ENHANCED RELEASE OF LIDOCAINE FROM SUPERSATURATED SOLUTIONS OF LIDOCAINE IN A PRESSURE SENSITIVE ADHESIVE

DISSertation

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

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2003

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ABSTRACT

Transdermal drug delivery systems consisting of a pressure sensitive adhesive (PSA) supersaturated with drug have been studied with the objective of enhancing drug release. Lidocaine (LC) and Duro-Tak®87-2287 (PSA) were the model components. *In vitro* release of drug through a composite membrane consisting of multiple layers of cellulose membrane and a silicone membrane was significantly higher from supersaturated LC/PSA systems compared to systems in which drug had crystallized. Drug loading was an important factor influencing the release of lidocaine from the prototype transdermal delivery systems. The DT2287 PSA hydrated when in contact with water, and the presence of LC accelerated this process. Slow crystallization was also observed during the drug release experiments and was highly dependent on the hydration state of the drug/PSA systems. This suggests that hydration of drug/PSA systems may be an important factor in drug release when water is present. e.g., from the stratum corneum when a transdermal system occludes the skin, and may account for the non-Fickian release of LC from these systems.

The physical stability of the systems was evaluated kinetically and thermodynamically using thermal analysis and then applying theories of nucleation, e.g., the Fisher-Turnbull equation; and phase transformation, e.g., the Avrami equation. From this analysis nucleation rather than the crystal growth process appears to govern the crystallization of LC from the supersaturated LC/PSA systems. Nucleation is a diffusion-
controlled process, which is therefore closely dependent on the viscoelastic properties of the PSA medium. Nonetheless some of the thermodynamic features of the crystallization of LC in drug/PSA systems, i.e., $T_{crit}$, were retained from crystalline LC. Crystallization of LC in the PSA systems also had a two-phase temperature dependence with the values of key kinetic parameters, such as the Avrami exponent and the Avrami constant, remaining constant over a low temperature range. Over a higher temperature range, however, the crystallization behavior of LC cannot be explained by the conventional Avrami theory, and a new hypothesis has been proposed suggesting that the nucleation rate increased exponentially with time. To reconcile the apparent differences between the classical theory of nucleation and the proposed hypothesis, a two-step nucleation process is suggested. Before nuclei are stably formed, the nucleation rate follows the classical theory of nucleation, which indicates that the nucleation rate is time independent. However, after the nuclei are stable the nucleation rate increases exponentially with time. It appears that the frequent branching that occurs as crystals grow may account for the time dependence of the nucleation rate after nuclei are formed; i.e., each branch is essentially a nucleus.

To further explore the mechanisms of crystallization in the model systems, the physical and chemical properties of LC/PSA systems were characterized using thermal analysis, hot stage microscopy, and FT-IR. LC/PSA interactions were evaluated using thermal analysis, specifically the composition dependence of the glass transition temperatures. The interactions between LC and the PSA were then characterized by FT-IR. An intermediate interaction between LC and the PSA was found, which resulted in a conformation entropy relaxation of the polymer systems. Although no specific interaction, such as hydrogen
bonding, was found between the two components, LC is actively involved in the relaxation of the PSA, and no simple dilution effect was found when LC was added in the PSA systems. This may contribute to the physical stability of the supersaturated LC/DT2287 systems by reducing the amount of free LC in the systems.
Dedicated to my parents, my wife and my son
I would like to give special thanks to my advisor, Dr. Sylvan G. Frank, for his intellectual mentorship and insightful directions, for his encouragement and patience, for his trust and confidence in me, and especially for his dedication to my personal growth, which will perpetually support me throughout my career and life.

I am indebted to my committee members, Dr. William Hayton, Dr. Robert Curley, and Dr. Jim Dalton for their valuable comments and suggestions, and for their time. I am grateful to Dr. Arne Brodin for his invaluable comments and inspiring discussions with me on my project.

I would like to appreciate my labmate Carmen and Kathy for their help and friendship, especially Carmen, whose instruction has helped me take full advantage of the resources of our laboratory. Thanks also to Mrs. Karen Lawler and Ms. Kathy Brooks for their help and encouragement on numerous occasions.

I thank AstraZeneca AB and The OSU College of Pharmacy for financial support.

I am deeply grateful to my family, especially my wife, for her love and support; and my parents, for their underlying faith in me.

My sincere gratitude also extends to all the faculty, staff, and friends at OSU College of Pharmacy, and particularly the Division of Pharmaceutics, whose names are
not mentioned. Your friendship, trust, and love have supported me through these years, and do not go unrecognized by me.
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CHAPTER 1

INTRODUCTION

The transdermal route is one of the major pathways for delivering potent therapeutic agents to the human body. The potential advantages of transdermal drug delivery may include:\(^1\)

- Avoidance of first-pass metabolism by the gastrointestinal tract and liver in the case of oral delivery.

- Ease of use and withdrawal of drug. Compared with parenteral injections, the transdermal route is easier for patients to use and compliance can be improved due to its non-invasive nature. In addition, ease of withdrawal is a unique advantage of transdermal drug delivery in most cases, allowing medication to be discontinued in time to avoid adverse effects due to overdosing.

- More uniform drug concentrations in the blood. Transdermal delivery usually gives a zero-order absorption of drug, thereby maintaining relatively constant plasma drug levels up to the end of the dosing interval or until drug is exhausted. This can improve the therapeutic effect and reduce side effects resulting from alternating high-to-low
plasma drug concentrations characteristic of non-controlled release oral and parenteral drug delivery systems.

- Sustained-release of drug for long durations to reduce dosing frequency. Compared with controlled release oral delivery systems which typically have the limitation of 24 hours of drug release, transdermal delivery systems can be formulated to continuously release drug for up to 7 days.

The applications of the transdermal delivery route may encompass both local and systematic drug therapies. For local therapy, drugs are delivered through the epidermis and act in the local areas of the skin or subcutaneous tissues. For example, local anesthetics can penetrate through the skin and act in the region adjacent to administration. On the other hand, drugs that penetrate through the skin may enter the systemic circulation and be distributed to the entire body or to specific target organs to achieve therapeutic effects. In either case, penetration of drug through the epidermis is generally required.¹²

Transdermal drug delivery, however, is often limited by the low permeability of the skin.³⁴ As a result, the bioavailability of drugs delivered by this route is generally low and the amounts of percutaneously absorbed drugs may not reach minimum therapeutic levels even for many potent drugs.¹ As a result, the number of drugs that can be potentially used by this pathway is small. Therefore, there has been a consistent demand for novel and effective methods to enhance drug permeation through the skin.⁵
1.1 Skin structure and its barrier function

The skin of an adult body has a total surface area of ~2 m² and utilizes about one-third of the blood supply of the body.\textsuperscript{6} The physiological functions of the skin include:\textsuperscript{6}

- Separating the internal organs from the outside environment;
- Protecting the body against physical, chemical and microbial attacks, and ultraviolet light;
- Maintaining body temperature.

Human skin is a remarkably effective barrier to permeants, due to its unique multilamellar structure. The skin is essentially composed of two major layers, the epidermis and the dermis. The epidermis is the outer epithelial layer of the skin and is an unvascularized layer consisting of cells which are differentiated from stem cells on the basal membrane at the interface between the epidermis and dermis.\textsuperscript{3} The inner layer of the skin is the dermis which contains abundant capillaries, nerves, sweat glands, sebaceous glands, and hair follicles.\textsuperscript{7} The outermost layer of the epidermis, the stratum corneum, consists of ~15 layers of dead cells, which are also referred to as “corneocytes”. The corneocytes are embedded in an intercellular lipid matrix which can be stylized as having a “brick-and-mortar” structure (see Figure 1.1). The corneocytes, the “bricks”, are composed mainly of fibrous and water-insoluble keratin, which is about 20% cross-linked
Figure 1.1. The structure of the stratum corneum and intercellular lipids of human skin (from Ref. 7).
and packed tightly making the corneocytes almost impermeable to most solutes. The intercellular area of the stratum corneum, the “mortar”, consists of a complex lipoidal mixture in a uniquely arranged matrix. Compared with the corneocytes, the intercellular lipid matrix has a looser structure and is relatively more permeable to solutes.4

The stratum corneum, although only about 20 μm thick, provides most of the barrier effect of the skin.8,9

Drug penetration through the stratum corneum may follow one or more routes: transcellular, intercellular, or shunts through the appendages, e.g., sweat glands or hair follicles. The contribution of the transappendal pathways, however, is usually believed to be small because the appendages occupy only about 0.1% of the total human skin surface.7 Many studies have suggested that the intercellular transepidermal route, which is mainly through the intercellular lipid matrix, is the most significant pathway for passive drug penetration.10 Therefore, the barrier effects of intercellular lipids become the rate-limiting factor for the percutaneous transport of solutes. Additionally, the key role of intercellular lipids is indicated by the fact that the lipid matrix, which occupies ~20% of the total volume of the stratum corneum, forms a continuous phase; whereas the corneocytes by contrast are enveloped by the lipid matrix and are essentially discontinuous islands. Consequently, any molecule permeating through the stratum corneum has to diffuse across this continuous lipid phase, thereby making it a crucial step for transdermal drug delivery.11,12

The resistance to drug penetration presented by the intercellular route is attributed to the highly tortuous diffusion pathway and the composition and structure of the lipid
It has been found that the intercellular lipids, composed mainly of ceramides (42%), cholesterol (27%), and cholesterol esters (10%), form a highly ordered multiple lamellar structure (see Figure 1.1), in which the lipids are densely packed into a crystalline-like structure. In the matrix, the lipids, especially the ceramides whose molecules contain hydrophobic and hydrophilic moieties, assemble into multi-lamellar structures with alternate hydrophobic and a hydrophilic domains (see Figure 1.1). The long, straight, and saturated hydrocarbon chains of the ceramides help to pack the lipid bilayers tightly and orderly by chain-chain interactions, and make the structure of the lipid matrix close to that of a crystal, i.e., a liquid crystal. This arrangement of the lipid matrix forces a diffusant molecule to pass sequentially through a number of densely packed layers with different regions of polarity. Generally, compounds with good solubilities in both lipids and water have the highest skin permeability. Furthermore, the high melting points of the lipids in the stratum corneum make the matrix mostly “solid” at physiologic temperature with a small portion in a gel phase. Consequently, a diffusant with a relatively large molecular weight may have difficulty penetrating through this dense lipid matrix. Therefore, the properties of a drug molecule allowing optimal permeability across the skin can be summarized as follows:

- Lipophilicity: Log P of 1-3.
- Molecular size: MW < 500 Daltons.
- Hydrogen bonding groups: ≤ 2.
- Melting point: ≤ 200 °C.
1.2 Theoretical basis for passive transdermal delivery and its enhancement

Permeation of drugs through the skin or other membranes, as indicated by Higuchi,\textsuperscript{17} is a process of passive diffusion and can be described by Fick’s laws.\textsuperscript{10} In conditions of steady-state, the flux is given by:

\[ J = D_m \left( \frac{C_{s,m}}{L} \right) \left( \frac{C_v}{C_{s,v}} \right) \quad (1.1) \]

where \( J \) is the flux of drug, \( D_m \) the diffusion coefficient of the drug in the membrane, \( C_{s,m} \) the solubility of the drug in the membrane, \( L \) the length of the diffusion pathway, \( C_v \) the concentration of drug in the vehicle and \( C_{s,v} \) the solubility of drug in the vehicle.

Drug transport across a membrane can be considered to be a balance between driving forces and resistances. In Equation 1.1, the ratio \( C_v/C_{s,v} \), the degree of supersaturation or supersaturation ratio,\textsuperscript{18} represents the relative chemical potential of the donor system. Under sink conditions, this value reflects the gross chemical potential gradient across a target membrane. Thus, it can be regarded as the thermodynamic driving force (thermodynamic activity gradient) for drug permeation through a membrane or skin. On the other hand, the diffusion coefficient \( D_m \), which is virtually the reciprocal of the viscosity of the barrier medium according to the Stokes-Einstein equation,\textsuperscript{19} essentially represents the kinetic resistance of the barrier to drug penetration. Therefore, transdermal drug delivery is a thermodynamically favored, but kinetically suppressed process.
Based on Equation 1.1, enhancement of drug flux across the skin may be achieved by: 1) increasing the drug diffusion coefficient, $D_m$, by decreasing barrier resistance; 2) increasing drug solubility, $C_{s,m}$, in the skin, or 3) strengthening the driving force for penetration by increasing drug concentration in the vehicle. Most of the strategies for enhancing transdermal permeation of drug utilize one or a combination of these mechanisms.

1.3 Transdermal drug delivery systems

1.3.1 System designs

Transdermal drug delivery systems (TDDS) are usually in form of “patches” incorporating pressure sensitive adhesives. There are two basic designs for the transdermal patches: matrix or reservoir types. Matrix-type patches include monolithic adhesive and polymer matrices, whereas reservoir-type patches include liquid and solid-state reservoirs. Schematic illustrations of these designs are given in Figure 1.2.

1.3.2 Components

As shown in Figure 1.2, a TDDS may contain the following components:

- Pressure sensitive adhesives (PSAs), within which drugs and other excipients may be incorporated.
Figure 1.2 Schematic illustrations of transdermal drug delivery systems (from Ref. 1).
- A polymer matrix or other vehicle serving as the drug reservoir.
- Backing materials.
- Rate-controlling membranes.
- Release liners.

These components will be discussed below.

1.3.2.1 Pressure sensitive adhesives (PSAs)

Pressure sensitive adhesives (PSAs) are generally defined as “materials that can adhere to a substrate with light pressure and which leave no residual adhesive upon their removal”\(^2\). PSAs are the most important components of a TDDS other than the drug. They are unique bioadhesives that can adhere to the skin to ensure intimate contact between the patches and the skin surface. To achieve this goal, some thermodynamic as well as kinetic requirements have to be satisfied\(^4\). Thermodynamically, for skin adhesion to occur, the surface energy of the adhesive must be equal to or less than that of human skin. Kinetically, the adhesive must be balanced between its ability to adhere to the substrate surface and its cohesive strength. The former, the ability to adhere, requires the material to possess sufficient mobility to flow so that intimate molecular contact between the adhesive and the substrate surface can be achieved with light pressure. On the other hand, sufficient cohesive strength of the adhesive is also necessary to ensure clean removal without leaving any residue on the skin. These mechanical properties are defined as “viscoelastic properties”, which means the materials are partly “viscous” and
deformable under mechanical stress, while “elasticity” of the materials is retained to a certain extent so that deformations are partly recoverable after the stress is withdrawn.\textsuperscript{20} Since the PSAs in a TDDS must function under various conditions such as high humidity, wide-ranging temperatures, bathing, and sweating; the viscoelastic properties of the PSAs must be maintained during the entire period of application.\textsuperscript{4}

In addition to these viscoelastic properties, formulation compatibility and biocompatibility also need to be considered for the PSAs used in a TDDS.\textsuperscript{2} Formulation compatibility requires that the PSAs be physically and chemically inert in the presence of drug and excipients, and should offer desired solubility and permeability for the drug and other excipients. Biocompatibility requires that the PSAs should not produce skin irritation or sensitization and have no systemic toxicity.\textsuperscript{2}

Four types of PSAs that have been most widely used in TDDS are karaya gum, polyisobutylanes (PIBs), polysiloxanes (silicones), and polyacrylate copolymers (acrylics).\textsuperscript{1} Among these, karaya gum-based adhesives are being superceded by the other three types of synthetic adhesives.\textsuperscript{1} More recently, hydrophilic PSAs have been developed and used in TDDS.\textsuperscript{2} For example, hydrogels composed of high molecular weight polyvinylpyrrolidone and low molecular weight polyethylene glycol have been used as PSAs in TDDS for a number of drugs.\textsuperscript{21-23}
Polyisobutylene (PIBs)

PIBs are among the earliest types of PSAs used in TDDS. They are composed of homopolymers of isobutylene as shown in Figure 1.3a. Due to their paraffinic structure, PIBs are nonpolar and chemically inert. The high flexibility and tack of PIBs are imparted by their low glass transition temperatures (T_g) at ~62 °C. The glass transition temperatures are the temperatures at which polymers or amorphous materials convert from a glassy state, in which the molecular movements are exclusively inhibited at the lower temperature, to a plastic state, where these movements are re-activated by increasing temperature. The glass transition temperatures indicate the molecular mobility of a polymer material, i.e., a lower T_g generally reflects a higher molecular mobility at room temperature. Therefore, a low T_g is one of the important characteristics of PSAs and determines their high molecular flexibility at room temperature.

