Amorphous magnesium carbonate nanomaterials

Synthesis, characterization and applications

JIAOJIAO YANG
Abstract

High surface-to-volume ratio materials, including nanoparticles and mesoporous materials, have a number of applications due to their large surface area and special structures. Traditional approaches for synthesizing high surface-to-volume ratio nanomaterials are often complicated, expensive or environmentally unfriendly. Considering aspects such as availability and safety in terms of environmental or biological contact, magnesium carbonate-based nanomaterials are an interesting and potentially valuable candidate for novel applications. The overall aim of this thesis was to develop novel high surface-to-volume ratio amorphous magnesium carbonate nanomaterials and investigating their possible applications.

Amorphous magnesium carbonate nanoparticles (AMN) were successfully synthesized via a simple and low-temperature pathway. The structure and resulting properties of the material can be tailored by changing the final steps in the synthesis process.

The ability of AMN to stabilize ibuprofen (IBU) in the amorphous state was investigated. Nanocomposites with IBU:AMN mass ratios as high as to 5:1 were shown to enhance the release rate of IBU \textit{in vitro} by as much as 83 times compared to IBU in crystalline form. A related nanostructured material, mesoporous magnesium carbonate (MMC), was evaluated as a drug carrier for stabilizing amorphous drugs through the incorporation of the drug within its pores. In this study, MMC was used to release and sustain two poorly soluble drugs (tolfenamic acid and rimonabant) in the supersaturated state with the assistance of hydroxypropyl methylcellulose.

AMN was also used to synthesize a novel adhesive together with IBU without the addition of a polymer. This adhesive was transparent, self-healing, shapeable, stretchable and reusable. In addition, the adhesive was able to glue a variety of materials, including metals, glass, paper and plastics (even Teflon).

Finally, AMN was used to prepare flexible, transparent and UV-shielding films when incorporated into a PMMA matrix. These films exhibited both UV-shielding properties and moisture absorbance and retention abilities. In addition, the UV- and thermo-stability of these films were enhanced by the addition of AMN.

The work presented in this thesis show that the nanomaterials AMN and MMC possess great potential for an extremely broad range of applications, from pharmaceutical applications dealing with poorly soluble drugs to structural applications such as adhesives to applications in optics or electronics such as UV-shielding or moisture barrier films.

Keywords: high surface-to-volume ratio, nanoparticles, mesoporous, magnesium carbonate, amorphous drugs, supersaturated concentration, general adhesives, UV-shielding

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


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The author’s contribution to the included papers

I  I planned the study, performed the experimental work except the TEM operation, and performed data analysis. I wrote the first draft of the manuscript and contributed to the continued writing process.

II  I planned the study, performed the experimental work except the cytotoxicity test, and performed data analysis. I wrote the first draft of the manuscript and contributed to the continued writing process.

III I took part in planning the study, performed the experimental work, performed data analysis and wrote the first draft except the part of determination of initial release rate. I contributed to the writing revised process.

IV  I planned the study, performed the experimental work, and performed data analysis. I wrote the first draft of the manuscript and contributed to the continued writing process.

V  I planned the study, performed the experimental work except UV-vis transmittance studies of films, and performed data analysis. I wrote the first draft of the manuscript and contributed to the continued writing process.
Also published

Journal articles


Conference papers


Patent application

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<th>Description</th>
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<tr>
<td>0D</td>
<td>Zero dimensional</td>
</tr>
<tr>
<td>1D</td>
<td>One dimensional</td>
</tr>
<tr>
<td>2D</td>
<td>Two dimensional</td>
</tr>
<tr>
<td>AMN</td>
<td>Amorphous Magnesium Carbonate Nanoparticles</td>
</tr>
<tr>
<td>APIs</td>
<td>Active pharmaceutical ingredients</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DLS</td>
<td>Dynamic light scattering</td>
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<tr>
<td>FDA</td>
<td>U. S. food and drug administration</td>
</tr>
<tr>
<td>FFT</td>
<td>Fast Fourier transform</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared spectroscopy</td>
</tr>
<tr>
<td>HDF</td>
<td>Human dermal fibroblasts</td>
</tr>
<tr>
<td>HPMC</td>
<td>Hydroxypropyl methylcellulose</td>
</tr>
<tr>
<td>HRTEM</td>
<td>High resolution transmission electron microscopy</td>
</tr>
<tr>
<td>IBU</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>LMW</td>
<td>Low-Molecular-Weight</td>
</tr>
<tr>
<td>MMC</td>
<td>Mesoporous Magnesium Carbonate</td>
</tr>
<tr>
<td>PMMA</td>
<td>Poly(methyl methacrylate)</td>
</tr>
<tr>
<td>RIM</td>
<td>Rimonabant</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning electron microscopy</td>
</tr>
<tr>
<td>SSA</td>
<td>Specific surface area</td>
</tr>
<tr>
<td>TEM</td>
<td>Transmission electron microscopy</td>
</tr>
<tr>
<td>TGA</td>
<td>Thermogravimetric analysis</td>
</tr>
<tr>
<td>TOL</td>
<td>Tolfenamic acid</td>
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<tr>
<td>UV</td>
<td>Ultraviolet</td>
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<tr>
<td>XRD</td>
<td>X-ray diffraction</td>
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1. Introduction

Nanotechnology is typically described as the manipulation of matter on an atomic, molecular or supramolecular scale, and therefore involves the study of materials that have features of interest with at least one of their dimensions in the nanometer range, i.e., from 1 to 100 nm. Therefore, nanosized materials can be divided into 0D nanomaterials (e.g., nanoparticles, C$_{60}$ or “buckyballs”), 1D nanomaterials (e.g., nanowires, nanorods), 2D nanomaterials (e.g., nanosheets, graphene) and nanostructured materials (e.g., mesoporous materials) [1, 2].

At the nanoscale, many of the physical and chemical properties of materials are significantly different from those of the bulk materials with the same chemical composition. For example, nanoparticles may exhibit quantum effects and mesoporous structures (i.e., structures such as pores with dimensions between 2 and 50 nm) can suppress the recrystallization of loaded molecules in pores due to geometrical constraints. Therefore, nanomaterials have been widely used in medicines [3], environmental sciences [4], optics [5], energy applications [6] and so on [7].

While nanomaterials can be generated by ‘top-down’ methods such as grinding, attrition and milling, ‘bottom-up’ methods have been generally developed to more effectively synthesize nanomaterials as they provide better control of sizes, shapes and functionalization [8, 9]. Bottom-up, or self-assembly, approaches for nanofabrication use chemical or physical forces to induce smaller components to arrange into larger structures. In order to synthesize nanomaterials, an extremely broad range of substances or compounds have been utilized, including metals and metallic compounds [10], carbon materials [11], polymers [12] and silica materials [13], and even nanomaterials themselves can assemble into more complex nanostructures [14]. Many different methods have been used to synthesize nanomaterials, including colloidal methods [15], sol-gel processing [16], microemulsion methods [17], hydrothermal or solvothermal syntheses [18] and polyol methods [19]. Despite impressive progress in the field of nanomaterial synthesis, many if not most of the synthesis routes involve the use of toxic raw materials or rigorous, complex or expensive steps. Thus, in order to aid in the commercial realization of new nanomaterials, the development of simple, cost-effective and environmentally friendly synthesis routes using non-toxic materials are urgently needed.
Recently, an amorphous magnesium carbonate nanomaterial with a mesoporous structure was successfully synthesized using only magnesium oxide, carbon dioxide and methanol [20]. This amorphous and mesoporous form of magnesium carbonate (designated as MMC) does not exist in nature and has excellent properties such as high specific surface area [20] and has been investigated for use in different applications [21-23]. In this thesis, a novel structure of amorphous magnesium carbonate, amorphous magnesium carbonate nanoparticles (AMN), was developed based on a modification of the synthesis route for MMC. Possible applications in pharmaceutics, structural materials and optics for these amorphous magnesium carbonate nanomaterials (both AMN and MMC) were also examined herein.
2. Aims of the thesis

The work presented in this thesis was aimed at developing a novel nanostructure of amorphous magnesium carbonate without the use of organic surfactants as templates. The possibilities of using amorphous magnesium carbonate nanomaterials in a wide range of application areas were also investigated.

The specific aims of the thesis are detailed in the aims of the included papers as follows:

**Paper I:** To synthesize and characterize a novel amorphous magnesium carbonate nanomaterial, amorphous magnesium carbonate nanoparticles (AMN).

**Paper II:** To explore the ability of AMN to stabilize amorphous forms of drugs with limited aqueous solubility, and thus improve their dissolution rate. Ibuprofen (IBU) was used as the model drug.

**Paper III:** To explore the ability of amorphous mesoporous magnesium carbonate (MMC) in combination with hydroxypropyl methylcellulose (HPMC) as a drug delivery system to both induce and prolong the supersaturation of drugs with limited aqueous solubility. Tolfenamic acid (TOL) and rimonabant (RIM) were used as model substances.

**Paper IV:** To explore the possibility of AMN in combination with Low-Molecular-Weight (LMW) molecules to prepare a novel adhesive without the use of a polymer. IBU was used as the model LMW molecule.

**Paper V:** To explore the possibility of AMN as fillers in combination with poly(methyl methacrylate) (PMMA) to produce transparent, UV-shielding, moisture absorbing and flexible thin films.
3. Background

3.1 Nanotechnology

Nanotechnology is typically described as the manipulation of matter on an atomic, molecular or supramolecular scale and as such deals with the synthesis, characterization, and application of nanosized and/or nanostructured materials. A nanometer (nm) is $10^{-9}$ m, which is approximately the length of 5 silicon atoms aligned in a line. At the nanoscale, materials can exhibit different physical, chemical and/or biological properties from the corresponding bulk materials, including strength, thermal behavior, catalytic activity and biocompatibility [24].

Although nanomaterials have been developed rapidly in recent decades, nanomaterials are known to have been used hundreds if not thousands of years ago. For example, Chinese used gold nanoparticles as a noble dye to incorporate red color into ceramics in ancient times; Romans adjusted the colors of glass artefacts by using different metal nanoparticles long ago; and Europeans used nanoparticles to decorate cathedral windows in medieval times [9]. Unknown to these early chemists was the theory behind why their compositions produced different colors, which are due to the absorption and scattering properties of nano-sized metallic particles. These optical properties can be tuned simply by changing the size or shape of the metallic nanoparticles.

Today, nanotechnology has matured into a complex combination of fundamental and engineering sciences. Depending on the number of dimensions of the nanostructured material/system of interest on the nanoscale, nanomaterials can be divided into (a) 0D structures, e.g., nanoparticles or $C_{60}$ “buckyballs”; (b) 1D structures confined in one dimension, e.g., nanowires whose length is significate greater than the cross-sectional dimension such as carbon nanotubes; (c) 2D structures confined in two dimensions, e.g., layered or sheeted structures such as graphene; (d) Materials with nanostructure, e.g., mesoporous structured materials (see Fig.1).
Figure 1. Schematic classification of nanomaterials: (a) 0D nanomaterials; (b) 1D nanomaterials; (c) 2D nanomaterials; and (d) Nanostructured materials.

