–H or N–H). Van der Waals forces, that is, dipole–dipole, dipole–induced dipole, and induced dipole–induced dipole forces, are important intermolecular forces in nonionic species while ionic bonds are present in charged compounds.\(^\text{17}\)

The vast majority of pharmaceuticals are administered as solid dosage forms. Examples of the most common solid dosage forms are tablets, capsules, and inhalation or nasal powders. Further, pharmaceuticals might be stored as powders before being dissolved and administered, as may be the case for injectibles. Solids are popular because they are convenient to administer and are more stable in storage than liquid formulations. Thus, the study of solid state properties is of enormous pharmaceutical importance.

Solids may exist in the amorphous\(^a\) or in the crystalline state (Figure 1). Crystalline materials are of high order in which the molecules are packed in a defined order that repeats over and over again. Amorphous materials lack this long-range order and more resemble liquids in their molecular confirmation with disordered molecules and greater molecular mobility. An example of an amorphous solid found in daily life is window glass. As we shall see, the difference in molecular structure and molecular mobility between crystalline and amorphous materials translates into large differences in material properties, such as physical stability, dissolution rate, apparent solubility, density, mechanical properties, and humidity sorption capacity.

\(^a\) From the Greek word ἄμορφ-ος (ámorphos), without form, shapeless, and deformed.
Polymorphism

Another source of variation in material properties is polymorphism (Figure 2). The molecules can arrange in several ways in crystals, that is, different polymorphic modifications, either in single component crystals or in mixtures with other materials (pseudopolymorphs). These other materials are often water (hydrates) or other solvents (solvates), but they can also be neutral “guests” (cocrystals). In addition, the molecules may form salts, which are crystals of charged molecules counterbalanced by oppositely charged ions.

The polymorphic modifications have varying strong intermolecular forces which are reflected in variations in melting temperature \( (T_m) \). In general, compounds with monotropic polymorphism—the polymorph with the highest \( T_m \)—are the most thermodynamically stable form. However, the most stable form varies with temperature and pressure in compounds that demonstrate enantiotropic polymorphism.\(^{16,19}\)

Materials strive to have as low energy as possible, that is, as strong intermolecular forces as possible. Therefore the less stable (metastable) polymorphic modifications transform towards the thermodynamically stable form.\(^{19}\) This transformation rate may be extremely slow and is dependent on activation energy. For these reasons, it is very important for a pharmaceutical formulator to have good knowledge of the available polymorphs of a substance; great effort is normally put into studying the substance properties at the drug formulation development. The first-hand choice is to formulate the drug compounds in the thermodynamically stable form to prevent undesired transformations during the manufacturing process.\(^{18,19}\) Correct choice of
polymorph through screening is important as sudden modifications of a polymorph may affect the drug compound. It may also have implications for intellectual property considerations. For example, ampicillin, a broad spectrum antibiotic, could crystallize as either an anhydrate or a trihydrate. Several years later, a monohydrate made its appearance, and the anhydrate has never since been prepared.

The Amorphous State

Amorphous materials have very different properties compared to their crystalline counterparts. The lack of crystal lattice in amorphous solids means it is not possible to speak of a $T_m$, since melting per se is the breaking up of the crystal lattice. Instead the amorphous state is highly energetic and resembles a liquid. On the other hand, amorphous materials do have a characteristic temperature not present in their crystalline counterparts, that is, the glass transition temperature ($T_g$). Very little is known about the theoretical aspects of the $T_g$, but the transition involves dramatically lowered molecular mobility, viscosity, thermal expansion, and heat capacity (Note the slope change in Figure 3).

When a liquid is cooled below its $T_m$ (Figure 3), it enters into a supercooled liquid state, also known as the rubbery state due to its resemblance with rubber. From this state it is thermodynamically favorable for the material to

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*The viscosity is a measure of a fluid’s resistance to flow.

The thermal expansion is defined as the tendency of a material to change shape, area, and volume in response to a change in temperature, through heat transfer.

The heat capacity or thermal capacity is defined as the amount of energy required to raise the temperature of a given quantity of the substance by one degree Celsius.*
Figure 3. Enthalpy/density–temperature diagram of solids. $T_m$ is the melting point, $T_g$ is the glass transition temperature, $T_a$ is the annealing temperature, $\Delta H_m$ is the melting enthalpy, and $\Delta H_a$ is the annealing endotherm (adopted from reference 24).

crystallize and the heat released at recrystallization is equivalent to the melting enthalpy ($\Delta H_m$). However, the molecules will not have time to form a crystal if the cooling is performed at a sufficiently high rate below the $T_g$; instead, a brittle amorphous material termed *glass* may form. The molecular motions are significantly lowered below the $T_g$.

The method of preparation—for example, the cooling rate—determines whether an amorphous is formed or not; methods such as spray-drying, melt-extrusion, or milling may produce amorphous products (see further discussion in the *Preparation of Amorphous Materials* chapter). However, the glass forming ability of a compound is dependent on the molecular weight ($M_w$), \(^25\) or more specifically, the number of hydrogen acceptors and Hückel pi atomic charges.\(^26\) Typically, drug compounds with $M_w >300 \text{ g/mol}$ have higher probability of forming glasses than drug compounds with $M_w <300 \text{ g/mol}$.\(^25\) Furthermore, big bulky compounds such as polymers are so large and flexible that they cannot form perfect crystals at all. However, they may possess regions of higher order and are then described as semi-crystalline. The continuation of this discussion will address low molecular weight drug-like compounds.

There are a few things to consider when using the amorphous state in drug formulation. In fact, it is incorrect to speak of an amorphous state. It may seem counterintuitive, but there can be several different amorphous structures of a compound. This can be illustrated by plotting different configurations of the molecules in a solid versus the potential energy in the system.\(^27\) This type of illustration is termed an energy landscape. Figure 4 shows the energy landscape of a hypothetical solid. In the figure there are two states of
lower potential energy, that is, two crystalline states. In between these two crystalline states, the energy is higher and the solid is in the amorphous state. Actually, the term polyamorphism has been introduced—in analogy with polymorphism—to describe the different amorphous modifications of a compound with a phase transition between the amorphous phases. Nevertheless, polyamorphism is a very uncommon phenomenon for pharmaceutical systems.\textsuperscript{28}

The method of preparation influences the properties of an amorphous compound, for example, the physical stability.\textsuperscript{29-32} Storage of a glass may lead to it developing density and enthalpy (arrow downwards in Figure 3).\textsuperscript{33} Since the molecular mobility is relatively high in glasses, especially close to the $T_g$, the molecules move into more favorable positions. This process is termed aging or structural relaxation. This phenomenon will be discussed more thoroughly in the Physical Characterization of Amorphous Solids chapter. The differences in the amorphous state are illustrated by slightly different energy levels in the amorphous megabasin in Figure 4. The term pseudopolyamorphism has been suggested for such kinetic differences in the amorphous state.\textsuperscript{34}

In summary, there is greater variation in the properties of amorphous compounds than in those in the crystalline state because glasses are not thermodynamically stable. Thermodynamic instability is, of course, negative in a drug formulation perspective since the drug performance needs to be predictable and reproducible.
Preparation of Amorphous Materials

There are three basic methods by which amorphous solids can be produced. The first two are by solidification of a melt—either by a rapid cooling, or by dissolving the substance, followed by a rapid removal of the solvent thereby bypassing the crystallization. The third method is by mechanical activation, for instance milling, which introduces disorder to the crystal structure. The first two techniques “freeze” the disordered structure that is found in the melt or the solution, whereas mechanical activation induces structural disorder to the material little by little. These principles are applied in several preparation techniques including melt quenching, melt extrusion, freeze-drying, spray-drying, granulation, and ball milling. The preparation techniques in this thesis were freeze-drying and spray-drying, and are described below.

Freeze-Drying

Freeze-drying is time-consuming and therefore expensive. Still, freeze-drying, or lyophilization as it is also termed, is a drying method that is widely used to increase the shelf-life of pharmaceuticals and biologics such as peptides, proteins, bacteria and valuable foods. Historic reasons and the high-quality of the produced products contribute to the widespread use of freeze-drying.

The freeze-drying process can be divided into three steps. In the first step the sample is frozen. In the second step, the pressure is lowered to remove most of the frozen water (ca. 95%) by sublimation—the primary drying (Figure 5). Finally, the remaining water residue is removed in a secondary drying by increasing the temperature. This process leads to a porous cake that normally is amorphous.
Spray-Drying

Spray-drying has a much lower production cost than freeze-drying and is widely used within the pharmaceutical, food, and other manufacturing industries.\textsuperscript{55} It is possible to spray-dry solutions, emulsions, and dispersions of a large variety of different materials, including heat sensitive ones such as peptides and proteins.\textsuperscript{56} A great advantage over freeze-drying is that it produces powders rather than cakes. Despite this, spray-drying is less commonly used to produce biopharmaceuticals.\textsuperscript{56}

One example of the application of spray-drying in pharmaceutics is commercially available spray-dried lactose. It is produced from spray-drying of partially dissolved $\alpha$-lactose monohydrate. This results in a powder of $\alpha$-lactose monohydrate particles with amorphous lactose on them. This product has better tableting properties than $\alpha$-lactose monohydrate.\textsuperscript{15}

When spray-drying (Figure 6), the liquid sample is pumped into an atomizer that atomizes it into an aerosol. The aerosol droplets are introduced into a cylinder in which hot gas is flowing, typically air or nitrogen. The temperature at the liquid inlet (inlet temperature) is normally 100–200°C when spray-drying water-based liquids, but lower for organic solvents. The liquid evaporates in the hot gas in milliseconds and a dry powder can be collected using a cyclone.