The close molecular packing of PIBs results in their low permeabilities to air, moisture, and drugs. Therefore, PIBs are usually used with drugs with a low polarity. Typically, these types of PSAs are formulated by blending two PIBs, one of high and the other of medium molecular weight (MW), or by blending a high MW PIB with a low MW polybutene. The high MW polymers are used to impart cohesive strength, while the low MW polymers are used as tackifiers which give the PSAs sufficient fluidity to ensure intimate contact between the adhesive and the skin. The viscoelastic properties of the
Figure 1.3 Chemical structures of three types of pressure sensitive adhesives.
adhesives can be adjusted by changing the ratio between the high and low MW components. In general, this sort of blending provides PSAs with medium tack.\textsuperscript{4}

**Polyacrylates (acrylics)**

Polyacrylates are poly (acrylic esters) produced by copolymerization of acrylic esters, acrylic acid, and other functional monomers (see Figure 1.3b). Acrylics have a saturated hydrocarbon backbone, and thereby are resistant to oxidation. Acrylic copolymers have a $T_g$ between $\sim -55$ to $-15\, ^\circ\text{C}$, and are inherently tacky. Therefore, they do not need additional low MW tackifiers. In addition, acrylics offer many advantages including biocompatibility, compatibility with a wide range of drugs and excipients, and good skin adhesion.\textsuperscript{2} Another unique advantage of acrylics is that the properties of these PSAs can be tailored according to special application requirements by changing the various types of monomers used in their copolymerization reactions. Compared with PIBs, acrylics provide better solubility and permeability for many drugs and excipients.\textsuperscript{2}

**Polysiloxanes (silicones)**

Polysiloxane PSAs are produced by condensation of two major components: a polysiloxane polymer and a silicate resin (see Figure 1.3c), which results in a network of
polymer crosslinked by the resin molecules. By changing the ratio between the polysiloxane polymer and the resin, the degree of crosslinking can be changed resulting in an adjustment of adhesive properties.

Polysiloxane PSAs are unique in their high molecular mobility. Their low glass transition temperatures ($T_g$) of ~$-127 \, ^\circ C$ make the silicones highly flexible polymers with greater free volumes at room temperature. Therefore, silicone PSAs have a high permeability to air, moisture, and many drugs. In addition, their chemical and biological inertness is also well documented. It should be noted that the silanol end group is reactive and is incompatible with amine-functional drugs, although end-capping of the silanol group may help solve this incompatibility. Another drawback of silicone PSAs is that they are relatively more expensive than the other PSAs.

1.3.2.2 Backing materials

Backings are polymer films that are either permeable or occlusive to moisture depending on the design of a TDDS. The polymer materials can be occlusive materials, such as synthetic polyesters, or semi-occlusive films, such as polyurethanes and polyolefins, or nonocclusive fiber-based materials. Selection of the backing films essentially depends on the active ingredient to be delivered. Since occlusive backings can cause hydration of the stratum corneum, and thereby promote the permeation of drugs through the skin (see Section 1.5.1.1), it may be desirable to use these backings to enhance the delivery of drugs to deeper dermal tissues or systemic circulation. On the
other hand, nonocclusive fiber-based materials may be preferred for those TDDS systems in which it is not necessary to enhance the transdermal permeation of the active ingredient.\(^1\)

**1.3.2.3 Rate-controlling membranes**

Rate-controlling membranes are used in reservoir or multilaminate patches to control the rate of drug release when the rate of drug transport through the skin is too rapid. These membranes are used to regulate drug release from the patches and thereby control the amounts of drug absorbed. Additionally, they may also provide physical support of a liquid reservoir or a multilaminate patch. Rate-controlling membranes in TDDS include nonporous ethylene vinyl acetate films or microporous polyethylene films.\(^1\)

**1.3.2.4 Release liners**

Release liners protect the PSA layer of a TDDS until the time of use. Usually, they are polyester films coated with a thin layer of polymers which can be PSA releasable. These polymers include polysilicone, polyfluorosilicone, and polyperfluorocarbons.\(^1\)
1.4 Methods for study of *in vitro* drug release from a transdermal delivery system

*In vitro* methods for evaluating the rate of drug release from a TDDS play a significant role in its development. However, as reviewed by Finnin, *et al.*, there is not yet a generally accepted standardized methodology for *in vitro* testing of a TDDS. Most *in vitro* drug release studies use various types of diffusion apparatuses and a variety of barrier membranes. As summarized in Ref. 6, there are three major types of diffusion cells: horizontal, vertical, and flow-through.

The hydrodynamic and thermal characteristics of these diffusion apparatuses can affect the *in vitro* rate of drug release from a TDDS. Temperature variation and mixing conditions may affect the thickness of the stagnant diffusion layers on the interfaces between the donor or receiver media and the barrier membranes, and thereby can affect drug release profiles. This is one of the reasons that the reported rates of drug release or permeation through the skins often vary from one laboratory to another.

Diffusion cells used for *in vitro* drug release studies typically contain donor and receiver ("receptor") compartments, and are usually made of glass. Although there are no standard diffusion cell designs, the vertical-type Franz cell (see Figure 1.4) has been shown to have minimal temperature variation and good mixing conditions to ensure uniform drug concentration, and is used often. Therefore, it was used in the present work.
Figure 1.4 Schematic depiction of a Franz cell for drug release studies.
Another key component for *in vitro* testing of TDDS is the barrier membrane. Barrier membranes differ in their effects on drug permeation, and therefore can affect drug release profiles. Theoretically at least, human skin preparations or other animal skins should resemble viable skin *in vivo*, and therefore should function as appropriate barriers in *in vitro* testing. However, after storage and the necessary preparative procedures, these skins are no longer viable and the stratum corneum of the skin preparations may be hydrated to different extents. Consequently, large variations in drug release have been frequently observed in *in vitro* testing involving skin preparations as the barriers. Therefore, direct extrapolation from *in vitro* rate of drug release to clinical application still remains to be improved.

In addition to skin preparations, artificial membranes may be used as barriers in drug release studies. These membranes include nonporous silastic or ethylene vinyl acetate membranes or porous water-permeable cellulose membranes. They do not necessarily mimic human skin either in structure or in composition. However, in terms of the barrier effects, they are commonly used in *in vitro* tests to replace skin preparations and to differentiate between drug release from different prototype formulations. In the present work where supersaturated drug/PSA systems were used to enhance drug release, the artificial membranes may substitute for skin to test the effectiveness of this approach because drug permeation through both skin and artificial membranes has been shown to follow Fick’s laws of passive diffusion.

Silastic, or “silicone” membranes have been widely reported as an *in vitro* barrier for drug release evaluation. Chemically, silicone membranes have a similar
structure to that of silicone PSAs (see Section 1.3.2.1 and Figure 1.3c). This type of polymer material, as discussed in Section 1.3.2.1, has a high molecular mobility and free volume. Therefore, silicone membranes typically have a relatively high permeability to many drugs. On the other hand, silicone membranes are hydrophobic nonporous films and are water impermeable.

The SpectroPor® membranes are microporous water-permeable films made from amorphous regenerated cellulose. After being soaked in distilled water for a sufficient period of time, small pores will form on the membrane which can sieve solutes according to their molecular sizes. For example, SpectroPor® 1 membrane has molecular weight cut-off (MWCO) at 6,000-8,000 Dalton, which means that solutes with molecular weight larger than this range cannot penetrate through the pores on the membranes.

1.5 Enhancement technologies for transdermal drug delivery

As discussed in Section 1.1, the skin, especially the stratum corneum, functions as the barrier to the permeation of drugs and other substances. As such, transdermal drug delivery has been limited by the generally low drug bioavailability and the limited number of drug candidates that can be delivered by this route. In this context, therefore, there has been a consistent demand for novel and effective methods to enhance drug penetration through the skin.
Numerous physical and chemical strategies have been developed for the purpose of enhancing penetration of drug through the skin. Physical strategies include occlusion,\textsuperscript{31} iontophoresis,\textsuperscript{32} electroporation and phonophoresis,\textsuperscript{33} while chemical methods have been mainly the application of certain chemicals as penetration enhancers.\textsuperscript{34} As discussed in Section 1.2, passive approaches for enhancing transdermal permeation of drug have been through one or a combination of three mechanisms: increasing the diffusion coefficient of the drug, enhancement of drug solubility in the stratum corneum, and increasing the driving force by increasing drug concentration in the vehicle. Generally, chemical enhancers exhibit their enhancement effects through the first two approaches, whereas the physical strategies mainly focus on increasing the driving force for drug permeation.

While these approaches have exhibited effectiveness in promoting drug penetration across the skin, they have encountered various kinds of challenges.\textsuperscript{10} For example, the physical approaches can suffer from complex and cumbersome delivery devices; whereas chemical penetration enhancers often alter the physiological barrier properties of the stratum corneum and thereby may induce skin irritancy or toxicity. The effectiveness and limitations of these technologies will be reviewed below.
1.5.1 Chemical enhancers

Chemical enhancers should reversibly reduce the resistance of the skin to drug penetration without affecting the normal function of the skin. Drug is driven by the concentration gradient of the drug across the skin as indicated by Equation 1.1. Therefore, passive diffusion is the mechanism for drug penetration. The chemical enhancers act essentially by reducing the diffusional resistance of the skin. Table 1.1 lists the properties of an ideal penetration enhancer.35

1.5.1.1 Permeation enhancement by increasing the diffusion coefficient of the drug

As indicated in Section 1.2, an increase in the diffusion coefficient of the drug is one of the strategies to promote drug penetration through the skin. By disordering the lipid bilayers, many chemical enhancers increase the diffusion coefficient of the drug in the stratum corneum and thereby enhance penetration.7,13 The barrier function of intercellular lipids of the skin is attributed to several factors: a highly ordered multi-lamellar arrangement, a densely packed crystal-like structure, and solid phase at physiologic temperature. Disturbances of these structures will result in a more disordered lipid matrix, thereby increasing the permeability of solutes. In general, chemical enhancers affect the arrangement of a lipid bilayer at two locations, the polar head groups or the hydrophobic tails.
• Pharmacologically inert
• Nontoxic, nonirritating, and nonallergenic
• Rapid onset of action, predictable and suitable duration of action for the drug used
• Following the removal of the enhancer, the stratum corneum should immediately and fully recover its normal barrier property
• The barrier function of the skin should decrease in one direction only, and efflux of endogenous materials should not occur
• Chemically and physically compatible with the delivery system
• Readily incorporated into the delivery system
• Inexpensive and cosmetically acceptable

Table 1.1. Properties of an ideal penetration enhancer (from Ref. 35).
A simple example is water, which can interact with the polar head groups of the lipid bilayer and thereby interfere with their packing. Only a small amount of water aggregates in the polar head regions with larger amounts either adsorbed on the corneocytes or as a separate phase in the intercellular lipid matrix. Nevertheless, it has been found that the limited amount of water located at the polar regions can induce a phase transition of the solid lipids and thereby enhance the mobility of the lipid acyl chains. This will induce gelation or fluidization of the solid lipid phase and resulting in faster diffusion of hydrophobic compounds. On the other hand, adsorbed water that forms a separate water phase will provide a transport route for hydrophilic solutes with less resistance to their penetration. Hence, hydration of the stratum corneum enhances the penetration of both hydrophilic and hydrophobic compounds.

Fatty acids and fatty alcohols are another class of enhancers and function by interfering with the packing of lipid bilayers by inserting themselves between the hydrophobic tails of the lipids. This disorder may induce alteration of the arrangement of polar head regions as well, so that diffusion of both hydrophilic and hydrophobic molecules can be enhanced. An example of such an enhancer is oleic acid, which has been shown to increase molecular mobility by inducing a phase transition in the lipid matrix by interacting with the hydrophobic tails of the lipids. Given this mechanism, it is not surprising to find that many enhancers share a common type of hydrocarbon chain. The permeation enhancement effects of this class of enhancers are related to the length and conformation of their hydrocarbon chains. An appropriate length of the hydrocarbon chain will anchor the enhancer molecules more firmly in the hydrophobic domain of the
lipid bilayers, while appropriately located unsaturated double bonds in *cis-* conformation on the hydrocarbon chain may result in a greater disruption of the lipid bilayers. It has been reported that a maximum effect was achieved with chain lengths of about 12 carbons, and with the unsaturated double bonds in the middle of the chains. Noticing that the lipids in the stratum corneum are primarily saturated and therefore can form highly ordered structures, it is reasonable to assume that an unsaturated hydrophobic chain inserted in the lipid bilayer may cause significant disruption.

Similarly, Azone® and many other alkylazacycloalkanone derivatives, which also possess a polar head group and a long alkyl tail, can intercalate with the hydrophobic chains of the lipid bilayers and upset the packing of the lipids. The disturbance caused by Azones® on the self-assembly of lipids can be remarkable. It has been reported that a multiple-lamellae structure can be disrupted and result in a disordered mixture of single layers of lipids in the presence of Azone®. Additionally, it was found that Azones® increased the diffusion coefficient of drug in the stratum corneum while the partition coefficient remained constant, showing that enhancement of diffusion accounted for the increased permeation. Different from the behavior of many fatty acids, Azone® can also interact with the polar head regions of the lipid bilayers by insertion of its large seven membered ring between polar groups of the lipids. This is why Azone® has been reported to be able to enhance the permeation of several types of drugs with different polarities.

Diffusion coefficients may be increased by mechanisms other than disorder of the arrangement of lipids. As discussed above, changes in phase behavior of the lipids
may be an effective way. Some enhancers, such as terpenes, may penetrate into the lipid matrix and form separately dispersed liquid regions in the matrix which co-exist with the liquid crystal multiple-lamellae domains. This will then induce phase transitions in the solid crystal-like domains and fluidize the boundary regions between them, which may provide a liquid pathway for easier diffusion. In other words; some enhancers may form miscible solutions with the gel phase in the lipid matrix and lead to a liquid medium with less resistance to diffusion. This mechanism was reported to account for the diffusion enhancement effects of many enhancers such as the terpenes, as well as 8-cineole, eugenol, D-limonene, menthone, and nerolidol.

Lipid extraction can be another mechanism of action for some penetration enhancers. For example, ethanol has been reported to selectively extract polar lipids from the lipid matrix, leading to a greater free volume in the lipids, thereby enhancing drug permeation. Further studies also suggested that selective extraction of intercellular lipids may result in the formation of pores in the stratum corneum lipids.

In addition to the intercellular lipids serving as a major target for enhancement technologies, the protein components, mainly keratins in the corneocytes, may also be targets for enhancers. The extensively crosslinked water-insoluble keratins make the corneocytes, and then in turn the transcellular pathway highly impermeable. Therefore, hydration or structural alteration of the proteins may lead to a decrease in diffusional resistance. For example, protein crosslinking inhibitors, such as dithiothreitol (DTT), can reduce the degree of crosslinking of the keratins and thereby increase permeation. Similarly, propylene glycol and dimethylsulfoxide (DMSO) can replace the water...
environment of the proteins and thereby cause conformational changes of keratins which may contribute to the penetration enhancement effects of these agents.

1.5.1.2 Permeation enhancement by increasing solubility of drug in the skin

Many solvents can penetrate into the intercellular lipid matrix and change its solubility parameter so that the partition coefficients of some drugs in the stratum corneum can be increased.\textsuperscript{50} For example, propylene glycol can change the solubility parameter of the stratum corneum so that the penetration of a number of drugs, e.g., ibuprofen and metronidazole, can be enhanced.\textsuperscript{7} Similarly, other solvents, such as ethanol, Transcutol\textregistered, and N-methyl pyrrolidone, may also enhance drug permeation in the same way.\textsuperscript{50}

Solvent drag can also account in part for the penetration enhancement effects of some solvents. For example, ethanol can pass rapidly through the stratum corneum and drag solute with it.\textsuperscript{51} A similar effect also occurs for propylene glycol.\textsuperscript{52}

It should be noted that many chemical enhancers act through a combination of several mechanisms, such as those which have been proposed for the effects of ethanol: causing alteration of the arrangement of the lipid polar head region,\textsuperscript{53} promoting extraction of polar lipids, enhancement of drug solubility in the stratum corneum, and the solvent drag effect. This appears to be common for many enhancers, e.g., propylene glycol and terpenes.\textsuperscript{54}
Although chemical enhancers have exhibited effectiveness in promoting permeation of drugs across the skin, only a few chemical enhancers have been successfully applied clinically. Some of the reasons, as summarized by Finnin, et al., are:

1. The lack of in vitro/in vivo correlations. Many in vitro permeation studies use various types of membranes including artificial membranes and animal skin preparations as models and are not, or cannot be, extrapolated to in vivo clinical applications.