A large part of nanomaterial research presently focuses on the manipulation of materials on the nanoscale, as well as the understanding interactions of these materials at the nano- and even atomic level. For example, nanofibers are used for reinforcement of composite materials; nano-thin films are used to make products lighter and stronger; nanoparticles are used as UV-shielding materials; nanosized vehicles are used for drug delivery in the body, etc.

3.1.1 High surface-to-volume ratio materials

Among nanomaterials, materials with high surface-to-volume ratios play important roles in our lives. Large surface area enables chemical transformations to occur with high reaction rates and high product selectivity. Nanoparticles and porous materials are typical examples of high surface-to-volume materials. Properties of nanoparticles are governed by their small, solid size, while properties of porous materials are governed by nano-sized cavities in their condensed state. In addition to the effect due to the physical dimensions of the materials, the surface chemistry can strongly affect the properties of nanoparticles and porous materials, for example mesoporous materials, which have attracted the attention of many researchers in recent years [25]. Nanoparticles and mesoporous materials have been synthesized via several different methods [9, 26] and have found a wide range of applications [27, 28].

3.1.1.1 Nanoparticles

Nanoparticles are defined as particles between 1 and 100 nm in size according to IUPAC. Nanoparticles can be synthesized by several different chemical methods as described below.

Metal nanoparticles are usually prepared by the decomposition of organometallic precursors, e.g., metal carbonyls [29], metal oleates [30] and metal carboxylates [31] in hot surfactant solutions.

The process with mixing two microemulsions containing appropriate reactants is another method used to synthesize various nanoparticles, where the microemulsion consists of a ternary mixture of water, surfactants and oil.
This method has been successfully applied to prepare Ag nanoparticles [32], Cu nanoparticles [33] and cobalt ferrite nanoparticles [34].

The hydrothermal/solvothermal method of nanoparticle fabrication is generally employed for the synthesis of inorganic nanoparticles. Reaction parameters such as time, temperature, reactant and surfactant concentration, pH and relative volume can strongly affect the reaction and size of nanoparticles. TiO$_2$ [35], MnO [36] and ReO$_3$ [37] have been prepared via this method.

Sol-gel synthesis is a common method for the synthesis of metal oxide nanoparticles as well as oxide nanoparticles. The sol-gel method includes the hydrolysis and condensation of metal precursors and has been used to synthesize Fe$_2$O$_3$ nanoparticles [38], ceria nanoparticles [39] and TiO$_2$ nanoparticles [40].

The phase-transfer method of nanoparticle fabrication involves the transfer of reactants from a polar phase to a non-polar phase in which the reaction occurs. This method is widely used to synthesize noble metal nanoparticles [41] and metal chalcogenides nanoparticles [42].

The microwave synthesis route is based on the rapid decomposition of precursors in a microwave reaction and presents a new route for synthesizing inorganic nanoparticles [43]. This method provides a supersaturated solution, where nucleation and growth occur. Microwave synthesis has been applied to synthesize Au nanoparticles [44], CdSe and PbSe nanoparticles [45].

Nanoparticles can also be formed at the liquid-liquid interface, because certain precursors are often highly mobile at the interface, and molecules are able to assemble due to low interfacial energy. This technique can be used to prepare metal nanoparticles such as Au, Ag and Pd, or metal compound nanoparticles CdS and NiS [46].

3.1.1.2 Mesoporous materials

Mesoporous materials are defined as porous materials with pore diameters between 2 to 50 nm according to IUPAC. In the past decades, many synthesis methods and techniques have been explored. Most mesoporous materials are generally prepared under ‘hydrothermal-like’ conditions. However, the synthesis temperature normally ranges from room temperature to 150 °C. A sol-gel process involving surfactants for pore formation is typically used to synthesize mesoporous materials. Either basic or acidic conditions can be applied to produce mesoporous materials.

A general procedure for synthesizing mesoporous materials includes several steps. First, the surfactant(s) are dissolved in water to obtain a homogeneous solution. Second, inorganic precursors are added into the solution in which they hydrolyze in presence of a catalyst. Third, the solution is allowed to transform from a sol to a gel. Fourth, the product undergoes a hydrothermal treatment and cools to room temperature, and then is filtered, washed
and dried. Finally, the resultant mesoporous material is obtained after removing organic template(s), \textit{i.e.} surfactant(s) [47]. Various mesoporous structures, including mesoporous silica [48] and carbon [49], have been synthesized by this method.

An alternative way to synthesize mesoporous materials is described as a hard-template method. Ordered mesoporous templates are used to form ordered arrangements [50]. Highly ordered mesoporous carbons and metal oxides are synthesized by this method [51, 52]. However, this method depends on the order of the original templates, which limits wide application of this technique.

3.1.2 Templates

As described in section 3.1.1, synthesis of both nanoparticles and mesoporous materials usually requires the participation of surfactants as templates. Traditionally, many different surfactants have been used in the synthesis of ordered materials [53], \textit{e.g.}, cationic surfactants for mesoporous silica [54], anionic surfactants for mesoporous silica [55] and non-ionic surfactants for BaSO$_4$ nanoparticles [56].

It has been reported that the nature and structure of surfactants observably affects structures and the surface area of the final products. The use of surfactants in the synthesis of nanoparticles often results in nanoparticles with uniform size and surface structure, while the use of surfactants in the synthesis of mesoporous materials often results in materials with ordered and unidirectional pores. However, surfactants are usually environmentally unfriendly because of their toxicity and/or difficulty to be removed [57]. Therefore, attempts have been made to develop synthesis routes that do not require surfactants, \textit{e.g.}, CaCO$_3$ nanoparticles [58], but such pathways usually generate materials with much lower surface area than that possible using templates.

3.2 Magnesium carbonate

Magnesium is one of the most abundant elements on earth and of critical importance for life as it is essential for all cells. In nature, magnesium often exists in the compound magnesium carbonate, MgCO$_3$, which is a ‘generally recognized as safe’ material by the FDA and has attracted the interest of researchers for different applications [59, 60].

Magnesium carbonate normally consists of the hydrate, the basic hydrate, and the anhydrous forms. Basic magnesium carbonate is the most common form, and varies in formula between (MgCO$_3$)$_3$·Mg(OH)$_2$·3H$_2$O and (MgCO$_3$)$_4$·Mg(OH)$_2$·5H$_2$O [61]. (MgCO$_3$)$_3$·Mg(OH)$_2$·3H$_2$O (M$_w$ = 365.30) is described as light magnesium carbonate, while (MgCO$_3$)$_3$·Mg(OH)$_2$·4H$_2$O (M$_w$ = 383.32) is described as heavy magnesium carbonate. Magnesium
carbonate occurs as light, white masses or as a bulky, white powder. The typical properties of magnesium carbonate are shown in Table 1.

Table 1. *Typical properties of Magnesium carbonate.*

<table>
<thead>
<tr>
<th></th>
<th>Heavy magnesium carbonate</th>
<th>Light magnesium carbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
<td>42-50° for granular type [62]</td>
<td></td>
</tr>
<tr>
<td>Density (true)</td>
<td>1.966-2.261 g/cm³ [59]</td>
<td></td>
</tr>
<tr>
<td>Moisture content</td>
<td>1% w/w (^a), 5% w/w (^b) [62]</td>
<td></td>
</tr>
<tr>
<td>Particle size distribution</td>
<td>7-43 µm [59]</td>
<td>44.5 µm [59]</td>
</tr>
<tr>
<td>Solubility</td>
<td>Insoluble</td>
<td>Insoluble</td>
</tr>
<tr>
<td>Specific surface area (SSA)</td>
<td>7.8-18.2 m²/g for granular type [62]</td>
<td></td>
</tr>
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</table>

\(^a\) at relative humidities between 15% and 65% at 25°

\(^b\) at relative humidities above 75% at 25°

Recently, to meet the requirements of the wide range of applications, magnesium carbonates have been synthesized with different morphologies or structures. Mistuhashi et al. developed a carbonation method of magnesium hydroxide suspension to synthesize needle-like MgCO\(_3\)·3H\(_2\)O [63]. Yan et al. synthesized nest-like Mg\(_5\)(CO\(_3\))\(_4\)(OH)\(_2\)·4H\(_2\)O via a self-assembly of MgO nanosheets [64]. Li et al. prepared rosette-like Mg\(_5\)(CO\(_3\))\(_4\)(OH)\(_2\)·4H\(_2\)O spheres via a hydrothermal route [65]. In recent years, MgCO\(_3\)-based nanomaterials have also attracted the interest of an increasing number of researchers. Crystalline magnesium carbonate nanoparticles were successfully synthesized via encapsulation of precursors [66]. However, additional stabilizers, surfactants, were involved in this method.

3.2.1 Mesoporous magnesium carbonate (MMC)

As described in section 3.1.2, surfactants may generate environmental toxicity and can be difficult to remove. Thus, the development of a non-surfactant route of manufacture for magnesium carbonate nanomaterials is significantly important.

MMC produced in the amorphous state was first successfully achieved via a low temperature synthesis route involving only MgO, CO\(_2\) and CH\(_3\)OH at the Division for Nanotechnology and Functional Materials, Uppsala University [20, 67]. Different from other amorphous porous magnesium carbonate xerogels and aerogel [68], MMC shows a well-defined pore-size distribution.

The synthesis first involves pressurizing a mixture of MgO and methanol under 4 bar CO\(_2\) with stirring for a period of days until a homogeneous solution is obtained, after which the pressure is released and the product under-
goes gelation and then is dried to form the final, solid mesoporous material, in which desorbing CO$_2$ and evaporating CH$_3$OH play a role as pore-foaming agents.

Interestingly, MMC is composed of randomly oriented nanoparticle aggregates (Fig. 2), and these primary nanoparticles are produced in an intermediate step in the synthesis [69]. Significant aggregation of nanoparticles occur when the solvent and CO$_2$ are evaporated/desorbed, leaving pores in the spaces between the primary nanoparticles or aggregates [69]. The mesoporous structure of this material shows great promise in environmental, biomedical and pharmaceutical applications [21-23, 70-73]. However, the spontaneous aggregation behavior of these primary nanoparticles limits the development of magnesium carbonate nanomaterials with smaller size, which could allow for the exploitation of further applications such as in injectable drug vector systems.

Figure 2. A SEM (scanning electron microscopy) image of MMC.

In this thesis, a novel amorphous magnesium carbonate based nanomaterial, amorphous magnesium carbonate nanoparticles (AMN), was successfully synthesized and characterized (Paper I).

3.3 Applications of high surface-to-volume materials
3.3.1 Enhancing the dissolution rate and/or solubility of poorly water-soluble drugs

The bioavailability of active pharmaceutical ingredients (APIs) is a critical factor in drug discovery and development for oral administration. Normally, the dissolution rate and solubility of APIs in water strongly affect their bioavailability, because APIs should first dissolve in the gastrointestinal juice, then be absorbed into the bloodstream and be thus able to participate in a therapeutic action [74]. However, around 75% of developing drugs and 40%
of marketed drugs are poorly water-soluble [75]. To meet the therapeutic requirements for dissolution rate and/or solubility of APIs, numerous approaches have been studied and reported.