The droplets in the spray cylinder are kept at a relatively low temperature due to the energy that is required to evaporate the liquid. (This resembles the cool feeling you experience when getting out of the shower and the water
evaporates from your wet body.) The outlet temperature at the end of the spray cylinder is significantly lower than at the inlet. The outlet temperature is used to follow the drying process because it is the highest temperature that the spray-dried product is in contact with. The outlet temperature is affected by inlet temperature, pump rate, solvent, drug concentration, etc.

The solid-state of the spray-dried product is either amorphous or crystalline. The solid-state of the product is determined by the outlet temperature, which may not exceed the $T_g$ if an amorphous product is to be attained.
Aims of the thesis

The overall aim of this thesis was to increase the knowledge of amorphous pharmaceutical formulations by studying pharmaceutical composites. More specifically, the aim was to gain a mechanistic understanding of pharmaceutically relevant functionalities of amorphous composites consisting of disaccharides and filler particles. The method to reach the aim was by searching for the answers of following questions: What is the relationship between the nanofiller arrangement in the nanocomposites and moisture sorption capacity, physical stability, and compression mechanics? How does the molecular mobility of the amorphous phase at the interface of the nanofiller particles and as a whole relate to the physical stability? Finally, do morphological changes of the nanocomposite particles at moisture sorption affect the physical stability?
Materials

Amorphous pharmaceutical composites consisting of an amorphous component and of filler particles were examined in this thesis. Sucrose and lactose were used as model substances for the amorphous component. Pharmacologically relevant, inert particles in the lower micron range were used as fillers in the first paper\(^a\) and nanoparticles in the other papers.\(^b\)

Amorphous Phase

The disaccharides sucrose and lactose were tested separately as the amorphous components in the pharmaceutical composites. Disaccharides are widely used as pharmaceutical excipients and in foods. They are found as diluents or fillers in tablets, capsules, or inhalables, lyoprotectants, coatings, granulating agents, sweetening agents, and viscosity increasing agents. Disaccharides are convenient to work with because they are non-toxic and inexpensive.\(^3\)

Disaccharides are readily rendered amorphous for spray- or freeze-drying. Amorphous sucrose has a \(T_g\) at ca. 70°C and lactose at ca. 120°C. The amorphous state is relatively stable for amorphous sucrose and lactose in dry conditions. However, the amorphous form of the disaccharides is extremely hygroscopic due to the many hydroxyl groups in the molecular structure which sorb large amounts of water when stored at elevated humidity. This leads to plasticization and dramatically increased recrystallization rate of the amorphous sugars (see the Moisture sorption chapter).

Filler Particles

In the first paper, five types of filler particles were used to alter the amorphous state in the pharmaceutical composites.\(^c\) These were 1–5\(\mu\)m in

\(^{a}\) Paper I
\(^{b}\) Papers II–VI
\(^{c}\) Paper I
Table 1. Characteristics of the micro-particle fillers.a

<table>
<thead>
<tr>
<th>Filler particles</th>
<th>CaCO₃</th>
<th>MCC</th>
<th>Oxazepam</th>
<th>Starch</th>
<th>Talc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface area / (m²/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- BETi</td>
<td>0.52</td>
<td>3.40</td>
<td>2.71</td>
<td>1.12</td>
<td>5.80</td>
</tr>
<tr>
<td>- Blaine slip flowii</td>
<td>0.60±0.01</td>
<td>2.4±0.06</td>
<td>2.2±0.4</td>
<td>1.5±0.01</td>
<td>5.5±0.06</td>
</tr>
<tr>
<td>Particle diameter/µmiii</td>
<td>1.3±1.3</td>
<td>3.2±1.5</td>
<td>4.3±1.5</td>
<td>4.7±1.0</td>
<td>2.3±1.4</td>
</tr>
<tr>
<td>Density/(kg/m³)ii</td>
<td>2.7</td>
<td>1.6</td>
<td>1.4</td>
<td>1.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Chemical formula</td>
<td>CaCO₃</td>
<td>(C₆H₁₀O₅)ₙ</td>
<td>C₁₅H₁₁ClN₂O₂</td>
<td>(C₆H₁₀O₅)ₙ</td>
<td>Mg₃Si₄O₁₀(OH)₂</td>
</tr>
<tr>
<td>Crystalline?</td>
<td>Yes</td>
<td>Semi</td>
<td>Yes</td>
<td>Semi</td>
<td>Yes</td>
</tr>
<tr>
<td>Hygroscopic?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

i Values represent mean.
ii Values represent mean ± SEM.
iii Values represent median ± quartile deviation.

Table 1. Characteristics of the micro-particle fillers.a

Nanoparticles, due to their limited size, have a greater surface area per weight than micron-sized particles. Three nanoparticle types with different shapes and surface characteristics were used in Paper II–VI—fumed silica, cellulose nanocrystals (CNC), and sodium montmorillonite (Na-MMT).

Fumed Silica

Fumed silica consists of nearly spherical SiO₂ particles (Figure 7); these particles are available in both hydrophilic and hydrophobic grades and a wide range of sizes. In this thesis, a hydrophilic grade of fumed silica was used, namely Aerosil® 200 Pharma (A200). It has a specific surface area of ca. 200 m²/g. The primary particle size of A200 is ca. 12 nm, but the nanoparticles agglomerate into larger aggregates.36 A200 has traditionally been used as a pharmaceutical excipient to improve the flow properties of powders, but it has many uses, for instance as an anti-caking agent, tablet disintegrant, reinforcer of polymers, and thickening agent.35

Cellulose Nanocrystals

Cellulose nanocrystals (CNC) are also referred to as cellulose whiskers. They are produced by acid hydrolysis of the amorphous regions of cellulose

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a Paper I
Figure 7. Cryo-transmission electron microscopy (TEM) image of the nearly spherical Aerosil® 200 Pharma (A200) particles. The A200 particles are aggregated into ca. 100 nm large aggregates. The A200 particles are seen as dark grey areas in the image.

Figure 8. Cryo-transmission electron microscopy (TEM) image of the rod-shaped cellulose nanocrystals (CNC). The CNC particles are seen as dark grey areas in the image.

raw material, leaving the acid-resistant, rod-shaped crystals as a product (Figure 8). The dimensions of the nanoparticles vary depending on the type of raw material. The particles in this study were produced from wood pulp and are typically 5–10 nm in diameter and 100–300 nm in length. MCC is a very common excipient in tablets. However, CNC is not, to my knowledge, manufactured on a large-scale or used in any marketed pharmaceutical products. CNC has been proposed for applications as a binder, controlled release excipient, and reinforcer of polymer nanocomposites.

Montmorillonite

Montmorillonite (MMT) is the main constituent of bentonite and consists of about 1-nm thick clay sheets with diameters of ca. 200–1000 nm (Figure 9). It is a 2:1 phyllosilicate mineral that belongs to the smectite group. Clay particles consist of layered clay sheets that are termed tactoids (right image in Figure 9). However, the clay sheets can also acquire an exfoliated
structure when mixed with other components. Isomorphous substitution in the clay sheets induces a negative net charge which is counter-balanced by cations in the interlayer space and at the outer basal surfaces.

MMT with sodium cations, sodium MMT (Na-MMT), was used in this thesis. It is possible to prepare nanostructured mixtures of Na-MMT and other substances due to its layered structure. New materials with novel and/or improved properties are achieved in this way, which is not possible with simple mixtures of the two components. For instance, clay-polymer nanocomposites have improved mechanical properties, increased heat resistance, gas permeability, flammability and biodegradability of polymers. MMT is also used as a pharmaceutical excipient, including transdermal formulations, tablets for oral administration, and extended release agent for tablets.

The distance between the base of two adjacent MMT clay sheets in a tactoid is referred to as the basal spacing ($d_{001}$). The $d_{001}$ is influenced by the intercalation of counter ions, water, and other types of intercalated substances such as organic materials. The thickness of the MMT sheets is estimated to be 9.3 Å, on the basis of the mineral pyrophyllite, which has the same basic structure as MMT but without anything intercalated. In dry conditions Na-MMT has a $d_{001}$ at 9.6 Å. Water is intercalated into the Na-MMT interlayer space in one to three water-layers leading to $d_{001}$s at 12.8, 15.6, and 18.9 Å.

Production of Composites
The composites were prepared by mixing water solutions of sucrose or lactose with fillers dispersed in water, followed by drying away the water with
freeze-a or spray-drying. b The fillers were used as received from the manufacturer and preprocessed only to a minor extent before being mixed with disaccharide solutions. The micron-sized fillers were fractionated with an air classifier to produce a relatively consistent particle size. c

Much effort was made to find good conditions for dispersion of the nanofillers without additions of dispersion agents. This was accomplished by introducing high-energy sonics using an ultra-sonication horn with a high effect, which deagglomerated the nanoparticles.

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a Paper I  
b Papers II-VI  
c Paper I
Physical Characterization of Amorphous Solids

Many aspects of pharmaceutical solids need to be studied to understand their performance. This section describes the methods used in this thesis to study these aspects. The reader is referred to the appended papers for a more specific description of the methods.

Size, Surface, Morphology, and Density Characterization

Particle size, morphology, and density are characteristics that significantly influence the bulk powder properties of a material. It is critical to understand these properties.

Microscopy techniques such as optical light microscopy, scanning electron microscopy (SEM), and transmission electron microscopy (TEM), visualize the studied sample and can be used to study the particle size distribution and morphology of the powders. Microscopy techniques were applied throughout the production of this thesis on both the fillers and nanocomposite particles.