2. Chemical enhancers in many cases are good solvents for drugs. Therefore, the presence of enhancers in considerable amounts in the vehicles may reduce the thermodynamic activities of drug in the vehicles, thereby reducing drug permeation.

In addition, a more important factor is the clinical safety of chemical enhancers. It has been reported that Azone®, one of the most widely known transdermal enhancers, had concerns raised on its potential to cause skin irritation and therefore is not used clinically. Moreover, fatty acids and fatty acid esters, classes of enhancers which have been believed to be safe for skin application, are also known to have potential for skin irritation. In fact, safety concerns and the related regulatory questions are major considerations when a chemical enhancer is evaluated clinically. The rigorous toxicity requirements present a formidable hurdle to any chemical enhancer that is newly proposed for transdermal application.
1.5.2 Physical enhancement strategies

Many transdermal penetration enhancement approaches that do not involve chemical enhancers may be categorized into the class of physical strategies. Compared with chemical enhancers, physical enhancement approaches may offer unique advantages, such as enhancing the delivery of polar or ionic drugs, including peptides and proteins; and the ease by which pulsatile or programmable drug delivery can be achieved. Among the physical methods, electrically-assisted transdermal delivery (EATDD) methods and phonophoresis are the most well known. EATDD refers to a number of methods that facilitate the transdermal delivery of drug by the use of an electromotive force, whereas phonophoresis enhances drug penetration through the skin using therapeutic ultrasound.

1.5.2.1 Electrically-assisted transdermal delivery (EATDD) methods

EATDD includes a number of approaches that facilitate the transdermal delivery of drug by means of an electromotive force. Based on their specific mechanisms, EATDD can be further divided into iontophoresis, electroporation, electroosmosis, and electroincorporation. Compared with other transdermal enhancement approaches, such as chemical enhancers, a unique advantage of EATDD is that it can facilitate the penetration of ionized polar molecules, including some peptides and proteins, across the skin, which are otherwise very difficult to deliver via the transdermal pathway.
Iontophoresis

Iontophoresis uses a low voltage (typically $\leq 10$ V) and constant current (typically 0.5 mA/cm²) to drive a charged drug across the skin. Presently, it is the best-characterized EATDD method and is involved in most EATDD related systems. Iontophoresis enhances drug penetration through the skin by three mechanisms: 1) the electric field provides a driving force in addition to the concentration gradient to push or pull the charged drug through the skin; 2) the electric current reduces the resistance of the skin to drug penetration; and 3) an electroosmotic effect causes a bulk flow of the solvent which may carry ions or neutral molecules. In an electric field, a positive ion will be driven toward the cathode and a negative ion toward the anode. Therefore, for delivery of a positively charged drug, it should be put in the donor chamber together with anode.

Theoretically, the basic principles of iontophoretic delivery can be described by the Nernst-Planck equation:

$$J = -D \left( \frac{dc}{dx} \right) - \left( \frac{DzFc}{RT} \right) \frac{dE}{dx}$$

(1.2)

where $J$ is the drug flux through the barrier membrane; $D$, $c$, and $z$ are the diffusion coefficient, concentration, and charge of drug; $x$ the length of the diffusion pathway; $F$ the Faraday constant; $R$ the gas constant; $T$ the temperature; and $E$ the electrical potential.

When the molecule is neutral ($z = 0$) or there is no electrical potential applied ($dE/dx = 0$), the Nernst-Planck equation reduces to.
\[ J = -D \frac{dc}{dx} \]  

(1.3)

which is Fick’s first law of diffusion. On the other hand, if there is no concentration difference across the membrane \((dc/dx = 0)\) or the diffusion coefficient \(D\) in the skin is extremely small, such as in the case of hydrophilic or ionized molecules, then the contribution of passive diffusion can be neglected and the Nernst-Planck equation becomes:60

\[ J = -\left( \frac{DzF}{RT} \right) \frac{dE}{dx} \]  

(1.4)

which is the equation for electrophoresis. It can be seen then that the Nernst-Planck equation gives drug flux as the linear sum of the fluxes contributed by passive diffusion and electrophoresis, respectively. Therefore, if a voltage difference is applied across a barrier membrane, flux of ionic drug will be enhanced by the electric field in addition to passive diffusion due to a concentration gradient.

The route by which drugs are delivered through the skin by iontophoresis has not yet been completely determined. It is generally agreed, however, that iontophoretic flux is highly localized and that drug transport occurs primarily through preexisting pathways, especially sweat glands and other skin appendages.61 The sweat glands, among all the skin appendages, have been suggested to be of the greatest importance.62 In skin with a high density of hair follicles, follicular transport may predominate although penetration of the stratum corneum must also occur.63
It should be noted that the structure of the skin may be altered by the flow of electric current to the extent that some macropores in the skin appendages might form. Evidence for this is the observation that the resistance of the skin to drug penetration was reduced by an electric current.\textsuperscript{64}

The safety issues of iontophoresis are of special interest. Although the clinical application of iontophoresis is generally believed to be safe, unwanted side effects can occur.\textsuperscript{65} The side effects range from erythema and tingling sensations to painful burns. Optimization of the procedures, such as the pH of the donor formulation, the type of electrolytes, the type of the electrodes, and the mode of the applied electric field, may alleviate cutaneous effects.\textsuperscript{66}

**Electroosmosis**

Electroosmosis is a convective flow of bulk solvent relative to a fixed charged porous membrane when an electric voltage is applied across the membrane. This bulk flow of solvent is caused by the preferential transport of the counterions in the solution, and therefore is always in the same direction of movement as the counterions. This convective flow of solvent can carry ions or neutral molecules with it,\textsuperscript{59} and therefore, it is one of the mechanisms that contribute to iontophoretic drug delivery. It is believed to be the major force for enhancement of the transdermal penetration of peptides and proteins during iontophoresis.\textsuperscript{67} Since human skin is negatively charged at pH values above 4, electroosmotic flow in transdermal drug delivery is primarily from anode to
cathode. Therefore, delivery of drugs from anode to cathode is enhanced and delivery in the opposite direction is retarded. A recent development in electroosmosis is to apply reverse electroosmosis to extract endogenous materials from the systemic circulation such as glucose to the skin surface so that blood glucose levels can be continuously monitored.68

Since electroosmosis uses the same method and devices as does iontophoresis, the specific safety considerations of this technique are therefore generally believed to be mild.65,67

**Electroporation**

While iontophoresis enhances drug penetration primarily by providing an electromotive driving force, electroporation functions by increasing the permeability of the skin. Using an electric pulse with a high voltage (typically $>100V$) and very short duration ($\mu$s-ms), electroporation induces structural changes in biological membranes leading to transient losses of semipermeability. These changes can facilitate the penetration of ions, metabolites, and even DNA molecules.69 After the electric field is withdrawn, the pores may anneal and the membrane returns to normal function.

Although the creation of aqueous pores is generally believed to be the mechanism of electroporation, the detailed process is still not completely clear.70 It has been shown, however, that unlike a single cell membrane which can anneal immediately after the electroporation pulse, the non-viable complex intercellular lipid matrix structure of the
stratum corneum usually requires a longer time (several minutes) to recover after an electric pulse is applied,\textsuperscript{71} which leaves a longer period of time for large ionic molecules to penetrate through the pores in the stratum corneum generated by the electric pulse.\textsuperscript{57}

Despite the fact that electroporation has been shown to be effective in enhancing drug permeation, the safety and biological effects of this method remain to be evaluated further, especially in clinical settings.\textsuperscript{72} It has been shown that the effects of electroporation and iontophoresis on the skin were different, implying that their biological safety is not likely to be equivalent.\textsuperscript{58} Since electroporation acts more directly on the structure of the stratum corneum, this has raised more concerns.

Another drawback of electroporation is that miniaturization of this technology to a portable size is currently not available because the high voltage electric pulses require a bulky capacitor.\textsuperscript{73}

**Electroincorporation**

Similar in function to electroporation, electroincorporation uses high voltage electric pulses applied to the skin to enhance the penetration of particles, such as microspheres and liposomes. The mechanism of this method has not yet been defined. A hypothesis is that the particles are typically dielectric and will help to focus the electric potential at the contact points of the particles with the stratum corneum. Consequently, electroporation may occur at these contact points and the dielectric particles may be
pushed along the pores by the electric field.\textsuperscript{74} Since this is a relatively new technique and has not yet received much attention, many questions remain to be answered concerning both its effectiveness and safety.\textsuperscript{57}

\textbf{1.5.2.2 Phonophoresis}

Phonophoresis uses ultrasound to increase the transdermal delivery of drugs. Having been used since the 1950’s in physiotherapy and sports medicine, phonophoresis is assumed to enhance drug absorption locally. There are however many conflicting reports on the effectiveness of this method.\textsuperscript{75} It is now generally agreed that the frequency of the ultrasound is a crucial factor, and that low frequency (20-100 kHz) rather than standard therapeutic high frequency (1-3 MHz) is more effective and reliable in facilitating the transdermal penetration of drugs, especially large molecules, such as insulin and low molecular weight heparin.\textsuperscript{76}

The effects of low frequency ultrasound on the skin are currently believed to be related to disturbance of the structure of the intercellular lipid matrix in the stratum corneum by cavitation resulting from the ultrasonic vibration.\textsuperscript{77} Cavitation induced by ultrasound can be unstable and may implode creating a shock wave, which may increase the free volume in the lipids and therefore transiently increase the permeability of the stratum corneum.\textsuperscript{78} In extreme cases, macroscopic alterations, such as holes up to
5-15 mm diameter have been found, as well as epidermal and dermal lesions.\textsuperscript{79} Some of these are delayed responses to ultrasound radiation, and damage in blood vessel and muscle tissue have also been documented.\textsuperscript{80}

Despite remarkable developments in physical transdermal enhancement approaches that have been achieved during the past several decades, especially in the last ten years, two major weaknesses, as reviewed by Barry,\textsuperscript{67} limit their wide application. First, the effectiveness, and especially the clinical safety, of these methods remain to be validated. Second, the instrumentation for most physical transdermal enhancement approaches, particularly for electroporation and phonophoresis, may not lend themselves to miniaturization necessary to facilitate their use.

\section*{1.6 Supersaturation in permeation enhancement}

\subsection*{1.6.1 Theoretical basis and current development}

While the physical approaches can be limited by skin irritation, chemical penetration enhancers often alter both the physiological barrier properties of the stratum corneum as well as the normal functions of viable cell membranes, and thereby may also induce skin irritation or toxicity.\textsuperscript{67} In fact, these drawbacks are so serious that clinical applications of these technologies are significantly limited.\textsuperscript{67}

Alternatively, supersaturated systems have been utilized to successfully enhance the permeation of a number of drugs through the skin. The potential of supersaturated
systems in topical drug delivery was first indicated by Coldman, et al. based on the early work of Higuchi. Theoretically, the permeation of drugs through the skin, as discussed in Section 1.2, can be described by Fick’s first law, which postulates that enhancement of drug flux across the skin can be achieved by increasing the thermodynamic activity of drug in a vehicle. By creating a higher degree of saturation, as shown by an increase of the ratio \( C_v/C_s,v \) in Equation 1.1, supersaturation may thereby achieve a larger driving force to enhance the flux of penetrant.

In addition to theoretical predictions, experimental evidence also supports the validity of Fick’s first law in describing the permeation enhancement effect of supersaturation. For example, it has been reported that the same diffusant in different solution systems (all at saturation concentration) has the same flux even though its solubility in these solvent systems may have varied over two orders of magnitude. Moreover, it has been found that drug flux across various membranes and skin preparations was linearly proportional to the degree of saturation. Pellett, et al. also found that drug concentrations in different strata of the skin were in direct proportion to the degrees of saturation. Recently, it has been reported that supersaturation had no influence on the magnitude of drug diffusion coefficients and partition coefficients, suggesting that supersaturation enhances permeation entirely by increasing the thermodynamic driving force.

In fact, since it was first reported by Coldman, et al. in the late 1960’s, it has been found that a number of supersaturated systems of model drugs have enhanced penetration through several types of skins and synthetic membranes. For example,
Theeuwes, et al.\textsuperscript{86} reported that the flux of hydrocortisone alcohol across a synthetic membrane was maximal from a supersaturated solution in an acetone/water system. Similarly, a supersaturated ethanol/propylene glycol/water system was also reported to promote the \textit{in vitro} penetration of minoxidil through human skin.\textsuperscript{87} Other model compounds that have been successfully tested for the same purpose include nifedipine,\textsuperscript{88} hydrocortisone acetate,\textsuperscript{27} fluocinonide,\textsuperscript{28} lavendustin derivative (SDZ LAP 977),\textsuperscript{89} piroxicam,\textsuperscript{90} ibuprofen,\textsuperscript{5} indomethacin,\textsuperscript{91} oestradiol,\textsuperscript{29} and bupranolol.\textsuperscript{92} The vehicles that have been used to generate supersaturation include acetone/water cosolvent,\textsuperscript{86} ethanol/propylene glycol/water cosolvent,\textsuperscript{87} propylene glycol/water cosolvent,\textsuperscript{27,90,91} ethanol/propylene cosolvent,\textsuperscript{89} ethanol/propylene glycol/water/glycerol cosolvent,\textsuperscript{28} microemulsions,\textsuperscript{92} creams,\textsuperscript{89} water-soluble gels,\textsuperscript{27} and oily gels.\textsuperscript{93} In these studies, either synthetic membranes,\textsuperscript{27,28,90,91} such as silicone membrane, or excised animal\textsuperscript{89} or human skin preparations\textsuperscript{28,29,89,90} were used as \textit{in vitro} model barriers. In addition, \textit{in vivo} studies also support the same conclusion that supersaturation may enhance the percutaneous absorption of drug.\textsuperscript{94}

From all of these examples, a temporal conclusion may be drawn that the enhancement of penetration through skin and synthetic membranes achieved from supersaturated systems may be a common phenomenon. In fact, it has been suggested that supersaturation due to solvent evaporation is partly responsible for drug permeation through the skin from conventional topical solution vehicles.\textsuperscript{28,81,87} On the other hand, Hadgraft pointed out that de-supersaturation through crystallization during a period of storage may be responsible for decreases in efficacy of some transdermal systems.\textsuperscript{50}
1.6.2 Significance and challenges

Compared with other permeation enhancement strategies, supersaturation has some unique advantages as well as challenges. Unlike many chemical penetration enhancers, which as indicated earlier often alter the structure of the stratum corneum and cause irritation and inflammation; supersaturation, in principle, should not have an effect on the stratum corneum, thereby avoiding alterations of the normal physiological barrier function of the skin. In addition, supersaturation can be achieved by relatively simple and inexpensive designs, unattainable by most physical enhancement methods, such as iontophoresis and phonophoresis. Considering that transdermal drug delivery is generally a sustained-release strategy with a relatively long duration of action, a simple dosage form that is easy to apply and retain would be important to ensure success in real-life applications. Furthermore, from the research experience in past decades it has been generally concluded that synergy between different penetration enhancement strategies is of particular importance for practical applications. Combinations of different enhancement technologies may offer strengthened effects and reduced side effects. For example, synergism in penetration enhancement effect has been found between oleic acid as an enhancer and supersaturation.

Although supersaturation provides safety and simplicity, it also has significant challenges. The most important consideration with regard to supersaturated systems is their physical instability. A saturated solution implies a thermodynamic activity of unity, which is equal to that of the pure drug crystal. Thus, when there is excess drug in a
drug/solvent system, a saturated solution is in equilibrium with excess drug crystals. A supersaturated solution, on the other hand, has a thermodynamic activity above unity,\(^5\) which means it tends to promote crystallization to remove solute and thereby reduce its thermodynamic activity to unity. Therefore, a supersaturated system is thermodynamically unstable and drug crystallization may occur over time. In fact, potential physical instability is the major problem that hinders the use of supersaturation in transdermal drug delivery.\(^7\)

In order to circumvent the physical instability problem, it has been found that the stability of supersaturated solutions can be prolonged by the addition of certain polymers.\(^{95-97}\) For example, methyl cellulose (MC), hydroxypropyl methyl cellulose (HPMC), polyvinyl pyrrolidone K30 (PVP), polyvinyl alcohol (PVA), polyethylene oxide (PEO) and polyethylene glycol (PEG) have been shown to be stabilizers, but to different extents.\(^{27,98}\) In most cases, the mechanism of stabilization is believed to be interference of the polymers with nucleation and crystal growth.\(^{27}\) Some other polymers such as cyclodextran may stabilize supersaturated solutions by shifting phase equilibria.\(^5\) This shift results from an increase in drug solubility due to the presence of the polymer and may thereby reduce the degree of penetration enhancement. Furthermore, there is also some evidence that polymer stabilization may be quite specific in nature. Megrab, \textit{et al.}\(^{29}\) found that PEGs are ineffective in stabilizing supersaturated solutions of oestradiol, while others \(^{95}\) have shown that PEGs stabilize supersaturated solutions of hydrocortisone acetate. This specificity may be explained by a specific interaction, e.g., hydrogen bonding, between the drug and polymers that produce an anti-nucleating effect.\(^{95}\)
Since physical instability may be the major limitation for the application of supersaturated systems in topical drug delivery, it will be presented in greater detail in Chapter 3.