The distinction between solubility and dissolution rate should be first considered. The solubility is the equilibrium concentration of a substance, defined as the maximum quantity of that substance which completely dissolves at a certain temperature and pressure in a certain amount of solvent. On the other hand, dissolution is a kinetic property, defined as the process of dissolving a solute into a solvent, and thus the dissolution rate is used to describe whether the dissolution process is fast or slow.

Adjusting the pH of a solution using a buffer can increase the proportion of a weakly acidic or basic drug in the ionized form, which increases the polarity of APIs and therefore increases the dissolution rate and the aqueous solubility of APIs. Salt formations provide a similar effect via an ionic interaction between weakly acidic or basic drugs and an oppositely charged basic or acidic counterion. When salts subsequently dissolve or dissociate in water, the acidic or basic counterion from the salt formation changes the pH of the solution to provide the equivalent of a pH adjustment [76, 77]. However, salt formations may suffer from a reduction in the apparent solubility because ions in the dissolution media existing with the counterion used for salt formation may form in situ new salts that may have lower solubility compared to the free acid or free base.

Polymorphism and cocrystal formation change the packing of drug molecules within a crystal structure, which influence a range of different drug properties, including apparent solubility and dissolution rate. These approaches, unlike salts, can be used by non-ionizable drug compounds [78, 79]. However, polymorphism and cocrystal formation involve complex processing. In addition, polymorphism results in thermodynamic instability of solid drug formations. These disadvantages limit their application in the pharmaceutical industry.

Cosolvents are water-miscible organic solvents, which are less polar than water, and therefore decrease the polarity of the bulk solvent. In this case, the polarities of cosolvents are selected to be close to the polarity of the nonpolar molecule of interest, i.e., poorly water-soluble drugs [80, 81]. However, because of the additional cosolvents, formulations may lose solubilization power on dilution and lead to cell-based toxicity after administration.

Surfactants are commonly used to enhance the solubility of poorly water-soluble drugs by incorporating the drug into surfactant micelles, whose outer surface is hydrophilic [82, 83]. However, surfactants may induce hypersensitivity and affect the transporter/metabolic enzyme activity.

Cyclodextrins (CDs) have a hydrophilic outer exterior and a hydrophobic inner cavity. Poorly water-soluble drug molecules are able to be loaded in the cavity of CDs and form dynamic inclusion guest-host complexes. Therefore, the solubility of the drug-CD complexes is higher than the drug alone
However, CDs-based formations are often non-stable, because the interactional force between drugs and CDs is usually weak.

Particle size reduction is widely used for increasing the solubility and dissolution rate of drugs [86, 87]. Particle size reduction of drug yields higher surface area, which provides an equivalent increase in dissolution rate. Particle size reduction can also increase the solubility of compounds according to the Ostwald-Freundlich equation [88]. However, the need for high shear to reduce particles requires the use of specialized equipment, which increases the cost when applied in industry.

Solid dispersions can enhance dissolution rate and solubility for poorly water-soluble drugs via several mechanisms, including a reduction in effective particle size, enhanced solubilization, improved wetting and changes in crystal structure of the drug [89, 90]. Solid dispersions can be prepared with glass, silica, polymers and so on. However, the stability of solid dispersions, especially for polymer based solid dispersions, is difficult to predict a priori.

3.3.1.1 Amorphous drugs

Unlike crystals, the arrangement of molecules in the amorphous state is irregular, i.e., amorphous solids have no crystal lattice barrier. Therefore, the energy states of amorphous solids are higher than those in the crystal forms. Amorphous solids usually show very different properties from those in the crystal form, especially exhibiting higher apparent solubility and faster dissolution rate compared to the bulk crystalline form. Because their chemical structures and components of molecules are same, dissolved amorphous drugs and dissolved crystal drugs have the same clinical effects.

Drugs in the amorphous state have been obtained in salt formations [91], surfactants [92], cyclodextrins [93] and solid dispersions [94]. However, because the amorphous state is metastable, a drug component in the amorphous state is spontaneously able to recrystallize. Thus these formulations cannot stabilize drug molecules in the amorphous state over a long period of time, and add to some other disadvantages for these formulations as described above.

A number of strategies for stabilizing drugs in the amorphous state and subsequently improving the aqueous solubility and dissolution rate of poorly water-soluble drugs have emerged in recent years. One successful approach is to utilize the high surface-to-volume ratio structures of carrier materials, which can also be regarded as one type of solid dispersions, to adsorb or load drugs and thereby suppress the recrystallization of drugs because of strong interactions between the drugs and carriers (nanoparticles) [95] or because of geometric space constraints (mesoporous materials) [96, 97]. Fig. 3 illustrates schematically the means by which nanoparticles and mesoporous materials stabilize drugs in the amorphous state.
Mesoporous structures can be used for various drugs but the pore volume or size may restrict the amount or size of drug molecules that can be loaded into the pores, whereas nanoparticles can stabilize drugs with different sizes and at the same time stabilize high amounts of drug in the amorphous state.

In this thesis, AMN was used to stabilize ibuprofen, IBU, in the amorphous state. The dissolution rate of IBU from IBU@AMN composites and stabilization of formulations were investigated (Paper II).

3.3.1.2 Supersaturating drug delivery systems (SDDSs)

A high drug concentration in intestine provides for the possibility that more drugs can be absorbed into the bloodstream. Therefore, maintaining a high drug concentration is very important for increasing the bioavailability of poorly water-soluble drugs. As described in section 3.3.1, an poorly water soluble substance in the amorphous state can be rapidly dissolved in aqueous media, creating a ‘spring effect’ that can result in a supersaturated solution when a large amount of substance is used. However, supersaturation is thermodynamically unstable. Once the system starts to equilibrate, substances will aggregate and begin to precipitate, lowering the concentration of drug towards the equilibrium solubility level. In order to take advantage of the high intraluminal drug concentration, the supersaturation state should be stabilized for a time period. Therefore, a ‘parachute’ can be added to form a supersaturating drug delivery system (SDDS) to hinder the precipitation and stabilize this supersaturation of the drug [91]. Schematic profiles of drug concentration as a function time for different release profiles are shown in Fig.4.
Figure 4. Schematic drug concentration vs time profiles for the spring and parachute approaches of supersaturating drug delivery systems. Profile 1: dissolution of a crystalline drug. Profile 2: dissolution of a ‘spring’ form of an amorphous drug. Profile 3: dissolution of a ‘spring’ form of an amorphous drug in presence of ‘parachute’ form of precipitation inhibitors. $C_{eq}$ represents the equilibrium solubility.

Commonly used precipitation inhibitors include surfactants [98], CDs [99] and polymers [100, 101]. The mechanisms involved in achieving precipitation inhibition are different for these inhibitors. Surfactants at concentrations exceeding their critical micelle concentration (CMC) can increase the solubility of drugs, thereby decreasing the degree of supersaturation and reducing the rate of nucleation and crystal growth [102]. CDs or CD aggregation have solubilization effects similar to surfactants due to their cavities [103]. Polymers may interact with dissolved drug molecules to prevent nucleation and crystal growth [104]. Because of their convenient incorporation, high efficiency and excellent biocompatibility, polymers as precipitation inhibitors have been reported quiet often.

In this thesis, MMC in combination with the polymer HPMC were used as a SDDS to both induce and prolong the supersaturation of two model drugs, namely tolfenamic acid (TOL) and rimonabant (RIM), two poorly water-soluble drugs (Paper III).

3.3.2 Low-molecular-weight materials

The discovery and design of low-molecular-weight (LMW) based materials to mimic and replace polymer materials is a novel and rapidly expanding area of research. LMW materials can be derived from biocompatible components, making them environmental friendly. LMW based materials are synthesized by noncovalent forces (hydrogen bonds, van der Waals forces, $\pi-\pi$ stacking, dipole-dipole, charge-transfer and coordination interactions, and solvophobic effects), meaning that LMW based materials are easy to reuse. LMW molecules have a well-defined and stable chemical structure and self-assemble in a controlled manner [105]. Recently, many LMW molecules with molecular weight less than 2000 Da have been used to prepare LMW gels and have been applied in biomedicine, environmental applications, etc. [106, 107]. However, mechanical strengths of these LWM based
materials are usually very low and thus these materials do not have a high load bearing capability, and therefore are limited in achieving wider applications.

Utilizing adhesives to glue materials together has been applied in different situations for thousands of years. The discovery and development of adhesives are related to various sciences: surface chemistry, polymer chemistry and physics, materials sciences, mechanical engineering, etc. The formation of a bonded joint can be described by three stages. Initially, the adhesive must be a liquid (or fluid) so that it can spread on and wet the surface of adherends, where an intimate molecular contact occurs between the adhesive and the surface to be bonded. Secondly, the liquid (or fluid) adhesive must harden to support the loads. Most adhesives usually are initially in the monomer state and polymerize to form a polymer, except for pressure-sensitive adhesives. Pressure-sensitive adhesives do not harden, but remain permanently sticky. Finally, adhesives must have the durability to carry the load. Therefore, general adhesives are traditionally made of natural or synthetic polymers. [108]. However, polymeric adhesives are often environmentally unfriendly. For example, one of the most common building adhesives are formaldehyde based resins which can release the ‘known to be human carcinogen’ compound, formaldehyde [109]. Polymeric adhesives are often irreversible and cannot be reused, because once the polymerization completes, the structure of the polymer will be very stable and result in a solid joint [110]. Due to the polydispersity of polymers, it is very difficult to generally describe the molecular structure of polymeric adhesives [111].

Incorporating inorganic nanoparticles in polymer matrixes or networks can significantly increase the mechanical strength of the resulting composite material. In general, the presence of nanoparticles in polymer matrixes or networks can be used to either cross-link polymer chains or polymeric structures, or to adsorb or attach to polymer chains (Fig. 5) [112].

![Nanoparticle and Polymer](image)

*Figure 5. Schematic of the polymer/nanoparticle composite. There are interactions between polymers and nanoparticles.*
In this thesis, a novel adhesive that integrates the features of LMW organic molecules and inorganic nanoparticles was synthesized. An ethanol solution of AMN and IBU was used to form an AMN-IBU hybrid adhesive (Paper IV).

3.3.3 UV-shielding materials

Ultraviolet (UV) light is a type of high energy electromagnetic radiation with a wavelength from 100 nm to 400 nm. On one hand, the high energy of this light has been exploited for applications in label tracking, optical sensors, medical imaging, light therapy and so on. On the other hand, the high energy of UV light can lead to harmful effects for human health and the environment [113, 114]. For example, people exposed to a strong UV environment for a long time run an increased risk for cancer. Transparent materials with UV-shielding can be used to reduce such risks, and are used in applications such as contact lenses, UV-protecting glass or coatings for furniture or vehicles. In these cases, physical flexibility of these materials is very important as well.

