Ceramic Materials for Administration of Potent Drugs

BING CAI
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Abstract


This thesis aimed to investigate and document the potential of applying ceramics in two specific drug delivery applications: tamper-resistant opioid formulations and transdermal enhancement protrusions.

Geopolymers were developed into the matrix for a tamper-resistant formulation, aiming to protect drug substances from non-medical abuse. The synthesis conditions and excipients composition of the geopolymer-based formulation were modified in this work to facilitate a stable and extended drug delivery. Results showed that 37°C 100% humidity for 48 hours were applicable conditions to obtain geopolymer with suitable mechanical strength and porosity. Moreover, it was found that the integration of poly(methyl acrylate) into the geopolymer-based formulation could reduce the drug release at low pH and, meanwhile, maintain the mechanical strength. Therefore, the geopolymer-based drug formulations concluded from these studies were applied in oral and transdermal delivery systems. Evidence of the tamper-resistance of geopolymer-based oral and transdermal formulations was documented and compared to the corresponding commercial opioid formulations. The results provided experimental support for the positive effects of geopolymers as drug carriers for the tamper-resistance of oral and transdermal delivery systems.

Self-setting bioceramics, calcium phosphate and calcium sulfate were fabricated into transdermal enhancement protrusions in this work for the first time. Results showed that, under mild conditions, both bioceramics could form pyramid-shaped needles in the micron size. The drug release from these needles could be controlled by the bulk surface area, porosity and degradation of the bioceramics. An in vitro insertion test showed that the bioceramic microneedles had enough mechanical strength to insert into skin. Further optimization on the geometry of needles and the substrate material was also performed. The higher aspect-ratio needles with a flexible and self-swellable substrate could release most of the drug content within 4 hours and could penetrate through the stratum corneum by manual insertion. This study explored the potential application of bioceramics in transdermal enhancement protrusions and showed promising indication of their future developments.

Keywords: Tamper-resistance, Oral formulation, Transdermal formulation, Biomaterials, Microneedles

Bing Cai, Department of Engineering Sciences, Applied Materials Sciences, Box 534, Uppsala University, SE-75121 Uppsala, Sweden.

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To my family
List of Papers

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


VI **Cai, B.**, Xia, W., Li, H., Bredenberg, S., Engqvist, H., Bioceramic microneedles with flexible and swellable substrate, submitted.

Reprints were made with permission from the respective publishers.
Author’s Contributions to the listed papers:

Paper I  Part of sample preparation and compressive strength measurement and major part of evaluation and writing.

Paper II  Part of sample preparation, drug release experiments, evaluation and writing.

Paper III  Major part of planning, experimental work, evaluation and writing.

Paper IV  Part of planning, major part of experimental work excluding patch preparation and \textit{in vivo} test, major part of evaluation and writing.

Paper V  Major part of planning, experimental work, evaluation and writing.

Paper VI  Major part of planning, experimental work, evaluation and writing.
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<td>β-TCP</td>
<td>β-tricalcium phosphate</td>
</tr>
<tr>
<td>BCMN-G</td>
<td>Bioceramic microneedle with gelatin substrate</td>
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<tr>
<td>CaP</td>
<td>Dicalcium phosphate dihydrate; Brushite</td>
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<td>CaS</td>
<td>Calcium sulfate dihydrate</td>
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<td>ER</td>
<td>Extended release</td>
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<td>FDA</td>
<td>U.S. Food and Drug administration</td>
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<tr>
<td>HPLC</td>
<td>High pressure liquid chromatography</td>
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<tr>
<td>MCPM</td>
<td>Monocalcium phosphate monohydrate</td>
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<tr>
<td>MicroCT</td>
<td>X-ray computed micro-tomography</td>
</tr>
<tr>
<td>MN</td>
<td>Microneedle; Transdermal enhancement protrusions</td>
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<tr>
<td>PMA</td>
<td>Poly(methyl acrylate)</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene glycol</td>
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<td>RH</td>
<td>Relative humidity</td>
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<tr>
<td>SCMN</td>
<td>Self-setting bioceramic microneedle</td>
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<tr>
<td>SEM</td>
<td>Scanning electron microscope</td>
</tr>
<tr>
<td>SSS</td>
<td>Synthetic skin simulator</td>
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<tr>
<td>XRD</td>
<td>X-ray diffraction</td>
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<tr>
<td>USP</td>
<td>The United State Pharmacopeia</td>
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1. Introduction

As the title implies, this thesis focuses on an evaluation of the potential to apply ceramics to deliver potent drugs into patients, specifically through oral and transdermal routes. The great variation in physical and chemical properties of ceramics has been used to meet the demand of different drug delivery strategies. Due to the high compressive strength, adjustable porosity, good biocompatibility and mild manufacturing conditions of some ceramics, this work intended to utilize a few ceramic materials in two specific drug delivery applications: tamper-resistant formulations and transdermal penetration enhancement micro-protrusions.

To put this theme into context, the Introduction states the aim and objectives of this thesis and also briefly presents the readers with the necessary background of the work presented. The purpose of drug delivery, different types of controlled release formulations and some of the release mechanisms will be described. The chemical structure, physical and chemical properties and current medical application of the ceramics that have been used in this thesis will also be presented.

After the presentation of the background, two sections, Geopolymer-based tamper-resistant formulations and Bioceramic transdermal enhancement protrusions, will state the therapeutic motivations, describe the conducted experiments and summarize the major findings of the studies.

The section Geopolymer-based tamper-resistant formulations first presents the motivation behind this study: opioid therapy for chronic pain and the abuse situation related to prescription opioids. Subsequently, the current state-of-the-art in tamper-resistant formulations will be introduced briefly. The section will also describe the synthesis procedures and major experiments performed to evaluate these formulations. Lastly, the main findings for geopolymer-based formulations (mainly from Paper I-IV) will be summarized.

The section Bioceramic transdermal enhancement protrusions will first briefly present the problems of transdermal penetration and current studies in the field of transdermal enhancement protrusions. It also describes the fabrication procedures of the bioceramic protrusion arrays and the major experiments performed to evaluate their drug releases and ex vivo skin penetration. The main findings for bioceramic transdermal enhancement protrusions (Paper V and VI) will then be summarized.
The Concluding remarks and Future outlook section mainly review the thesis and present suggestions for future work. At the end of thesis, Analytical techniques describes the experiments performed to characterize the ceramics that have been used.

1.1 Aim and objectives

This thesis aims to document the suitability of geopolymers, calcium phosphate and calcium sulfate as drug carriers for oral and transdermal delivery, mainly in tamper-resistant formulations and transdermal enhancement protrusions. Although there are previous studies that have investigated these ceramics as drug delivery systems, exploration of the applications in these two specific areas is still in an early stage. To achieve this ultimate aim, the objective is to evaluate whether the desired material properties for these applications could be achieved by these ceramics.

Geopolymers were developed as a matrix for the oral and transdermal formulations with controlled drug release and low abuse liability in the first study. To achieve this, the effect of curing temperature, humidity and time on the mechanical strength and porosity of geopolymers was investigated to determine suitable curing conditions for the following studies. Next, a screening study of several polymer excipients was performed in order to acquire a suitable excipient composition that could retard the drug release from the geopolymer-based formulation at low pH. Their influences on the mechanical strength of the geopolymer matrix and drug release rate at low and neutral pH were evaluated. The geopolymer-based oral formulation with the selected polymer excipient was then evaluated for its performance in terms of tamper-resistance compared to a commercial opioid oral tablet. The resistance was assessed through tests simulating some tampering methods commonly used by abusers. Some additional properties of this geopolymer-based formulation were documented as well. Last but not least, the geopolymer-based drug carrier was further used to improve the tamper-resistance of a fentanyl transdermal patch. The drug-loaded geopolymer particles were integrated into the matrix layer, and the tamper-resistance of this patch was compared with a control patch and a commercial fentanyl patch using the tests simulating some common tampering methods used by abusers.

The desired properties of the materials for transdermal enhancement protrusions could be: mild manufacture condition, high drug capacity, controlled release, good biocompatibility and sufficient mechanical strength to penetrate into the skin. In this context, bioceramics were prepared into micro-sized protrusions for the first time. Two bioceramics were molded into pyramid-shaped needles, and their applications as protrusions were evaluated by in vitro drug release test and ex vivo skin penetration. A further development on the bioceramic protrusions was performed aiming to reduce the
effort required for skin insertion and accelerating drug release. A higher aspect ratio of the needles and a flexible and self-swelling substrate were designed for this purpose. To estimate the function of this bioceramics protrusion in practice, the in vitro drug release and ex vivo skin penetration were studied.

1.2 Drug delivery

Different drug delivery strategies are developed to achieve a predictable and desired therapeutic effect in the human body. This effect is reached when the drug plasma concentration at the relevant site is within the therapeutic window—that is, below the toxic level but above the effective level (Figure 1). To attain a concentration within that range, drug molecules can be introduced into the patient’s body through various administration routes with the help of delivery formulations.

The common administration routes of a drug into the body include oral, intravenous, intramuscular, inhalation and transdermal [1]. Oral administration is the most straightforward and convenient option for patients. Oral formulations, such as tablets and capsules, are easy to administer, relatively inexpensive to prepare and require less medical knowledge during treatment than some of the alternatives (e.g., injections). Transdermal administration, on the other hand, has shown great potential due to its avoidance of first-pass metabolism, prevention of gastrointestinal degradation, relatively steady release and good patient compliance. Patches, as one of the most common transdermal formulations, are suitable to release a constant and controlled dosage over extended period for systemic delivery. Depending on the chosen route and formulation, the physiologic responses change accordingly—that is, the rate of pharmacokinetic phases: absorption, distribution, metabolism and excretion.
1.2.1 Controlled release formulations

Controlled release formulations restrain the amount and time of drug release for the targeted treatment. The immediate release dosage form gives an impulse of medication into the body after administration. However, the resulting concentration boost in plasma usually accelerates the elimination process at the same time. If a continuous treatment is required, patients need to take these dosage forms periodically to maintain the concentration within the therapeutic window, as shown in Figure 1, which results in a frequent fluctuation of plasma concentration. Hence, the immediate dosage form is suitable for acute treatment but not for continuous therapy.