1.6.3 The methods and materials to create supersaturated systems

Even though polymers have been shown to be effective in stabilizing supersaturated solutions, the stability of these systems still does not allow for long-term storage. Therefore, it is usually necessary to generate supersaturation immediately prior to or during administration of the formulation. There are several methods to achieve supersaturation in situ: 1) by water or other solvent uptake from the skin, 2) by evaporation of a volatile solvent, and 3) by mixing co-solvent systems. All these approaches create supersaturation by changing or reducing the solute capacity of the solvent systems. Their limitations include: 1) the need for organic solvents, propylene glycol and ethanol being the most common; and 2) that the vehicles are generally in liquid form, which may not be feasible for sustained-release drug delivery systems which need a prolonged duration of application to the skin.

An alternative approach to create supersaturation in situ is heating followed by cooling. The advantages of this method are that it is simple in nature, no organic solvents are needed, and that on-site mixing is not required. The heating/cooling technique is especially good for semi-solid systems such as ointments or creams and PSA
patches where solvent mixing is not easily handled at the clinic or patient level. Considering that semi-solids make up a large proportion of topical drug delivery systems, it would be of importance to develop a simple method for generating supersaturation in these systems.

Although it seems no more complicated to heat a transdermal patch than to mix two liquids together before application, there appears to have been little attention paid to this method. The heating/cooling technique has only been used for cream or oily based semi-solid systems where solvents are not usually involved.

One concern about this approach is that heating may result in chemical decomposition of drug. Nevertheless, the fact that many target drugs for transdermal delivery have low melting points limits the amount of heat that must be applied. For example, among marketed transdermal products, scopolamine monohydrate (m.p. 59 °C), nicotine (liquid at room temperature), clonidine (m.p. 130 °C), fentanyl (m.p. 83 °C) and lidocaine (m.p. 67 °C) all have low melting points. In fact, a low melting point is one of the considerations for selecting target drugs for the transdermal pathway.

Another concern is whether the physical stability of the supersaturated systems generated by the heating/cooling method is equal to or similar to that created by other methods such as solvent mixing. For supersaturated creams and oily ointments, it has been demonstrated that the physical stability of these systems generated by the heating/cooling method is sufficient for in situ application.
1.7 Enhancement of transdermal drug delivery by supersaturated drug/pressure sensitive adhesive patches

1.7.1 Strategy

In the present work, pressure sensitive adhesive (PSA) patches containing drug in a supersaturated state in the PSA are proposed as a novel delivery system to enhance drug release. The monolithic drug-in-adhesive matrix design (see Figure 1.2) will be adopted for the PSA patches. Patches containing supersaturated solutions of drug in a PSA will be produced by heating the patches in an oven to melt the drug, followed by cooling at room temperature. Although the design of packaging and heating equipment suitable for clinical applications of these types of patches is not included in this study, aluminum bags with hermetic sealing may be appropriate for packaging. A portable heating device using rechargeable battery power may be suitable for heating the patches.

The present work will consist of the following parts: formulation and the physical stability of the transdermal patches containing supersaturated drug/PSA systems; studies of in vitro drug release from the PSA patches; studies of the crystallization kinetics of the model drug from the supersaturated drug/PSA systems; studies of factors that may affect the crystallization process; and physical chemical characterization of the drug/PSA systems. Since physical instability is the major limitation for the application of supersaturated systems in transdermal drug delivery, it is of importance to put sufficient emphasis on the study of the mechanisms and characteristics responsible.
1.7.2 Materials

1.7.2.1 Lidocaine

Lidocaine (LC), a local anesthetic, will be the model drug since: 1) it has a relatively low melting point of \(\sim 67 \, ^\circ\text{C}\), which is appropriate for testing the heating/cooling technique; 2) it has good heat stability; and 3) it has been well documented that it has a relatively high transdermal flux.\textsuperscript{102} A transdermal patch containing lidocaine (Lidoderm\textsuperscript{®})\textsuperscript{103} is currently marketed. The properties of lidocaine related to this work are:

- Molecular Formula: \(\text{C}_{14}\text{H}_{22}\text{N}_{2}\text{O}\)
- Molecular Weight: 234.33
- Structure:

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\text{NH} - \text{C} - \text{CH}_2 - \text{N} \\
\text{C}_2\text{H}_5 \\
\text{C}_2\text{H}_5 \\
\end{array}
\]

- Melting Point: 67-68 °C
- Solubility: insoluble in water; soluble in alcohol, ether, benzene, oils.
- Density: 1.04 g/cm\textsuperscript{3}
1.7.2.2 Pressure sensitive adhesives (PSAs)

Three types of PSAs were used to formulate the model systems with lidocaine:
1) polyacrylate copolymers (PA), which are commonly used in medical applications;\(^2\)
2) polyisobutylene (PIB), a classic medium-tack PSA,\(^4\) and 3) poly(vinylpyrrolidone)/polyethylene glycol (PVP/PEG) blend, an extensively studied hydrophilic PSA.\(^{21-23}\) This group covers the most common PSA types currently used in transdermal drug delivery.

Preliminary studies indicated that some of the PSAs might not be appropriate candidates for this work. For example, PIB, a very hydrophobic PSA, formed immiscible mixtures with lidocaine even when both components were heated to melt. In this case, the melted drug formed “supercooled” droplets rather than a supersaturated homogeneous solution in the PIB medium when the systems were cooled to room temperature, which appears opaque and can be observed by optical microscopy. Consequently, the physical stability of the supercooled systems is not sufficient for the purpose of transdermal drug delivery.

Another example is the hydrophilic PVP/PEG blend. It was possible to form a supersaturated solution of lidocaine in PVP/PEG which had sufficient physical stability at room temperature. Unfortunately, the supersaturated system was very sensitive to moisture and crystallization of LC occurred upon contact with water. This is because LC is water insoluble while the PSA is water soluble, and hydration of the system may force crystallization of LC.
Finally, a medical grade polyacrylate PSA containing free -OH groups (Duro-Tak® 87-2287, National Starch & Chemical Company) was found to be acceptable for this study. Duro-Tak® is a class of copolymers comprising monomers such as 2-ethylhexylacrylate, butyl acrylate, and vinyl acetate (see Figure 1.5). Polyacrylate PSAs are known for their biocompatibility, good skin adhesion, and compatibility with many drugs. By modifying the monomer composition and the amount of crosslinking agents, the properties of the PSAs, including mechanical properties and compatibility with water and drugs, can be tailored. Therefore, the present work involving polyacrylate PSAs may provide important information on optimization of the properties of this class of PSAs.

1.7.2.3 Others

The patches were formulated using nonporous occlusive backing materials (Scotchpak™, polyester film, 3M Co.) and release liners (Scotchpak™, polyester, 3M Co.), both of which have good heat tolerance.

1.7.3 Theoretical considerations for the physical instability of supersaturated systems

Since physical instability is the major limitation for the application of supersaturated systems in topical drug delivery, it is of importance to put sufficient emphasis on the study of the mechanisms and characteristics responsible. Theoretically,
Figure 1.5 Molecular structures of the monomers in DuroTak® 87-2287.
the physical stability of a supersaturated solution is determined by the process of crystallization, which consists of two consecutive steps: first nucleation, and then crystal growth. Both nucleation and crystal growth are kinetic processes with different activation energies. In the case of small organic compounds in a liquid solution state, nucleation may be the rate-limiting step, and the rate of nucleation can be described by the classical theory of nucleation, which stems from the work of Gibbs and Volmer. Basically, the rate of nucleation is given below:

\[
J = A \exp \left[ - \frac{16 \pi \gamma^3 v^2}{3 k^3 T^3 (\ln S)^2} \right]
\] (1.5)

where \( J \) is the rate of nucleation, \( A \) a constant, \( \gamma \) the interfacial tension between the developing crystal surface and the supersaturated solution, \( v \) the molecular volume of the solute, \( k \) Boltzmann’s constant, \( T \) temperature and \( S \) is the degree of supersaturation. This equation indicates the three major variables governing the rate of nucleation: temperature, \( T \); degree of supersaturation, \( S \); and interfacial tension, \( \gamma \). Among these, temperature is especially important because it also determines the degree of supersaturation.

The influence of temperature on nucleation rate is multi-fold. According to Equation 1.5, a decrease in temperature will reduce the rate of nucleation by itself, but may also increase the degree of supersaturation and thereby raise the nucleation rate. Due to the presence of a logarithmic factor \((\ln S)\), Equation 1.5 also suggests there might be a “critical” temperature \((T_{\text{crit}})\) and a “critical” degree of supersaturation beyond which the nucleation rate may sharply decrease (see Figure 1.6). In addition, it has been found that
Figure 1.6 Temperature dependence of crystallization rate (from Ref. 108).
when temperature decreases to a certain point, although the degree of supersaturation is still increasing, the rate of nucleation usually reaches a maximum and subsequently decreases. This is due to inhibited molecular movement caused by a sharp increase in the viscosity of the system. Figure 1.6 shows the features of the temperature dependence of the nucleation rate of supersaturated systems.

Based on this analysis, the physical stability of a supersaturated system may be optimized if the temperature of the system can be controlled to be above \( T_{\text{crit}} \), or below \( T'_{\text{crit}} \) (through quenching). Additionally, it is also important to pay special attention to the concentration of drug in the systems because a higher concentration of drug in the system may increase the critical temperature and the system will be more prone to crystallization.

Although the classical theory of nucleation, as indicated above, describes the kinetics of the crystallization process, there is no evidence at this point that it can be applied to a supersaturated semi-solid or a highly viscoelastic PSA system.

Compared with nucleation, crystal growth is a much more complicated process. Numerous models and theories have been developed to describe the kinetics of this process. However, due to its complexity, it seems that there is not yet a universally applicable theory. The Avrami relation and its modified forms are probably the most commonly used. The following is one form of the Avrami relation:

\[
\ln(1 - \alpha) = -k t^n \quad (1.6)
\]
where $\alpha$ is the fraction of the crystal formed at time $t$, $k$ the Avrami constant, and $n$ the Avrami exponent, a constant related to the dimensions of the crystal growth.

Data analysis based on the Avrami relation may give insight into the microscopic dimensions and the corresponding kinetics with which crystals grow. A more detailed discussion on this approach will be given in Chapter 3.

1.8 Objectives

The overall goal of this research is the development of transdermal drug delivery systems with an enhanced drug permeation effect. This will be accomplished from pressure sensitive adhesive (PSA) systems supersaturated with drug by an *in situ* heating/cooling method. The specific objectives are:

1. The formation of a supersaturated drug solution in pressure sensitive adhesives with a pharmaceutically acceptable physical stability through an *in situ* heating/cooling method.

2. The enhancement of drug release across artificial membranes by PSA systems supersaturated with the drug.

3. Determination of the mechanism of the physical stability of supersaturated drug/PSA systems and the factors that affect it. Specifically, it is of interest to study the drug crystallization process in polymeric PSAs and the influence, if any, of the PSAs on this process.
CHAPTER 2

ENHANCEMENT OF \textit{IN VITRO} RELEASE OF DRUG FROM
SUPERSATURATED DRUG/PRESSURE SENSITIVE ADHESIVE
TRANSDERMAL DELIVERY SYSTEMS

\textit{CONCEPT MAP}

- The solubility of the model drug lidocaine (LC) in the pressure sensitive adhesive DuroTak® 87-2287 (DT2287) was measured using DSC and hot stage microscopy.
- Pressure sensitive adhesive patches supersaturated with drug (LC) were prepared using an \textit{in situ} heating/cooling method. The patches have exhibited pharmaceutically acceptable physical stability.
- PSA patches supersaturated with LC can enhance its \textit{in vitro} release across a composite barrier membrane consisting of one layer of silicone membrane and five layers of SpectroPor® membrane.
- Drug loading has a significant influence on the accumulated amount of drug released, especially for supersaturated systems.
• Microscopy indicated that appreciable hydration of the PSA occurred when water was present and that LC enhanced the hydration of the systems. This may account for the non-Fickian release of LC from the patches through the water permeable SpectroPor® membranes.

• Microscopy further indicated that slow crystallization of LC may be induced by hydration of the supersaturated PSA systems, accounting for the decrease in drug release from the supersaturated drug/PSA patches.

2.1 Experimental

2.1.1 Materials

Lidocaine (LC) was provided by AstraZeneca AB (Södertälje, Sweden). Duro-Tak® 87-2287 was a gift from National Starch and Chemical, Co., and patch backing materials (Scotchpak™, polyester film) and release liners (Scotchpak™, polyester) were gifts from 3M Co. (St. Paul, MN). Silicone membrane (Sil-Tec®, non-reinforced, medical grade) with a thickness of 0.005 inch (∼127 µm) was purchased from Technical Products Inc. of Georgia, U.S.A (Decatur, Georgia), and Spectra/Por® regenerated cellulose dialysis membrane (Spectra/Por® 1, MWCO: 6,000-8,000, width: 52 mm) was purchased from Fisher Scientific Co. (Pittsburgh, PA). Deionized, distilled water was used throughout the experiments. All other chemicals were purchased from Fisher Scientific Co. (Pittsburgh, PA) and used as received.
2.1.2 Equipment

A list of equipment and their manufacturers is given in Table 2.1.

2.1.3 Experimental methods

2.1.3.1 Solubility measurements

The solubility of LC in the PSA was measured separately by differential scanning calorimetry (DSC, Mettler Model TA4300)\textsuperscript{102} and hot stage microscopy.\textsuperscript{89} The DSC method was used to measure the solubility of LC in the PSA at room temperature and at the temperature of the drug release study (31 °C), while hot stage microscopy was used to quantify the temperature dependence of drug solubility in the PSA.

For the DSC method, a series of LC/DT2287 mixtures were prepared by dissolving appropriate amounts of both LC and DT2287 in ethyl acetate followed by evaporation of the solvent at 50 °C for 12 hours until constant weight was reached. After cooling and storage at room temperature or 31 °C for 1 week, 5-10 mg of the LC/DT2287 mixtures were accurately weighed and DSC thermograms obtained over the range of -100 to 100 °C at 20 °C/min. The areas of the crystal melting endotherms were plotted as functions of the weight fractions of drug and the intercept on the drug weight fraction axis was taken as the solubility of the drug.\textsuperscript{102}
<table>
<thead>
<tr>
<th>Equipment</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion Cells</td>
<td>Crown Glass Co., New Jersey</td>
</tr>
<tr>
<td>Circulating Bath</td>
<td>HAAKE Mess-Technik GmbH u. Co., Karlsruhe, Germany</td>
</tr>
<tr>
<td>Milli-Q® Water System</td>
<td>Millipore Co.</td>
</tr>
<tr>
<td></td>
<td>Bedford, MA</td>
</tr>
<tr>
<td>Magnetic Stirrer, IKAMAG Model RET</td>
<td>IKA-Works, Inc.</td>
</tr>
<tr>
<td></td>
<td>Cincinnati, OH</td>
</tr>
<tr>
<td>Microbalance, Model AE 240</td>
<td>Mettler-Toledo International Inc.</td>
</tr>
<tr>
<td></td>
<td>Hightstown, NJ</td>
</tr>
<tr>
<td>HPLC</td>
<td>Beckman Instruments, Inc.</td>
</tr>
<tr>
<td>Beckman 110B pump</td>
<td>San Ramon, CA</td>
</tr>
<tr>
<td>UV Detector model 167</td>
<td></td>
</tr>
<tr>
<td>Analog interface, model 406</td>
<td></td>
</tr>
<tr>
<td>Injector, 200 µL</td>
<td></td>
</tr>
<tr>
<td>Software, System Gold™</td>
<td></td>
</tr>
<tr>
<td>HPLC Column, PRP-1 polymeric column</td>
<td>Hamilton Company</td>
</tr>
<tr>
<td>Particle size 5 µm, 25×2.3 mm I.D.</td>
<td>Reno, NV</td>
</tr>
<tr>
<td>Light Microscope equipped with polarizers</td>
<td>Ernst Leitz Wetzlar, Germany</td>
</tr>
<tr>
<td>Hot Stage</td>
<td>Mettler FP2</td>
</tr>
<tr>
<td>DSC, Model TA4300</td>
<td>Mettler-Toledo International Inc.</td>
</tr>
<tr>
<td>Software TA 72.5</td>
<td>Hightstown, NJ</td>
</tr>
<tr>
<td>FT-IR Spectrometer</td>
<td>Protégé 460 E.S.P.</td>
</tr>
<tr>
<td></td>
<td>Nicolet Corporation</td>
</tr>
</tbody>
</table>

Table 2.1 List of equipment.
For hot stage microscopy, the values of the melting temperatures \( T_m \) of LC crystals in the LC/PSA mixtures were determined at a heating rate of 0.2 °C/min. Since melted LC forms a homogeneous solution with the PSA as indicated by polarized light microscopy, the weight percentage of LC in a drug/PSA mixture can be assumed to be the solubility of LC in the PSA (DT2287) at the melting temperature \( T_m \). All data reported are the average of three independent measurements.