To meet the requirements of transparent, flexible materials with UV-shielding properties, nanoparticles have been incorporated as UV filters into transparent polymer matrixes, as shown in Fig. 6. The UV-shielding property of these composite materials depends on the transition of electrons from the valence band to the conduction band of such nanofillers upon adsorption of incident photons when the photon energy is higher than the band gap energy. On the other hand, the visible light transmittance depends on the transparency of the polymer matrix and the interface between the inorganic nanoparticles and matrix. Various inorganic nanoscale nanoparticles, including titanium dioxide, zinc oxide, calcium carbonate, etc. have been reported to be UV filters. Common polymer matrixes include poly(methyl methacrylate) (PMMA), polycarbonate (PC) and polystyrene (PS), whose visible light transmittances rival that of transparent glass [115-117]. In situ synthesis of nanoparticles can result in homogeneous nanocomposites but requires rigid control of both the synthesis process of nanofillers and polymerization of the matrix under the same reaction conditions, which limits the wide application of this fabrication technique [118]. Ex situ methods of incorporating nanoparticles are suitable for choosing a wide combination of inorganic nanofillers and polymer matrixes, but frequently cause inhomogeneous materials due to nanoparticle aggregation [5]. Recently, a simple casting route of nanocomposite fabrication has been developed to obtain the desired product via casting a homogenous solution consisting of surfactant-modified nanofillers and a polymer.
Incorporating nanoparticles into polymer matrixes may also result in additional advantages. Common transparent polymers will normally degrade under a high energy light environment (e.g., UV-B or UV-C irradiation) or high temperature, but incorporation of nanoparticles can actually increase resistance to UV degradation and thermostability due to effects such as the limiting of motion of polymer chains due to the strong interactions between nanoparticles and the polymer [119-122]. In addition, some nanoparticles that have water sorption properties, such as calcium carbonate nanoparticles, can increase the moisture absorption and retention ability of the composite materials, which is important for industrial electronics applications [123].

In this thesis, a novel transparent and UV-shielding film based on AMN and PMMA was synthesized using a simple and inexpensive casting method. Stearic acid was used as a surfactant to modify the AMN and aid in the dispersion of the nanoparticles in the polymer matrix. The stability and moisture absorbing abilities of composite films were also characterized (Paper V).
4. Methodology

4.1 Materials preparation

4.1.1 AMN Synthesis

The AMN were synthesized through a modified route previously used for amorphous mesoporous magnesium carbonate (MMC). In the synthesis, MgO (Sigma-Aldrich) was dispersed in methanol at a 1:15 (g:mL) ratio in a glass bottle and placed under 4 bar CO₂ (Air Liquide) pressure with stirring for 4 days at room temperature. The pressure was then released and 5 mL of product from the reaction was added dropwise to 250 mL ethyl acetate (Sigma-Aldrich) under stirring.

The product was divided in four groups (Paper I): Samples designated AMN-25 and AMN-50 were directly dried at 25 °C and 50 °C, respectively, while samples designated AMN-25C and AMN-50C were first centrifuged at 4696 g for 10 min to collect solids, which were then dried at 25 °C and 50 °C, respectively. After drying, all samples were calcined at 250 °C with a temperature ramp rate of 1 °C/min and a hold time of 30 min. After that, the obtained materials were ground using a mortar.

AMN-25 was used in Paper II, IV and V, and designated as AMN.

4.1.2 Amorphous APIs stabilized using AMN or MMC

A solvent evaporation method was used to adsorb drugs onto the surface of AMN or into the pores of MMC.

IBU was dissolved in anhydrous ethanol (Sigma-Aldrich) and then a specific amount of AMN was added to the solution to achieve samples with 0.8, 1.5, 3 and 5 IBU/AMN mass ratios. The mixtures were stirred for 24 h at 25 °C and then heated at 50 °C to obtain the dried samples, designated as IBU@AMN-X with X representing the IBU/AMN mass ratio (Paper II).

TOL and RIM were dissolved in ethanol, respectively. Then two separate batches of MMC (Disruptive Materials AB, Paper III) were added to the solutions, respectively. The mixtures were placed on an orbital shaker at 500 rpm for 72 h at 25 °C and finally heated at 80 °C to obtain the dried samples, designated as MMC-TOL and MMC-RIM, respectively.

The bioavailability of the three APIs used in this thesis is limited by their low dissolution rate and/or solubility (Table 2).
Table 2. Melting points and molecular structures of studied drugs.

<table>
<thead>
<tr>
<th>API</th>
<th>Abbreviation</th>
<th>Related paper</th>
<th>Melting point (°C)</th>
<th>Molecular structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>IBU</td>
<td>II</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Tolfenamic acid</td>
<td>TOL</td>
<td>III</td>
<td>213.5</td>
<td></td>
</tr>
<tr>
<td>Rimonabant</td>
<td>RIM</td>
<td>III</td>
<td>97.2</td>
<td></td>
</tr>
</tbody>
</table>

4.1.3 Adhesive preparation (Paper IV)

A simple solvent method was used to prepare the adhesive. Generally, equivalent volumes of an ethanol solution of 10 mg/mL IBU and a 1 mg/mL suspension of AMN were mixed and vigorous stirred. After the mixture became transparent, ethanol was evaporated at room temperature until the materials could be molded stretched. The mixture was then heated at 50 °C to remove free ethanol and obtain the adhesive.

To obtain adhesives containing different ratios of AMN to IBU, the concentration of IBU in ethanol was adjusted. All other procedures were the same as with the adhesive described above.

4.1.4 PMMA-AMN composite films preparation (Paper V)

A casting method was used to prepare nanocomposite films. Fifty milligrams AMN were dispersed in a solution of 15 mL acetone and 25 mg stearic acid, and the suspension was sonicated for 30 min to obtain suspension A. One gram of PMMA (Sigma-Aldrich, Sweden) was dissolved in 20 mL of acetone, and the solution was stirred for 30 min to obtain solution B. A specific amount of suspension A was added dropwise into solution B to achieve an AMN concentration corresponding to 1, 2 or 4% of the total mass of PMMA,
AMN and stearic acid. The resulting suspension was stirred 2 h to ensure a homogenous dispersion of nanoparticles and then cast into a petri dish. The acetone was allowed to evaporate at room temperature to obtain a 260 µm thick AMN-PMMA composite film. A neat PMMA (i.e., 0 wt.% AMN) film was also prepared without the addition of suspension A.

4.2 Materials characterization

4.2.1 Scanning electron microscopy (SEM)

SEM produces images of samples by scanning the material surface with a focused beam of electrons. The interaction between electrons and atoms in the surface of the sample can produce different signals such as backscattered electrons, secondary electrons and X-rays, which can be collected to analyze information about the topography and composition of sample surface. The secondary electrons are produced during inelastic scattering of the beam after knock out of k-shell electrons from sample atoms. Because the secondary electrons have relatively low energies, only ones generated close to the surface can escape and be received by detector, resulting in the ability of secondary electrons to image the surface morphology of samples. In addition, the in-lens detector can only receive secondary electrons in the lens, which eliminates the impact of other electrons, resulting in a higher resolution of the surface morphology.

The SEM images in Papers I and III were carried out using a Leo 1550 FEG SEM (Zeiss, Germany) operating at an acceleration voltage of 2 - 3 kV. The SEM images in Papers II, IV and V were carried out using a Merlin SEM (Zeiss, Germany) operating at a voltage of 2 kV. All samples were sputtered with a thin Au/Pd coating prior to imaging to reduce charging effects and then imaged using the in-lens detector.

4.2.2 X-ray diffraction (XRD)

When the spacing of planes in a crystal lattice of a crystalline substance is similar to the wavelengths of incident X-rays, the substance can act as a diffraction grating for the X-rays. In XRD, constructive interference between X-rays diffracted from different parallel planes will generate a signal. The diffraction follows Bragg’s law (nλ = 2d sinθ), where λ is wavelength of the X-rays, d is the distance between different parallel planes and θ is the incident angle of the X-rays. Therefore, XRD is used for determining the atomic and molecular structure of a crystal. Patterns of crystalline phases are recorded as strong signals (counts) in XRD instrument, while patterns of amorphous phases are recorded as no signal (materials with disorder in short range and long range) or weak signals. With an increase in atomic or molec-
ular order corresponding to a transformation from the amorphous state to the crystalline state, XRD signals will become stronger.

All samples in this thesis were measured using a D8 TwinTwin instrument (Bruker AXS GmbH, Germany) with Cu-Kα radiation (40 kV, 40 mA) and carried out a zero background. Measurements were made in the 2θ range from 15° to 70° (Paper I), 10° to 80° (Papers II and V) or 5° to 80° (Papers III and IV) at a rate of 0.02°/s.

4.2.3 Gas adsorption analysis

Structural information of a high surface-to-volume ratio material, including specific surface area, pore volume and pore-size distribution, can be obtained by the amount of adsorbed gas (e.g., N₂) onto this material at various relative pressures at a fixed temperature. The theory is as follows: At the liquid nitrogen temperature (77 K), the amount of adsorbed nitrogen on the surface of an adsorbate depends on the relative pressure \( P/P_0 \), where \( P \) is the partial pressure of nitrogen and \( P_0 \) is the saturated vapor pressure of nitrogen. The BET surface area is calculated from the amount of adsorbed nitrogen which forms a monolayer on the adsorbate; this is typically achieved when the \( P/P_0 \) is between 0.05 and 0.30 [124]. The total pore volume was calculated from the single point adsorption at \( P/P_0 \approx 1 \) using the Dubinin-Asthakov equation [125]. The isotherm is used to assess the pore size distribution of the adsorbate according to the density function theory (DFT) model in this thesis [126]. In the DFT model, it is assumed that the nitrogen condenses in the pores and the pore volume is the nitrogen volume, converted to a liquid volume. It also assumes that the experimental isotherm consists of many individual ‘single pore isotherms’ multiplied by their relative distribution. Therefore, a mathematical fit is made of the theoretical isotherms to the experimental isotherms to obtain the pore size distribution.

Nitrogen sorption in this thesis was carried out using an ASAP 2020 instrument (Micromeritics, USA). Prior to analysis, samples were degased in vacuum at 70 °C (Papers I and II) or 90 °C (Paper III) for 12 h, respectively. All analyses were operated at 77 K. The specific surface area was obtained according to the Brunauer-Emmett-Teller method in the relative pressure range of 0.05 – 0.30 of the adsorption isotherm. The pore-size distribution was obtained using the DFT methodology and the model for nitrogen sorption at 77K.

Water vapour sorption (Paper I) was conducted by the same equipment and pre-treatment as described above. The affinity coefficient for water vapour was set to 0.2 in the Dubinin-Asthakov equation, which was proven to be an appropriate value for the analysis of water sorption [127].
4.2.4 Thermogravimetric analysis (TGA)

TGA is a thermal analysis method used to examine the mass change of a sample as a function of temperature in the scanning mode or as a function of time in the isothermal mode. Therefore, changes in the mass of a sample due to desorption, absorption, sublimation, vaporization, oxidation, reduction and decomposition are recorded while the sample is set to a program of change in temperature. In this thesis, TGA traces were used to determine the amount of MgCO$_3$ (Paper I), APIs (Papers II and III) and ethanol (Paper IV) in these composites and the degradation behavior of films (Paper V). In this thesis, the amount of each compound is calculated based on the assumption that only MgO remains at the highest temperature during the TGA runs. Thus the mass percent of MgCO$_3$ before decomposition can be obtained from the TGA trace of the pure AMN or MMC trace. Then, the amount of AMN or MMC in composites can be calculated. Finally, the amount of APIs can be obtained.

A TGA/DSC 3+ (Papers I, II, IV and V) or TGA/SDTA 851e instrument (Paper III) (Mettler Toledo, USA) was used. Samples were placed into an alumina crucible under air flow (40 – 60 mL/min) and heated from 25 °C to 600 °C at a rate of 3 °C/min.