Alternatively, one can take a large dose of a drug that releases over a long period of time—in other words, extended release. Extended-release (ER) formulations aim to reduce dosing frequency, alleviate fluctuation of plasma concentration and thus improve patient compliance (Figure 1). These formulations usually liberate drug molecules continuously at a predictable and low rate. However, since the ER dosage forms contain a large amount of the drug dose, loss of the control of drug release can cause dose dumping, which can lead to severe or even lethal consequences.

1.2.2 Release mechanisms

In order to provide an efficient and reliable control of the responding therapeutic effects, the release behaviors from the drug formulations should be carefully managed. For the ER formulations, the control of the rate and extent of drug release is usually facilitated by the following processes [2]:

Figure 1 Illustration of the plasma concentration after administration of different formulations.
1. Diffusion of water into the device
2. Dissolution of drug
3. Diffusion of the dissolved drug from the device into the surroundings
4. Dissolution or swelling of the matrix.

Depending on the formulation design, some of these processes can be dominated, in absence or in a different order. The design parameters, such as incorporated dose, physicochemical properties of the drug and the properties of the matrix, can determine the rate-limiting process of drug release—that is, the dominant release mechanism. This thesis focuses mainly on adjusting the properties of the matrix to modify the drug release behavior.

Drug release behavior is usually evaluated by investigating the release profile, which is plotted by the cumulative amount of drug released in a certain environment versus time. If the release of drug molecules are mainly limited by drug dissolution at the given condition, the release profile will presumably follow first-order kinetics (Figure 2) [1]. The dissolution is usually the major rate-limiting mechanism when the drug has poor solubility or when the formulation releases the drug molecules in an immediate or pulsed manner [1].

To better manage the drug release, many designs of drug carrier use diffusion as the rate-controlling mechanism. If the dissolution is faster than the diffusion for the drug molecules dispersed in an inert matrix, diffusion is then considered as the rate-limiting mechanism. The release profile of a typical diffusion-based system often follows a square root of time curve (~t^{1/2}, Figure 2). For drug formulations based on the matrix with low porosity, as discussed in Papers II, III, IV, V and VI, diffusion can be treated as in a homogenous matrix with a modified diffusion coefficient. The porosity and tortuosity of the pores contribute to a reduction in the diffusion coefficient [3]. The drug dose, the pore properties of the matrix and the interaction between drug and matrix are the major formulation factors that affect the diffusion.

Erosion, which is mentioned as degradation for the ceramic drug carriers in this thesis, is another commonly used mechanism to sustain drug release. The matrix material in the eroding drug delivery system continuously dissolves from the surface and exposes the dissolved or dispersed drug to the surroundings, resulting in drug release. The drug release from an eroding system can often approximate to a zero-order profile for a significant part of the total release time [1]. However, as the diffusion can occur at the same time as erosion, the dominant mechanism of the system is the process that has a lower rate.
1.2.3 Modeling drug release

Mathematical model is an important tool for evaluating release profiles and reducing experimental work according to the underlying release mechanism. In Papers III and IV, the drug release profiles were evaluated with Higuchi and Hopfenberg models to understand their possible rate-limiting mechanisms [4].

Higuchi is a famous mechanistic model for describing the release profile that is regulated by the diffusion-controlled mechanism. The model is based on several assumptions:

- The drug is released into surroundings that are in the sink condition: the accumulated drug contents in the surroundings do not affect the drug dissolution and diffusion.
- The drug particle size is much smaller than the dimensions of the matrix, and the particles are homogenously dispersed within the matrix.
- The initial drug concentration is much higher than the solubility of the drug in the matrix material.
- The dissolution of the drug in the matrix is rapid compared to the diffusion of dissolved drug molecules through the matrix.
- The matrix is inert, and its swelling and dissolving is much slower than the diffusion during drug release.

*Figure 2* Release profiles of the dissolution- (first-order), diffusion- ($t^{1/2}$) or erosion- (zero-order) controlled release formulations.
Under these conditions, the Higuchi equation was first derived for the slab model. In order to apply it to various delivery systems, the initial equation was extended to other geometries as well [5]:

\[
\begin{align*}
\text{Slab} & \quad M_t = A \sqrt{D c_s (2c_{ini} - c_s)} \cdot t \\
\text{Spheres} & \quad \frac{M_t}{M_\infty} - 3 \left[ 1 - \left( \frac{M_t}{M_\infty} \right)^{2/3} \right] = -\frac{3D}{R} \frac{c_s}{c_{ini}} \cdot t \\
\text{Cylinders} & \quad \frac{M_t}{M_\infty} + \left( 1 - \frac{M_t}{M_\infty} \right) \ln \left[ 1 - \frac{M_t}{M_\infty} \right] = \frac{4D}{R^2} \frac{c_s}{c_{ini}} \cdot t,
\end{align*}
\]

where \(M_t\) and \(M_\infty\) denote the cumulative amounts of drug released at time \(t\) and infinite time, respectively; \(D\) is the diffusion coefficient of the drug within the system; \(c_s\) denotes the drug solubility in the wetted matrix; \(c_{ini}\) denotes the initial drug concentration in the system and \(R\) is the radius of the geometries.

The release profiles of the intact formulations in Paper III were evaluated by the cylindrical Higuchi model. The spherical model was used to evaluate the drug release from the residual particles of the milled formulations. In Paper IV, the release profiles of transdermal patches were fit into the slab model, in which the accumulated drug release has a relationship with the square root of time (~\(t^{1/2}\)).

Hopfenberg proposed a semi-empirical model to describe the drug release from an eroding drug delivery system. The model assumes the surface dissolving, which is the rate-limiting step, will result in the detachment of the drug. The general equation is [4]:

\[
\frac{M_t}{M_\infty} = 1 - \left( 1 - \frac{k_0 t}{c_0 a} \right)^n,
\]

where \(M_t\) and \(M_\infty\) denote the cumulative amounts of drug released at time \(t\) and infinite time, respectively; \(c_0\) represents the uniform initial drug concentration in the system; \(a\) is the radius of a cylinder or sphere or half-thickness of the slab and \(n\) is a shape factor representing spherical (\(n=3\)), cylindrical (\(n=2\)) or slab geometry (\(n=1\)). The intact formulations in Paper III were approximated by the cylindrical shape, and their release profiles were evaluated by the Hopfenberg model with \(n=2\). The residual particles of the milled formulations were approximated by the spherical shape, and their release profiles were evaluated with \(n=3\).
1.3 Ceramics for drug delivery

1.3.1 Ceramics

Ceramics are inorganic nonmetallic materials formed by the application of heat and sometimes pressure as well [6]. Since the atoms in the ceramic materials are mainly held by ionic or covalent bonds, ceramics tend to have high mechanical strength. They exhibit from highly crystalline to amorphous state with different physical and chemical properties, depending on the regularity of the atomic arrangement. Their various properties make them suitable for numerous engineering applications. Different porous and biocompatible ceramics have been used as drug carriers as well to achieve timely, reproducible and efficient delivery [7, 8]. Medications, from small molecule drugs to biopharmaceuticals, have been loaded into ceramic matrices for treatment of the targeted body parts. For the cements based on ceramics that can cure under mild conditions, the drug molecules can be both incorporated into the whole matrix volume or coated on the surface.

In the sections below, the focus will be on three types of ceramic materials: geopolymers, calcium sulfate and calcium phosphate, as they constitute the foundation of the work that follows. Their physical properties and their suitability in some biomedical applications are also presented.

1.3.2 Geopolymer

Geopolymers have been referred to as “inorganic polymers,” “alkali-bonded ceramics” and “hydroceramics” [9]. The basic unit of geopolymers, polysialates, has the structure that SiO$_4$ and AlO$_4$ tetrahedra were linked alternatively by sharing all oxygen. The charge of tetrahedral Al$^{3+}$ is balanced by alkali ions, such as Na$^+$ and K$^+$ (Figure 3) [10]. Geopolymers are formed by a reaction between an aluminosilicate and an aqueous alkali solution. Metakaolin, a dehydrated form of kaolinite, is one of the most commonly used aluminosilicates for geopolymer synthesis. When an alkali solution is mixed with metakaolin, alkali ions and hydroxyl ions react on the outer surface and inter layer spaces of the metakaolin, but other additives, such as siloxonates, react only with the outer surfaces [10].
The reaction of geopolymer formation is generally divided into 3 steps (Figure 4) [10]:

1. Alkalination of orthosialates to form tetrahedral Al ends. Negatively charged tetrahedral Al is balanced with sodium ions. The orthosialates are released from solid aluminosilicate with the presence of sodium hydroxide silicate solution.
2. Orthosialates conjugate with other orthosialates or oligo-siloxonates and condense into oligomers.
3. The oligomers reorganize and polycondense into nanometer-sized micelles. The geopolymeric micelles agglomerate into solid material with mesopores.