2.1.3.2 Preparation and stability of PSA patches supersaturated with drug

In an \textit{in vitro} drug release study, the effect of drug depletion on the rates of release from a transdermal delivery system is different from a supersaturated solution or a suspension. In a suspension, drug crystals can function as reservoirs which would keep the thermodynamic activity of the drug constant until the crystals are completely dissolved. By contrast, the apparent thermodynamic activity of drug in a supersaturated solution continuously decreases during the period of release. To eliminate this effect of drug depletion in supersaturated systems, a sufficiently large drug loading can be used to ensure that the degree of drug depletion is negligible during the course of the release studies. As such, an apparent steady state release can be achieved assuming sink conditions are maintained and drug loading remains sufficiently large. According to Equation 1.1, steady state release reflects a nearly constant drug concentration in the vehicle if sink conditions are maintained over the course of the release experiment. Therefore, the effect of drug depletion on the rate of release should be negligible during
the period of steady state release since drug concentration in the vehicle is approximately constant from a practical point of view. Experimentally, this can help eliminate the effects of drug depletion on the rates of release from a supersaturated solution and from a suspension. Based on this, a series of LC/DT2287 mixtures at different weight fractions of LC were prepared by first dissolving appropriate amounts of both LC and DT2287 in ethyl acetate. A general casting method was then used to prepare PSA patches with diameters of 3.5 cm. The rates of LC release from these patches were determined. An appropriate drug loading was selected and regarded as “sufficiently large” based on these results. Specifically, the drug loadings of LC per patch were 44.9, 89.9, 135 and 449 mg. After casting, solvent was evaporated at 50 °C for 12-24 hours, leaving excess drug crystals suspended in a saturated solution in the highly viscous PSA. These patches were used in drug release studies and labeled as patches containing crystallized drug or “crystallized patches”. Patches containing DT2287 supersaturated with LC, i.e., “supersaturated patches”, were produced by an in situ heating/cooling procedure prior to the release studies. The supersaturated systems were produced by heating the crystallized patches in an oven at 80 °C for 10 minutes, followed by cooling at room temperature.

The physical stabilities of the supersaturated LC/DT2287 patches generated by the heating/cooling method were examined at room temperature (23-25 °C). The presence of drug crystals turned the patches from transparent to opaque white, which can be detected first visually and then confirmed by brightfield microscopy at 320 ×. Further study of the kinetics of drug crystallization from supersaturated LC/DT2287 mixtures using DSC showed that the physical stability of the LC/PSA systems in these patches was
greater at 31 °C than at 25 °C (see Section 3.3.1 and Figure 3.3). Therefore, it was believed that this study at 25 °C provided reliable information on the physical stability of the supersaturated LC/PSA systems in the patches used for studies of drug release at 31 °C.

2.1.3.3 HPLC analysis

LC was quantified by a HPLC method using a Beckman 110B pump, a model 167 UV detector and a 406 analog interface. The mobile phase consisted of 53% methanol and 47% formate buffer solution (pH ≈ 3), which contained 0.398% (g/mL) formic acid, 0.103% (g/mL) sodium formate, 0.28% (v/v) triethylamine and deionized, distilled water. The stationary phase was a Hamilton PRP-1 polymeric column, particle size 5 µm, 25×2.3 mm I.D. The flow rate was 1.5 mL/min, detection wavelength was 254 nm and sample volume was 200 µL. Samples taken from the receiver compartment of the diffusion cell were injected directly into the HPLC. The retention time of LC was ~ 3.1 min.

2.1.3.4 Drug release studies

Drug release studies were performed using jacketed glass Franz cells (Crown Glass Co., New Jersey) with a diffusional area of 3.30 cm² and a volume of the receiving chamber of 16.5 mL. Vacuum degassed deionized, distilled water was used as the
receiving medium. A Teflon®-coated magnetic stir bar was used to ensure sufficient mixing in the receiving chamber, which was thermostated at 31 ± 0.5 °C (the cells were allowed to equilibrate for two hours prior to use). LC/DT2287 patches were carefully laid on the top of prepared barrier membranes to ensure good physical contact and then mounted in the diffusion cell. At predetermined intervals, 0.5 mL of the receiving medium was removed and replaced with an equal volume of fresh pre-thermostated receiving medium. The samples were assayed directly by HPLC. Drug concentration in all samples was below 17% of the saturation concentration of lidocaine in deionized, distilled water (~3.97 mg/mL); thus, it was believed that the drug release process was under sink conditions.

The drug release studies included the following:

1. The influence of loading on lidocaine release:

Five layers of Spectro/Por® 1 were used as the barrier membrane. Both supersaturated and crystallized LC/DT2287 patches containing 40% w/w LC (relative to the total weight of the LC/DT2287 mixture) at 44.9, 89.9, 135 and 449 mg LC per patch were studied in terms of drug release. The barrier membranes were prepared as follows: the Spectro/Por® 1 membranes were first soaked in deionized, distilled water for 12 hours to ensure sufficient hydration, and then laminated to each other by squeezing out excess water and removing it with tissue paper. The LC/DT2287 patches were then carefully laid on top of the barrier membrane and mounted in the diffusion cell.
2. **The effect of supersaturation on lidocaine release:**

A series of layers of silicone membrane and cellulose membrane were used. Specifically, 1 or 4 layers of silicone membrane; 5, 9 or 10 layers of cellulose membrane; and a combination of 1 layer of silicone membrane and 5 layers of cellulose membrane were evaluated. For preparation of the 4 layer silicone membrane barrier, silicone membranes were first immersed in propylene glycol and then laminated to each other as excess propylene glycol was squeezed out by pressure from a round glass cylinder and then removed from the edges with tissue paper. Propylene glycol was used to ensure good physical contact between the silicone membrane layers. The preparation of cellulose membrane barriers was described in the previous section. For preparation of the composite membranes, 5 layers of cellulose membrane were prepared as described in the previous section. The LC/DT2287 patches were then carefully laid on top of a layer of silicone membrane and this stack then laid on top of the 5 layers of cellulose membrane so that the silicone membrane was between the adhesive patch and the cellulose membranes. The composite system was then mounted in the diffusion cell.

All patches used in this study had a loading of 135 mg LC per patch, which was selected based on the results of the above section (see Section 2.2.3.1).

### 2.1.3.5 Hydration of the pressure sensitive adhesive systems

LC release through the cellulose membranes (Spectro/Por® 1) did not show a statistically significant difference between supersaturated and crystallized LC/PSA
patches. In order to further explore the mechanism behind this, the patches were studied
by light microscopy. An optical microscope (Leitz Wetzlar) coupled with a color video
camera (Sony, CCD/RGB, model DXC-151) and a video recorder was used.
Magnification was $320 \times$. LC/PSA patches that were treated with deionized, distilled
water or subjected to a drug release study were examined at predetermined time intervals.

2.2 Results and discussion

2.2.1 Solubility measurements

Measurement of the solubility of drug in a viscoelastic PSA is a challenge to
pharmaceutical scientists and recently it has been of increasing interest.\textsuperscript{113,114} As can be
seen in the theoretical analysis in Section 1.7.3, solubility of drug in a PSA is an
important parameter in both the drug release studies and in determination of the degree of
supersaturation. Unfortunately, there is no widely accepted method to accurately measure
this value in a PSA system, especially when the temperature dependence of solubility
must be considered. The difficulty of measuring drug solubility in semi-solid systems
such as creams, ointments, hydrogels and PSAs is due mainly to the difficulty in
separating excess drug crystals from the saturated but highly viscous, or even elastic,
medium. Nevertheless, many approaches have been tried to solve the problem, including
theoretical methods to predict the solubility of drug in the PSA systems.\textsuperscript{113,114} Toddywala
and Chien equilibrated a placebo PSA patch with saturated or half-saturated aqueous drug
solutions and then quantified the amount of drug extracted from the patch.\textsuperscript{115,116}

However, it was found in the present work that this method may underestimate drug solubility due to incomplete extraction of the drug from the PSA. Furthermore, hydration of some PSAs, i.e., polyacrylates, may complicate the situation because the water absorbed in a PSA may carry solutes with it or may change the solubility parameter of the PSA. Others have used microscopy to monitor the saturation point of a drug-containing cream or ointment base.\textsuperscript{89,117} Although the accuracy of this method may be affected by the uncertain equilibration times required for the viscoelastic PSA system since stirring is impossible, this method can be used to approximate the temperature dependence of LC solubility in a PSA as will be shown later in this section. Another potential problem of this method, as also discussed later in this section, is that crystallization of drug from drug/PSA mixtures at relatively low temperatures and low degrees of supersaturation may be required. This process can be extremely slow due to the high viscosity of the PSA systems and therefore may not be achieved within a reasonable time frame. Furthermore, it has been reported that DSC could be used to measure drug solubility in a PSA.\textsuperscript{102} However, since temperature is changing during the period of measurement, the accuracy of this method was not sufficient to allow quantification of the temperature dependence of LC solubility in a PSA. In the present work, the DSC method and hot stage microscopy have been used for different purposes. The DSC method was used to measure the solubility of LC in the PSA at room temperature and at the temperature of the drug
release studies (31 °C). Since it was not possible to quantify the temperature dependence of LC solubility in the PSAs by DSC, hot stage microscopy was used instead for this purpose.

As shown in Figure 2.1, linear correlations exist between the enthalpies measured by DSC and the weight fractions of LC in the LC/DT2287 mixtures. These correlations gave the solubilities of lidocaine in the PSA as 20.8% ± 0.43% and 21.3% ± 0.66% (w/w) at room temperature and 31 °C, respectively, by extrapolation to zero enthalpy. The $r^2$ values for the plots were 0.999 and 0.996, respectively, indicating that the DSC method was a simple and reliable method for solubility determination in the PSA systems. Additionally, the 10% and 20% LC/DT2287 mixtures were transparent while the 30% to 60% w/w mixtures were opaque white. Microscopy showed crystals present in the 30% to 60% w/w LC/PSA mixtures.

To study the crystallization kinetics of LC in the LC/DT2287 mixtures (see Chapter 3), the temperature dependence of the solubility of LC in the PSA, i.e., the solubility of LC over the temperature range of 5~25 °C, was needed. To determine this, the temperature dependence of the solubility of LC in the PSA over the temperature range of 26.0~67.5 °C was measured first by hot stage microscopy and the relationship between $T_m$ and solubility was then extrapolated to the temperature range of 5~25 °C. This extrapolation was necessary because direct measurement of the solubility of LC over the temperature range of 5~25 °C cannot be achieved by hot stage microscopy due to the slow crystallization of LC from drug/PSA mixtures at low degrees of saturation (typically
Figure 2.1 Solubilities of lidocaine in Duro-Tak® 87-2287 at room temperature (23-25 °C) and 31°C (SD is indicated by the size of the symbols).
the weight percentages of LC were less than 20%) and at low temperatures. In principle, direct measurement of solubility over a certain temperature range by hot stage microscopy requires that crystallization of drug in drug/PSA mixtures which are just saturated within this specific temperature range, i.e., 5~25 °C in this case, should be achieved first. In the present work, therefore, this means that the weight fraction of LC in these LC/PSA mixtures should be less than 20% because the solubility of LC in the PSA mixtures is ~ 20% w/w at 25 °C. Unfortunately, due to the high viscosity of the PSA systems below ~20 °C and the low degree of supersaturation in these mixtures, crystallization of LC from LC/PSA mixtures at weight percentages of LC of less than 20% were extremely slow and could not be observed (see Table 2.2), which made the direct measurement of the solubilities of LC at temperatures below 20°C impractical by hot stage microscopy.

To extrapolate the relationship between $T_m$ and solubility to the temperature range of 5~25 °C, it should first be determined within the temperature range of 26.0~67.5 °C. The ideal behavior of $T_m$ as a function of mole fraction is described by the Hildebrand equation:118

$$ln \ (x) = \Delta H_f / R \ (1/T_x-1/T_p)$$

(2.1)

where $x$ is the mole fraction of LC in the mixtures, $\Delta H_f$ is the enthalpy of fusion per mole of pure LC, and $T_p$ and $T_x$ are the melting temperatures of pure LC and of LC in the mixtures, respectively, which were determined by hot stage microscopy. Since DT2287 is
a polymer of which the molecular weight is much larger than that of LC, it is not appropriate to use the mole fraction $x$ for the correlations. Therefore, the weight and volume fractions of LC in the mixtures were used instead. The volume fraction of LC in the mixture was calculated by $v_1 = (w_1/\rho_1) / (w_1/\rho_1 + w_2/\rho_2)$, where $v_1$ is the volume fraction of LC in the system, $w_1$ and $w_2$ are the weight fractions of LC and DT2287, respectively; and $\rho_1$ and $\rho_2$ are the densities of LC and DT2287, respectively, which are 1.04 g cm$^{-3}$ for LC and 0.979 g cm$^{-3}$ for DT2287. Other empirical relationships such as half-logarithm, double logarithm and rectangular hyperbolic relation ($T_s = T_p x / (K + x)$) were also attempted. The relationship between $T_m$ and the weight fractions of LC (solubility) with the best correlation was selected and extrapolated to the temperature range of 5~25 °C.

Table 2.2 lists the melting temperatures of LC/DT2287 mixtures as functions of the weight fractions of LC. To determine the relationship between $T_m$ and the weight percentage of LC, the Hildebrand equation, Equation 2.1, was first applied using weight fraction and volume fraction to substitute separately for mole fraction $x$. However, the two plots were not linear. Other empirical relations such as half-logarithm and double logarithm did not provide good linearity, except for the rectangular hyperbolic relation which gave linearity within the temperature range of 26~67.5 °C when weight fraction of LC was used in the correlation (see Figure 2.2). The correlation obtained from Figure 2.2 was extrapolated to the temperature range of 5~25 °C. The calculated solubilities of LC in the PSA mixtures at different temperatures are listed in Table 2.3. These solubility data will be used to calculate the degrees of supersaturation (see Chapter 3).
Table 2.2. Melting temperatures ($T_m$) of LC in LC/DT2287 mixtures.

<table>
<thead>
<tr>
<th>LC (%, w/w)</th>
<th>$T_m$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>26.0 ± 0.34</td>
</tr>
<tr>
<td>24</td>
<td>39.3 ± 0.28</td>
</tr>
<tr>
<td>27.3</td>
<td>45.0 ± 0.45</td>
</tr>
<tr>
<td>30</td>
<td>47.8 ± 0.36</td>
</tr>
<tr>
<td>40</td>
<td>55.9 ± 0.50</td>
</tr>
<tr>
<td>50</td>
<td>60.1 ± 0.48</td>
</tr>
<tr>
<td>60</td>
<td>62.8 ± 0.59</td>
</tr>
<tr>
<td>70</td>
<td>65.1 ± 0.39</td>
</tr>
<tr>
<td>80</td>
<td>65.4 ± 0.41</td>
</tr>
<tr>
<td>100</td>
<td>67.5 ± 0.53</td>
</tr>
</tbody>
</table>
Figure 2.2 The rectangular hyperbolic relationship between the melting temperatures ($T_m$) and the weight fractions of LC in LC/DT2287 mixtures. SD is indicated by the size of the symbols. The correlation is: $T_m = -2.9145 \left( \frac{T_m}{LC\%} \right) + 351.7$, $r^2 = 0.991$. 
<table>
<thead>
<tr>
<th>$T_n, (^\circ \text{C})$</th>
<th>Solubility of LC (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>11.0</td>
</tr>
<tr>
<td>10</td>
<td>12.0</td>
</tr>
<tr>
<td>15</td>
<td>13.2</td>
</tr>
<tr>
<td>16</td>
<td>13.7</td>
</tr>
<tr>
<td>17</td>
<td>14.3</td>
</tr>
<tr>
<td>18</td>
<td>14.6</td>
</tr>
<tr>
<td>25</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Table 2.3. Calculated solubilities of lidocaine in LC/DT2287 mixtures.
It should be noted that the solubility approximated by hot stage microscopy (~16.2% w/w at 25 °C) is lower than that measured by DSC (~20.8% ± 0.43% at 23-25 °C). This difference results from errors due to the increasing temperatures in the measuring processes of DSC and hot stage microscopy. Since DSC directly measures solubility of drug in the PSA, overestimation of solubility is possible due to overshoot as the temperature increases because solubility generally increases with temperature. On the other hand, hot stage microscopy measures the temperature at which drug completely dissolves in a system at a particular composition to form a saturated solution. The weight fraction of drug in a particular system is considered to be the solubility at the saturation temperature. However, due to the constantly increasing temperature, the saturation temperature may be overestimated by hot stage microscopy, and errors in solubility measurement may occur. Therefore differences may exist between the results of these two methods.