4.2.5 Transmission electron microscopy (TEM)

TEM is a microscopy technique in which a beam of high energy electrons is transmitted through a thin specimen to form an image. TEM has two imaging methods via contrast formation and diffraction, respectively. The contrast between different areas in a TEM image can be imaged due to different electron densities, which is caused by the scattering of the electron beam by the sample, the amplitude and phase change of the electron wave. The diffraction contrast can be imaged due to Bragg scattering of the electron beam through a crystalline sample. In this situation, disperse electrons go into discrete locations in the back focal plane. The diffraction pattern of a sample can be obtained via Fast Fourier transform (FFT) due to the correlation of images and molecular structures.

A Tecnai F30 microscope (FEI Co. USA) was used to carry out the TEM characterization. The TEM was operated at 300 kV with the high resolution mode. FFT images were obtained using the TEM instrument software.

4.2.6 Infrared (IR) spectroscopy

Mid-infrared light (4000 - 200 cm$^{-1}$) has suitable energy to excite vibrations or rotations of molecules and groups. Therefore, the wavelengths of IR absorption bands are characteristic of specific types of chemical bonds. IR spectroscopy therefore is used to identify these groups and thus to analyze
the structure of compounds. All frequencies in the spectrum can be collected simultaneously in an FTIR spectrometer, making it a quick analysis technique.

In this thesis, an IFS 66v/S spectrometer (Bruker, USA) was used to obtain IR spectroscopy. The resolution was 4 cm\(^{-1}\) and the spectrum was collected from 4000 to 400 cm\(^{-1}\). A blank scan was recorded for background removal.

4.2.7 Ultraviolet-Visible (UV-Vis) spectroscopy
The energy of ultraviolet or visible light can excite \(\pi\)-electrons or non-bonding electrons (\(n\)-electrons) of molecules to higher anti-bonding molecular orbitals. Therefore, light with a suitable wavelength can be absorbed by molecules when their electrons are easily excited.

In this thesis, UV-Vis transmittance spectrums of APIs (Paper II and III), AMN samples and films for degradation studies (Paper V) were measured by a UV-1800 UV/Vis spectrophotometer (Shimadzu, Japan). UV-Vis transmittance spectrums of films for UV-Vis transmittance studies (Paper V) were measured by a Lambda 900 spectrophotometer (Perkin-Elmer, USA). Each measurement was carried out from 800 to 200 nm.

4.2.8 Dynamic light scattering (DLS)
DLS measures the intensity of laser light which is scattered by molecules or particles in solution or suspension. Since the scattering behavior is related to the hydrodynamic radius and Brownian motion, particles with different size and aggregation status can be characterized by DLS.

In this thesis (Paper II), DLS was performed with a ZetaSizer NanoZS instrument (Malvern, UK). Samples were dispersed in ethanol and the measurements were carried out at room temperature.

4.2.9 Biocompatibility testing
Materials with good biocompatibility can be used in biomedical applications since they will not induce unwanted immune reactions. Therefore, biocompatibility testing of novel materials is necessary if they are intended for biomedical applications. The cell viability assay is an easy and effect means of evaluating a material’s biocompatibility. In a cell viability test, the viability of cells cultured in a medium containing the material to be tested (often at different concentrations) is compared to cells cultured with a benign or known biocompatible material (negative control) and cells cultured with a known toxic material or substance, \(e.g.,\) DMSO (positive control). Human dermal fibroblasts (HDF) are commonly used cells, because the skin is the body’s first line of defense in many regards.
An alamarBlue cell viability assay was performed to study the biocompatibility of AMN (Paper II). Human dermal fibroblasts were seeded into 96-well plates (20,000 cells/cm²) using Dulbecco’s Modified Eagle medium. Medium without AMN was used as the negative control, while 5% (v/v) dimethylsulfoxide (DMSO, Sigma-Aldrich) in medium was used as the positive control. Fluorescence intensities were measured using a spectrofluorometer (Tecan infinite M200 plate reader, Switzerland).

4.2.10 Drug-release study
Most oral drugs are absorbed in the intestine, so using in vitro experiments that mimic the intestinal environment, including temperature, pH and movement of liquid, is necessary in drug development to evaluate the dissolution of drugs.

IBU release from IBU@AMN samples was measured in a small-volume solubility and dissolution apparatus µDiss Profiler (pION Inc. USA). Experiments were conducted at 37 °C, using in situ probe heads with a stirring speed of 400 rpm. Samples at a total drug concentration of 35 mg/mL were placed in a buffer at pH 6.8 (Paper II).

APIs release from the crystalline API alone and MMC samples (Paper III) was measured in a AT7 Smart USP-2 dissolution bath (Sotax AG, Switzerland) using 500 mL of buffer medium (pH 6.8) containing sodium dodecyl sulfate (SDS, Sigma-Aldrich) for TOL and fasted-state simulated intestinal fluid (FaSSIF, Biorelevant.com, UK) for RIM. The release studies were carried out at 37 °C with a stirring rate of 100 rpm. One milliliter sample aliquots were collected at predetermined time intervals, filtered and measured in UV-1800 UV/Vis spectrophotometer.

4.2.11 Rheological characterization
Rheology is the study about the flow of liquids, soft solids, gels, pastes and even solid materials. When external shear forces are applied to these materials, the viscosity and flow speed of these materials will change. These changes are related to their shear modulus and molecular weights. Therefore, rheological characterization can help elucidate the structure of materials.

In this thesis (Paper IV), an AR2000 Advanced Rheometer (TA instrument, USA) was utilized for rheological characterization. At room temperature, experiments were performed at a fixed force (0.03 N) and a fixed strain (1%) as a function of frequency in the frequency interval between 0.1 and 10 Hz.
4.2.12 Shear strength test

One of the most common causes of damages to adhesive joints is due to shear force. Therefore, shear strength testing is usually used to evaluate the capabilities of adhesives.

In this thesis (Paper IV), lap-shear tests using glued PET sheets were performed with an AGS-X universal testing machine (Shimadzu, Japan). According to the ASTM D3163-01 standard (2014), each PET sheet was tailored to 101.6 mm * 25.4 mm * 2.4 mm, the overlap area for adhesive application on each PET lap joint was 12.7 mm * 25.4 mm * 2.4 mm, and the crosshead speed was 1.3 mm/min. Tests were carried out after setting times of 1 to 8 days and five lap joints were used for each experiment. Following the shear test of joints set for 8 days, the lap joints were rejoined immediately without any additional application of adhesive. The test was repeated 4 times to assess reusability.

Papers (Niceday, Sweden) used for lap-shear tests were tailored to 76 mm * 10 mm, the overlap area for adhesive application on each lap joint was 10 mm * 10 mm, and the crosshead speed was 50 mm/min. Experiments were performed after setting times of 30 min and 1 day. Following the shear test of joints set for 1 day, the lap joints were rejoined immediately without any additional application of adhesive. The test was repeated 4 times to assess reusability. Lap joints formed from commercial sticky paper (Niceday, Sweden) with same parameters as above were tested after 30 min setting time.

4.2.13 Moisture adsorption and desorption of films

Transparent materials, such as the screens of smartphones and TVs, are continuously exposed to the outside environment. One possible limitation to their utilization is their susceptibility to moisture damage. Therefore, before new materials can be implemented for such purposes it is important to test their performance in different moisture environments. The ability of transparent films to absorb and desorb or retain moisture can be of particular interest for applications in flexible transparent displays.

In this thesis (Paper V), each film was weighed before being stored in a desiccator at 25 °C and 75% relative humidity (RH). After 24h the films were weighed again to check for moisture adsorption and then placed in another desiccator at 75 °C and 75% RH. After 24h the films were weighed again to determine the amount of moisture desorbed. AMN-PMMA films at each concentration of AMN were tested in triplicate.

4.2.14 Ultraviolet light degradation analysis

UV radiation has relatively high energy, which can cause the degradation of polymer materials because the polymer chains can be disrupted by absorp-
tion of the high energy UV photons. Therefore, the evaluation of a material’s UV stability is useful for determining the longevity of materials exposed to UV light.

In this thesis (Paper V), after the moisture adsorption and desorption study (section 4.2.13), the nanocomposite films were dried in vacuum for 24 h and then irradiated with a UV-C lamp (Philips TUV PL-S 11W/2P, wavelength of 254 nm, intensity = 5 mW/cm²) for 1, 3 and 6 h. Transmittance spectra of the films were recorded with a UV-Vis spectrophotometer (UV-1800, Shimadzu) before and after each exposure interval (section 4.2.7).
5. Results and Discussion

5.1 Characterization of AMN

The synthesis route (described in Section 4.1.1) of mixing MgO and methanol under 4 bar CO₂ pressure followed by dispersing the product dropwise in ethyl acetate produced the AMN (Papers I, II, IV and V). AMN are composed of amorphous magnesium carbonate and small amount unreacted MgO, as evidenced by IR spectra and powder XRD (Fig. 8). The absorbance bands at ~1440 cm⁻¹, ~1100 cm⁻¹ and ~850 cm⁻¹ in the IR spectra correspond to carbonate groups while the halo peaks between 25° and 40° in the XRD pattern indicate the existence of an amorphous phase. The small, sharp peaks at approximately 29° and 42° are attributed to residual crystalline MgO (Papers I, II, IV and V).

![Figure 7. (a) IR spectra of the AMN. The \( \text{CO}_3^{2-} \) absorbance peaks are indicated at 850, 1100 and 1440 cm⁻¹. (b) XRD pattern of the AMN. The halo peak between 25° and 40° shows the existence of an amorphous phase. Unreacted MgO is evidenced by the small peaks at approximately 29° and 42°.](image)

Despite variations in synthesis parameters (see Section 4.1.1), all AMN are white powders and composed of aggregated nanoparticles (Papers I, II, IV and V). Detailed SEM and TEM images of typical AMN-25 samples are shown in Fig. 8.
Voids can form between these aggregated nanoparticles, resulting in an overall mesoporous structure when characterized by gas sorption analysis. The N$_2$ sorption isotherms of different AMN samples are shown in Fig. 9. Although no obvious morphological difference existed between these samples, the specific surface area (SSA) and pore structure of the AMN are shown to depend on both drying temperature and the centrifugation process (Paper I).

Data detailing the SSA and pore structure of the AMN sample are presented in Table 3 and Fig. 10. The BET equation was employed to calculate the SSA of these samples, which ranges from 188 to 410 m$^2$/g. Narrow pore size distributions were found for all AMN samples as shown in Fig. 10a. Both the pore volume and pore size of the centrifuged AMN samples were lower than those of the AMN materials dried at the same temperature without centrifugation, which supports the interpretation that the pores in the samples arise
from the voids between aggregates of nanoparticles, which become compressed during the centrifugation process. On the other hand, a lower drying temperature resulted in both larger pores and a greater pore volume than drying at high temperature, but also resulted in a lower SSA, which may be due to the speed of solvent evaporation, as well as the release rate of bound CO₂. It is noteworthy that AMN-25 had the highest pore volume of 1.72 cm³/g, which exceeds any alkali earth metal carbonate previously reported [20, 61, 67] (Paper I).