Depending on the different compositions and synthesis conditions, geopolymers can exhibit various physical and chemical properties. A previous study investigated how the Si, Na and water content in the geopolymer matrix affects its porosity, compressive strength and drug release behaviors [11]. Therefore, the influence of synthesis condition on the properties of geopolymers was investigated in this work.
In some previous studies, geopolymers were evaluated as the matrix material for controlled-release oral opioid formulation due to their good mechanical stability, adjustable porosity and low solubility in water [11, 12]. Diffusion is considered as the rate-limiting step of the drug release from geopolymer-based formulations [12]. However, drug release tests showed a faster release at pH 1 than that at pH 6.8 from the geopolymer matrix [11]. Pore opening at low pH is believed as one of the reasons for the increased drug release [11]. In the acidic environment, the alkaline ions in the geopolymer structure are replaced by $\text{H}^+$ or $\text{H}_3\text{O}^+$ [13]. Thus, the primary bonding, between polysialate and polysiloxon, is likely ruptured by proton attack, forming zeolites and gypsum-like crystals, which have much lower mechanical strength [13]. Therefore, in order to improve the consistence and the control of the release in acidic solutions, modifications on the acid resistance of geopolymers are necessary. Some of the commonly used tablet coating excipients were studied in this work for their effects on retarding drug release in low pH environment.
1.3.3 Calcium sulfate

The natural mineral form of calcium sulfate is calcium sulfate dihydrate (CaSO$_4$·2H$_2$O), also called gypsum. When gypsum is dehydrated at 110ºC, it loses structural water and forms calcium sulfate hemihydrate (CaSO$_4$·0.5H$_2$O). The hemihydrate exists in two forms, α and β, which are chemically identical but differ in structure and morphology of crystals. α-hemihydrate shows mainly in rod- and prism-shaped crystals, while β-form are less regular, containing the aggregates of irregular crystals with capillary pores. Due to the inherent crystal structure, α-form has lower solubility and requires less water to rebuild into dihydrate form [14]. In general, the dihydrate (referred to as CaS) formed from α-hemihydrate is denser and mechanically stronger [15].

Calcium sulfate is recognized as a biocompatible material and has a long history in medical applications. It has been used for bone regeneration, bone void filling and drug delivery. Many studies have reported a minimal inflammatory response subsequent to in vivo usage of CaS [16-18]. Studies also showed that CaS has fast and complete resorption compared to other bioceramics [16, 19]. A lump of CaS degrades in body fluid at a rate of about 1mm per week and dissolves into calcium and sulfate ions [20]. Despite orthopedic applications, CaS also works effectively as a drug carrier for growth factors, antibiotics and small molecule drugs [14, 20]. Due to the dissolution of CaS, the drug release mechanisms rely both on diffusion of the drug molecules and degradation of the CaS matrix.

1.3.4 Calcium phosphate

Calcium phosphate-based materials have been widely studied as biomaterials for over 100 years. Dicalcium phosphate dihydrate (CaHPO$_4$·2H$_2$O), or brushite (referred as CaP in this thesis), is one of the most interesting types of synthetic calcium phosphates which has a similar monoclinic crystal structure to that of gypsum. The brushite used in this work was synthesized using β-tricalcium phosphate (β-TCP, Ca$_3$(PO$_4$)$_2$), monocalcium phosphate monohydrate (MCPM, Ca(H$_2$PO$_4$)O$_2$·H$_2$O) and water. Since adequate handling time is necessary to mold the cements into the desired shape, retardants, such as citric acid (C$_6$H$_8$O$_7$) and disodium dihydrogen pyrophosphate (Na$_2$H$_2$P$_2$O$_7$), were added into the liquid or powder. The retardants can slow down the setting reaction by decreasing the solubility of β-TCP and reducing the nucleation rate of brushite [21, 22].

As CaS, CaP is another biocompatible material suitable for orthopedic applications and drug delivery. The delivery of antibiotics, anti-inflammatory drugs and even hormones by CaP have been studied [23]. Although CaP is also resorbable by the body, the rate of degradation is usually
much lower than the rate of drug diffusion in CaP drug carriers. Therefore, drug release from the CaP matrix is mainly diffusion-controlled [23].
2 Geopolymer-based tamper-resistant formulations

2.1 Motivation

2.1.1 Chronic pain and opioid therapy

According to surveys in Europe as well as worldwide, around one-fifth of the participants have suffered moderate or severe pain [24, 25]. Despite the persistent pain, many patients also suffer from physical, social and psychological disability due to chronic pain [26]. Opioid drugs are narcotic analgesics that bind to the receptors in the central and peripheral nervous systems and induce a pain-killing effect. Opioid therapies are strongly recommended for treating chronic pain by the key medical organizations and are prescribed by many physicians in practice [27]. In the U.S., retail sales of commonly used opioids have increased from 50.7 million grams in 1997 to 126.5 million grams in 2007—in other words, a 149% increase in a decade. During that time, sales of fentanyl and oxycodone increased 525% and 866%, respectively [28]. Moreover, the average sales of opioid medication per person increased 402% from 1997 to 2007 [28].

As chronic pain requires around-the-clock treatment, patients need to have a continuous administration of opioids. However, due to the severe or even lethal overdose symptoms of opioids, the plasma concentration should be carefully controlled within the therapeutic window during the therapy [29]. To sum up, the opioid dosage forms for treating chronic pain should be able to maintain a stable plasma concentration within the therapeutic window for an extended period to meet both safety requirements and patient compliance.

2.1.2 Abuse liability and tamper-resistant formulations

With the increase of opioid consumption, concern has been expressed over the escalating misuses and non-medical use of prescription opioids. Investigations have illustrated that drug abuse occurred in 18-41% of patients receiving opioids for chronic pain, with a 90% increase in the number of people from 1992 to 2003 [30]. A survey published in 2010 reported the number of the emergency department visits involving non-medical use of opioid medications doubled from 2004 to 2008 in the U.S.—from 144,644 to
305,885 [28]. Drug abuse has become an enormous burden economically and socially. It was estimated that drug abuse costs the U.S. government approximately $300 billion a year [31]. Therefore, the Food and Drug Administration (FDA) strongly recommended the assessment regarding the abuse potential to all opioid products starting in 2010 [32, 33].

Extended-release drug products are easily targeted for non-medical use as they generally contain larger drug doses than the corresponding immediate-release counterparts [34]. In order to deter manipulation of drug formulations, several tamper-resistant strategies have been developed: opioid antagonist, aversive agents and physical/chemical barriers. This thesis mainly focuses on using physical/chemical barriers to develop new tamper-resistant formulations. Such barriers create obstacles to intentional and illegal manipulation of the controlled release mechanism of opioid formulations [35]. The physical/chemical barrier makes the formulation less accessible and attractive for non-medical use.

For oral tablets, deformation of the matrix and extraction in solvents are the most commonly used abuse methods [36]. Reformulated OxyContin® and Remoxy® are the two tamper-resistant ER oxycodone tablets that have been approved in terms of their claims on tamper-resistance by the FDA. OxyContin® has a rigid polymer matrix that can form a viscous gel in water against extraction [37], while Remoxy® is a gelatin capsule that is difficult to crush and extract in water or alcohol [38]. More tamper-resistant oral formulations have been reviewed by Mastropietro and Omidian [35].

Transdermal patches are often abused by means of extraction, chewing, ingestion and smoking [39]. To reduce the abuse potential of opioid patches, several tamper-resistant patches have been designed. Patent documents WO2004098568 A2, US7182955 B2 and US8790689 B2 describe transdermal dosage forms with a compartment containing antagonist/aversive agent which is separated from active pharmaceutical ingredients [40-42]. The antagonists or aversive agents are not delivered during therapeutic use but will release during attempted abuse along with the opioids. US7511054 B2 illustrates a dosage form that contains opioid pro-drugs and a form of antagonist poorly absorbed through the skin [43]. The antagonists would be minimally delivered transdermally but would take effect when the dosage form is tampered with.

Since the resistance to tampering is not absolute, researchers are endeavoring to create new formulations and further minimize abuse potential without compromising the efficiency of the oral and transdermal opioid formulations [35, 44, 45]. The potential applications of geopolymers as drug carriers for oral and transdermal tamper-resistant formulations were evaluated in this study.
2.2 Methods

2.2.1 Synthesis process of geopolymer-based formulations

The geopolymer matrices in this study were synthesized by mixing metakaolin and sodium silicate solution using a mortar and pestle until a uniform paste was formed. Metakaolin (Al₂O₃·2SiO₂) was prepared by dehydroxylating kaolinite (Al₂O₃·2SiO₂·2H₂O) at 800ºC for 2 hours. A sodium silicate solution (waterglass) was prepared by mixing water, sodium hydroxide and fumed silica until a homogenous liquid was formed. The compositions of the geopolymer pastes in Papers I, II, III and IV are listed in Table 1.

Table 1 Geopolymer composition in this work (in molar ratio, except * in mass ratio)

<table>
<thead>
<tr>
<th>Paper</th>
<th>SiO₂/Al₂O₃</th>
<th>Na₂O/Al₂O₃</th>
<th>H₂O/Al₂O₃</th>
<th>Drug concentration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td>2.83</td>
<td>0.57</td>
<td>8.4</td>
<td>0mg/g metakaolin</td>
</tr>
<tr>
<td>Paper II</td>
<td>1.77</td>
<td>1.4</td>
<td>14</td>
<td>13mg zolpidem tartrate/g metakaolin</td>
</tr>
<tr>
<td>Paper III</td>
<td>3.88</td>
<td>1.2</td>
<td>12.3</td>
<td>5mg oxycodone hydrochloride/g metakaolin</td>
</tr>
<tr>
<td>Paper IV</td>
<td>2.13</td>
<td>1.47</td>
<td>14.9</td>
<td>530mg fentanyl base/g metakaolin</td>
</tr>
</tbody>
</table>

In Paper II, zolpidem tartrate powder (C₁₉H₂₁N₃O, Cambrex Corp., USA) and polymer excipients in dissolved or powdered form were added into the geopolymer paste. In Paper III, oxycodone hydrochloride solution (C₁₈H₂₁NO₄, 10mg/ml, Orion Pharma, Finland) was added into sodium silicate solution and poly(methyl acrylate) (PMA) powder was added into the geopolymer paste. In Paper IV, fentanyl base powder (C₂₂H₂₈N₂O, MacFarlan and Smith, UK) was added into the geopolymer paste. The pre-cured paste was molded in Teflon® molds into pellets (1.5 x 1.5 mm, diameter x height) or in rubber molds for rods (6 x 12 mm, diameter x height). In Paper I, the paste was cured under various curing temperatures (ambient, 37ºC and 90ºC), humidities (ambient and 100% relative humidity) and time periods (24, 48 and 96 hrs). In Papers II, III and IV, the geopolymer precursor was cured for 48 hrs at 37ºC under 100% relative humidity (RH) and dried in air for at least 24 hrs. The samples were demolded and stored under a low RH before testing. The synthesis process of the geopolymer pellets and rods in this thesis are shown in Figure 5.