2.2.2 Physical stability of drug/PSA patches at room temperature

Table 2.4 shows the physical stabilities of LC/DT2287 patches as functions of the weight fraction of LC in LC/DT2287 mixtures. The 40% w/w LC/DT2287 patch had sufficient physical stability (> 3 months) for drug release studies. Since the physical stabilities of the patches had been found to be higher at 31 °C relative to that at 25 °C (see Section 3.3.1 and Figure 3.3), it was believed that the stabilities found at room temperature would be sufficient for conducting the drug release studies.
<table>
<thead>
<tr>
<th>Drug Weight Fraction (w/w)</th>
<th>90%</th>
<th>80%</th>
<th>70%</th>
<th>60%</th>
<th>50%</th>
<th>40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystallization Time (min)</td>
<td>2.00±0.30</td>
<td>7.20±2.10</td>
<td>18.3±3.40</td>
<td>19.5±4.50</td>
<td>117±18.4</td>
<td>&gt; 3 months</td>
</tr>
</tbody>
</table>

Table 2.4 Times for crystallization of LC in LC/DT2287 mixtures at room temperature (23-25 °C).
2.2.3 Drug release studies

2.2.3.1 Influence of drug loading on lidocaine release

Figures 2.3 and 2.4 show profiles of the release of LC from supersaturated and crystallized 40% w/w LC/DT2287 patches as functions of drug loading across 5 layers of Spectro/Por® 1 membrane. It can be seen that for both supersaturated and crystallized patches, drug loading affected the rate of drug release from the patches, especially at the longer times. At times greater than 10 hours, for patches with drug loading at 44.9 mg LC/patch, the rate of LC release was significantly slower than that at higher loadings. Supersaturated patches seem to be more sensitive to drug loading since release from these patches (with 44.9 mg LC/patch) began to decrease at about 5-6 hours. It can be further estimated from the release profiles at 44.9 and 89.9 mg LC per patch as shown in Figure 2.3, that the rates of release began to decrease from the supersaturated patches after about 15-20% of drug was released (at ~6 hours for 44.9 mg/patch and ~12 hours for 89.9 mg/patch). Similar estimations for the crystallized patches indicated that after ~30% of drug was released, drug release tended to decrease. This indicates that supersaturated patches are more sensitive to drug loading than crystallized patches, which is reasonable because the apparent thermodynamic activity of LC in the supersaturated patches would be more easily affected by the amount of drug released from the patches. Drug release from crystallized patches, on the other hand, should not be affected by drug depletion.
Figure 2.3 Profiles of the release of LC from supersaturated 40% w/w LC/DT2287 patches as functions of drug loading across 5 layers of Spectro/Por® 1 membranes (n=3, + SD). Key: •: 449 mg LC per patch; ♦: 135 mg/patch; ■: 89.9 mg/patch; ▲: 44.9 mg/patch.
Figure 2.4 Profiles of the release of LC from crystallized 40% w/w LC/DT2287 patches as functions of drug loading across 5 layers of Spectro/Por® 1 membranes (n=3, + SD). Key: ▲: 449 mg LC per patch; ◆: 135 mg/patch; ■: 44.9 mg/patch.
before the suspended drug crystals are exhausted since these crystals function as reservoirs which would keep the thermodynamic activity of the drug in the patches constant over a longer period of time until the crystals are completely depleted. It should be noted here that for transdermal patches with drug directly dispersed in a PSA, the maximum drug loading is usually limited by the thickness of the PSA layer (typically about 50-100 µm). Therefore, drug release from this type of patch may have a higher dependency on drug loading, especially for those drugs that have a higher permeability in the skin and thereby would be depleted more easily. In this case, reservoir types of patches may be the favored delivery systems because larger amounts of drug can be loaded in them.

Figures 2.3 and 2.4 also indicate that drug release did not increase significantly after drug loading was increased to 135 mg LC per patch, especially during the first 10 hours. The linearity of the drug release profiles during the first 10 hours for patches at 135 mg/patch was ~0.998, which indicated that steady state release was achieved during this period of time. According to Equation 1.1, this may indicate that the effects of drug depletion on the rate of release are negligible during the period of steady state. Therefore, the loading of 135 mg/patch can be regarded as sufficiently large for the drug release studies, and comparisons of the rates of drug release should be performed within the time frame where steady state release can be achieved.
2.2.3.2 The effect of supersaturation on LC release

Figure 2.5 shows that drug release profiles from supersaturated and crystallized patches across 1 layer of silicone membrane were close to those of direct release (no barrier membrane was used), indicating that drug release across a single silicone membrane was rapid. An increase in the number of layers of membrane from 1 to 4 layers reduced fluxes, but not to the desired extent (see Figure 2.5). The accumulated amounts of drug released were 2500 µg/cm² in 2 hours for 1 layer of silicone membrane and 3400 µg/cm² in 10 hours for 4 layers of silicone membrane. Compared with the permeabilities of LC through hairless rat skin\textsuperscript{102} (where the accumulated amount of drug permeated at 24 hours was about 2000 µg/cm²), transport of LC across the silicone membranes was too fast to be of practical use. Further increases in the thickness of the individual silicone membranes or in the number of layers may have run the risk of turning the barrier membrane into a reservoir for drug which in turn may have significantly reduced the degrees of supersaturation of the patches. This would have made it difficult to differentiate between the release of drug from the supersaturated and crystallized patches. Therefore, silicone membranes may not be appropriate barriers for \textit{in vitro} tests of these LC-containing PSA patches.

Alternatively, cellulose membranes (5 layers of Spectro/Por\textsuperscript{®} 1), as shown in Figure 2.5, gave an almost zero-order release for both supersaturated and crystallized patches over 24 hours. The accumulated amounts of drug released in 24 hours were about 2800-3000 µg/cm², which was closer to the literature value measured for hairless rat skin
Figure 2.5 Profiles of the release of LC from 40% w/w LC/DT2287 patches as functions of barrier composition (n=3, + SD). Key: ×: no barrier membrane, supersaturated LC/PSA patches; +: no barrier membrane, crystallized patches; •: 1 layer of silicone membrane, supersaturated patches; ○: 1 layer of silicone membrane, crystallized patches; ■: 4 layers of silicone membrane, supersaturated patches; □: 4 layers of silicone membrane, crystallized patches; ▲: 5 layers of Spectro/Por® 1, supersaturated patches; △: 5 layers of Spectro/Por® 1, crystallized patches; ◆: 5 layers of Spectro/Por® + 1 layer of silicone membrane, supersaturated patches; ◇: 5 layers of Spectro/Por® + 1 layer of silicone membrane, crystallized patches.
Unfortunately, as can be seen from Figure 2.5, the differences in the accumulated amounts of LC released between the supersaturated (the degree of saturation was about 1.88 for supersaturated 40% w/w LC/DT2287 patches at 31 °C) and crystallized patches was not significant. LC release from the supersaturated patches appears to be faster than from the crystallized patches during the first 8 hours (the ratios between the accumulated amounts of drug permeated from the supersaturated and crystallized patches reached up to ~1.30 at 8 hours, although no statistically significant difference was found between the fluxes from these two patches.). However, after 8 hours, LC release from the supersaturated patches decreased to the same rate as that from the crystallized patches. The reasons for this will be explored in Section 2.2.4.

The LC release profiles obtained with a composite barrier consisting of 1 layer of silicone membrane and 5 layers of Spectro/Por® 1 are also given in Figure 2.5. It can be seen that the rate of LC release from supersaturated 40% w/w patches was significantly higher than that from crystallized 40% w/w patches. The linearity of these profiles is good since both have r² values above 0.998 which indicates that steady state release of LC has been reached. The calculated average LC fluxes over 2~24 hours were 103 µg/cm²h for supersaturated and 58.5 µg/cm²h for crystallized 40% w/w patches. The ratio between the fluxes is about 1.76, which is close to the degree of saturation (~1.88) of the supersaturated 40% w/w patches. Statistical analysis indicated that the rate of release of LC from the supersaturated patches was significantly larger than that from the crystallized patches (p = 0.001), showing that supersaturation of LC in a PSA can enhance the in vitro release of LC across the composite membranes. Compared with
silicone and cellulose membranes alone, the composite membrane functions as a barrier which can differentiate the rates of drug release from supersaturated and crystallized patches. Further characterization of this composite membrane will be discussed later in this section (see Figure 2.8).

A peculiarity of drug release across the Spectro/Por® membranes, as shown in Figure 2.6, was that the rate of release of LC from the crystallized 40% w/w patches was significantly higher than that from the supersaturated 30% w/w patches. This happened despite the fact that the apparent thermodynamic activity of the crystallized 40% w/w patches should be approximately equal to that of the 20% w/w patches since the solubility of LC in the PSA was about 21.3% w/w at 31 °C. In addition, no statistically significant differences in the rates of drug release were found between the supersaturated and crystallized patches of both the 30% and 40% w/w LC/DT2287 mixtures (see Figures 2.5 and 2.6). This indicates again that drug release from LC/DT2287 patches across Spectro/Por® 1 membranes apparently did not follow Fick’s first law. The mechanism behind this will be discussed also in Section 2.2.4.

The possibility of using greater numbers of stacked cellulose membranes to differentiate the rates of LC release was also evaluated. Both supersaturated and crystallized 40% and 30% w/w patches were studied. Figure 2.7 shows the release
Figure 2.6 Profiles of the release of lidocaine from supersaturated and crystallized 30% and 40% w/w LC/DT2287 patches with a barrier consisting of 5 layers of Spectro/Por®1 membrane (n=3, ± SD). Key: •: supersaturated 40% LC/DT23287 patches; o: crystallized 40% LC/DT2287 patches; ▲: supersaturated 30% LC/DT2287 patches; Δ: crystallized 30% LC/DT2287 patches.
Figure 2.7 Profiles of the release of lidocaine from supersaturated 30% and 40% w/w LC/DT2287 patches as functions of the number of layers of Spectro/Por® 1 membranes (n=3, + SD). Key: •: 5 layers of, 40% w/w supersaturated LC/PSA patches; o: 5 layers of, 30% w/w supersaturated patches; ▲: 9 layers of, 40% w/w supersaturated patches; Δ: 9 layers of, 30% w/w crystallized patches; ■: 10 layers of, 40% w/w supersaturated patches; □: 10 layers of, 30% w/w supersaturated patches.
profiles for LC from the supersaturated patches. It can be seen that the differences in the rates of drug release for the 30% and 40% w/w supersaturated patches decreased as the thicknesses of the barrier membranes increased. Similarly, increases in the thicknesses of the barrier membranes also reduced the differences in rates of drug release between the crystallized patches and their corresponding supersaturated patches. The latter is not shown because the release profiles from the crystallized patches were very close to those from the corresponding supersaturated patches (see Figures 2.5 and 2.6) and increased numbers of membranes made them even closer, therefore they are difficult to resolve schematically. This suggests that cellulose membranes alone might not be good release barriers to allow differentiation between the rates of LC release from the supersaturated and crystallized patches even though the rates of release across it could be reduced. The mechanism behind this will be discussed also in Section 2.2.4.

Figure 2.8 shows the profiles of LC release obtained with the composite barrier consisting of 1 layer of silicone membrane and 5 layers of Spectro/Por® 1. As indicated for Figure 2.5, supersaturation of LC in a PSA can enhance the in vitro release of LC across the composite membranes. Compared with silicone and cellulose membranes alone, the composite membrane functions as a good barrier which can differentiate the rates of drug release from supersaturated and crystallized patches. To further characterize the properties of the composite barrier membranes, LC/DT2287 patches containing 10%
Figure 2.8 Profiles of the release of LC from various LC/DT2287 patches determined with a composite barrier consisting of 1 layer of silicone membrane and 5 layers of Spectro/Por® 1 membranes (n=3, + SD). Key: ●: supersaturated 40% w/w LC/DT2287 patches; ○: crystallized 40% w/w LC/DT2287 patches; ▲: crystallized 50% w/w LC/DT2287 patches; ■: 20% w/w (saturated) LC/DT2287 patches; ★: 10% w/w (subsaturated) LC/DT2287 patches.
w/w LC (subsaturated; the degree of saturation ~0.47), 20% w/w LC (close to saturation; the degree of saturation ~0.94) and 50% w/w LC (saturated system with excess drug crystallized) were also tested on this barrier. The LC release profiles are shown in Figure 2.8, while the calculated steady-state fluxes over 4-24 hours are listed in Table 2.5. The linearity of these profiles is good, with r² values all over 0.997. It can be seen that the release profiles for the 40% w/w crystallized and 50% w/w crystallized patches were very close to that of the 20% w/w saturated patches, and statistical analysis shows that there are no significant differences between the steady state fluxes from these patches (p values between 0.236-0.819). On the other hand, the release profile of the 10% w/w subsaturated patches was significantly lower than that of the three patches containing higher weight fractions of LC. A statistically significant difference was found between the steady state fluxes from the 10% and 20% w/w patches (p = 0.005). The ratio of the fluxes from the subsaturated 10% w/w patches and 20% w/w patches was ~0.58, which was close to the degree of saturation (~0.47) of the 10% w/w patches. Similarly, as discussed for Figure 2.5, it can be concluded that the rate of LC release from the supersaturated 40% w/w patches was significantly larger than that from the crystallized 40% w/w patches (p = 0.001). Theoretically, the thermodynamic activities of 50% and 40% w/w crystallized patches should be equal to that of a saturated LC/DT2287 system, i.e., 20% w/w system, and almost twice that of the 10% w/w subsaturated patch. Therefore, LC release from the LC/DT2287 patches across the composite barrier membranes followed Fick’s first law,
<table>
<thead>
<tr>
<th>Drug in PSA (w/w)</th>
<th>10%</th>
<th>20%</th>
<th>50% crystallized</th>
<th>40% crystallized</th>
<th>40% supersaturated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flux, µg/cm²h</td>
<td>34.8±4.94</td>
<td>59.5±5.74</td>
<td>65.0±6.91</td>
<td>58.5±4.17</td>
<td>103±8.79</td>
</tr>
</tbody>
</table>

Table 2.5 Calculated steady-state fluxes across a composite membrane consisting of 1 layer of silicone membrane and 5 layers of SpectroPor® 1 (n=3) (see Figure 2.8).
which predicts that thermodynamic activity (or concentration) gradients rather than the weight fractions of drug in the PSA systems should determine flux. Therefore, it can be concluded that the composite membrane was a good barrier model for studying lidocaine release from these PSA systems.

It should be noted that the linearities of the drug release profiles in Figure 2.8 are better than those in Figures 2.3 and 2.6 over the time frame of 2~24 hours. Specifically, the rates of drug release through 5 layers of Spectro/Por® membrane (see Figures 2.3 and 2.6) decreased after 8~12 hours, which is shown by deviation of these drug release profiles from a linear relationship after 8~12 hours. This will be further discussed in the following section.

2.2.4 Hydration of the pressure sensitive adhesive systems

In the drug release studies, no statistically significant differences in the rates of drug release were found between the supersaturated and crystallized LC/PSA patches when the Spectro/Por®1 membranes were used as the barriers. Additionally, the rates of drug release decreased after 8~12 hours using the Spectro/Por®1 membranes as the barriers (see Figures 2.5 and 2.7). Spectro/Por® is a water-permeable dialysis membrane and back flow of water to the surface of the patches was observed during the drug release experiments. It was also found that the supersaturated patches, which were transparent at the beginning of a drug release experiment, gradually became hazy in appearance and finally opaque white after ∼5-8 hours. Therefore, it can be assumed that the presence of
water might cause changes in the drug/PSA systems. To evaluate this, a series of DT2287 patches with and without drug were exposed to water and subsequently examined by microscopy.