Table 3. Structural characteristics of AMN samples derived from N₂ sorption isotherms.

<table>
<thead>
<tr>
<th></th>
<th>AMN-25</th>
<th>AMN-50</th>
<th>AMN-25C</th>
<th>AMN-50C</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSAa (m²/g)</td>
<td>377.75</td>
<td>409.96</td>
<td>187.78</td>
<td>330.23</td>
</tr>
<tr>
<td>Total Pore Volumeb (cm³/g)</td>
<td>1.72</td>
<td>1.57</td>
<td>0.72</td>
<td>0.64</td>
</tr>
</tbody>
</table>

a BET surface area. b Single point desorption total pore volume. \( P_0/P = 1 \).

Figure 10. DFT-based pore size distribution for the 4 AMN samples.

As shown in Fig. 11, magnesium carbonate in each AMN sample decomposed at ~ 300 - 325 °C, which is lower than other types of amorphous mesoporous magnesium carbonate reported in previous studies [20, 22, 67, 70, 71]. The phenomenon can be attributed to the smaller particles of AMN, which correlates with previous studies for other types of nanoparticles [128]. It also can be found that the decomposition temperature of these four AMN materials increased as follows: AMN-50 < AMN-25 < AMN-50C < AMN-25C, which is inversely correlated to the SSA, i.e. the higher the surface area of the material, the lower the decomposition temperature (see Table 3). Similar findings that a high surface area induces a lowering of the thermo stability have been shown in a previous report [129]. In addition, all four AMN samples contain approximately 12 - 15 wt% unreacted MgO, which is similar to the composition of amorphous magnesium carbonate materials synthesized in previous studies (i.e., MMC) [20]. Therefore, the additional step of using ethyl acetate as a dispersant for the formation of individual nanoparticles...
cles did not significantly affect the chemical composition of the resultant material (Paper I).

Figure 11. TGA traces of the four AMN samples.

The moisture sorption properties of the AMN samples were characterized as well. As shown in Fig. 12a, AMN-25C and AMN-50C, which underwent centrifugation prior to drying, can absorb up to 24 mmol/g of moisture, which is higher than MMC [20] and many commercially desiccants [130]. It is noteworthy that the AMN samples without centrifugation (and thus having a higher SSA) can only absorb up to 13 mmol/g, which is lower than the AMN samples with lower SSA. The lack of correlation between SSA and moisture absorbance indicates that water is absorbed into the materials rather than, or in addition to being, adsorbed on the surface or into the pores. Additionally, a large hysteresis in the moisture sorption isotherm can be found on desorption, indicating that AMN have a tendency to retain moisture. It is likely that chemisorption leads to hydrate formation in the material, which is supported by the XRD measurements of AMN-25C after water sorption (Fig. 12b) (Paper I).
Figure 12. (a) Moisture sorption isotherms at room temperature for the four AMN samples. (b) XRD pattern of AMN-25C after water sorption and degas process. The emergence of distinct, broad peaks are observed.

AMN-25 was chosen for all further studies in this thesis. Henceforth, AMN-25 will be referred to as simply AMN (Paper II, IV and V).

The in vitro cytotoxicity of AMN is shown in Fig. 13. Even with exposure to AMN concentrations up to 1000 µg/mL for an incubation time of 24 h, the viability of human dermal fibroblasts was not negatively affected. This indicates that AMN has very low toxicity.

Figure 13. Cell viability of human dermal fibroblasts cultured in AMN for 24 hours as a function of concentration of AMN. “neg” is the negative control group using growth media alone, while DMSO is used as the positive control (toxic group) (n = 6 for all groups).

UV-Vis transmittance properties of suspensions of AMN in ethanol with concentrations ranging from 100 to 1000 mg/L are shown in Fig. 14. It can be observed that transmission decreases with decreasing wavelength of light,
particularly in the UV wavelength region, and for all wavelengths the trans-
mission decreases with increasing concentration of AMN. The insert to Fig
14 shows that in the visible region, transmittance decreases markedly at con-
centrations above 600 mg/L. (Paper V).

![Figure 14. UV-Vis transmittance of suspensions of AMN in ethanol with different concentrations of AMN.](image)

5.2 Nanocomposite IBU@AMN (Paper II)

A solvent evaporation method was used to obtain a nanocomposite of IBU
and AMN (IBU@AMN) with different IBU:AMN mass ratios. These
IBU@AMN composites are denoted IBU@AMN-0.8, IBU@AMN-1.5,
IBU@AMN-3 and IBU@AMN-5, in which the numeric suffix indicates the
mass ratio of IBU to AMN.

5.2.1 Characterization of IBU@AMN

A TEM image of the IBU@AMN-0.8 sample is shown in Fig. 15. The dis-
persed nature of the nanoparticles can be observed, which is attributed to the
negative charge of the nanoparticles due to adsorbed IBU, resulting in a re-
pulsion force between nanoparticles.
The higher IBU concentration in the suspensions of AMN leads to more negatively charged AMN particles, which was measured by zeta potential measurements (Table 4). The zeta potential increased from +18.53 mV for AMN to +6.87 mV for the IBU@AMN-5 sample. This suggests that nanoparticles in solutions with high IBU concentrations will be easier to disperse.

Table 4. Surface charge of AMN before and after adsorbing IBU.

<table>
<thead>
<tr>
<th>Sample</th>
<th>AMN</th>
<th>IBU@AMN-0.8</th>
<th>IBU@AMN-1.5</th>
<th>IBU@AMN-3</th>
<th>IBU@AMN-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeta potential (mv)</td>
<td>18.53</td>
<td>12.33</td>
<td>11.95</td>
<td>10.12</td>
<td>6.87</td>
</tr>
</tbody>
</table>

FTIR characterization shows a clear shift of the peak from 1706 cm\(^{-1}\) (\(\nu\)COOH) in pure IBU to 1581 cm\(^{-1}\) (\(\nu\)COO\(^{-}\)) in IBU@AMN samples, as shown by arrow in Fig. 16. This phenomenon suggests an electrostatic interaction between the Mg\(^{2+}\) of AMN and COO\(^{-}\) of IBU [131]. Indeed, the peak of 1581 cm\(^{-1}\) (\(\nu\)COO\(^{-}\)) strengthens with the increasing IBU content. However, a small peak at 1706 cm\(^{-1}\) (\(\nu\)COOH) can be detected in the IBU@AMN-5 sample, which indicates that some IBU in the sample does not interact with the magnesium ions of the AMN.
Figure 16. FTIR transmittance spectra for IBU@AMN and IBU samples. The arrow shows the peaks shifted from 1706 cm\(^{-1}\) (\(\nu\)COOH) in pure IBU to 1581 cm\(^{-1}\) (\(\nu\)COO) in IBU@AMN samples.

TGA of IBU and IBU@AMN samples was used to elucidate the composition of the IBU@AMN nanocomposites (Fig. 17). IBU@AMN samples display two distinct regions of mass loss in the TGA traces. The first region occurs around 315 °C, which is the decomposition temperature of AMN (Section 5.1). Interestingly, samples with less IBU content have more mass loss in this region, which may be attributed to the decomposition of AMN in IBU@AMN that is not interacting with IBU. The second region of mass loss occurs around 480 °C and is likely due to the IBU that is electrostatically interacting with AMN. The drug content of these IBU@AMN samples can be calculated from the relative mass losses in the curves and are found to be 43%, 58%, 71% and 82% for IBU@AMN-0.8, -1.5, -3 and -5, respectively. The highest drug content realized in this study (5 grams of drug per gram of carrier) is 2.2 to 12 times greater than previously reported using inorganic carriers or metal-organic frameworks (MOFs) to load ibuprofen [132-136], and 15 times greater than achievable with loading in the mesoporous structure of amorphous magnesium carbonate [22].
Figure 17. Normalized mass thermogravimetric analysis traces for IBU and IBU@AMN samples.

XRD analysis proves that the nanocomposites have the ability to stabilize IBU in the amorphous state (Fig. 18). As detailed in the enlarged view, a wide halo peak between $10^\circ$ and $30^\circ$ in XRD patterns of IBU@AMN samples exists, corresponding to the region of the strongest characterized peaks of pure crystalline IBU. This phenomenon indicates that drugs in the IBU@AMN nanocomposites are ordered in the short range (chemical groups), but disordered in long range (molecular level) [137]. Even though the intensity of the halo peak increases with increasing IBU content, there are no sharp peaks, indicating that the IBU has the stronger tendency to re-crystallize when the IBU content is higher.

Figure 18. X-ray diffraction patterns for IBU and IBU@AMN nanocomposites. The enlarged view is the pattern for the IBU@AMN samples for $2\theta$ between $10^\circ$ and $30^\circ$. 
5.2.2 In vitro IBU release

The in vitro dissolution profiles of IBU from the IBU@AMN-0.8 and IBU@AMN-5 samples are displayed in Fig. 19. IBU releases are very fast in both the two nanocomposites, and the IBU release rate increases with IBU content. For example, 88% of IBU was released from IBU@AMN-0.8 in the first 6 min whereas IBU@AMN-5 only needed 30 s (i.e. 12 times shorter than IBU@AMN-0.8). All IBU in IBU@AMN-5 was released in 2 min, while only 65% of IBU was released from IBU@AMN-0.8 at this time point; IBU@AMN-0.8 took 11 min to release all drugs. The time to release 50% IBU from IBU@AMN-5 was 10 to 60 times faster than from the mesoporous magnesium carbonate [22, 71] and 83 times faster than from crystal-line IBU [22]. The difference in release rates between that from IBU@AMN nanocomposites and that from the mesoporous magnesium carbonate study can be partly attributed to different release paths. IBU released from the latter is diffusion limited and thus retards the release rate compared to release from the nanocomposite. The much higher release rate from IBU@AMN may also be partly due to an increased solubility of the deprotonated IBU in the pH 6.8 release media.

![Figure 19. IBU release from IBU@AMN-5 and IBU@AMN-0.8 in pH 6.8 phosphate buffer.](image)

5.3 API-loaded MMC (Paper III)

The solvent evaporation method was used to load TOL and RIM into the pores of MMC and obtain the loaded materials MMC-TOL and MMC-RIM.
5.3.1 Characterization of MMC loaded with TOL and RIM

The endothermic peaks in the DSC trace at 213.5 °C for TOL (Fig. 20a) and 97.2 °C for RIM (Fig. 20b) correspond to the melting points of TOL and RIM, respectively. After loading into MMC, no corresponding peak was found in the DSC traces for MMC-TOL and MMC-RIM, indicating that the incorporated TOL and RIM were not in the crystalline state. A similar conclusion can be drawn from the XRD patterns for the crystalline APIs, unloaded MMC and MMC-API samples (Fig. 21). The lack of crystalline API peaks in both MMC-TOL and MMC-RIM samples indicates that the API was fully loaded into the pores of MMC, and that crystallization of the API was suppressed.