1 The composition varied between papers due to continuous adjustment of the mechanical strength and drug release behavior.
2.2.2 In vitro evaluation of geopolymer-based formulations

In vitro dissolution test

The United States Pharmacopeia (USP) apparatus II dissolution bath (Sotax AG, Switzerland) was used to evaluate and compare the drug release performance of different drug formulations. Samples were placed at the bottom of vessels with dissolution media at pH 1±0.5 (0.1 M HCl) or pH 6.8±0.5 (50 mM phosphate buffer), which simulated the conditions in the stomach and intestine tract, respectively. The stirring rate was 50 rpm and the temperature was 37ºC. An illustration of the setup is shown in Figure 6. The sink condition for all dissolution tests was approximated by a well-mixed bath in which the accumulated drug concentration would not exceed 10% of the drug solubility during the whole test.

In Paper II, the dissolution tests were performed with 400 mL of dissolution media in each trial. In Paper III, 400 mL of dissolution media was used for all trials with the same drug-to-solvent ratios of 1 mg drug added to 80
mL dissolution media. The release tests were also performed in 400 mL of 5 vol% or 40 vol% ethanol in pH 1±0.5 solution, simulating conditions in the stomach with codigestion of alcoholic beverages. In both studies, aliquots (1 mL) were manually withdrawn at the predetermined time points. The drug concentrations in the solutions were determined by photospectrometry (UV/VIS spectrophotometer, Shimadzu Corp., Kyoto, Japan).

In Paper IV, the preliminary drug release test of geopolymer granules or commercial patches were performed in 200 mL of phosphate buffer at pH 6.8±0.5 or 50 vol% ethanol aqueous solution by mini vessels and paddles. Subsequently, the drug release from the patches was performed in 500 mL of pH 1±0.5, pH 6.8±0.5 and 40 vol% ethanol in pH 1±0.5 dissolution media with a drug-to-solvent ratio of 1 mg drug added to 238 mL dissolution media. The investigated patch was fixed on a metal plate at the bottom of the dissolution beaker. The drug concentrations were determined by isocratic reversed-phase high-pressure liquid chromatography (HPLC) with a photodiode array detector (Waters, Corp., Milford, MA) and a YMC-Triart C18 column (2.0mm ID × 12mm, 3µm; YMC, Japan).

![Figure 6](image)

**Figure 6** The setup of drug release test in a standardized USP II dissolution bath.

**Tamper-resistant tests**

Tamper-resistant tests were performed in Papers III and IV to evaluate the difficulty level of defeating the controlled release mechanism of a formulation to achieve rapid-onset effects. Since the tamper-resistance cannot be measured as an absolute value, the performance of geopolymer-based formulations was compared with that of the existing products: in Paper III, the geopolymer-based oral formulation was compared to the commercial ER tablets, OxyContin®, while in Paper IV, the geopolymer-integrated patch was compared to a controlled patch and a commercial fentanyl patch, Durogesic®.
In **Paper III**, the tests simulating physical deformation, chemical extractions and co-digestion with alcoholic beverages were performed to evaluate the tamper-resistance of the oral geopolymer-based formulation and that of a commercial tablet. Drug formulations were crushed with two spoons, a coffee grinder or milled for 15 minutes with a mortar and pestle. The particle size of residue, which indicates the degree of difficulty for physical manipulation, was estimated under a scanning electron microscope (SEM). Both intact and ground formulations were extracted in the following solvents over a two-hour course: ethanol aqueous solution (20 or 40% ethanol, ambient temperature), distilled water (50°C or 70°C), pH 1±0.5 (0.1M hydrochloric acid (HCl) aqueous solution, ambient temperature) and pH 12±0.5 (Sodium hydroxide (NaOH) aqueous solution, ambient temperature). All extractions were performed with the same drug-to-solvent ratio of 1 mg drug added to 20 mL extraction media. Co-digestion of opioid formulations with alcoholic beverages was simulated using the USP II apparatus as described in the previous section. The drug concentrations were determined by the HPLC method as described above.

In **Paper IV**, tests simulating chemical extractions, chewing, smoking and oral ingestion were performed to evaluate the tamper-resistance of the geopolymer-integrated patch compared to that of a control patch and a commercial patch. The patches were extracted in the following solvents over a two-hour course: ethanol aqueous solution (40 vol% ethanol, ambient temperature), distilled water (70°C) and pH 1±0.5 (0.1M HCl solution, ambient temperature). Extractions were performed with the same drug-to-solvent ratio of 1 mg drug added to 20 mL extraction media. Milling using a mortar and pestle with 5 mL of pH 6.8±0.5 phosphate buffer simulated intentional chewing on the patches. Heating the patches at 120°C for 20 minutes simulated smoking. The amount of the residual drug after heating was determined by extracting the patches in 500 mL pH 1±0.5 solution by the USP II apparatus as described in the previous section. The evaporated drug fraction was calculated by the difference of the released fraction from the patch before and after heating. The oral ingestion of the patches was simulated by the USP II apparatus as described in the previous section. The drug concentrations were determined by the HPLC method as described above.

Although the tests used in **Papers III and IV** cannot represent all tampering methods that are accessible to abusers, the design of the method aimed to cover some of the most common practices used by abusers according to previously published studies and regulations [32, 33, 37, 38, 44].
Table 2 Summary of the tamper-resistant tests used in Papers III and IV.

<table>
<thead>
<tr>
<th>Oral geopolymer-based tamper-resistant formulation (Paper III)</th>
<th>Physical manipulation</th>
<th>Extraction in solution for 2 hours</th>
<th>Co-digestion with alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crushing with two spoons</td>
<td>20 % ethanol aqueous solution</td>
<td>400 mL 5 vol% ethanol pH 1±0.5 HCl aqueous solution</td>
</tr>
<tr>
<td></td>
<td>Coffee grinder</td>
<td>40 % ethanol aqueous solution</td>
<td>400 mL 40 vol% ethanol pH 1±0.5 HCl aqueous solution</td>
</tr>
<tr>
<td></td>
<td>Milled with a mortar and pestle</td>
<td>50°C water</td>
<td>70°C water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pH 1±0.5 HCl aqueous solution</td>
<td>pH 12±0.5 NaOH aqueous solution</td>
</tr>
<tr>
<td>Transdermal geopolymer-integrated tamper-resistant patch (Paper IV)</td>
<td></td>
<td>Extraction in solution for 2 hours</td>
<td>40 % Ethanol aqueous solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70°C water</td>
<td>pH 1±0.5 HCl aqueous solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chewing Milling using a mortar and pestle with 5 mL of pH 6.8±0.5 phosphate buffer</td>
<td>Smoking Heating at 120°C for 20 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mL pH 1±0.5 HCl aqueous solution</td>
<td>400 mL pH 6.8±0.5 phosphate buffer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mL 40 vol% ethanol pH 1±0.5 HCl aqueous solution</td>
<td>400 mL 40 vol% ethanol pH 1±0.5 HCl aqueous solution</td>
</tr>
</tbody>
</table>

2.3 Determination of suitable curing conditions for geopolymerization (Paper I)

Both drug release performance and resistance to abuse of the geopolymer-based formulations are closely related to the physical properties of geopolymers, especially in terms of porosity and compressive strength. Thereby, this study started with investigating the effect of the curing conditions on the porosity and compressive strength of geopolymers. Geopolymer samples were cured under different curing conditions in terms of time, temperature and humidity and their properties were measured accordingly.

Curing time is an important factor in the geopolymerization process. Samples with extended curing time did not have obvious changes in X-ray diffraction (XRD) patterns but showed coarser microstructures under SEM. Moreover, longer curing time improved the compressive strength in the first 48 hours and resulted in slightly lower porosity after 96 hours (Figure 7).
The mechanical strength of the samples cured at 22°C for 24 hours was significantly lower than those cured for 48 hours (p=4.57E-05 by t-test).

Heating accelerated strength development, which was more obvious for the samples cured for 24 hours since the geopolymers had not fully developed yet (Figures 7a and 7b). The samples cured at 22°C for 24 hours in air had lower mechanical strength than those cured at 90°C (p=5.72E-07 by t-test). However, according to the XRD patterns, the curing temperature did not influence the crystallinity of the reaction product. After 48 hours of incubation, the elevated temperature resulted in a decrease of mechanical strength for the samples cured under low RH above 22°C. The mechanical strength decreased significantly between the samples cured at 90°C for 24 and 96 hours in air (p=2.23E-03 by t-test).

The geopolymers cured at high RH generally had higher mechanical strength but also slightly higher porosity than those cured in the air (Figure 7). The p value calculated by t-test was 8.031E-07 between the mechanical strength of the samples cured at 90°C for 96 hours under 100% RH and air.