As shown in Figure 2.9, upon exposure to water both LC-containing and non-LC-containing (control) DT2287 systems underwent changes with time, i.e., numerous droplets appeared and grew in size. These droplets were found not only on the surfaces, but also in the interiors after equilibration with water. The higher the LC weight fraction in the PSA systems, the faster the droplets grew. Meanwhile, it was observed that both LC-containing and control (non-LC-containing) PSA systems turned hazy and then opaque. The degree of opacity was also related to the weight fraction of drug in the systems since the control PSA systems were the most transparent. After removal from water, the droplets quickly disappeared (see Figures 2.10), and all patches recovered their transparency. The reversibility of the presence of these droplets and its relation to dehydration can be seen more clearly in Figure 2.11 at a higher magnification (400×).

Similar findings were observed from drug release studies using Spectro/Por® membranes as the barriers (see Photomicrograph A in Figure 2.12), but were not found when water impermeable barriers such as silicone membranes or the composite membranes (1 layer of silicone membrane and 5 layers of Spectro/Por® membrane) were used.

The direct relationship between the occurrence of the droplets and the presence of water suggests that these droplets may be caused by hydration of the PSA systems upon contact with water. DT2287 is a polyacrylate PSA which has ester groups that can hydrate. Due to the relative hydrophilicity of LC, the degree of hydration occurring
Figure 2.9  Photomicrographs of control and LC/DT2287 patches exposed to distilled, deionized water (320×).  Panel 1: control DT2287 patches; Panel 2: 30% LC/DT2287 Patches; Panel 3: 40% LC/DT2287 Patches.  A, E and I: before exposure to de-ionized water; B, F and J: after exposure to de-ionized water for 1 hour; C, G and K: after exposure to deionized water for 24 hours.
Figure 2.10 Photomicrographs of dehydrated control and LC/DT2287 patches after exposure to distilled, deionized water (320×). Samples were stored at ambient temperature for 1 hour after exposure to water for 24 hours.
Figure 2.11 Photomicrographs of the dehydration of control DT2287 patches (400×). The photographs were taken at different time points when the samples were stored at ambient temperature after exposure to distilled, deionized water for 8 hours; A: 5 minutes; B: 10 minutes; C: 15 minutes; D: 20 minutes; E: 25 minutes; F: 30 minutes.
Figure 2.12 Photomicrographs of 40% LC/DT2287 patches used in drug release studies with 5 layers of Spectro/Por 1 Membranes (320×). A: after 5 hours; B: after 18 hours; C: crystals formed by evaporating solvent at 50 °C; D: stored at ambient temperature for 5 min after 12 hours in drug release experiment; E: stored at ambient temperature for 20 min after 12 hours in drug release experiment; F: stored at ambient temperature for 30 min after 12 hours in drug release experiment. B, D, E, and F were taken under polarized light.
in the LC/PSA systems can increase as the weight fraction of drug in the systems increased. This explains why the LC/PSA systems containing a higher weight fraction of LC had a higher degree of hydration and thereby more droplets in the systems as shown in Figure 2.9.

Furthermore, scanning electron microscopy (SEM) showed that the surfaces of the water-treated 40% w/w LC/DT2287 patches were very smooth in appearance (see Figure 2.13), indicating that no significant morphological changes had occurred upon exposure to water and that the droplets are not caused by, nor did they cause, morphological deformation of the systems despite the fact that LC has apparently dissolved out of these systems.

Based on this hypothesis, the non-Fickian release of LC from the LC/DT2287 systems across the Spectro/Por® membranes may be explained by hydration of the LC/DT2287 systems. The presence of water droplets in the LC/DT2287 systems, resulting from hydration of the systems, could provide two alternative pathways for drug release: by diffusion within the PSA medium or by partitioning into water droplets and diffusion through the water. Drug diffusion in water should be faster than in the PSA and this “shortcut” pathway provided by water droplets in the hydrated LC/PSA systems would function to facilitate drug release. Accordingly, the higher the extent of hydration of the drug/PSA systems, the larger would be the total interfacial area between the droplet water phase and the PSA, as well as between droplets. The latter could create finite clusters of water droplets leading eventually to infinite clusters as the number of droplets increases. This would provide an alternative pathway for LC diffusion through
Figure 2.13 Scanning electron microscopy (SEM) of the surface of the 40% w/w LC/DT2287 system after exposure to water.
the PSA. Since the degree of hydration of the LC/PSA systems is related to the weight fraction of LC in the mixtures, drug release would therefore depend on the weight fraction of LC. Considering that transdermal delivery patches usually block water evaporation from the skin, thereby promoting hydration of the stratum corneum, it can be assumed that hydration of polyacrylate PSA systems would also occur. In fact, it has been reported that drug release from another type of polyacrylate PSA patch was also drug weight fraction dependent in an in vitro animal skin test.\textsuperscript{102}

To determine why there were no significant differences in the rates of drug release from supersaturated and crystallized patches (see Figures 2.5), the patches were examined by microscopy at predetermined time intervals during a drug release experiment using 5 layers of SpectroPor\textregistered 1 membrane as barrier and the results are given in Figure 2.12.

It can be seen in Photomicrograph B of Figure 2.12, that drug crystallization occurred during the release experiment. The crystals were much larger than the needle-like crystals formed from solvent evaporation or from crystal seeding (see Photomicrographs B and C in Figure 2.12), suggesting that they grew at much slower rates. Further studies showed that between 7 to 16 hours after the drug release experiments began, large crystals could be observed by polarized light microscopy (n = 15). After 16 hours all patches contained large crystals, however, few needle-shaped crystals were found during this time frame. After the patches were removed from the diffusion cell, needle-shaped crystals did grow rapidly on the large crystals (typically
crystal growth completed within 30 min), while at the same time the sizes of the droplets decreased (see photomicrographs D ~ F). Furthermore, no crystallization occurred in the drug/PSA patches when drug release studies used the water-impermeable silicone membranes or the composite membranes. This suggests that hydration of the drug/PSA systems has a direct relationship to the slow crystallization process.

As shown in Figures 2.3 and 2.5, the rate of drug release from supersaturated patches across the Spectro/Por® membranes slowed after about 8 hours which generally corresponds to the appearance of the large crystals at 7-16 hours. Considering that there might be a considerable lag time for nucleation and crystal growth, nucleation probably occurred earlier than when the crystals were first observed. Therefore, nucleation and crystallization induced by hydration of the LC/PSA systems might be the reason the rate of drug release decreased over time since nucleation may significantly decrease free drug concentration in the PSA even before crystals started to grow. On the other hand, drug release through the composite membrane (1 layer of silicone membrane and 5 layers of Spectro/Por® membrane) was not affected because the silicone membrane was water-impermeable.
CHAPTER 3

PHYSICAL STABILITY OF SUPERSATURATED LIDOCAINE/POLYACRYLATE PRESSURE SENSITIVE ADHESIVE SYSTEMS

CONCEPT MAP

• Isothermal crystallization of LC in supersaturated LC/Duro-Tak® 87-2287 pressure sensitive adhesive systems was studied by DSC, and analyzed using the classical theory of nucleation and the Avrami relation.

• Crystallization of LC in supersaturated LC/DT2287 systems is primarily controlled by the nucleation process, which in turn is highly affected by temperature and the composition of the systems.

• A critical temperature, $T_{crit}$, for crystallization of LC in LC/DT2287 systems was found to be $\sim 26 \, ^\circ$C, above which the crystallization process becomes very slow.

• A critical degree of saturation, $S_{crit}$, of $\sim 4$ was found, above which the nucleation rate sharply increases.

• The lack of dependence of $T_{crit}$ on the compositions of the systems indicates that the presence of the PSA affected the kinetics (diffusion) rather than the thermodynamics of the nucleation process.
• The nucleation of LC in the PSA medium is a diffusion-controlled process.

• The activation energy for nucleation has a two-phase dependence on temperature, whereas both the Avrami constant, $k$, and the Avrami exponent, $n$, exhibit two-phase temperature dependence. This suggests that the mechanism of crystallization may change at the transition temperatures.

• Over the low temperature range, crystal growth can be described both by the Avrami equation and the classical theory of nucleation. The values of $n$ indicate that crystals are formed by two-dimensional disc-like growth from sporadic nuclei in the 40% and 50% w/w systems, and by three-dimensional spherulitic growth from sporadic nuclei in the 60% and 70% w/w systems.

• Over the high temperature range, the Avrami exponent $n$ is rather large and cannot be explained by conventional Avrami theory. In this context, a hypothesis has been proposed suggesting that the nucleation rate increases exponentially with time.

• A two-step nucleation process has been suggested over the high temperature range. Before nuclei are stably formed, the nucleation rate may be described by the classical theory of nucleation, while the nucleation rate increases exponentially with time after the nuclei are stable.

• It appears that frequent branching which occurs as crystals grow may account for the time dependence of the nucleation rate after nuclei form.
3.1 Purpose of the studies

Although supersaturation has some unique advantages, it also presents significant formulation challenges, such as the inherent physical instability of a supersaturated system. With thermodynamic activity above unity, supersaturated systems are thermodynamically unstable and drug crystallization may occur over time. In fact, physical instability is the major hurdle that limits the application of supersaturation in transdermal drug delivery.7

To enhance the physical stability of supersaturated drug/PSA systems, it is necessary to understand the drug crystallization processes from such systems. The aim of this study was therefore to determine the crystallization kinetics of drug from a PSA system supersaturated with drug and the factors that may affect it.

As mentioned briefly in Section 1.7.3, crystallization from supersaturated systems is essentially a two step process: nucleation followed by crystal growth.121,122 The kinetics of homogeneous nucleation can be described by what is called “the classical theory of nucleation” which stems from the work of Gibbs106 and Volmer107 (see Equation 1.5), whereas the overall crystallization process may be described by the Avrami relation.110

In this work, isothermal crystallization kinetics of LC from supersaturated LC/PSA systems was analyzed sequentially using the classical theory of nucleation and the Avrami relation (see Equation 1.6).
3.2 Experimental

3.2.1 Sample preparation

A series of LC/DT2287 mixtures with different weight fractions of LC were prepared by dissolving appropriate amounts of both LC and DT2287 in ethyl acetate followed by evaporation of the solvent at room temperature for one month. The samples were then stored in desiccator at room temperature for at least two weeks prior to use.

3.2.2 Isothermal crystallization

Thermal analysis methods such as differential scanning calorimetry (DSC) have been used to determine isothermal crystallization kinetics in various types of materials including metals, polymers, fats, and glass-forming solids.\textsuperscript{123-126} In this work, DSC was used to determine the isothermal nucleation kinetics of a drug in PSA systems. Accurately weighed samples (~10 mg) of drug/PSA systems were placed in aluminum DSC pans and hermetically sealed. To eliminate the effects of prior thermal history, all samples were first heated to 100 °C for 20 minutes. They were then cooled to predetermined crystallization temperatures at a rate of 20 °C/min. Samples were kept at these temperatures until crystallization was complete. Due to the limited amount of coolant in the liquid nitrogen reservoir, the longest isothermal period was 15-24 hours depending on the crystallization temperatures that needed to be maintained.
From the isothermal DSC thermograms, the time of the deflection point of the crystallization exotherm was taken as the induction time $\tau$, while the baseline peak width was taken as the crystallization growth time. All data reported are the average of three independent experiments.

From the isothermal DSC thermograms, the fractions of crystal transformed, $\alpha$, as functions of time were calculated as:

$$\alpha = \frac{\Delta H_t}{\Delta H_T}$$

where $\Delta H_t$ is the integrated exotherm at time $t$ and $\Delta H_T$ is the total integrated exotherm. The calculation was performed by the thermal analysis software (Mettler GraphWare TA 72.5).

### 3.2.3 Crystal growth studies

Light microscopy (Leitz Wetzlar) was used to study crystal growth. The linear crystal growth rate ($G, \text{mm/min}$) was measured using a stage micrometer (2mm, Leitz) and a stop watch. Crystallization in supersaturated LC/DT2287 systems at ~24 °C was induced by seeding with small amounts of LC/DT2287 mixtures containing LC crystals. All data reported are the average of three independent measurements.
3.3 Results and discussion

3.3.1 Isothermal crystallization

A sample DSC thermogram is given in Figure 3.1, and the crystal fractions, $\alpha$, as functions of time were determined by the thermal analysis software (Mettler GraphWare TA 72.5) based on Equation 3.1, and are shown in Figure 3.2. It can be seen from Figure 3.2 that DSC is capable of accurately quantifying the crystallization kinetics of LC in LC/DT2287 mixtures based on the fractions of crystallization exotherms as functions of time. The crystallization induction times $\tau$ and crystal growth times as functions of crystallization temperature $T_c$ are shown in Figures 3.3 and 3.4, respectively.

Figure 3.3 indicates that the nucleation process in supersaturated LC/DT2287 systems depends strongly on the crystallization temperature. The higher the temperature, the longer is the induction time. Although all systems showed a two-phase dependency, i.e., an inflection point, and a transition temperature $T_{tran}$ above which the nucleation rate decreased rapidly, i.e., $\tau$ increases, systems with different weight fractions of drug had different values of $T_{tran}$. The values of $T_{tran}$ are about 15, 17, 22 and 23 °C for the 40%, 50%, 60% and 70% w/w LC/DT2287 systems, respectively. It should be noted that for the pure LC melt, the temperature dependence of the nucleation rate is so large that with an increase of only 0.5 °C, i.e., 25.5 to 26 °C, the induction time jumps from ~1 minute to more than 24 hours. This increase in induction time becomes smaller as the weight
Figure 3.1 Typical DSC thermogram for the isothermal crystallization of LC from a 70% w/w LC/DT2287 system at 25 °C.
Figure 3.2 Crystallization of LC from a 70% w/w LC/DT2287 system at 25 °C (as shown in Figure 3.1). $\alpha$ is the calculated crystal fraction.
Figure 3.3 Crystallization induction times of LC in LC/DT2287 systems as functions of temperature. Key: ■, 40% w/w LC/DT2287; ♦, 50% w/w LC/DT2287; ▲, 60% w/w LC/DT2287; ×, 70% w/w LC/DT2287; and o, 100% LC.
fraction of drug decreases, indicating that the presence of the PSA inhibited the nucleation of LC. Nevertheless, none of the samples crystallized within 24 hours at temperatures above 26 °C, indicating that this temperature is crucial in inhibiting nucleation in LC/DT2287 systems. This suggests that the nucleation rate becomes very slow when the crystallization temperature approaches 26 °C, irrespective of the composition of the systems. The lack of dependence of this critical temperature \( T_{\text{crit}} \) on the compositions of the systems may indicate that the presence of the PSA affected the kinetics (diffusion) rather than the thermodynamics of the nucleation process.

However, the crystal growth times, as shown in Figure 3.4, are essentially independent of temperature except for the 40% w/w mixture. Combined with the data in Figure 3.3, it can be concluded that nucleation rate rather than crystal growth rate is the determining factor in the crystallization process, especially at or above room temperature. Therefore, for the purpose of stabilizing a supersaturated transdermal PSA system, the nucleation process and related factors should be carefully controlled.

Figure 3.5 gives the crystallization induction times as functions of the degrees of saturation. It can be seen that there is a critical degree of saturation \( S_{\text{crit}} \) below which the nucleation rate may significantly decrease. The value of \( S_{\text{crit}} \) is \( \sim 4 \), irrespective of temperature. Obviously, \( S_{\text{crit}} \) is another important parameter in evaluating the potential of these systems for enhancement of transdermal delivery, as well as the physical stability of the supersaturated systems. Therefore, based on the inflection points of the curves, it may
Figure 3.4 Crystal growth times of LC in LC/DT2287 systems as functions of temperature. Key: ♦, 40% w/w LC/DT2287; ■, 50% w/w LC/DT2287; ▲, 60% w/w LC/DT2287; ⋯⋯⋯, 70% w/w LC/DT2287.
Figure 3.5 Crystallization induction times of LC in LC/DT2287 systems as functions of the degrees of saturation $S$ and temperature. $S$ is the ratio between the actual concentration and the saturation concentration of LC in DT2287 and was calculated based on the solubility data in Table 2.3.
be concluded that the degree of saturation of LC/DT2287 systems should not exceed ~4 for the purpose of enhancing drug release since the supersaturated LC/DT2287 systems tend to undergo crystallization above this value.