Somewhat simplified, it can be said that light microscopy magnifies samples with the use of lenses for particles down to ca. 1 µm. Light microscopy was used to study the size distribution of the fillers and to follow the swelling behavior (humidity sorption) of the nanocomposites upon exposure to water-saturated nitrogen.

By dispersing the samples in oil and applying a polarization filter to the light microscopy, it is possible to determine whether the dispersed particles contain any crystalline structures (Figure 10), since such structures illuminate. This technique is extremely sensitive and makes it possible to get a qualitative perception of the degree of crystallinity of a powder.

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a Paper I
b Papers II and IV
c Paper II
Electron microscopy uses electrons instead of visible light to image a sample. The much smaller wavelength of electrons compared to visible light makes it possible to get much higher magnification. It is possible to image particles down to ca. 0.1 µm with SEM and down to ca. 0.1 nm with TEM. SEM provides a 3D image, while TEM produces a 2D image of a thin sample. SEM was applied to image the morphology of the nanocomposites. TEM provided sufficiently high resolution to image the nanofillers.

It can be very time-consuming to attain a particle size distribution with microscopy. Luckily, particle size distributions can be determined with several other techniques. The following techniques have the advantage of analyzing a large number of particles and relatively quickly.

Blaine permeametry was applied to determine the particle size distribution of the micron-sized filler particles. It builds on the principle that it takes longer time for air to flow through a powder bed of small particles than large ones.

Laser diffraction was applied to determine the size distribution on the nanofillers and to determine the size distribution of the spray-dried nanocomposites. It can be performed on a relatively broad range of particle sizes from ca. 100 nm–1 mm, in both liquid and dry modes. Laser diffraction determines the particle size of a powder by applying either the Mie scatter theory or the Fraunhofer theory to the diffraction pattern created when a laser beam is passed through a sample.

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*a Papers III and VI*  
*b Papers II, III, and IV*  
*c Paper I*  
*d Papers II and III*  
*e Paper VI*
Photon correlation spectroscopy, also known as dynamic light scattering, was also applied to determine the size distribution on the nanofillers. This technique determines the size distribution of submicron particles by measuring their Brownian motion.

Surface area measurements were performed on the fillers with nitrogen gas adsorption and were estimated according to Brunauer, Emmett and Teller’s model (BET surface area). The same technique was also applied to determine the porosity of neat spray-dried nanofillers.

The apparent particle density of the fillers and the nanocomposites was determined using helium pycnometry, which is a technique that measures the gas displacement of a sample. It allows determinations of the apparent particle density. The powder density was determined by gently pouring the powders into a measuring cylinder followed by recording the height of the powder.

### X-ray Diffraction

X-ray Diffraction (XRD) was used throughout the thesis and is considered to be the gold standard for determining the solid state atomic and molecular structure of a crystal. It is also an important tool in detecting crystalline content in partially amorphous materials.

Depending on the distances between the atoms and the molecules in a solid, incident X-ray beams diffract at different angles. The molecules in a crystal are ordered which leads to diffraction peaks at specific angles (top diffractogram in Figure 11). These angles are specific for each crystal type due to different distances between the atoms and molecules in each crystal type. This can be described with Bragg’s law:

\[ n\lambda = 2dsin\theta \]

where \( n \) is an integer that describes the order of reflection, \( \lambda \) is the wavelength, \( \theta \) is the angle, and \( d \) is the distance between the planes in the crystal (Figure 12).
Figure 11. XRD diffractogram of α-lactose monohydrate (crystalline, top), amorphous lactose (bottom), and partially amorphous/crystalline lactose (middle).

Figure 12. Illustration of Bragg’s law.

Amorphous materials lack long-range order. Therefore XRD of amorphous materials results in an amorphous halo (bottom diffractogram in Figure 11). A material that consists of both amorphous and crystalline regions has a mixture of these two X-ray diffraction types (middle diffractogram in Figure 11).

XRD gives quantitative information about the degree of crystallinity since each component in a mixture gives rise to X-ray diffractograms independent of each other. There are however, numerous error sources in quantitative XRD including preferential orientation of crystals; this has implications for sample preparation. Micro-absorption in a mixture can cause loss of signal since the X-rays have to pass through several phases on their way to the detector. Varying particle and crystal size are also sources of error, since small crystals cause peak broadening and large particles absorbs X-rays. It is very complicated to control for all these error sources and the information obtained is of a semi-quantitative nature.
One-Dimensional XRD Profile Modelling

XRD can be used to study MMT clay sheet arrangement since their arrangement in tactoids gives rise to diffraction peaks known as 00l reflections. However, the reflections in clay minerals are generally broad and may deviate significantly from the expected Bragg angles due to interstratification, small particle size, defects, etc. Also, at intercalation in the interlayer space of the MMT tactoids, the \( d_{001} \) increases, which leads to alterations of the 00l reflections according to Equation 1. The electron density in the clay interlayer space becomes altered, which also influences the diffractogram. Therefore it is necessary to perform one-dimensional XRD profile modelling, that is, profile fitting, to get a correct understanding of the XRD data of clay material. This type of modelling not only gives the values and an average of the \( d_{001} \) (\( d_{001,Ave} \)), but also the fraction for each population in the sample. For an in-depth description of one-dimensional XRD profile modelling please see references 62 and 63. The one-dimensional XRD profile modelling was performed on the lactose/Na-MMT nanocomposites in cooperation with Michael Holmboe at Umeå University, Sweden.

Calorimetry and Thermal Analysis

A calorimeter detects transformations that induce heat flow by measuring the difference in heat flow between a sample and a reference as a function of temperature and/or time. Transformations that can be studied with calorimetry are physical changes such as glass transitions, recrystallization, melting, or structural relaxations, as well as chemical reactions and bacterial growth. Upon physical transition, intermolecular bonds are broken or formed which leads to heat transfer to or from the sample. This heat change is referred to as the enthalpy change, \( \Delta H \). Uptake of heat by a sample is an endothermic transition while heat released is exothermic. Calorimetry was applied to detect physical transitions in the composites. Two types of calorimetry were applied—differential scanning calorimetry (DSC) and microcalorimetry (MC).

Differential Scanning Calorimetry

The temperature is normally ramped in DSC at, for instance, 10°C/min from a temperature below to a temperature above the transition of interest. This detects at what temperature a transition occurs and the enthalpy change (\( \Delta H \)) of the transition, for instance the melting. A typical DSC thermogram of amorphous lactose is illustrated in Figure 13a. Transitions possible to
observe are water loss, glass transition, recrystallization, melting, and decomposition. As already discussed, an amorphous compound lacks a \( T_m \). Instead, \( T_g \) is the key feature of such materials (see The Solid State chapter). At heating through the \( T_g \), the molecular mobility in the sample dramatically increases and the sample transforms from a glass to a super-cooled liquid state. This induces a change in the heat capacity, that is, the energy required to increase the temperature of the sample. This leads to a baseline shift in the DSC thermogram, where the size of the baseline shift is referred to as change in heat capacity at \( T_g \)(\( \Delta C_p^{T_g} \)).

Modulated DSC (mDSC) is a variant of DSC where the temperature is modulated on top of the linear heating rate. This makes it possible to deconvolute the total heat flow into a kinetic component and a heat capacity component (Figure 13b).\(^6^5\) This is especially valuable when studying \( T_g \) since this transition normally consists of both a heat capacity baseline shift and an endothermic transition due to aging of the glass.

Microcalorimetry
MC is normally performed under isothermal conditions, that is, the temperature is constant. Several different stresses can be used to induce transformations in the sample depending on the transition of interest, including humidity. Since water absorbs into amorphous structures and lowers the \( T_g \), that is, it acts as a plasticizer,\(^6^6\) it can be used as a suitable stress to induce recrystallization. This method was used in this thesis. Moisture sorption and

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**Figure 13.** a) Typical differential scanning calorimetry (DSC) thermogram of amorphous lactose with transitions marked, and b) the same thermogram deconvoluted into reversed heat flow and nonreversed heat flow.
plasticizing will be discussed further in the *Moisture sorption* chapter. The humidity level can be controlled by the aid of saturated aqueous salt solutions. A typical MC thermogram of the recrystallization of amorphous sucrose upon humidity exposure is illustrated in Figure 14. MC records the heat flow as a function of time. This makes it a suitable technique to determine transformation kinetics, for instance recrystallization rate constant, $k$. MC has higher sensitivity than DSC and smaller heat transfers can hence be detected.

### Structural Relaxation

The molecular mobility of the samples was studied with structural relaxation determinations. As already discussed in *The Solid State* chapter, a glass relaxes during storage toward the equilibrium super-cooled liquid state (Figure 3). This process is also referred to as structural relaxation or aging of the sample. Energy decreases and is released from the sample when the molecules in the glass find more favorable positions/intermolecular bindings. Hence, the structural relaxation can be detected with calorimetry.

The relaxation rate is strongly dependent on the molecular mobility of the sample of interest. It is more common to use DSC to study structural relaxation, but it can also be studied using MC. In practical terms, the sample is held at a temperature below the $T_g$ to let the sample relax (anneal)—the annealing temperature ($T_a$). In DSC measurements, the sample is heated through the $T_g$ to break the formed intermolecular bonds which results in an endothermic peak in the thermogram (arrow upwards in Figure 3). This is referred to as enthalpy recovery ($\Delta H_a$). This process is repeated at different

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*a Papers II–IV*
aging times. The $\Delta H_a$ increases in size with aging times and can be fitted to a Kohlrausch–Williams–Watts (KWW) equation:

$$\Phi(t) = \exp \left[ -\left( \frac{t}{\tau} \right)^\beta \right]$$

where $\Phi(t)$ is a decay function describing the relaxation at the time $t$, $\tau$ represent relaxation time, and $\beta$ is a constant ($1 < \beta < 0$) that reflects to what extent the relaxation process deviates from exponential behavior and is often called the “stretching parameter”.