![Figure 20. DSC curves for the APIs prior to loading, MMC prior to loading, and loaded MMC (panel a for TOL and panel b for RIM).](image)

![Figure 21. XRD patterns for the API prior to loading, MMC prior to loading and loaded MMC (panel a for TOL and panel b for RIM).](image)

Results of the nitrogen sorption analysis of MMC prior to loading and the API-loaded MMC samples are shown in Table 5 and Fig. 22. Table 5 shows that the pore volume in the MMC was decreased by 46% on loading TOL, and 22% on loading RIM. In other words, there were empty pores remaining after loading APIs in both two MMC, indicating that it was theoretically possible to add more API. However, not all of pores were necessarily availa-
ble for loading [22]. As shown in Fig. 22a, the pore distribution centered at approximately 5 nm decreased in volume without changing position of the peak location, indicating that some pores were completely filled while others were not accessible, rather than indicating that pores were partially filled, which would have been reflected in a shift to the left in peak location of the pore distribution. A pore volume reduction can also be observed in the MMC-RIM sample, but in addition there is a noticeable shift to the left in the location of the distribution’s peak, indicating a small overall decrease in pore size of the remaining pores.

Table 5. SSA and pore volume of MMC prior to loading and API-loaded MMC samples.

<table>
<thead>
<tr>
<th></th>
<th>MMC prior to loading TOL</th>
<th>MMC-TOL</th>
<th>MMC prior to loading RIM</th>
<th>MMC-RIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA (m²/g)</td>
<td>252.9 ± 1.6</td>
<td>168.0 ± 0.6</td>
<td>180.5 ± 1.6</td>
<td>150.7 ± 0.8</td>
</tr>
<tr>
<td>Pore volume (cm³/g)</td>
<td>0.35</td>
<td>0.19</td>
<td>0.23</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Figure 22. Pore-size distributions (circles, left ordinate axis) and cumulative pore volume (squares, right ordinate axis) for the unloaded MMC and API-loaded MMC (panel a for TOL and panel b for RIM).

The TGA traces of samples are shown in Fig. 23. In the API-loaded samples, there was no discernable mass loss at the temperature of evaporation of the corresponding crystalline API. Instead, the mass loss occurred at a higher temperature, which was coincident with the decomposition of the carrier MMC. This increase in the evaporation temperature of the loaded API may be explained by the Kelvin equation, which describes the phenomenon that a higher temperature is needed to evaporate compounds in nanometer-sized pores. Similar phenomena have been reported previously [22, 138, 139]. By analyzing the mass losses in the TGA traces of the loaded samples compared to the traces of the unloaded MMC, the amount of loaded API can be calculated and was found to be 8.5% and 7.6% for the MMC-TOL and MMC-RIM samples, respectively.
5.3.2 In vitro release of APIs from MMC

The in vitro release profiles for the crystalline APIs, API-loaded MMC, and API-loaded MMC combined with different HPMC concentrations are presented in Fig. 24. As shown in Fig. 24a, TOL dissolved faster from MMC-TOL than crystalline TOL. At the 10 min point, the concentration of TOL from MMC-TOL was 7 times higher than that from the crystalline TOL. These initial values of TOL concentration from MMC-TOL and from MMC-TOL with different concentrations of HPMC were above the equilibrium solubility of crystalline TOL, indicating that supersaturation was achieved. The equilibrium solubility of crystalline TOL was measured to be 39 µg/mL in this buffer after 48 h. The highest concentration of TOL from MMC-TOL samples was achieved after 20 min release, followed by a rapid decrease to the equilibrium solubility of TOL within 40 min, indicating recrystallization of the dissolved TOL in the supersaturation state. The supersaturated state could be prolonged by the addition of HPMC, and this effect increased with an increase in HPMC concentration. In this case, supersaturation was maintained for the entire 240 min of the release study. This effect may be due to hydrogen bonds formed between HPMC and TOL [91, 98], which reduces the crystallization rate rather than totally inhibiting recrystallization [140].

Similar release results for RIM were found as shown in Fig. 24b. The initial dissolution of RIM from MMC-RIM was faster than the dissolution of crystalline RIM. The concentration of dissolved RIM from MMC-RIM was 12 times greater than that from crystalline RIM 5 min after start of release. Supersaturation was achieved and lasted approximately 40 min (the equilibrium solubility of crystalline TIM was measured to be 17 µg/mL in this release media). In the case of RIM combined with HPMC, a HPMC concentration of 0.001% and 0.005% extended the supersaturation for approximately 50 and 140 min, respectively.
Figure 24. API dissolution profiles for crystalline APIs, API-loaded MMC, and API-loaded MMC mixed with 0.001% and 0.005% HPMC. (panel a for TOL and panel b for RIM) (data are given as mean of 3 values with error bars representing standard deviation)

5.4 AMN-IBU adhesive (Paper IV)
The adhesives were prepared from the mixture of AMN, IBU and ethanol via an evaporation method.

5.4.1 Characterization of the AMN-IBU adhesive
In the first step of the synthesis process, a suspension of AMN in ethanol was slowly added to a solution of IBU in ethanol under vigorous stirring until the mixture became transparent (Fig. 25a to b). In the second step, the adhesive was formed through solvent evaporation without stirring (Fig. 25b to c). The ratio of AMN to IBU is important for the adhesive synthesis; a too low (≤ 1:20) or too high (≥ 1:5) ratio results in a powder. This mass-ratio dependency is likely caused by the number of Mg$^{2+}$ linkers inhibiting self-assembly of IBU when AMN content is too high, and also by the recrystallization of IBU occurring when AMN content is too low. Mechanical forces are important in the formation of supramolecular structures [141]. In the present work, stirring in the first step disperses AMN and prevents the nanoparticles from coagulating, while the lack of stirring in the second step helps to maintain a supramolecular structure. The molecular size is also crucial for adhesive formation, as it is in a typical polymer adhesive [142]. $p$-Toluic acid and benzoic acid, which have a smaller molecular size than IBU, were found to be unable to form an adhesive with AMN under similar conditions, even though they have similar structures and functional groups.
The AMN-IBU adhesive dissolves slowly in ethanol and maintains its adhesive ability for ~ 30 min, but completely dissolves after ~ 12 h. It fully recovers to an adhesive after ethanol evaporation (Fig. 26). However, the adhesive also dissolves in water, but cannot recover after water evaporation due to the recrystallization of IBU.

The adhesive can easily form a transparent film by spreading the material (Fig. 27a). The letter ‘J’ on the paper underneath the adhesive film can be clearly read. When two pieces of the adhesive are placed in contact, they rapidly display a self-healing property (Fig. 27b). The adhesive is soft but tough, so it can be formed into different shapes (Fig. 27c). Similar to pliable plastics, the adhesive can be stretched into very long fibers without any elastic recovery (Fig. 27d).
Figure 27. Functional features of the AMN-IBU adhesive.

As shown in Fig. 28a, the lyophilized AMN-IBU adhesive shows a non-porous film structure in the SEM image. Small AMN can be discerned in the TEM image of the dry adhesive (Fig. 28b).

Figure 28. Morphology of the AMN-IBU adhesive characterized by SEM (a) and TEM (b).

The amorphous states of MgCO$_3$ and IBU in the adhesive are verified by the XRD and DSC (Fig. 29). These results indicate that recrystallization of IBU molecules was inhibited.
The FTIR spectra (Fig. 30) confirm the coulomb interaction between the COO\(^-\) of IBU molecules and the Mg\(^{2+}\) of AMN, which stabilizes the IBU molecules in the amorphous state. The peaks at 1628 cm\(^{-1}\) and 1419 cm\(^{-1}\) in the AMN-IBU adhesive correspond to the \(\nu(\text{COO}^-)\). The peak at 1709 cm\(^{-1}\) corresponds to the \(\nu(\text{COOH})\) [131]. Hydrogen bonding between IBU molecules can be detected by the peaks at 2725 cm\(^{-1}\) and 2628 cm\(^{-1}\).

The shear modulus of the AMN-IBU adhesive varies with the angular frequency (Fig. 31). The dynamic loss modulus (\(G''\)) is significantly higher than storage modulus (\(G'\)), meaning that the adhesive is flexible and plastic. This property provides the adhesive with good tack ability allowing it to bond a variety of substrates. The high values of \(G' (> 10^9 \text{ Pa})\) at frequencies above 2 Hz and \(G'' (> 10^5 \text{ Pa})\) at frequencies above 4 Hz are most likely due to the incorporation of a large amount of inorganic nanoparticles [131, 143, 144].
5.4.2 Glueing ability of the AMN-IBU adhesive

The AMN-IBU adhesive can be used to glue different types of materials, such as metals (stainless steel), glass (microscope slide), and plastic (Teflon, polytetrafluoroethylene) as shown as Fig. 32. The LMW organic molecules may provide the good wetting ability, and the adherence ability for different surfaces was sustained at room temperature for more than two months.

As shown in Fig. 33a, when the AMN-IBU adhesive was spread on a PET sheet surface and another PET sheet was pressed against it, a strong adhesion was observed after a few seconds of contact and a lap joint was formed. The measured failure stress, \( i.e. \) the shear strength, of the lap joints increased with time, \( i.e. \) during setting of the adhesive (Fig. 33b). The AMN-IBU ad-
hesive could be repeatedly re-used. The shear strength (Fig. 33c) and failure behavior (Fig. 33d) had no significantly change during four re-attachments of the lap joint.

**Figure 33.** a) A glued lap joint fixed in a universal testing machine. b) Failure shear stress for glued lap joints at different time points after setting. c) Failure shear stress for glued lap joints in repeated measurements after 8d setting. d) Force-displacement curves for one glued lap joint after 8d setting in repeated measurements. (data are presented as the mean of 5 measurements with errors bars representing standard deviation)

Compared with commercially available sticky notes, the AMN-IBU adhesive has better adherence ability (Fig. 34).

**Figure 34.** a) A glued lap joint fixed in the universal testing machine. b) Failure shear stress for glued lap joints at different time points after setting and for commercial sticky notes after 30 min curing. c) Failure shear stress for glued lap joints in repeated measurements after 1d setting. d) Force-displacement curves for one glued lap joint after 1d setting in repeated measurements. (data are presented as the mean of 5 measurements with errors bars representing standard deviation)

### 5.5 PMMA-AMN films (Paper V)

A simple casting method was used to obtain thin, transparent nanocomposite films (260 µm in thickness) of PMMA and AMN with different AMN concentrations (0, 1, 2 and 4 wt.% AMN in PMMA).
5.5.1 Characterization of PMMA-AMN films

As shown in the SEM images (Fig. 35), the neat PMMA film appears featureless, while some nanoparticles can be observed at the surface of films containing AMN. These nanoparticles were more evenly dispersed at the surface of the 1 wt.% film compared to the 2 wt.% and 4 wt.% films.

Figure 35. Scanning electron microscopy images for AMN-PMMA nanocomposite films. The proportions of AMN in the films are 0 wt.% (a), 1 wt.% (b), 2 wt.% (c) and 4 wt.% (d).

No crystalline phases were found to exist in either the neat PMMA or any of the nanocomposite films when tested with XRD (Fig. 36), indicating that all components of the film (PMMA, AMN and the surfactant, stearic acid) are in the amorphous state.

Figure 36. X-Ray diffraction patterns for neat PMMA and AMN-PMMA nanocomposite films
The incorporation of nanoparticles results in an increase in thermal stability of the PMMA films (Fig. 37). As shown in Fig. 37a, the DSC trace shows that the endothermic peak at approximately 160 °C, corresponding to the glass transmission temperature of the polymer, increases slightly with the incorporation of AMN. In both the DSC and TGA traces, the decomposition temperature of PMMA at approximately 350 °C is also increased with increasing AMN content. These results are supported by previous reports of enhanced thermal stability of PMMA due to incorporated inorganic nanoparticles [121, 122, 145].