**Figure 7** Compressive strength and porosity of the samples cured in air (a, c) and 100% humidity (b, d).
Table 3 P value calculated by t-test between the mechanical strengths of the geopolymer samples cured under different conditions. (n=6, condition to accept null hypothesis: p>0.05)

<table>
<thead>
<tr>
<th>Condition 1</th>
<th>Condition 2</th>
<th>p value</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>22ºC air 24hr</td>
<td>22ºC air 48hr</td>
<td>4.57E-05</td>
<td>Significant</td>
</tr>
<tr>
<td>22ºC air 24hr</td>
<td>90ºC air 24hr</td>
<td>5.72E-07</td>
<td>Significant</td>
</tr>
<tr>
<td>90ºC air 24hr</td>
<td>90ºC air 96hr</td>
<td>2.23E-03</td>
<td>Significant</td>
</tr>
<tr>
<td>90ºC air 96hr</td>
<td>90ºC humidity 96hr</td>
<td>8.03E-07</td>
<td>Significant</td>
</tr>
<tr>
<td>90ºC humidity 48hr</td>
<td>90ºC humidity 96hr</td>
<td>6.88E-02</td>
<td>Random</td>
</tr>
<tr>
<td>37ºC humidity 48hr</td>
<td>90ºC humidity 48hr</td>
<td>5.11E-01</td>
<td>Random</td>
</tr>
</tbody>
</table>

It was found that the geopolymer samples required at least 24 hours to acquire full mechanical properties. Denser geopolymers would form if the liquid alkali silicate had more time filling into the layered structure of metakaolin. Heating was believed to accelerate dissolution of aluminates and silicates from metakaolin and condensation, resulting in fast strength development [46]. Elevated temperature during curing was found to cause more cracks and slightly higher porosity in geopolymers, which corresponded with previous studies [46-48]. Moreover, it was shown in this study that humidity could prevent dehydration during the reaction and thus might reduce cracking and shrinkage of the products [49].

Considering the efficiency and the products’ properties, the conditions at 37ºC 100% RH for 48 hours were concluded as the suitable conditions for the following studies.

2.4 Screening of polymer excipients for geopolymer-based formulations (Paper II)

As observed in the previous study, the drug release from the geopolymer matrix was faster in the acidic than neutral solutions [11]. Thereby, this study aimed to screen several polymer excipients to reduce the drug release at low pH, according to their effects on the drug release and mechanical strength of geopolymer-based formulations. Poly(methyl acrylate) (PMA), polyethylene-glycol (PEG) and alginate, which are commonly used to modify the drug release of tablets, were chosen to retard drug release. These polymers were integrated into the geopolymer matrix in pre-dissolved (denoted as D) or powder (denoted as P) form.

As observed under SEM, the integration of pre-dissolved PMA (denoted as Ko D and Ko-h D) formed a homogenous layer on the geopolymer surface, while the integration of powder-form PMA (denoted as Ko P) would leave micro-sized voids with a smooth polymer layer covering the interior void surface. The integration of pre-dissolved PEG (denoted as PEG D) and
powder-form alginate (denoted as Alg-G P and Alg-M P) resulted in voids in the geopolymer structure as well. The mechanical strength of the samples was varied due to the difference in the microstructures. Adding pre-dissolved PMA did not significantly influence the mechanical strength of geopolymers, while incorporating other excipients led to an obvious decrease in mechanical strength (Figure 8a).

The drug release test at pH 1 showed that Ko D had a slower drug release compared to the control (Figure 8b). Reducing the integrated amount of PMA by half (denoted as Ko-h D) led to a faster drug release. Alg-G P and Alg-M P retarded the drug release at low pH as well, but the drug molecules leached out from PEG D faster than that from the control. Both PMA and alginate slowed down the drug release at pH 6.8, the pH condition which mimics the fluid in the intestinal tract.

Figure 8 The compressive strength (a) and drug release profiles at pH1 (b) of the geopolymer with/without polymer excipients.

With low solubility at low pH, the layer of PMA formed on the geopolymer pore surface acted as an extra diffusion barrier against rapid drug release in acidic solutions. Thereby, the drug release from Ko D was significantly slower than that from the control at pH 1. Reduction in the amount of PMA or blending powder form of PMA resulted in a less obvious effect on the drug release at pH 1. The slower drug release from the samples with PMA at pH 6.8 indicated that the dissolved polymer might be hindered from diffusing out, which results in slower drug diffusion at neutral pH as well.

The integration of pre-dissolved PEG in the geopolymer resulted in a slight decrease in the compressive strength, which was probably due to the voids formed by phase separation in the microstructure. Moreover, the voids and dissolution of PEG might increase the surface area of the composite and thus lead to a higher drug release rate than the control at low pH. Therefore,
PEG was not further considered as a suitable polymer excipient to sustain the drug release from the geopolymer matrix at lower pH.

Adding the powder of alginate (denoted as Alg-G P and Alg-M P) into the geopolymer also formed some micro-size voids in the structure, which might cause the reduction in compressive strength. However, Alg-G P and Alg-M P have good swelling ability and electrostatic interaction with zolpidem tartrate, which retarded the drug release at low pH. As the swelling ability of alginate is not pH sensitive, their drug releases at neutral pH were slowest of all the samples. The difference of the drug release rates between Alg-G P and Alg-M P was believed to be the result of their variations in swelling ability and electrostatic interaction with drug molecules.

It was concluded that PMA could reduce the drug release from the geopolymer matrix at low pH with little influence to the mechanical strength. Therefore, PMA was used in the next study as the excipient through which to improve the geopolymer-based delivery system.

2.5 Evaluation of the resistance of geopolymer-based oral formulation against tampering (Paper III)

Although previous studies showed that geopolymers could be used as matrix material to deliver potent opioids in a controlled manner, the abuse potential, which is strongly recommended by the FDA for all opioid formulations, has not yet been assessed [32, 33]. This study evaluated the tamper-resistance of the geopolymer-based oral formulation (denoted as Formulation A) by tests that simulate some commonly used abuse methods [32, 33, 37, 38, 44]. The performance of the formulation was compared with that of a commercial ER oral tablet (denoted as Formulation B). Oxycodone, a commonly prescribed opioid, was used in this study.

Formulations A and B were tested to evaluate their resistance against some common tools that abusers use: spoons, a coffee grinder and a mortar and pestle. The average size of residue of Formulation A was larger than that of Formulation B after crushing with spoons and a coffee grinder. Formulation A required 15 minutes of continuous grinding with a mortar and pestle to become the particles of an average size similar to those in the residue from Formulation B, which was obtained after several strokes. Therefore, we concluded that Formulation A was mechanically stronger and required more effort and a longer time to crush into fine particles than did Formulation B.

Intact and ground Formulations A and B were also challenged with extraction tests in several common solvents, as shown in Figure 9. The results showed that after crushing between spoons, Formulation A only released less than 30% of the total drug content while Formulation B released over 80% in most of the solvents. The intact and milled Formulations A and B showed
similar resistance to the extraction in most of the solutions. It is interesting to notice that the released amount from all forms of Formulation A in heated water was lower than that from the corresponding form of Formulation B. The intact Formulation A released a larger amount of the drug than Formulation B at pH 1. However, the milled Formulation A had better resistance at pH 12 than the milled Formulation B.

![Image](image.png)

*Figure 9* The release fraction of oxycodone from Formulations A and B and their particles after extraction for 2 hours. The error bars denote a confidence interval for three independent repeats.

The drug release from intact Formulations A and B was studied in pH 1, pH 6.8, pH 1 with 5 vol% ethanol and pH1 with 40 vol% ethanol solutions. The drug release profiles of intact Formulations A and B in pH 1 and pH 6.8 are shown in Figure 10. Both intact Formulations A and B released the drug in a controlled manner: less than 40% of the drug content was released during the first hour in all media. Their release profiles were evaluated by the mathematical models of Higuchi and Hopfenberg. It was shown that the release profiles of both formulations at pH 1 and pH 6.8 followed a square root of time curve, which could indicate that diffusion was the controlling mechanism for both intact formulations.

Residue of both formulations milled by a mortar and pestle into particles with similar sizes were also tested under the same dissolution conditions. The drug release profiles of milled Formulations A and B in pH 1 and pH 6.8 are shown in Figure 10. However, although 50-60% of the drug content
was released during the first hour, the milled Formulation A still retained a slower drug release at later hours. The release profile of the milled Formulation A fit into the Higuchi model best but fit into the Hopfenberg model as well, which indicates that the control of drug release was still maintained even after harsh grinding. On the other hand, the release from the milled Formulation B presented in an immediate-release manner: it liberated almost all the drug content within 30 minutes, which, however, could not fit into the models used due to the rapid release.

Figure 10 The release profile of intact and milled Formulations A and B in pH 6.8 (a); pH 1 dissolution media in 6 hours (b).

Physical manipulation is usually the first step that abusers take to defeat the controlled-release mechanism of an oral tablet. Formulation A showed a better resistance to mechanical manipulation than Formulation B. The results showed that Formulation A had better resistance than Formulation B against extraction after crushing: the crushed Formulation A released less drug amount in all of the tested solutions. The significant difference of the release amounts between the two crushed formulations could be due to the size difference of the crushed residue. The physical integrity of the geopolymer-based delivery system increased the difficulty of the abuse assisted with size reduction.

The extraction of opioids into a concentrated drug solution using different household solvents is also a common practice by abusers. Formulation A showed better resistance against heated water. Polymer materials usually experience more thermal expansion than ceramics. The expansion can result in enlarged spaces for the drug molecules to diffuse and thus the faster release from Formulation B at higher temperatures. Therefore, Formulation A, whose matrix is mainly composed of ceramics, had an advantage in the resistance against extraction in heated water than Formulation B.