The procedure is somewhat different when using MC to study structural relaxation. DSC measures the heat required to break the formed intermolecular bonds upon relaxation by heating the sample above $T_g$. In contrast, MC measures the release of heat due to formation of intermolecular bonds during the aging (This is represented by the downwards arrow in Figure 3). To minimize the influence of the thermal history of the sample, the amorphous sample is put directly in the MC after manufacturing or after heating it over the $T_g$.

The MSE equation expressed for heat power $P$, $\mu$W/g, with time in hours, was used to evaluate the MC relaxation data

$$P = 277.8 \cdot \frac{(\tau_2 - \tau_0) \Delta C_p}{\tau_0} \left( 1 + \frac{\beta t}{\tau_1} \right) \left( 1 + \frac{t}{\tau_1} \right)^{\beta-2} \exp \left[ -\left( \frac{t}{\tau_0} \right) \left( 1 + \frac{t}{\tau_1} \right)^{\beta-1} \right]$$

where $\tau_1$, $\tau_2$, and $\beta$ are constants. $\tau_1$, $\tau_2$, and $\beta$ were determined by fitting $P$ as a function of $t$ to Equation 3. The relaxation time $\tau$ could then be calculated from $\tau_1$, $\tau_2$, and $\beta$, as in the following

$$\tau = \tau_0^{1/\beta} \cdot \tau_1^{(\beta-1)/\beta}$$

Thus, calorimetric determinations of relaxation can be used to determine the molecular mobility of an amorphous sample. Since molecular mobility is a key feature of the recrystallization, this is valuable information about the process.

**Thermogravimetric analysis**

Thermogravimetric analysis (TGA) is a technique where a sample is heated with a constant heating rate up to maximum 2000°C in a controlled gas atmosphere while recording the sample weight using a precision balance. This procedure makes it possible to detect weight loss of substances. It can,
Dynamic Vapor Sorption (DVS)

Absorbed water strongly influences the physical and chemical properties of pharmaceutical solids. The water can lead to recrystallization and sintering, and also influence behaviors such as powder flow, compaction, dissolution, and chemical stability. Weight gain of a sample can be measured with DVS at various levels of humidity using a very sensitive balance. The most common and fundamental manner of studying the sorbed water vapor of a solid is by water sorption–desorption isotherms (Figure 15a). These are attained by determining the equilibrium weight gain as a function of RH (Figure 15b). The fillers and the composites in this thesis were studied with DVS.

Solid State Nuclear Magnetic Resonance Spectroscopy

Solid state nuclear magnetic resonance spectroscopy (NMR) was used to probe the local environment of specific atomic species to get structural information about the studied material. The solid state NMR experiments were performed on the lactose/Na-MMT nanocomposites by collaborators at the University of East Anglia, UK.

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Figure 15. a) Sorption isotherms of amorphous lactose derived by b) determining the equilibrium weight gain as a function of RH with dynamic vapor sorption. The red line indicates absorption, the blue line indicates desorption, and the green line indicate humidity level. The reduction in moisture content at 60% relative humidity is due to recrystallization of the amorphous lactose.

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a Paper III  
b Papers I, II, IV, and V  
c Papers III and V
Molecular Dynamic Simulations

Molecular dynamic (MD) simulations were performed to get an atomistic insight into the molecular interactions occurring in the lactose/Na-MMT nanocomposites to calculate the electron density, that is, the $G$-factor. This factor is needed to perform the one-dimensional XRD profile modelling.$^a$ These MD simulations were performed in collaboration with Michael Holmboe at Umeå University, Sweden.

Powder Compression Analysis

There are several methods to gain information about the mechanical properties of a powder including testing of single particles, indentation, and uniaxial confined compression.$^{73-76}$ Mechanical properties of the nanocomposites were evaluated using a standardized protocol for uniaxial confined compression.$^b$ $^{77}$ The powder compression was acquired using a materials testing machine in which the position and the force were recorded during the compression. The powder compression data were analyzed with a pressure–engineering strain relationship, using the Kawakita equation:$^{78}$

$$\frac{P_c}{C} = \frac{1}{ab} + \frac{p}{a}$$  \hspace{1cm} (5)

where $P_c$ is the applied compression pressure and $C$ is the engineering strain, calculated as:

$$C = \frac{V_0 - V}{V_0}$$  \hspace{1cm} (6)

where $V_0$ is the initial powder volume calculated from the bulk density and $V$ is the volume of the powder column at pressure $P_c$. This relationship gives information of particle rearrangement during particle compression.$^{79}$

The powder compression data were also analyzed with a porosity–pressure relationship, using the Shapiro–Konopicky–Heckel (SKH) equation$^{80}$

$$lnE = lnE_0 - cP - fP^{0.5}$$  \hspace{1cm} (7)

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$^a$ Papers III and V
$^b$ Paper VI
where $E$ is the porosity of the compact, $E_0$ is the initial porosity of the powder bed, $P$ is the compaction pressure, $c$ is a constant, and $f$ is the Shapiro compression parameter. A common interpretation of the SKH-profile is to divide it into three regions (Figure 16).\textsuperscript{81-83} The first nonlinear region with a falling derivative is indicative of particle rearrangement and particle fragmentation, which is normally followed by a linear part for which particle deformation is the main mechanism. From this region, the Heckel yield pressure is derived which can give an indication of the plasticity of the investigated material. The last region is a nonlinear part with an increasing derivative that is normally interpreted as elastic deformation of the formed tablet.\textsuperscript{81-83}

**Design of Experiments**

Experimental work is often conducted by studying one factor at a time. Experimental designs varying one factor at a time lead to problems when the factors are interdependent upon each other. A solution to this problem is to vary several factors at the same time using a design of experiment (DoE) approach.\textsuperscript{84} The factors are varied in a statistical manner using a factorial design between the low-end and the high-end values of the factors plus three center-points to sample the design space (Figure 17). However, the number
of experiments quickly adds up as the number of factors increases. To address this problem, the experiments are performed in stages. In the first stage, the screening phase, possible influencing factors are identified and screened. A fractional factorial design is used in this stage, which reduces the number of experiments required. However, it can only detect which factors influence the result and not to what extent. In the second stage—the optimization—the significant factors are further evaluated, to investigate the entire design space.

Spray-drying is a good example of a manufacturing technique where several factors influence the product and thus the DoE approach is well suited for describing and optimizing its design space. DoE was applied to study the influence of the spray-drying process relative to the composition of the formulation on the physical stability of the lactose/A200 nanocomposites. a

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*a Paper II*
Structure, Molecular Mobility, and Morphology

The foundation of this thesis is a structural investigation of lactose co-spray-dried with nanofillers into nanocomposites. This was done to understand functionalities of the materials, such as humidity sorption, physical stability, and compression mechanics. The focus was on the intraparticle structure of the nanocomposite particles, especially on the nanofiller arrangement in the nanocomposite particles and on the interface between the nanofiller surface and the lactose phase, but we have also studied the morphology of the spray-dried nanocomposite particles.

Intraparticle Structure

The structure of a composite material is influenced by the composition. The material properties vary greatly depending upon whether the components exist in high or low quantities. Percolation theory is a standard model for disordered systems and can be used to understand, for example, the material intraparticle structure and thus properties of composites.\textsuperscript{85, 86} Percolation theory has been applied to a large variety of systems, including micro-emulsion systems,\textsuperscript{87} drug release from matrix tablets,\textsuperscript{88} and tablet compaction.\textsuperscript{89}

The percolation theory can be applied to understand the intraparticle structure of the lactose/nanofiller nanocomposites. Imagine a composite material consisting of filler particles and an organic phase, for example, lactose. At low filler content in the composite, the filler particles have little contact with each other and the organic phase is continuous. However, as the filler content increases the number of contact points between the filler particles will increase. Eventually, there is a transition from a state of local connectedness between the filler particles to one in which the connection extends indefinitely. This is referred to as the geometrical percolation threshold.\textsuperscript{86, 90} The shape and density of the filler particles and aggregation forces between the particles influence at which weight fraction the geometrical percolation threshold appears. Further, as the filler content continues to increase, the
organic phase transitions from a continuous one into discrete domains. This transition is the second geometrical percolation threshold and can be referred to as the reversed percolation threshold since the organic phase stops being percolated.

It might be easier to grasp the structure of nanocomposites at high nanofiller content if one imagines the neat filler material in which the organic material is added and distributed. In the neat filler-material, the nanofiller particles adhere closely to each other. They may form a porous material depending on the shape and orientation of the nanofiller particles. When the organic material is introduced, the possible extra-particle pore voids fill with organic material. Eventually, the nanofiller particles begin to separate from each other. Thus, the domains in the organic phase are size-limited.

No nanofiller aggregates larger than 1 µm were formed in the dispersions before being co-spray-dried with lactose (Figure 7-9). Therefore the nanofiller particles were assumed to be relatively evenly distributed in the nanocomposites. Consequently, at co-spray-drying lactose and nanofillers at high nanofiller content, a material bearing resemblance to a mesoporous material forms. In this material, the amorphous lactose phase locates into the extra particle voids.

Neat spray-dried A200 possesses a porous structure, while the other nanofillers do not possess any major porosity (Figure 18 and Figure 22d). Thus, higher lactose content can be introduced into the lactose/A200 nanocomposites before the dimensions of the extra-particle voids start to increase, unlike with the other nanofillers.