Figure 37. a) Differential scanning calorimetry traces for neat PMMA and AMN-PMMA nanocomposite films. b) Normalized mass thermogravimetric analysis traces for neat PMMA and AMN-PMMA nanocomposite films. Insert shows the rate of weight loss of films during the heating process.

Fig. 38 portrays the transparency of the AMN-PMMA films. The addition of AMN is not detectible with the unaided eye with 1 or 2 wt.% AMN. At 4 wt.% AMN, a very slight decrease in transparency is noticeable, which may be due to the larger aggregates of AMN that form (c.f. Fig. 35). However, even at 4 wt.% the flexibility of the film is maintained as shown by the insert in Fig. 38.
5.5.2 UV shielding and moisture resistance properties of PMMA-AMN films

The UV shielding properties of the PMMA-AMN films are shown in Fig. 39. In the visible region, these composite films were transparent with transmittances close to that of the neat PMMA film, except for the 4 wt.% film which had a slightly lower transmittance (Fig. 39a). However, in UV-B and UV-C wavelengths, transmittance decreased as a function of AMN concentration in the film. Transmittances at a wavelength 310 nm of the films containing 0 wt.%, 1 wt.%, 2 wt.% and 4 wt.% AMN were 87%, 73%, 71% and 66%, respectively, whereas for 256 nm the corresponding transmittances were 68%, 30%, 25% and 15%. The UV-shielding abilities of these composite films were greater than pure AMN (Section 5.1) or pure PMMA (Fig. 39), which could be attributed to the quantum coupling of exciton states in closely spaced quantum dots which was previously reported in a ZnO-PMMA composite material [146].

Table 6 presents the moisture absorption and desorption properties of the AMN-PMMA films. The addition of 4 wt.% AMN increased the amount of
moisture absorbed by 29% compared to the neat PMMA film, which showed a weight increase of 1.65% after 24 h at 75% RH and 25 °C. Interestingly, when the temperature was increased to 75 °C, the neat PMMA film released nearly all the absorbed moisture (only 0.76% of the absorbed water was retained), whereas 48% of the absorbed water was retained in the AMN-PMMA composite film with 4 wt.% AMN. This is of particular importance in applications with thin flexible screens that act as moisture barriers to protect sensitive electronic components that are easily damaged by moisture, such as OLEDs.

Table 6. Absorbed and retained moisture in neat PMMA and AMN-PMMA films.

<table>
<thead>
<tr>
<th>Percentage of water absorbed at 25 °C, 75 % RH (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>0</th>
<th>1 wt.%</th>
<th>2 wt.%</th>
<th>4 wt.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of absorbed water retained after temperature increase to 75 °C (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.65 ± 0.11</td>
<td>1.80 ± 0.59</td>
<td>2.05 ± 0.51</td>
<td>2.13 ± 0.51</td>
</tr>
<tr>
<td>0.76 ± 0.16</td>
<td>19.81 ± 0.74</td>
<td>25.23 ± 0.79</td>
<td>47.98 ± 0.81</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> calculated by the weight change before and after absorption of water, divided by the weight of the film x 100%.

<sup>b</sup> calculated by the weight change before and after desorption, divided by the weight change before and after absorption x 100%.

Incorporated AMN can protect the film from UV degradation and the results are shown in Fig. 40. After 1 h of UV treatment the degradation of the neat PMMA film is seen as a significant decrease in transmittance of light at wavelengths approximately 450 nm and lower. This manifests itself as a slight yellowing of the film upon visual inspection. From Fig. 40b-d it can be seen that increasing the wt.% of AMN reduces this degradation by both shifting the degradation to lower wavelengths and increasing the irradiation time to achieve equivalent degrees of degradation. The greatest protection is seen with 4 wt.% AMN where very little degradation is seen after 1 h irradiation, and after 6 h irradiation, significant degradation in the film is only observed for wavelengths less than 400 nm, indicating that the visible properties of the film are unaffected.
Figure 40. UV-Vis transmittance spectra of the nanocomposite films after UV-C (254 nm) treatment.
6. Summary and Conclusions

Among nanomaterials, materials with high surface-to-volume ratios have attracted great interest and have been widely used in different areas. Traditional approaches for synthesizing high surface-to-volume ratio nanomaterials are often complicated, expensive or environmentally unfriendly. Considering aspects such as availability and safety in terms of environmental or biological contact, magnesium carbonate-based nanomaterials are an interesting and potentially valuable candidate for novel applications. The overall aim of the work presented in this thesis was to develop novel high surface-to-volume ratio amorphous magnesium carbonate nanomaterials. Investigating the possible applications of these materials was also an important aim of the work.

Amorphous magnesium carbonate nanoparticles, denoted AMN, were successfully synthesized via a simple and low-temperature pathway. The structure of the material can be tailored by changing the final steps in the synthesis process, including centrifugation and drying temperature, leading to changes in properties such as the specific surface area. The unique water sorption properties of AMN were also examined.

The ability of AMN to stabilize ibuprofen (IBU) in the amorphous form was investigated. It was found that nanocomposites with IBU:AMN mass ratios as high as 5:1 were able to be formulated and enhanced the release rate of IBU in vitro under simulated physiological conditions with a rate 83 times higher than that of IBU in crystalline form.

A related nanostructured material, mesoporous magnesium carbonate (MMC), was evaluated as a drug carrier that can stabilize amorphous drugs through the incorporation of the drug within its pores. In this study, MMC was used to release and sustain two poorly soluble drugs, toltenamic acid and rimonabant, in the supersaturated state with the assistance of the polymer hydroxypropyl methylcellulose (HPMC). With the increase in concentration of HPMC, the duration of supersaturation of the drugs could be further increased.

AMN was also used to synthesize a novel adhesive together with IBU without the addition of a polymer. This adhesive was transparent, self-healing, shapeable, stretchable and reusable. In addition, the adhesive was able to glue a variety of materials, including metals, glass, paper and plastics (even Teflon).
Finally, AMN was used to prepare flexible, transparent and UV-shielding films when incorporated into a PMMA matrix. Depending on the amount of AMN added to the film, these films exhibited different UV-shielding efficiencies and moisture absorbance and retention abilities. In addition, the UV- and thermo-stabilities of these films were found to be enhanced with the addition of AMN.

The work presented in this thesis show that the nanomaterials AMN and MMC possess great potential for an extremely broad range of applications, from pharmaceutical applications dealing with poorly soluble drugs to structural applications such as adhesives to applications in optics or electronics such as UV-shielding or moisture barrier films.
7. Future work

Amorphous magnesium carbonate materials, including AMN and MMC are still relatively new materials. These materials have been investigated in and proven promising for several different application areas, including biomedical, structural and optics/electronics applications. However, there are many mechanisms and many more possible applications to be examined, as suggested below.

The primary nanoparticles of AMN are observed to have a relatively wide size distribution, as is the aggregation of these particles, and thus future studies should be made with the aim of controlling the particle size and aggregation of AMN.

AMN and MMC have both been investigated for use in pharmaceutical applications. However, only in vitro studies were performed and therefore the next step in the development of this application area is to move towards in vivo studies in order to better simulate the complex environment of the human body. In addition, since it was discovered that a main force involved in the stabilization of IBU in the amorphous state by AMN is coulomb interactions, more drugs with anion groups should be investigated for their ability to be stabilized by AMN.

The gluing mechanism behind the AMN-IBU adhesive is not very well understood, and should be investigated further, which will hopefully provide key information that will allow other LMW molecules to be combined with AMN or other inorganic nanoparticles for future development of novel adhesives.

As a high surface-to-volume ratio material and a special surface chemistry with the possibility to interact with magnesium or carbonate ions, AMN seems to be a viable candidate as a material to be used for the adsorption and separation of chemicals, and as such this application area should also be investigated.
8. Svensk sammanfattning

Nanomaterial som har en stor yta i förhållande till dess volym har väckt stort intresse och har använts i stor utsträckning inom olika områden. Traditionella tillvägagångssätt för att syntetisera nanomaterial som har en hög kvot mellan yta och volym är ofta komplicerade, dyra eller miljöskadliga. Om man ser till aspekter som tillgänglighet och säkerhet när det gäller miljö eller biologisk kontakt, är nanomaterial bestående av magnesiumkarbonat intressanta och potentiellt värdefulla kandidater för nya tillämpningar. Det övergripande syftet med arbetet som presenteras i denna avhandling var att utveckla nya amorfa nanomaterial av magnesiumkarbonat med en hög kvot mellan yta och volym. Att undersöka möjliga applikationerna av dessa material var också ett viktigt syfte med arbetet.

Amorfa magnesiumkarbonat nanopartiklar (AMN) syntetiserades via en enkel process vid låg temperatur. Materialets struktur kan skäddas genom att ändra de sista stegen i syntesprocessen, som centrifugering och torkningstemperatur, vilket leder till förändringar i materialets egenskaper som den specifika ytarean. De unika egenskaperna för vattensorption hos AMN undersökes också.

AMNs förmåga att stabilisera ibuprofen (IBU) i dess amorfa form undersöks. Det visade sig vara möjligt att formulera nanokomponenter med ett högt massförhållande mellan IBU:AMN (5:1) och därigenom förbättra frisättningstiden för IBU in vitro under simulerade fysiologiska betingelser med en hastighet 83 gånger högre än den för IBU i kristallin form.

Ett liknande nanostrukturerat material, mesoporöst magnesiumkarbonat (MMC), utvärderades som en läkemedelsbärare som kan stabilisera amorfa läkemedel genom inkorporering av läkemedlet i dess porer. I denna studie användes MMC för att frisätta och bibehålla effekten av två läkemedel med låg löslighet, tolfenaminsyra och rimonabant i ett övermättat tillstånd med hjälp av polymeren hydroxipropylmetylcellulosa(HPMC). Genom enökning av koncentrationen av HPMC kan varaktigheten av övermättad för läkemedlen ökas ytterligare.

AMN användes också för att syntetisera ett nytt bindemedel tillsammans med IBU utan tillsats av en polymer. Detta bindemedel var transparent, självhärdande, formbart, töjbart och återanvändbart. Dessutom kunde det fästa en mängd olika material, inklusive metaller, glas, paper och plast (även Teflon).
Slutligen användes AMN för att framställa flexibla, transparenta och UV-avskärmande filmer när de adderades till en PMMA-matris. Beroende på mängden AMN tillsatt till filmen uppvisade dessa filmer olika UV-avskärmningseffekter, fuktabsorbans och retentionskapacitet. Dessutom förbättrades UV- och termostabiliteten hos dessa filmer med tillsatsen av AMN.

Arbetet som presenteras i denna avhandling visar att nanomaterialet AMN och MMC har stor potential för en stor variation av olika användningsområden, från läkemedelsapplikationer som hanterar svårlösliga läkemedel till strukturella applikationer som bindemedel för applikationer inom optik eller elektronik som UV-avskärmning eller fuktbarriärfilmer.
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与君一生，予珺一世
References


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