However, the extraction test showed that intact Formulation A released more drug than Formulation B in pH 1 extraction solution. A change in the polymer composition in the geopolymer matrix could be one of the solutions to improve the resistance of Formulation A against extraction at low pH.
The drug release tests in pH 1, pH 6.8 and pH 1 with 5 or 40 vol% ethanol solutions showed that the drug was leached from the milled Formulation B rapidly. Meanwhile, Formulation A could still maintain controlled-release after milling and thus can reduce the risk of dose dumping.

The results of this study provided evidence for the potential use of a geopolymer-based matrix for tamper-resistant oral formulations. It showed that the geopolymer-based formulation had much better resistance to physical manipulation and extraction by heated water compared to the commercial ER tablet. Its high mechanical strength presents an obstacle to the abusers who attempt to crush the formulation for a fast-onset drug release. The drug release profiles obtained by a standard USP method showed that the geopolymer-based matrix can sustain the release and reduce the risk of dose dumping even if the formulation is ground into fine granules.

2.6 Assessment of aluminum release from geopolymer-based oral formulation

As geopolymers contain aluminum in their structure, the potential aluminum ion leakage from the geopolymer matrix could be a concern. Exposure to high levels of aluminum for a long period of time can cause health problems related to the kidneys and nervous systems [50]. Therefore, it is necessary to evaluate the aluminum ion release from the geopolymer-based oral formulation.

The aluminum ion releases from a single dose of both intact and milled geopolymer-based formulation were investigated in pH 1±0.5 and pH 6.8±0.5 media from 30 minutes to 24 hours (Figure 11) [51]. The results showed that the aluminum release from the milled formulation after 24 hours, which represents the maximum possible aluminum leakage, was significantly lower than the non-observed-adverse-effect levels (between 10-42 mg aluminum/kg bw/day) issued by the European Food Safety Authority in 2008.

Therefore, the results of this study indicate that the aluminum ion release from the geopolymer-based oral formulation should not present a health concern for patients.
2.7 Evaluation of the resistance of geopolymer-integrated transdermal patch against tampering (Paper IV)

As the previous study showed that the geopolymer matrix could enhance the tamper-resistance of oral opioid formulations, this study aimed to use geopolymers to improve transdermal opioid patches.

The study started by comparing the geopolymer granules (particle size between 315 and 710 µm) and Patch C (a commercial patch). The dissolution tests in a pH 6.8 buffer and 50 vol% ethanol aqueous solution showed that the drug release from geopolymer granules was slower than that from Patch C. Moreover, a pilot in vivo study showed that the geopolymer granules could achieve a similar plasma concentration response to that of one-fourth of Patch C through transdermal delivery on the backs of male Sprague Dawley rats.

To ensure the consistency and adhesiveness of the patch, the geopolymer granules with smaller particle sizes of between 50 and 100 µm were subsequently integrated into the adhesive layer of the patch. The geopolymer-integrated patch (denoted as Patch A) was compared with a control patch (denoted as Patch B) and a commercial patch (denoted as Patch C) in terms of their tamper-resistance in this study. The adhesives used in Patches A and B were acrylates copolymer (DuroTak® 87-4098), which is similar to the DuroTak® 87-4287 that is used in Patch C. The control patch, Patch B, with the same adhesive as Patch A, was integrated with powder-form fentanyl.

The tamper-resistance tests simulating some common abuse methods on transdermal patches were designed according to regulations and similar studies [32, 33, 52]. In general, Patch A had better resistance than Patch C in all tested extraction methods, which indicated that this new formulation would have lower abuse liability than the commercial patch (Figure 12). Compared

Figure 11 The aluminum release from intact and milled geopolymer-based oral formulation at pH 6.8 (a) and pH 1 (b) [51].
to Patch B, Patch A had better resistance against extraction in heated water, 40 vol% ethanol and smoking. However, Patch A released a higher drug fraction at pH 1 than Patch B: 19% from Patch A and 11% from Patch B.

Figure 12 The release fraction of fentanyl from Patches A, B and C after extraction tests.

The patches were also evaluated with a dissolution test in media simulating gastrointestinal conditions (Figure 13). At both pH levels, Patch C released almost all the drug content within 6 hours, while Patches A and B released the drug in a more controlled manner. The release profiles from all three patches in the tested dissolution media had a linear relationship with the square root of time, which indicates the releases were all diffusion controlled.

Figure 13 The drug release profile from Patches A, B and C at pH 6.8 (a) and pH 1 (b) over 24 hours.

The resistance of Patch A against the tampering tests was compared to that of a commercial patch. The result showed that Patch A had better resistance
than Patch C in all tests, which indicates that Patch A would be less attractive to abusers and thus might have lower abuse potential.

Patch A was also compared to a control patch, Patch B. Patch B was prepared with the same adhesives and similar drug content as those of Patch A but contained the drug without the protection of geopolymer matrix. In Patch A, geopolymer granules replaced part of the space that was occupied by the adhesives in Patch B. Therefore, the drug released from Patch A would diffuse through the geopolymer matrix, partition at the interface and continue to diffuse through a thinner adhesive layer compared to Patch B. The difference in the drug diffusion rate through the same volume of geopolymer and adhesives in the testing condition and partition rate at the interface for Patch A were believed to cause the difference in the extractability of Patches A and B. Patch A was better than Patch B in the tests involving heating: extraction in heated water and smoking (Figure 12). As discussed in the previous study, heating affects the drug release from ceramics to a lower extent than polymers. However, Patch A released a larger amount of the drug after extraction at pH 1 than Patch B. As observed in the previous study, the drug release of the geopolymer matrix is promoted in low pH conditions, and polymer excipients, such as PMA, could improve the acid resistance of geopolymers. Therefore, polymer excipients should be integrated into the geopolymer granules for the further development of this patch.

As the number of abuse cases regarding opioid formulations has increased significantly in recent years, this study explored the possibility of improving the tamper-resistance of fentanyl patches using ceramics. The geopolymer granules incorporated in the matrix could increase the difficulty of compromising the controlled release at elevated temperatures. The drug release profiles showed that the geopolymer-integrated patch retarded the drug release in the simulated gastrointestinal conditions compared to the rapid release from the commercial patch.
3 Bioceramic transdermal enhancement protrusions

3.1 Motivation

3.1.1 Skin and the challenges of transdermal delivery

Skin is the largest organ on the human body and protects the body from the external environment and prevents water loss. The stratum corneum, situated on the top layer of the skin, is the main barrier and protects the underlying tissue from infection, chemicals and mechanical stress (Figure 14). The stratum corneum is 10-15 µm in thickness and composed of dead, flattened corneocytes. Below is the viable epidermis, which is 50-100 µm in thickness. Immune cells, such as Granstein cells and Langerhans cells, are located in the middle of the epidermis. Deeper still is the dermis, which is 1-2mm in thickness. Rich capillary and nerve cells are sited in the superficial dermis, just below the epidermis. The capillaries in dermis are suitable for uptaking drug molecules into systemic circulation.

Regardless of the easily accessible capillaries, transdermal delivery is mainly limited by the stratum corneum, the major barrier to the drug transportation through intact skin. The drug molecules released from the patch have to pass a multi-step process of diffusion and partition through the skin layers to reach systemic circulation. Hence, candidate drugs for transdermal delivery preferably have the following physicochemical properties: a molecular weight less than 500 Dalton, a melting point below 200ºC and a dose less than 10 mg per day [53]. The octanol-water partition coefficient and pharmacokinetic behavior of the drug are the other important parameters constraining the design of a patch. Therefore, although transdermal delivery is an attractive option for drug administration, only a limited amount of drug is available currently as transdermal products: about 40 products of about 20 drug molecules are on the market [54]. The major challenge facing the development of the transdermal patch is to expand the number of drug molecules that could be effectively delivered through skin [55].
3.1.2 Transdermal enhancement protrusions

To enhance percutaneous penetration, some physical and chemical methods have been developed. Microneedle (MN) technology, referred to as transdermal enhancement protrusions in this thesis, is one of the most extensively investigated enhancement methods in recent years. With minimal invasiveness, the micro-sized needles create pores in the stratum corneum, increasing the permeability of the epidermis (Figure 15). As the needles are usually not long enough to reach the dermis where nerves and capillaries are mainly located, the risk of pain and infection is reduced.

Due to the higher skin permeability after MN treatment, drug molecules can be administered transdermally in a larger dose [56]. Another popular application is to deliver biotherapeutic drugs that are difficult to be administered by oral formulations or traditional transdermal patches [57].

Materials for transdermal enhancement protrusions

For successful insertion, both design and physical properties of the material are important to avoid breakage and bending of the needles during insertion.

Silicon was the first MN material studied as it is easy to fabricate using a photolithographic process and silicon etching. These needles have extremely sharp tips and can be fabricated into different shapes. However, breakage of
silicon needles in the skin can increase the risks of infections and inflammations. Metal needles have been developed as they have higher mechanical strength to avoid breakage. These needles are usually expensive to manufacture and leave biohazardous sharp waste after usage. Moreover, as both types of needles are solid, the drug content is usually deposited on the needles as a coating by the techniques such as dipping or spraying. The preparation of the coating solution and the mechanical strength of the coating are the key challenges [57].

Dissolving MNs are usually cheaper to manufacture. They are mainly made by micromolding into a negative mold. Other methods, such as drawing lithography and electro-drawing, have also been used. Various biodegradable polymers and sugars have been molded into MNs. The biodegradable needles are intended to completely dissolve in the skin and leave no biohazardous sharp waste after use. Depending on the dissolution rate of materials, the drug could be released in a controlled manner at different rates. However, mechanical strength and stability are the major challenges for some of the dissolving MNs [57].