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\(^{a}\) Papers II–IV

\(^{b}\) Paper IV
Figure 19. a) Glass transition width ($\Delta T_g$) and b) change in heat capacity at the glass transitions temperature ($\Delta C_p^{T_g}$) as functions of nanofiller content for the lactose/fumed silica (A200) △, lactose/cellulose nanocrystals (CNC) •, and the lactose/sodium montmorillonite (Na-MMT) ● nanocomposites.

Calorimetric Insights to the Intraparticle Structure

The $T_g$ constitutes a very important factor for amorphous materials. Indeed it may give structural information about the amorphous phase. The width of the $T_g$ ($\Delta T_g$) is the temperature range from the onset to the endpoint of the transition and is related to the homogeneity of the amorphous phase. An increase of the $\Delta T_g$ can be interpreted as a heterogeneous amorphous phase, since slight differences in relaxation time-scales of amorphous microdomains lead to a broadening of the glass transition. The $\Delta T_g$ increased as a function of nanofiller content (Figure 19a), which subsequently indicates an increased heterogeneity of the amorphous lactose phase in the nanocomposites. This was likely due to an increased solid surface–lactose phase ratio.

The $\Delta C_p^{T_g}$, can be used to quantify amorphous content, for example in a recrystallizing sample, where a lowering of the $\Delta C_p^{T_g}$ relates to crystallization of the amorphous phase. However, the $\Delta C_p^{T_g}$ may be lower than the expected value for other reasons than recrystallization. In polymer nanocomposites, a lowered $\Delta C_p^{T_g}$ has been attributed to interactions between filler particles and polymers in the amorphous polymer phase. A two-layer model has been suggested to explain the results. According to this model, a partially or completely immobilized interfacial layer of the amorphous component develops near the nanofiller surface and does not contribute to the magnitude of the $\Delta C_p^{T_g}$. This immobilized fraction has been termed rigid amorphous fraction. Another reason for a low $\Delta C_p^{T_g}$ is intercalation of a fraction of the amorphous phase into the interlayer space of layered clay, which prevents these molecules from contributing to the cooperative molecular motion at the glass transition.
In the lactose/nanofiller nanocomposites, the surface properties and the arrangement of the nanofillers influenced the lactose molecules at the interface of the nanofillers. This was evident from differences in the $\Delta C_p^{T_g}$ (Figure 19b). No change in $\Delta C_p^{T_g}$ was detected for the lactose/CNC nanocomposites, while the lactose/A200 and the lactose/Na-MMT ones had a lowered $\Delta C_p^{T_g}$ as a function of nanofiller content. In the lactose/A200 nanocomposites, this lowering was attributed to immobilization of the lactose, most likely due to lactose–A200 surface interactions, while intercalation of lactose into the Na-MMT interlayer space could explain the results in the lactose/Na-MMT nanocomposites.

In the lactose/Na-MMT nanocomposites, the surface properties and the arrangement of the nanofillers influenced the lactose molecules at the interface of the nanofillers. The $\Delta C_p^{T_g}$ (Figure 19b) was changed. No change in $\Delta C_p^{T_g}$ was detected for the lactose/CNC nanocomposites, while the lactose/A200 and the lactose/Na-MMT ones had a lowered $\Delta C_p^{T_g}$ as a function of nanofiller content. In the lactose/A200 nanocomposites, this lowering was attributed to immobilization of the lactose, most likely due to lactose–A200 surface interactions, while intercalation of lactose into the Na-MMT interlayer space could explain the results in the lactose/Na-MMT nanocomposites.

Intraparticle Structure of Lactose/Na-MMT Nanocomposites

Intercalation by ion exchange into MMT is a well-studied phenomenon, especially for polymer materials, but only few report on intercalation of low-molecular weight organic compounds. The possibility of a layered clay structure with intercalated lactose in the lactose/Na-MMT nanocomposites demanded a more detailed structural investigation than the nanocomposites with the other nanofillers. Indeed, spray-drying of neat Na-MMT led to an arrangement of the clay sheets into tactoids (clay particles).

The $d_{001}$ of neat MMT without anything intercalated (including counter-ions) was estimated from the mineral pyrophyllite to be 9.3 Å. However, due to intercalation of Na$^+$ and water in the interlayer space, the average basal spacing ($d_{001,Ave}$) of neat Na-MMT was 10.0 Å. The $d_{001}$ increased to ca.14 Å or 18 Å, depending on the lactose content in the nanocomposites, upon co-spray-drying with lactose; higher lactose content gave increasingly higher values of the $d_{001,Ave}$. Thus, the increase in $d_{001}$ to 14 Å represents an increase in $d_{001}$ equivalent to ca. 4.7 Å. This corresponds with the size of the lactose molecule (the smallest dimension of crystalline lactose unit cell is 4.8 Å). Thus, the observed increase $d_{001}$ can be attributed to intercalation of lactose in the Na-MMT interlayer space.

The lactose intercalation was further confirmed with MD simulations and one-dimensional XRD profile modelling based on the MD simulations. The best fit of the one-dimensional XRD profile was achieved with a model that took the lactose intercalation into account. The MD simulations indicated a monolayer lactose configuration in the lactose/Na-MMT phase with $d_{001}$ at

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a Paper II

b Paper IV
c Paper III
Figure 20. Quantification by solid state NMR of the non-intercalated lactose content in the lactose/sodium montmorillonite (Na-MMT) nanocomposites, as estimated from signal loss in intensity.

Figure 21. A 2D illustration of the intraparticle structure of lactose/sodium montmorillonite (Na-MMT) nanocomposites demonstrating non-intercalated lactose and lactose/Na-MMT phase with basal spacing ($d_{001}$) at ca. 14 Å and ca. 18 Å, respectively. The brown lines illustrate the edge-on-view of the montmorillonite (MMT) sheets, while the black and red objects represent lactose molecules.

14 Å, but a partial overlapping configuration of the lactose molecules in the phase with $d_{001}$ at 18 Å. Also, the lactose content was estimated to be higher in the phase with $d_{001}$ at 18 Å.

It was expected to find domains of non-intercalated lactose when the amount of added lactose exceeded the maximum amount possible for intercalation in the Na-MMT interlayer space. Indeed, the detection of a $T_g$ confirmed the presence of non-intercalated lactose up to ca. 90% Na-MMT content. The presence of non-intercalated lactose was further confirmed with solid state NMR measurements. These results and the $\Delta C_p^{T_g}$ were used to quantify the fraction of the lactose being intercalated and non-intercalated (Figure 20). Figure 21 shows the structure of the lactose/Na-MMT nanocomposites.
Molecular Mobility

The glass transition is of special significance for the understanding of the physical stability of an amorphous substance. The molecular mobility and other properties of the amorphous state transform drastically at this temperature. The molecules need to be mobile to rearrange from an amorphous to a crystalline structure, so the physical stability of amorphous materials is strongly correlated with the molecular mobility in the amorphous phase.

Molecular motions can occur on a global or local scale. Molecular motions of the molecule as a whole are termed global mobility (or structural or α-relaxation). Local mobility (also termed secondary or β-relaxation) is associated with local motions of individual molecules or parts of molecules. It has been debated which scale is more relevant for the physical stability of pharmaceutical systems. In this thesis, the focus was on α-relaxations of the materials.

The $T_g$ was higher for the sucrose/micro particle composites than the neat amorphous sucrose and was dependent on filler type. For the lactose/nanofiller nanocomposites, the maximal $T_g$ was observed at the maximum investigated nanofiller content, that is, 1°C for the lactose/A200 nanocomposites, 3°C for the lactose/Na-MMT nanocomposites, and 9°C for the lactose/CNC nanocomposites. As already discussed, the $ΔC_p^{-T_g}$ decreased as a function of A200 content (Figure 19), which was related to immobilization of the lactose at the surface of the A200 particles.

To further scrutinize the molecular mobility in the nanocomposites, the α-relaxation of the amorphous lactose was estimated with structural relaxation experiments. The molecular mobility decreased in the lactose/A200 and the lactose/CNC nanocomposites, but increased in the lactose/Na-MMT nanocomposites compared with neat spray-dried lactose. Furthermore, there was a loss in the solid state NMR signal that could be correlated with lactose content in the Na-MMT interlayer space. This was likely due to increased molecular mobility of the intercalated lactose, which prevented detection of the intercalated lactose molecules.

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a Paper I  
b Paper II  
c Papers III and IV  
d Paper IV  
e Papers II–IV  
f Paper III
Figure 22. Scanning electron microscopy (SEM) images of spray-dried A) lactose, B) sodium montmorillonite (Na-MMT), C) cellulose nanocrystals (CNC), and D) fumed silica (A200).

Morphology

The particles of a spray-dried powder are produced from initially spherical droplets, and therefore the resultant powder is often spherically shaped particles. However, the drying process and the composition of the material also influence the powder morphology. The spray-drying process is very rapid and the droplets undergo fast evaporation. The morphology of the particles is dependent on the evaporation time and the diffusional motions of the solutes at spray-drying. The diffusional motions of low molecular solutes in the droplets are generally higher than the receding drying droplet surface. Thus, low molecular solutes migrate toward the droplet center as the drying droplet is reducing at spray-drying, which leads to spherical and dense particles. A good example of this is the spherically shaped spray-dried lactose particles in Figure 22A. However, the diffusional motions of high molecules solutes or suspended particles are slower than the receding surface of the drying droplet. The solutes are therefore enriched at the surface of the droplets, which instead leads to formation of light hollow particles or particles with altered morphology. This type of altered morphologies can be seen when neat nanofiller materials are spray-dried (Figure 22B–D).
Morphology upon Moisture Sorption

Amorphous lactose particles swell upon water sorption which may lead to sintering of adjacent particles and to formation of a continuous solid cake (Figure 23A–B). However, the nanoparticles in the lactose/nanofiller composites obstructed, to a varying degree, the swelling of the particles. In the lactose/Na-MMT nanocomposites, the swelling was prevented already at 20 wt% Na-MMT content (Figure 23C–D),\(^a\) while it was necessary with higher loads of A200 (40 wt%)\(^b\) and CNC (60 wt%)\(^c\) to prevent the sintering of the nanocomposite particles. The obstruction of the particle swelling and sintering likely depends on nanoparticle enrichment at the surfaces of the nanocomposite particles, due to low diffusional motions of nanofiller particles during spray-drying.

\(^a\) Paper IV
\(^b\) Paper II
\(^c\) Paper IV
Moisture sorption

Water is all around us in the form of humidity and has a unique ability to sorb into materials and on surfaces. Sorption of atmospheric water by hydrophilic materials and surfaces may cause degradation,\textsuperscript{7} relaxations,\textsuperscript{33} or recrystallization,\textsuperscript{7, 21, 119} and subsequently affect product quality. It is therefore essential to understand water sorption and the impact of humidity on solid materials when formulating products with high quality and long storage stability.

Good examples of the importance of water sorption are mixtures of cellulose-based excipients with hydrolysis sensitive substances. The chemical degradation rate of the hydrolysis sensitive substances is strongly dependent on the location and availability of the moisture, which in turn depends on the degree of crystallinity of the cellulose and the amount water sorbed.\textsuperscript{120, 121} The absorbed water is loosely bound to crystalline cellulose fibers, while the cellulose–water interactions are stronger in amorphous regions of the cellulose. Even though the water content is equal in two mixtures prepared from different cellulose grades, the degradation rate of, for instance, the hydrolysis sensitive acetylsalicylic acid, is higher when the cellulose is highly crystalline than when it is amorphous.\textsuperscript{120, 121}

Plasticizing

When water absorbs into an amorphous material, the $T_g$ of the mixture changes. By assuming perfect volume additivity and no specific interactions between the components in the mixture, it is possible to estimate the $T_g$ of the mixture ($T_g$ mix) with the Gordon-Taylor equation:\textsuperscript{66}

$$T_{g\text{ mix}} = \frac{w_1 \cdot T_{g1} + K \cdot w_2 \cdot T_{g2}}{w_1 + (K \cdot w_2)}$$

(8)

where $w$ is the weight fraction of the individual components, and

$$K = \frac{\rho_1 \cdot \Delta \alpha_2}{\rho_2 \cdot \Delta \alpha_1}$$

(9)

where $\rho$ is the true density of the material and $\Delta \alpha$ is the change in thermal
expansion at $T_g$. Thus, pharmaceutical materials yield a lowered $T_g$ upon absorption of water, since water has an extremely low $T_g$, $-138^\circ$C.66 This effect of water sorption is termed plasticizing. If sufficiently high amounts of water are sorbed, the $T_g$ will be lowered below the storage temperature. In this state, the recrystallization rate is dramatically increased due to increased molecular mobility. The $T_g$ of amorphous sucrose is lowered below 25°C at relative humidity (RH) levels above ca. 25% RH; for lactose this occurs at ca. 40% RH.122

![Figure 24](image)

**Figure 24.** Deviation from expected moisture content at 40% relative humidity (RH) as a function of sodium montmorillonite (Na-MMT) content in the lactose/Na-MMT mixture.

**Moisture Sorption of Lactose/Nanofiller Nanocomposites**

The moisture sorption was studied for the lactose/A200 nanocomposites.$^a$ The nanocomposites absorbed the amount of moisture that could be expected from the component weight percentages. In other words, the moisture sorption of the amorphous phase was the same regardless of A200 content.

The moisture sorption for the lactose/Na-MMT nanocomposites was also investigated.$^b$ These nanocomposites, however, were less hygroscopic than expected for a simple mixture, with down to 47% less sorbed water than an ideal mixture (Figure 24). The reason for the lowered hygroscopicity was investigated with one-dimensional XRD profile fitting, MD simulations, and solid state NMR. It was found that the non-intercalated lactose phase was unaffected by the nanofiller incorporation; it absorbed the amount of moisture that was expected. The intercalated lactose, however, interacted with the

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$^a$ Paper II
$^b$ Paper V

50
Na$^+$ and the clay surfaces in the Na-MMT interlayer space. The cations in the interlayer space play an essential role in the water sorption of MMT.\textsuperscript{123-126} Subsequently, the out-concurred Na$^+$–water interactions could account for the lowered hygroscopicity of the lactose/Na-MMT nanocomposites.
Physical Stability

Since amorphous materials are thermodynamically unstable, they tend to crystallize during storage. Recrystallization from the amorphous state depends on the interplay between nucleation and crystal growth. A critical nucleus is the smallest cluster of molecules that may constitute a seed for crystallization and nucleation is the process whereby nuclei are formed. According to the classical theory of nucleation, Gibbs free energy change $\Delta G$ for nucleus formation has two contributions. These are formation of new surface between the nucleus and the surroundings, and secondly, the formation of intermolecular bonds between the molecules in the nucleus. The formation of a new surface is described by $\Delta G_s$ and the formation of new bonds is described by $\Delta G_v$. The first process requires energy and the second process releases energy. This can mathematically be written as:

$$\Delta G = \Delta G_s + \Delta G_v = 4\pi r^2 \gamma + \frac{4}{3} \pi r^3 \Delta G_v$$

where $r$ is the radius of the spherically (for simplicity) formed cluster, and $\Delta G_v$ is the free energy change of the transformation per unit volume. The two terms on the right-hand side of Equation 10 have different signs and depend on $r$ which implies that $\Delta G$ passes through a maximum corresponding to a critical nucleus size with a specific $r$, $r_c$ (see Figure 25). The $r_c$ is specific for each molecular species, but is typically around a few nm. In other words, as the molecule cluster increases in size, the $\Delta G_s$ increases due to the formation of intermolecular bonds in the cluster. Therefore, the molecule cluster needs to be larger than $r_c$ to be stable if the crystallization process is to progress to crystal growth.

Spontaneous nucleation is termed homogeneous nucleation. Nucleation induced by the presence of foreign particles is called heterogeneous nucleation. As soon as a stable nucleus forms, it begins to grow into a crystal and crystal growth dominates the crystallization process. The kinetics of the crystallization is dependent on both the nucleation and crystal growth. Although crystal growth and nucleation are separate processes, most studies focus on them as a combined process due to difficulties in characterizing them separately. One way to describe the kinetics is the Johnson–Mehl–Avrami–Kolmogorov (JMAK) model.
Figure 25. Free-energy diagram for nucleation explaining the existence of a critical nucleus.

For homogeneous nucleation and isotropic 3D growth:

\[
f_{\text{cryst}}(t) = 1 - e^{-(kt)^m}
\]

(11)

where the isothermal time \((t)\) is the evolution of the fraction of crystallized material \((f_{\text{cryst}}(t))\), \(k\) is the crystallization rate constant, and \(m\) is the JMAK exponent that describes the dimensionality of the space in which the nucleation and growth proceed \((m=\delta+1\), where \(\delta\) is the number of dimensions).

The physical stability of amorphous materials is governed by the crystallization, which is complex and controlled by several factors in amorphous materials. The molecular mobility is regarded as the most relevant factor governing the physical stability of amorphous materials since the molecules need to be mobile in order to arrange into a crystal. However, the thermodynamic driving force for the crystallization and factors—such as the preparation method (see The Solid State chapter) and moisture content (see the Moisture sorption chapter)—may also affect crystallization behavior. Further, additives may influence the physical stability of an amorphous substance and, for example, cause heterogeneous nucleation.

The molecular mobility is strongly dependent on the storage temperature. It has been suggested that it is negligible at 50 K below the \(T_g\), and that amorphous materials therefore may be stored without crystallizing at such temperatures.\textsuperscript{130, 131} However, even though the molecular mobility of an amorphous material is significantly lower for a glass than in its rubbery state, the molecular mobility and the internal energy are still higher than in a crystal. Somewhat simplified, unless the amorphous material is physically stabilized it will eventually recrystallize, that is, transform into the crystalline state.
It is crucial to stabilize amorphous solids against recrystallization to prevent it occurring in systems where long-term physical stability is desired. To achieve this, nucleation must be suppressed. There are two main formulation strategies for doing this—either by forming an *amorphous solid dispersion* (ASD) or by loading the substance into a *mesoporous* carrier material.

**Amorphous Solid Dispersions**

The conventional way of stabilizing amorphous solids is based on reducing the molecular mobility by processing the amorphous substance with a carrier to form an intimate mixture denoted ASD. Typically these carriers are polymers and the drug can be either miscible or immiscible in them. When the drug is completely miscible in the polymer matrix, a one-phase solid solution can form. When the drug has limited solubility in the polymer, it disperses as amorphous particles in the matrix. The one-phase solid solution is the desired state.

The lowered molecular mobility is a result of intermolecular interactions between the polymer and the amorphous drug. Thus, a careful choice of carrier is required to obtain the desired properties of the ASD. Further, even though a one-phase solid solution is formed, water sorption, for example, may cause phase separations during storage. However, the impact of phase separations on the stabilizing effect of polymers is poorly understood.

A conventional ASD is made up of only a drug and a carrier. Researchers have exploited the possibility of adding more components to improve the performance of ASDs. For example, A200 has been used to improve the powder flowability and to further improve the physical stability.