Ceramics could serve as alternative materials for MNs due to their good mechanical strength and adjustable porosity. Bystrova and his colleagues developed nanoporous alumina MNs, which have sufficient mechanical strength to remain intact during skin insertion [58, 59]. Alumina needles have delivered the test compounds through human skin in an ex vivo test as well [59]. However, sintering at high temperatures was used for synthesis, which impedes encapsulation of the drug molecules in the ceramic material before molding into needles. In another study, porous calcium phosphate was coated onto stainless steel MNs to increase the drug loading capacity and improve the drug-release behavior [60]. The study showed that the calcium phosphate coating had good mechanical strength and adjustable porosity to deliver trehalose effectively into skin. However, both these needles are limited by drug loading capacity and would leave sharp waste after use. Therefore, bioceramics that are resorbable in the body fluid have great potential in MN application. The possibility of using self-setting CaP and CaS for MN application was investigated in this work for the first time.

Materials for the substrate of transdermal enhancement protrusions
In addition to the developments in the needle materials, the substrate of the MN array has been studied to improve efficiency on breaching the stratum corneum as well [61]. Due to the elasticity and toughness of the skin, the needle arrays with a rigid substrate often encounter the “bed of nails” effect—that is, the force is distributed on each needle, reducing the efficiency of insertion [62, 63]. In this case, some needles might not be successfully inserted and some might be easily pulled out with the movement of the substrate. Both could lead to insufficient and inconsistent drug delivery and also
waste of drugs. Therefore, different polymer materials are used to make flexible substrates in different studies and patents.

Silicon rubber, polymethyl methacrylate, polydimethyl siloxane, polyethylene and polypropylene have been made into MN substrates using ion implanting and etching [64]. A parylene substrate has also been assembled on silicon needles using micro processing techniques [65]. Both methods involve a series of microtechnology processes, which could increase the cost and retard production. A scalable and reproducible soft lithography approach has been developed to make a polymer MN patch with a flexible and water-soluble substrate made of polyvinylpyrrolidone/polyvinylacetate [61]. That study showed that this substrate could be removed easily after the needles have been inserted into the skin. However, the embossing process with high temperatures might affect the activity of the heat-sensitive drugs. A flexible and self-swelling substrate for bioceramic MN to improve the insertion and drug release profile was explored in this thesis.

3.2 Methods

3.2.1 Preparation of ceramic transdermal enhancement protrusions

CaP and CaS MNs in Papers V and VI were prepared by micromolding (Figure 16). The pyramid-shaped master molds were developed on silicon wafers or stainless steel by micro-fabrication. A negative replica of the master template, made of commercially available synthetic silicone, was prepared as an intermediate. A CaP paste was prepared by mixing $\beta$-tricalcium phosphate (45 wt%), monocalcium phosphate monohydrate (55 wt%) and a 0.5 M citric acid aqueous solution (liquid/powder ratio of 0.4). The CaS paste was prepared by mixing $\alpha$-calcium sulfate hemihydrate with water (liquid/powder ratio of 0.4). The cavities of negative replica were filled with the pastes under vacuum pressure.

In Paper V, CaP needle arrays were cured at 37ºC for 48 hours, while CaS needle arrays were cured under ambient humidity and temperature overnight.

In Paper VI, CaS needles were cured under ambient humidity and temperature. After the needles were cured overnight, a warmed gelatin solution (0.2 g/mL) was poured onto the top of needles, and the array was placed in the desiccators with 2 wt% of aqueous glutaraldehyde solution overnight under ambient conditions.
3.2.2 The modified *in vitro* drug release methods

A bench-top method based on a synthetic skin simulator (SSS) was used in Paper V to compare the drug release from different bioceramic microneedles. The illustration of the setup is shown in Figure 17 a. As the amount of moisture accessible to MN in the skin is limited, *in vitro* dissolution tests, USP II, are not suitable for evaluating performance. The SSS method, which was validated using a commercial transdermal patch, is an easy-to-handle alternative and suitable for providing preliminary screening of transdermal formulations under limited humidity [66]. A piece of cellulose drug reservoir—that is, a synthetic skin simulator (SSS) (Wettex®, Freudenberg, Sweden), was prepared in a square shape (2 x 2 cm$^2$) and moistened with 400 µL of pH 6.8±0.5 phosphate buffer. A self-setting bioceramics microneedle (SCMN) plate was placed on the cellulose reservoir and covered with Parafilm® to reduce the vaporization. The released drug was collected on the SSS during testing. At predetermined time points, SSS was collected and replaced by a new piece of moistened SSS. The drug containing SSS was then soaked in a pH 1±0.5 HCl aqueous solution to extract the collected drug molecules. The drug concentration was measured by the UV/VIS spectrophotometer, as described previously.

A vertical diffusion cell was used in Paper VI to compare the drug release from the bioceramic MNs with flexible and swelling substrates (Figure 17 b). The diffusion cell was composed of two chambers: receptor and donor. The receptor chamber was filled with 20 mL distilled water. A synthetic membrane was placed in between the chambers and fixed in position by the joint. Air was minimized under the membrane when positioning the membrane and joint. The MN array was placed on the membrane in the donor chamber and covered with Parafilm® to prevent evaporation. The diffusion cell was placed on a shaker at 40ºC during drug release. Aliquots of 1 mL were collected from the receptor chamber and replaced by 1 mL of distilled water. The drug concentration was determined using the HPLC, as described previously.
Figure 16 The micromolding process of bioceramic MNs in Papers V and VI.

(a)

(b)

Figure 17 Illustration of the setup of modified drug release methods: SSS method (a); diffusion cell (b).
3.3 Exploring self-setting bioceramic microneedle (SCMN) array (Paper V)

This study presented the first bioceramic microneedle array and its in vitro drug release performance. Two well-studied bioceramics, CaP and CaS, were molded into pyramid-shaped MNs under mild conditions which provides the possibility to integrate drugs into the ceramic needles. Therefore, two ways of drug loading were performed on SCMNs, and their drug release performances were investigated and compared.

The physical properties of these ceramics were documented: the surface areas of CaS and CaP were 27.1 m²g⁻¹ and 6.0 m²g⁻¹, respectively. The zeta potentials of CaS and CaP suspension in 0.05 M NaCl solution (pH 6 ± 0.1) were -15.74 mV (SD=1.79) and -16.184 mV (SD=2.2), respectively.

CaP and CaS were molded into needles under vacuum, and the cured needles were observed using SEM. CaS was densely packed into pyramid-shaped needles with small pores and distinct edges (Figure 18 a-c). In contrast, CaP needles had abundant micrometer-sized pores and channels forming needles with coarse surfaces (Figure 18 g-i).

![Figure 18 SEM images of CaS MNs: densely arranged (a), sparsely arranged (b) and magnified needles (c); cross section view of CaS: densely arranged (d), sparsely arranged (e) and magnified needles (f); CaP MNs: densely arranged (g), sparsely arranged (h) and magnified needles (i).](image)

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The drug release study was performed by the SSS method. In the first study, the drug was loaded into the SCMNs by blending into the ceramic paste before curing. Both CaS and CaP needles were prepared with two needle dimensions (sparsely arranged, denoted as –S, or densely arranged, denoted as –D) and two drug concentrations (single dose, denoted as 1, and double dose, denoted as 2). In general, CaP MNs released a smaller amount of drug than CaS MNs (Figure 19 a and b). The results showed that SCMNs with densely arranged needles released a higher fraction of drug content than the sparsely arranged needles. Moreover, there was an inverse relationship between initial drug content and the fraction of release.

In the second study, the drug solution (with 1 mg of zolpidem tartrate) was coated on the surface of SCMN (Figure 19 c). For the coated needles, the needle dimension did not influence the drug release. The coated CaP released faster than CaS MNs, which was in an inverse order from the results in the first study.

Figure 19 The drug release from SCMNs: CaP MNs with drug integrated in the matrix (a); CaS MNs with drug integrated in the matrix (b); CaP and CaS MNs with drug coating (c).

The in vitro insertion test evaluated the ability of SCMNs to penetrate porcine skin. The skin after insertion was observed by X-ray computed microtomography (microCT) with the SCMNs. After the reconstruction of mi-
croCT images, it showed that the needles were mostly retained in shape with no breakage (Figure 20). A brief investigation into the reconstruction image showed that SCMNs had adequate mechanical strength to allow manual insertion into porcine skin.

![Image](image_url)

**Figure 20** *In vitro* insertion of SCMNs into porcine skin: porcine skin after insertion (a); 3D reconstruction of microCT images; dark brown represents the SCMNs, yellow represents the skin and blue represents the air (indicated by the arrows) (b-d).

In the first study, the drug was integrated into SCMNs before curing. The result showed that CaP MNs released slightly less drug than CaS MNs. It was believed that the faster drug release from CaS MNs was mainly due to the higher water solubility and larger surface area of CaS. The SEM pictures taken before and after the drug release test corroborated this theory. The surfaces of CaS MNs were rougher after the drug release test, while the surface of CaP MNs did not show obvious change. In addition to the properties of ceramics, it was also found that drug release was affected by needle dimension and drug content. As the degradation occurred mainly on the needle tips, the densely arranged MN array with more needles was found to degrade more easily and thus promote drug release. The inverse relationship between drug content and drug release rate indicate that the drug release was not exclusively controlled by the drug dissolution. The total bulk surface area, 

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porosity and degradation rate of the matrix are thought to be the major parameters that influence the drug release from SCMNs.