**Mesoporous Systems**

The other strategy for stabilizing amorphous solids builds on *nanoconfine-ment* of the drug in domains with smaller dimensions than the critical nucleus size, $r_c$. The disordered-state drug substance is loaded into pores of a mesoporous material, 2–50 nm. This greatly reduces the nucleation tendency, and subsequently the crystallization propensity, in the amorphous material. This strategy has been demonstrated in materials such as mesoporous calcium carbonate, mesoporous amorphous magnesium aluminometasilicate (Neusilin® US2), chemically modified porous crystalline cellulose, mesoporous magnesium carbonate, and mesoporous silicate.
The molecular mobility of nanoconfined drugs is normally increased. However, immobilization of molecules at the pore surface may occur. These effects must be considered since they may influence the physical stability of drugs loaded into mesoporous materials with pore sizes above $r_c$.

**Pharmaceutical Composites**

An alternative and relatively unexplored approach for achieving long-term physical stability is to form composites of filler particles with the amorphous substances. Crystalline drugs, such as acetylsalicylic acid and phenacetin, physically mixed with graphite or silica nanoparticles, spontaneously transform into the amorphous form upon storage. Further, milling of drugs such as benzoic acid, chloramphenicol, and diazepam, lead to amorphization when mixed with MCCs. This is despite that milling of the neat drugs does not lead to transformation into the amorphous form. This effect is attributed to interactions between the drugs and the surfaces of the MCC.

Co-processing of drugs (indomethacin, ketoprofen, naproxen, progesterone, ibuprofen, and nitrendipine) and 50–90 wt% silicate nanoparticles (A200, Neusilin®, and kaolin) lead to amorphous pharmaceutical composites that are physically stable for months at 40°C/75% RH. This increased physical stability compared to the neat amorphous drugs has been attributed to surface immobilization of the drug at the filler particle surface due to interactions, such as hydrogen bonding, between the drug and the surface of the filler particles (rigidification). However, Bahl et al. co-milled indomethacin with silicate clay nanoparticles (MMT (Veegum®-F) and kaolin). They found that the composites were physically stable for 3–6 months at 40°C/75% RH at drug fractions that correspond to more than monolayer coverage of the nanofillers. Therefore, they pointed out that surface immobilization cannot be the single mechanism explaining the increased physical stability.

To deepen the understanding of the underlying mechanisms contributing to the altered recrystallization kinetics of pharmaceutical composites, we explored whether heterogeneous nucleation, moisture buffering, compartmentalization, and intraparticle confinement were possible mechanisms in addition to rigidification.

**Heterogeneous nucleation.** It is well known that foreign particles may induce heterogeneous nucleation. Heterogeneous nucleation may negatively influence the physical stability of amorphous solids since the overall crystallization rate may be increased. Crystalline surfaces have a greater tendency to induce nucleation than amorphous particles.
Moisture buffering. Stubberud and Forbes\textsuperscript{165} suggested that hygroscopic excipients such as PVP may act as internal desiccants in physical mixtures with amorphous lactose, thereby delaying the recrystallization of the lactose upon humidity exposure. Non-hygroscopic excipients do not have this effect.\textsuperscript{165} Our hypothesis was therefore that the filler particles in the composites act as moisture buffers and in that way influence the recrystallization kinetics.

Compartmentalization. Wu \textit{et al.},\textsuperscript{166} Nielsen \textit{et al.},\textsuperscript{167} and Priemel \textit{et al.}\textsuperscript{168} have demonstrated that amorphous powders have greater physical stability when divided into discrete compartments. When the crystallization is prevented from being transferred throughout the whole powder bed, the crystal growth rate is reduced.\textsuperscript{166-169} The overall recrystallization rate is strongly influenced by the nucleation rate in a compartmentalized system. A fast nucleating system will experience no or little effect of compartmentalization, while the recrystallization rate might be strongly reduced for a slow nucleating system.

Intraparticle confinement. A new structure is formed upon co-processing an amorphous substance with nanofillers. With sufficiently high filler content, the nanofiller particles may spontaneously form a porous network in which the amorphous substance is incorporated (see the \textit{Structure, Molecular Mobility, and Morphology} chapter). Our hypothesis was that the fillers form an interconnected network resembling a mesoporous material and that the organic amorphous phase is present in extra-particle voids with smaller domain size than $r_c$. This inhibits the nucleation and subsequently the recrystallization.

Sucrose/Micro-Particle Composites

To broaden the perspective and not only focus on silicate particles, we studied the recrystallization kinetics of sucrose freeze-dried into sucrose/micro-particle composites with 40 vol\% of five different particle types. These five were chosen to represent a wide range of crystallinity, hygroscopicity, hydrophobicity, and surface area (Table 1), and thereby enable a discussion of the mechanisms behind the physical stabilization of amorphous solids.\textsuperscript{a}

The crystallization temperature ($T_{cr}$) were significantly higher for the composites than the neat amorphous sucrose (Figure 26), but the crystallization rate was unaffected by the micro-particles and there were no indications

\textsuperscript{a} Paper I
that amorphous and crystalline fillers affected the crystallization kinetics differently. Thus, the alterations in recrystallization kinetics could not be correlated with heterogeneous nucleation. The recrystallization rate constant \( k \) of the sucrose in the sucrose/micro-particle composites was unaffected by the micro-particle additive and compartmentalization was therefore excluded as a mechanism for the alterations in recrystallization kinetics. We could not, however, exclude rigidification. This possibility was supported by the lowered molecular mobility, as indicated by increased \( T_g \). Further, talc, the filler with the largest surface area, gave higher \( T_g \) and \( T_{cr} \), while incorporation of CaCO\(_3\) into the sucrose phase led to the lowest values of \( T_g \) and \( T_{cr} \).

The stabilization effect was altered upon humidity exposure at an RH that was specific for each micro-particle type. Micro-particles of oxazepam (non-hygroscopic) only stabilized at dry conditions. CaCO\(_3\) (non-hygroscopic) delayed the onset of the recrystallization up to 33% RH, while talc (non-hygroscopic), starch (hygroscopic), and MCC (hygroscopic) delayed the recrystallization upon exposure to 43% RH. The stability against recrystallization in the sucrose/micro-particle composites could not be correlated with hygroscopicity of the filler particles and the humidity levels, as the moisture buffering hypothesis proposes. Instead, we believe that the water disrupted the intimate contact between the filler particle surface and the amorphous sucrose phase for the sucrose/oxazepam and sucrose/CaCO\(_3\) composites upon humidity exposure.

Lactose/Nanofiller Nanocomposites
We investigated humidity induced recrystallization of lactose co-spray-dried with 0–60 wt% (0–50 vol%) A200, 0–80 wt% CNC, or 0–80 wt% Na-MMT.
into lactose/nanofiller nanocomposites to further understand stabilization of the amorphous phase in pharmaceutical composites. Specifically we wanted to study how the shape of the nanofillers influences the nano- to micrometer length-scale filler arrangement in the composites and how that arrangement influences the physical stability.

The lactose/CNC and the lactose/Na-MMT nanocomposites at 80 wt% nanofiller content were physically stable for at least 2 months at 60% RH. Further, most particles of the lactose/A200 nanocomposites with 60 wt% A200 content were still amorphous after 1 week at 84% RH. The k was lowered as a function of nanofiller content for lactose/A200 nanocomposites at 43–94% RH, (see Figure 27 for k at 94% RH). By extrapolation, 64 wt% A200 was needed to completely inhibit recrystallization. The lactose/CNC and the lactose/Na-MMT nanocomposites demonstrated lowered k with high nanofiller content (≥42% w/w Na-MMT or ≥60% CNC) at 60–94% RH, (see Figure 27 for k at 94% RH).

Moisture buffering could be excluded as a mechanism for the increased physical stability. The nanofiller incorporation into the amorphous lactose phase did not influence the moisture sorption capacity in the lactose/A200 nanocomposites or in the non-intercalated lactose of the lactose/Na-MMT nanocomposites (see the Moisture sorption chapter).

The morphology of the nanocomposite particles upon moisture sorption was studied to evaluate the effect of compartmentalization in them (see the Structure, Molecular Mobility, and Morphology chapter). The physical stability

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Figure 27. Recrystallization rate constant (k) as a function of nanofiller content. The rate was determined with calorimetry at 94% relative humidity (RH) for neat spray-dried lactose and lactose/fumed silica (A200) ▲, lactose/cellulose nanocrystals (CNC) ●, and lactose/sodium montmorillonite (Na-MMT) ●.
correlated with the ability to prevent sintering of the lactose/A200 and the lactose/CNC nanocomposites. Nevertheless, the nanocomposite with 20% Na-MMT prevented sintering but had a higher $k$ than the neat amorphous lactose. A likely explanation is heterogeneous nucleation exerted by the Na-MMT sheet surfaces. An indication of this is lowered time to crystallization as a function of Na-MMT content. Thus, compartmentalization cannot be a general mechanism for the increased physical stability. Furthermore, compartmentalization is likely to only make minor contributions to the overall stabilization effect for the lactose/A200 and the lactose/CNC nanocomposites.

The molecular mobility was lowered for the lactose/A200 and the lactose/CNC nanocomposites, but was increased for the lactose/Na-MMT nanocomposites, as indicated by the structural relaxation (see the Structure, Molecular Mobility, and Morphology chapter). Further, $\Delta C_p T_g$ was lowered as a function of A200 content (Figure 19), which was attributed to immobilization of the lactose at the A200 surface. However, no signs of surface immobilization were detected for the lactose/CNC or the lactose/Na-MMT nanocomposites (Figure 19).

Even though the molecular mobility decreased in the lactose/CNC nanocomposites, the stabilization effect was at the same levels as for the lactose/Na-MMT. Thus, it seems that a general lowering of the molecular mobility does not have a great impact on the physical stability in the nanocomposites upon humidity exposure. Nonetheless, surface immobilization of the nanofiller particles may be desirable (as seen for the lactose/A200 nanocomposites and in earlier studies$^{158-163}$).