In the second study, the drug was coated on the SCMN surface. The faster drug release from coated CaP MNs than from CaS MNs was possibly caused by the difference in their microstructures. The loosely packed CaP MNs would allow the moisture to diffuse rapidly into the ceramic structure and thus release the drug molecules from the pores more easily. On the other hand, the more densely packed CaS MNs might hinder the release of drug from the pores with smaller openings.

This study showed the potential of resorbable bioceramics for biodegradable MN application. Self-setting CaS and CaP, as outlined here, could be molded into MNs under mild conditions. The drug loading, porosity and ceramic degradation rate can be used to regulate the release behavior. Successful penetration of this SCMN through skin indicated its potential application in transdermal drug delivery.

3.4 Improvement of bioceramic microneedle array with higher aspect ratio and flexible substrate (Paper VI)

As bioceramics appeared to have potential in MN applications, a further development on higher aspect ratio needles with flexible and self-swelling substrates was performed to improve drug release performance and insertion of the SCMN into skin. Gelatin was used as the substrate material for this study. Needles were made of CaS with heights of 450 \( \mu \text{m} \) (denoted as BCMN-G450) and 600 \( \mu \text{m} \) (denoted as BCMN-G600)

As observed through SEM, the bioceramic microneedles with flexible and swelling substrates (BCMNG) had sharp tips and tight binding with the gelatin substrate (Figure 21). The ceramic needles had clear edges and surfaces with abundant pores and channels.
The drug releases from BCMN-Gs were studied using vertical diffusion cells. The drug, clonidine HCl, was blended into the ceramic paste or coated on the cured needles. In general, the drug release was in a sustained manner and scarcely influenced by the MN geometry. The needles with the drug coating released significantly faster than the needles with preloaded drug content. The needle arrays and the diffusion membrane were examined using SEM after drug release (Figure 22). The ceramic crystals left on the membrane provided evidence of ceramic degradation after four-hour drug release.
Porcine skin after BCMN-G insertion was sectioned by cyro-cutting and then examined. The pictures under light microscope showed that stratum corneum was penetrated by the BCMN-G after manual insertion and a clear mark from the needle was left on the skin. This histology study of the skin after insertion showed the insertion ability of BCMN-G.

The image of BCMN-Gs under florescent microscope showed that the loaded model compound could homogenously distribute in the needles from tip to base. The SEM pictures showed that the bioceramic needles were dissolved and re-crystallized on the diffusion cell membrane. It was believed
that the gelatin substrate could swell and detach from the needles after contact with moisture. Moreover, *in vitro* insertion using porcine skin showed that the BCMN-G could be inserted manually into the skin without any help from an extra device.

However, due to the uneven water absorption of the gelatin substrate, there was variation of drug release between BCMN-G samples. Further control on the filming, cross-linking and drying of the gelatin substrate could reduce the variance. Moreover, other water swellable materials that could form a flexible film would be an alternative to improve the drug release performance for the bioceramic MNs.

This study showed the potential of fabricating bioceramic MNs with a higher aspect ratio and a flexible substrate to assist drug release and insertion. In addition to providing insertion with less effort, the gelatin substrate was believed to be able to detach from the needles after needle contact with subcutaneous fluid, leaving the needles in the skin for extended release. The *in vitro* result of this bioceramics MNs showed the potential of further enhancement in transdermal drug delivery.
4 Concluding remarks

The work presented in this thesis demonstrates the possibility to use ceramic materials—specifically, geopolymer, CaP and CaS—as matrix materials for oral and transdermal drug delivery. Specifically, the applications were in two tracks: tamper-resistant formulations and transdermal enhancement protrusions.

In the first track, it was demonstrated that geopolymers could be developed into oral and transdermal tamper-resistant formulations. The important physical properties of the drug-loading geopolymer matrix—specifically, mechanical strength and porosity—could be altered with curing conditions. Curing under 100% RH at 37°C for 48 hours was found to be the suitable condition, balancing between efficiency and resulting properties of geopolymers. The results showed that PMA was effective in reducing the drug release rate from the geopolymer matrix at low pH, while it had little influence on its compressive strength. Subsequently, the tamper-resistance of this geopolymer-based oral formulation was evaluated and compared to a commercial tablet. The geopolymer-based formulation showed good resistance to tampering, especially against mechanical crushing and heat-assisted extraction. This oral opioid formulation could maintain controlled release even after milling into fine particles. Moreover, the possibility to integrate the geopolymer-based drug carrier in transdermal patches to improve tamper-resistance was investigated as well. The patch with geopolymer granules had much better resistance to extraction in small volume, chewing and smoking compared to the commercial opioid patch. Moreover, the geopolymer-integrated patch could maintain controlled release in the simulated ingestion condition, while the commercial patch instantly released 80% of the drug content within 3 hours.

The second track of the work explored the possibility of using self-setting bioceramics in MN applications due to its high compressive strength, biocompatibility and resorbability in vivo. SCMNs were fabricated and evaluated for the first time. Their microstructures, in vitro drug release and in vitro insertion were investigated. The bioceramic MN array with higher aspect ratio needles and a flexible substrate were further developed. The study showed that the substrate could swell and detach from the needles, which could lead to faster degradation of the needles. Moreover, a histological study provided strong evidence of its ability to penetrate stratum corneum.
5 Future outlook

The work in this thesis presents a few properties of geopolymer-based formulations and bioceramic transdermal enhancement protrusions. Nonetheless, there are still many interesting and unresolved issues related to these drug formulations. In the following, a few are presented:

**Ethanol and acid resistance of oral and transdermal geopolymer-based formulations.** It was shown that the geopolymer-based formulations did not perform significantly better than the commercial products in the resistance to ethanol and acid extraction. Other polymer excipients or combination of excipients could be explored to improve the resistance against extraction in these solutions.

**Drug and matrix interaction.** The drug molecules were embedded in the matrix and released by diffusion. The interaction between drugs and the negatively charged ceramic matrix is important for predicting the release behavior of other types of drugs from these drug formulations.

**Polymorphism of the drug in the formulation.** The drug in salt form was mixed into cement paste during synthesis, as in Papers II, III, V and VI. The solubility of the drug and the local pH condition in the bioceramic matrix could both influence the polymorphism of the drug, which is closely related to the stability and drug release performance of the drug formulation.

**Optimization of SCMN.** Although it has been shown that bioceramic MNs can be successfully inserted into skin without extra help from other devices, the shape, aspect ratio, sharpness of tip and porosity of bioceramics could be optimized to further reduce the effort required to apply the SCMNs on skin.

**Fast disintegrating bioceramic microneedles.** It could be interesting to explore whether bioceramics microneedles could achieve immediate drug release for acute treatment, such as vaccine delivery and local anesthesia.

**In vivo evaluation.** As the current studies on these two formulations are all based on in vitro studies, it would be interesting to know their in vivo performance.
Future applications of SCMNs. Due to the rich immune cells in viable epidermis, SCMNs could be explored to deliver vaccines to stimulate immune responses.
Keramer har använts som material för många applikationer, allt från konstruktionsmaterial i byggnader till vattenrening. Porösa och biokompatibla keramer har också använts som läkemedelsbärare för att åstadkomma tidsstyrda, reproducerbara och effektiva läkemedelsadministrationer [7, 8]. Läkemedel, från små molekyler till biomolekyler, har laddats in i keramiska matriser för att skapa riktad läkemedelsadministration och därmed behandling i specifika delar i kroppen.

Avhandlingen syftar till att använda keramiska material för läkemedelsadministration för två specifika användningsområden: missbrukssäkring av opioid-läkemedel och biokeramiska mikronålar för transdermal administrering av läkemedel.


I denna avhandling utvecklades biokeramiska mikronålar. Resultatet visade att de biokeramiska nålarna kan frisätta läkemedel på ett kontrollerat sätt och kan tryckas in i hud utan hjälpmedel. Vidareutveckling av produkten visade att det går att nå snabbare frisättning av läkemedlet och minska kraften för att föra in mikronålarna i huden.
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you for your love and patience. And also thanks to our coming family member. I love you all!
8 Analytical techniques

8.1 Compressive strength
The compressive strength was taken as an indicator of the mechanical strength of a material in this work. The measurements were prepared according to a standard testing method using the Autograph AGS-H universal testing machine (Shimadzu corp., Japan) [67]. The compressive strength of a material was recorded at the maximum stress that the material in the defined geometry could tolerate before breakage, as described in the following formula:

\[ \sigma_{\text{max}} = \frac{F_{\text{max}}}{A} \]

8.2 Scanning electromicroscopy
A scanning electron microscope (SEM) was used to produce high-resolution images of material surfaces. When observing a material through an SEM, a beam of electrons interacts with the sample surface and generates the signals that can be detected and converted to reveal surface information. Secondary electrons signals were mainly used to provide images in this work. Secondary electrons are the knocked-out electrons from the atoms on the material surface that could present information on the morphology, porosity and grain sizes of the sample. Poorly conductive samples, such as ceramics, require a thin conductive coating layer, usually Au/Pd, to reduce the charging effect. In this thesis, a LEO 1550 microscope (Zeiss, Germany) was used to obtain high-resolution images.

8.3 Powder X-ray diffraction
Powder X-ray diffraction (XRD) was used in this work to obtain the crystallization information about a material using a D5000 diffractometer (Siemens/Bruker, Germany) and a D8 Advance diffractometer (Siemens/Bruker, Germany) with CuKα radiation at 45 kV and 40 mA. Parallel X-ray beams scan the sample over a range of angles. For crystalline materials, such as the
angle changes, some constructive interference of the beams would occur. The angles at which constructive interference occurred are recorded and compared to the database of the International Center for Diffraction Data (Newton square, PA, USA). By comparison, the information on the unicell and polymorphism is revealed and used to identify the phase and composition of the sample, according to Bragg’s law:

\[ n\lambda = 2d \sin \theta \]
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