As discussed, the amorphous lactose phase is present in the extra-particle voids with restricted dimensions in the nanocomposites, especially at high nanofiller content (see the Structure, Molecular Mobility, and Morphology chapter). Subsequently, nanoconfinement probably contributes strongly to the increased physical stability due to formation of lactose domains with smaller dimension than $r_c$.

The increased in $T_g$ of the lactose in the nanocomposites might be understood in terms of nanoconfinement. The $T_g$ of ezetimibe loaded into mesoporous materials is 0.8–6.7°C higher than neat amorphous ezetimibe,$^{147}$ and the $T_g$ of glycerol is increased as a function the pore size when confined in MCM-41.$^{170}$ This is in agreement with the $T_g$ changes for the lactose at 80% nanofiller content in the nanocomposites. However, this is not a conclusive argument for nanoconfinement of the lactose in the composites, since decreased $T_g$s has also been demonstrated upon nanoconfinement.$^{170}$
The differences between the different nanofillers in their ability to stabilize against recrystallization are likely due to the shape and the surfaces of the nanofillers. It is reasonable to assume that the rod-shaped CNC and the sheet-like MMT are not as good at forming mesopores as A200. In addition, the demonstrated immobilization of the lactose at the A200 surface also contributes to the greater ability of A200 to stabilize lactose against recrystallization.

Importance of Spray-Drying Production

As discussed in *The Solid State* chapter, production processes may influence the characteristics of amorphous products. Therefore, the influence of the spray-drying process on the physical stability was studied with DoE. However, multivariate analysis suggested that the manufacturing did not influence physical stability under the production conditions that were used. This has likely to do with the excellent glass-forming ability of lactose and the small differences in the intraparticle structure of the nanocomposite particles.
Compression Mechanics

Compression mechanics of a material is a central pharmaceutical functionality since the majority of pharmaceuticals are administered as tablets. The compression mechanical properties of crystalline materials are altered upon amorphization and excipients may also influence them. For example, nanofillers are widely used to produce polymer nanocomposites because they have better mechanical properties than the neat polymer. In this context, we found it interesting to study the compression mechanics of the lactose/nanofiller nanocomposites and to relate this property to the structural knowledge about the nanofiller arrangement in the nanocomposites from our previous studies.

The limited particle size of ca. 5 µm of the nanocomposites strongly influenced the initial compression due to particle rearrangement. Indeed, the lactose/A200 nanocomposites continued to rearrange throughout the whole compression profile, prohibiting an in-depth characterization of this nanocomposite material. The lactose/CNC and the lactose/Na-MMT nanocomposites demonstrated higher yield pressure than physical mixtures of the spray-dried neat components (Figure 28), which can be interpreted as increased particle hardness. The largest effect was achieved at 40–60 wt% nanofiller content.

The higher yield strength can be understood in the light of polymer nanocomposites. Nanofillers are commonly used to reinforce polymers by nanofiller skeleton formation within the composite particles to achieve materials with improved mechanical properties. Thus, the increased yield pressure of the lactose/nanofiller composites is likely due to such skeleton formation.

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* Paper VI
Figure 28. Heckel yield pressure, $P_y$ (MPa) as a function of nanofiller content for the lactose/nanofiller nanocomposites and for the physical mixtures with cellulose nanocrystals (CNC) and sodium montmorillonite (Na-MMT).
Conclusions

Amorphous materials are highly topical, something that is reflected in the number of publications and pharmaceutical products on the market. Amorphous materials are used both as excipients, for example in freeze- and spray-dried peptides and proteins, and as active pharmaceutical ingredients. ASD and mesoporous systems are central formulation strategies for amorphous pharmaceuticals. To better understand the functionality of such formulations, it is necessary to study microstructure and component interactions.

The investigated nanocomposites have many similarities with ASDs and mesoporous systems, for example in the importance of small domains of the amorphous compound to inhibit nucleation\textsuperscript{153, 174-176} and the interactions between the excipient and the amorphous phase.\textsuperscript{132, 144-146, 176, 177} Furthermore, nanofillers are increasingly being used as a third component in conventional ASDs.\textsuperscript{138-143}

This thesis showed that fillers change the properties of the amorphous phase in which they are dispersed. The most interesting alterations were achieved at high filler contents, typically above 60 wt%. Amorphous lactose that normally recrystallizes within a few minutes upon humidity exposure could withstand recrystallization for several months at 60% RH in nanocomposites with 80% CNC or Na-MMT.\textsuperscript{a} Further, 64 wt% A200 was estimated to give a similar effect.\textsuperscript{b} Also, the nanocomposite formation led to increased particle hardness for the lactose/CNC and the lactose/Na-MMT nanocomposites\textsuperscript{c}. The hygroscopicity of the latter composites\textsuperscript{d} also decreased more than for ideal simple mixtures of the neat components.

Our studies on the structure and mobility of the spray-dried nanocomposites demonstrated that the nanofillers were evenly distributed in the amorphous lactose phase.\textsuperscript{e} At low nanofiller content the amorphous phase was continuous, but the nanofillers most likely formed a porous network at high

\textsuperscript{a} Papers II and IV
\textsuperscript{b} Paper II
\textsuperscript{c} Paper VI
\textsuperscript{d} Paper V
\textsuperscript{e} Papers II-VI
nanofiller content, leading to a separation of the amorphous phase into domains smaller than $r_c$. The different nanofillers varied in their ability to form such domains, most likely due to differences in their shapes. Also, the molecular mobility of the amorphous lactose was mainly dependent on nanofiller type. When lactose was co-spray-dried with Na-MMT, a fraction of the lactose was intercalated in the clay interlayer space.

The most important mechanism in stabilizing the amorphous lactose against recrystallization was intraparticle confinement of the amorphous phase. However, rigidification caused by molecular interactions between the lactose molecules in the amorphous phase and the surface of the fillers also contributed under certain conditions to the reduced recrystallization tendency.

Decreased hygroscopicity in the lactose/Na-MMT nanocomposites was due to interactions between the sodium ions and the intercalated lactose in the Na-MMT interlayer space. Further, the greater particle hardness of the lactose/CNC and the lactose/Na-MMT nanocomposites compared to physical mixtures of the spray-dried neat components could be understood in terms of the nanofiller skeleton formation.

This thesis aimed to understand the structure−mobility−functionality relationship of pharmaceutical composites, which is applicable to amorphous formulations in general. In particular, the study of moisture sorption in the composites was fruitful in increasing our knowledge of amorphous formulations.

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[a] Papers II and IV  
[b] Paper IV  
[c] Papers II–IV  
[d] Paper III  
[e] Paper IV  
[f] Papers I, II, and IV  
[g] Paper V  
[h] Paper VI
Populärvetenskaplig sammanfattning

Majoriteten av alla läkemedel är fasta material, där tabletter är den vanligaste beredningsformen. Ett läkemedel består inte enbart av den aktiva komponenten. För att ett läkemedel ska kunna utöva sin effekt behöver läkemedelssubstansen formuleras eller beredas med andra komponenter, så kallade hjälpämnen. Dessa hjälpämnen tillsätts av flera olika anledningar, till exempel för att få tabletter att hålla ihop.


Farmaceutiska material är vanligen kristallina, men amorfa material kan ha egenskaper som är överlägsna den kristallina motsvarigheten. Till exempel är amorfa socker mycket viktiga hjälpämnen vid formulering av proteiner. Två andra exempel när det kan vara fördelaktigt med amorfa material i läkemedelsformuleringar är när upplösningshastighet och läsighet behöver förbättras eller när högre hållfasthet på tabletter eftersträvas.

Ett problem med de flesta amorfa material är att de är fysikaliskt instabila, dvs. de omvandlas så småningom tillbaka till kristallina. Denna kristallisation leder till förlust av de egenskaper som erhållits genom att amorfisera materialet och måste därför förhindras för att inte den avsedda effekten av läkemedelsformuleringen förstörs. För att förebygga detta kan drivkrafterna för kristallisationen minskas genom att formulera det amorfa materialet tillsammans med hjälpämnen.
Syftet med denna doktorsavhandling var att ge mer kunskap om amorfa läkemedelsformuleringar. Kompositmaterial bestående av en blandning av partiklar och modellsubstanser bestående av amorfa socker tillverkades. Genom att studera sambandet mellan strukturen på kompositmaterialen och egenskaper såsom motståndskraft mot kristallisation, fick vi information om vad som är viktigt vid formulerandet av sådana läkemedel. Ett flertal olika partiklar med olika form och ytegenskaper användes i kompositerna för att ge kunskap om hur dessa skillnader påverkade resultatet.

Det amorfa sockret var stabilt och den amorfa strukturen förblev bevarad i de kompositer som hade hög andel partiklar trots förvaring under förutsättningar där kristallisation normalt sker. Det finns två delförklaringar till detta resultat. För att kristallisation ska kunna initieras behöver det finnas tillräckligt med amorft material samlat på ett ställe. Det amorfa sockret delades upp i mycket små enheter i kompositerna och kristallisationsprocessen kunde därför inte initieras. Dessutom leddes interaktioner mellan ytan på partiklarna och sockermolekylerna till att ytslockermolekyler inte deltog i kristallisationsprocessen i vissa fall.

Denna avhandling bidrar med ökade kunskaper om amorfa läkemedelsbehandlingar. Dessa kunskaper är värdefulla vid exempelvis formulering av svårlosgående läkemedelssubstanser och proteinläkemedel.
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