3.3.2 Analysis of the kinetics of nucleation

As mentioned earlier, crystallization from supersaturated systems consists two steps: nucleation followed by crystal growth.\textsuperscript{121,122} The kinetics of homogeneous nucleation can be described by what is called “the classical theory of nucleation” developed by Volmer and Weber\textsuperscript{107}, Becker and Döring\textsuperscript{128} and Turnbull and Fisher.\textsuperscript{129} Taking into consideration the resistance of the medium to molecular diffusion, the rate of nucleation in a supersaturated solution can be expressed in the form of the Arrhenius reaction velocity equation:\textsuperscript{104}

\[
J = A \exp\left(-\frac{\Delta G_c}{kT}\right) \exp\left(-\frac{\Delta G_d}{kT}\right)
\]  

(3.2)

where $J$ is the rate of nucleation; $A$ the pre-exponential factor, which is often considered to be temperature independent; $k$ Boltzmann’s constant; $T$ temperature; and $\Delta G_c$ and $\Delta G_d$ are the activation energies to develop stable nuclei and for molecular diffusion, respectively. It can be seen from Equation 3.2 that nucleation rate $J$ is determined by two factors: a thermodynamic factor, $\Delta G_c$, and a kinetic factor, $\Delta G_d$. These two factors should have opposite effects on the rate of nucleation. The activation energy for nucleation, $\Delta G_c$,
as shown in Equations 3.3 and 3.4, determines the magnitude of driving force for nucleation and crystallization; while the activation energy for diffusion, $\Delta G_d$, represents the kinetic hindrance to nucleation and crystallization. Therefore, these two parameters should have opposite signs, and will exhibit opposite influences on the rate of nucleation when temperature changes (see Equation 3.2).\textsuperscript{104}

In a supersaturated solution, $\Delta G_c$ is associated with the degree of saturation, $S$, and the surface energy at the crystal/solution interface, $\gamma$, through the following equation:\textsuperscript{104}

$$
\Delta G_c = 16\pi\gamma^3 v^2 / 3k^2 T^2 (\ln S)^2
$$

(3.3)

where $S = C/C_s$, the ratio between the actual concentration and the saturated concentration; $v$ is the molecular volume and is equal to $M/\rho N$; $M$ the weight per mole of the solute; $\rho$ the density of the solute and $N$ is Avogadro’s number.

Similarly, in a supercooled melt, $\Delta G_c$ is related to the effective supercooling, $\Delta T$, through the following equation:

$$
\Delta G_c = 16\pi\gamma^3 (T_m)^2 / 3(\Delta H)^2(\Delta T)^2
$$

(3.4)

where $T_m$ is the equilibrium melting temperature; $\Delta T$, the effective supercooling, the difference between $T_m$ and the isothermal temperature of crystallization, $T$; and $\Delta H$ is the
heat of fusion. The factor $16\pi/3$ in Equations 3.3 and 3.4 is also called the “shape factor” and refers to spherical nuclei. For other geometrical shapes the appropriate values should be used, e.g., 32 for a cube.\textsuperscript{104}

If Equations 3.3 and 3.4 are incorporated into Equation 3.2, the rate of nucleation can be expressed as following for a supersaturated solution:\textsuperscript{104}

$$J = A \exp\left(-\frac{16\pi \gamma v^2}{3k^3T^3(\ln S)^2}\right) \exp(-\Delta G_d/kT)$$  \hspace{1cm} (3.5)

and for a supercooled melt:

$$J = A \exp\left(-\frac{16\pi \gamma^2 (T_m)^2}{3k(\Delta H)^2 T(\Delta T)^2}\right) \exp(-\Delta G_d/kT)$$  \hspace{1cm} (3.6)

In Equation 3.6, the pre-exponential factor can be substituted by $A = NkT/h$, where $h$ is Plank’s constant, to give Equation 3.7, which is the Fisher-Turnbull equation:\textsuperscript{129,130}

$$J = (NkT/h) \exp\left(-\frac{16\pi \gamma^2 (T_m)^2}{3k(\Delta H)^2 T(\Delta T)^2}\right) \exp(-\Delta G_d/kT)$$  \hspace{1cm} (3.7)

Since it is rather difficult to accurately quantify through experiment the rate of nucleation, $J$, the number of nuclei formed per unit time per unit volume, a method based on determination of the induction time, $\tau$, the time required to achieve nucleation after the
supersaturated/supercooled state has been reached, has been used previously.\textsuperscript{131-133} This assumes that the induction time is inversely proportional to the nucleation rate as shown in Equation 3.8: \textsuperscript{104,121,134}

\[
J = \frac{K}{\tau} \quad (3.8)
\]

where K is a constant.

If Equations 3.5 and 3.7 are substituted into Equation 3.8, the following are given:

\[
\tau = \frac{(K/A)}{\exp[16\pi\gamma^3v^2/3k^2T^2(\ln S)^2]} \exp(\Delta G_{\phi}kT) \quad (3.9)
\]

and,

\[
\tau = \frac{(hK/NkT)}{\exp[16\pi\gamma^3(T_m)^2/k(\Delta H)^2T(\Delta T)^2]} \exp(\Delta G_{\phi}kT) \quad (3.10)
\]

In Equation 3.10, the first exponential contains the factor $1/T(\Delta T)^2$. Compared with the second exponential, which contains the factor $1/T$, the magnitude of the first exponential would be influenced to a greater extent by a change of temperature, especially when $\Delta T$ is relatively large. The LC/DT2287 systems fall into this category as will be discussed later in this section. Therefore, within a small range of temperatures the second exponential may be treated as a constant and Equation 3.10 is then transformed into:
\[
\ln(\tau T) = \left[ \frac{(16\pi \gamma^2 (T_m)^2)}{3k(\Delta H)^2} \cdot \left( \frac{1}{T} \right)^2 \right] + A_1 
\]

(3.11)

where \( A_1 \) is a constant.

Similarly, Equation 3.9 is transformed into:

\[
\ln \tau = \left( \frac{16\pi \gamma^2 v^2}{3k^3} \right) \left[ \frac{1}{T^3} \left( \ln S \right)^2 \right] + A_2
\]

(3.12)

where \( A_2 \) is a constant. Equations 3.11 and 3.12 are for crystallization from melt\(^{130}\) and solution,\(^{131}\) respectively.

Crystallization of LC in supersaturated LC/PSA systems may be treated as if it was occurring in a supercooled melt. This is because crystallization of polymers or polymer blends is generally incomplete and a certain amount of amorphous state always exists in a crystallized polymer.\(^{132}\) Therefore, LC and PSA in the systems may be treated as crystalline and amorphous parts of polymer systems, and the Fisher-Turnbull equation, Equation 3.11, may be applicable to the crystallization of LC in such systems. Although the Fisher-Turnbull equation was originally derived for a single component system, it is applicable to multi-component systems as well.\(^{130,135}\)

On the other hand, crystallization of LC from supersaturated LC/PSA systems may also be regarded as a crystallization process from solution. In this case, Equation 3.12 may be applicable. This method requires that the drug solubilities as functions of temperature be known, which has been discussed in Section 2.2.1.
For the purpose of the present work, both approaches will be attempted and then compared. To characterize the thermodynamic and kinetic features of the nucleation process of LC in the LC/DT2287 systems, the activation energies, e.g., $\Delta G_c$ and $\Delta G_d$ were calculated based on both approaches. Briefly, the isothermal nucleation data were first analyzed by combining Equations 3.2 and 3.8 to yield:

$$
\ln \tau = (\Delta G_c + \Delta G_d)/kT + A_3
$$

(3.13)

where $A_3$ is a constant.

By plotting $\ln \tau$ against $1/T$, the magnitude of $(\Delta G_c + \Delta G_d)$ can be obtained by $\Delta G_c + \Delta G_d = \text{slope} \cdot k$.

Then, according to Equation 3.11, a plot of $\ln (\tau T)$ vs. $1/T (\Delta T)^2$ should yield a straight line with a slope equal to $16\pi \gamma^3 (Tm)^2 / 3k(\Delta H)^2$. Consequently, $\Delta G_c$ can be calculated by $\Delta G_c = \text{slope} k/\Delta T^2$.

Similarly, according to Equation 3.12, the slope obtained from a plot of $\ln \tau$ vs. $1/T (lnS)^2$ can be used to calculate $\Delta G_c$ through $\Delta G_c = \text{slope} k/T^2(lnS)^2$.

Plots of $\ln \tau$ versus $1/T$ for each sample are given in Figure 3.6 (see also Equation 3.13). Similar to that in Figure 3.3, each plot exhibits a two-phase temperature dependence, suggesting that changes may occur in crystallization mechanisms at these temperatures. Linear correlation was performed separately over two ranges, high and low temperature, and the slopes and $r^2$ values are listed in Table 3.1. The calculated values of $(\Delta G_c + \Delta G_d)$ are given in Table 3.2.
Figure 3.6 Data fitting for crystallization of LC in LC/DT2287 systems based on the classical theory of nucleation (Equation 3.13).
Table 3.1 Linear correlations of $\ln \tau$ values as functions of $1/T$ for crystallization of LC in LC/DT2287 systems over the high and low temperature ranges (based on Figure 3.6).

<table>
<thead>
<tr>
<th>LC (% w/w)</th>
<th>High Temperature Slope $\times 10^2$ K</th>
<th>$r^2$</th>
<th>Low Temperature Slope $\times 10^2$ K</th>
<th>$r^2$</th>
</tr>
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<td>$T_c$ (°C)</td>
<td>$\Delta G_c$ (kJ mol$^{-1}$)</td>
<td>$\Delta G_c + \Delta G_d$ (kJ mol$^{-1}$)</td>
<td>$\Delta G_d$ (kJ mol$^{-1}$)</td>
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<td>-----------</td>
<td>-----------------</td>
<td>-------------------------------</td>
<td>-----------------</td>
</tr>
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<td>7.70$^b$ 5.09 9.51 18.2</td>
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<tr>
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</table>

Table 3.2 Calculated values of $\Delta G_c$, ($\Delta G_c + \Delta G_d$) and $\Delta G_d$ for crystallization of LC in LC/DT2287 systems. Key: a: values of $\Delta G_c$ listed in this column were calculated based on the data from Figure 3.7 and Table 3.3; b: values of $\Delta G_c$ listed in this column were calculated based on the data from Figure 3.8 and Table 3.4; c: values of $\Delta G_d$ were calculated from $\Delta G_d = (\Delta G_d + \Delta G_c) - \Delta G_c$. $\Delta G_c$ was calculated by averaging the $\Delta G_c$ values in column a.
Figure 3.7 is the plot of $\ln(\tau T)$ vs. $T^{-1} \Delta T^{-2}$ for each sample (see also Equation 3.11). Linear correlation was performed over the high and low temperature ranges, and the slopes are given in Table 3.3, and the calculated values of $\Delta G_c$ in Table 3.2. The linearity, as shown in Table 3.3, is relatively good. This indicates that treating $\Delta G_d/kT$ as a constant over a short temperature range is feasible as long as the crystallization mechanism does not change over the specific range of temperature (see Equations 3.10 and 3.11). Similar results were obtained when $\ln \tau$ was plotted as a function of $T^{-3}(\ln S)^{-2}$ (see Figure 3.8 and Table 3.4). Based on the slopes, the values of $\Delta G_c$ were calculated.

Figure 3.8 gives plots of $\ln \tau$ as functions of $T^{-3}(\ln S)^{-2}$ at certain temperatures. The slopes obtained through linear correlation are given in Table 3.4, and the calculated values of $\Delta G_c$ in Table 3.2. Figure 3.8 and Table 3.4 show that plots of $\ln \tau$ vs. $T^{-3}(\ln S)^{-2}$ are close to linearity. According to some authors, this may indicate that crystallization occurs by homogeneous nucleation, in which the nuclei are essentially generated from LC rather than from other heterogeneous nuclei in the systems. Table 3.2 lists the values of $\Delta G_c$, $(\Delta G_c + \Delta G_d)$ and $\Delta G_d$ calculated from the slopes of Figures 3.6, 3.7, and 3.8. It can be seen that the magnitude of $\Delta G_c$ is much smaller compared with that of $\Delta G_d$, suggesting that crystallization of LC in the PSA systems is primarily a diffusion-controlled nucleation process. This would explain why it takes a long time for crystals of LC to form in the LC/DT2287 systems at relatively low temperatures, i.e., 0~20 °C, and at low degrees of supersaturation (see Section 2.2.1). It should also be noted that the signs of $\Delta G_c$ and $\Delta G_d$ are opposite, which reflects the
Figure 3.7 Data fitting for crystallization of LC in LC/DT2287 systems based on the Fisher-Turnbull equation for supercooled melt (Equation 3.11).
Table 3.3. Linear correlations of $ln \tau T$ as functions of $T^{-1} \Delta T^{-2}$ for crystallization of LC in LC/DT2287 systems over the high and low temperature ranges (based on Figure 3.7).

<table>
<thead>
<tr>
<th>LC (% w/w)</th>
<th>High Temperature Slope $\times 10^7$ K$^3$</th>
<th>$r^2$</th>
<th>Low Temperature Slope $\times 10^7$ K$^3$</th>
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</tbody>
</table>
Figure 3.8 Data fitting partly shown for crystallization of LC in LC/DT2287 systems based on the theory for supersaturated solutions (Equation 3.12).
Table 3.4 Linear correlations of \( \ln \tau \) as functions of \( T^{-3}(\ln S)^{-2} \) for crystallization of LC in LC/DT2287 systems.

<table>
<thead>
<tr>
<th>( T_c (°C) )</th>
<th>Slope ( \times 10^8 \text{ K}^3 )</th>
<th>( r^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3.29</td>
<td>0.992</td>
</tr>
<tr>
<td>10</td>
<td>2.31</td>
<td>0.979</td>
</tr>
<tr>
<td>15</td>
<td>1.42</td>
<td>0.974</td>
</tr>
<tr>
<td>17</td>
<td>2.56</td>
<td>0.989</td>
</tr>
<tr>
<td>20</td>
<td>4.64</td>
<td>0.986</td>
</tr>
<tr>
<td>25</td>
<td>6.93</td>
<td>0.981</td>
</tr>
</tbody>
</table>
opposite influences of thermodynamic and kinetic factors on the nucleation rate. This is predicted by the classical theory of nucleation (see Equation 3.2), indicating that this theory is also applicable to a PSA medium, and crystallization of LC in DT2287 occurs primarily by homogeneous nucleation.

On the other hand, it was observed also that $\Delta G_c$ and $\Delta G_d$ undergo similar sharp transitions when temperature increases to certain composition related values. Since $\Delta G_d$ and $\Delta G_c$ are unlikely to undergo sharp transitions around the same temperatures, this may imply that the calculations of $\Delta G_c$ and $\Delta G_c + \Delta G_d$ are not completely independent.

Figure 3.9 gives the temperature dependence of $\Delta G_c$ calculated from Equations 3.11 and 3.12, for the melt and solution, respectively. As shown in the figure, $\Delta G_c$ calculated based on Equation 3.11 undergoes a sharp transition between 15~23 °C depending on the weight fraction of LC in the systems. This two-phase temperature dependence of $\Delta G_c$ suggests that changes in crystallization mechanisms of LC may occur at the transition temperatures. However, it is not possible to draw unambiguous conclusions about mechanistic changes at this point. A possible explanation will be discussed later in Section 3.3.3. Over the low temperature range, where temperatures are lower than at the transition points, all systems exhibit virtually the same $\Delta G_c$ when Equation 3.11 was used to calculate $\Delta G_c$ except for 40% w/w LC/DT2287 which has a smaller value. These constant values cannot be explained by the classical theory of nucleation since $\Delta G_c$ should increase as the degree of saturation, $S$, decreases at a constant temperature (see Equation 3.3). By contrast, the $\Delta G_c$ values
Figure 3.9 Temperature dependencies of $\Delta G_c$. Key: —●—, ⋯◇⋯, 40% w/w LC/DT2287; —■—, ⋯□⋯ 50% w/w LC/DT2287; —▲—, ⋯▲⋯ 60% w/w LC/DT2287; —●—, ⋯○⋯ 70% w/w LC/DT2287. The solid symbols represent data calculated from Equation 3.11, while the open symbols represent data calculated from Equation 3.12.
calculated from Equation 3.12, as represented by the open symbols in Figure 3.9, exhibit a similar trend as those from Equation 3.11 (solid symbols in Figure 3.9), although the transition temperatures of $\Delta G_c$ are not as significant. Additionally, it can also be seen in Figure 3.9 that the values of $\Delta G_c$ obtained from Equation 3.12 also take the sequence of 40% > 50% > 60% > 70% w/w, which is different from those obtained from Equation 3.11 but conforms to the classical theory of nucleation. It is worth noting that $\Delta G_c$ reaches a minimum at about 15 °C for all samples, indicating that the nucleation rate of LC at this temperature is the most rapid. This is, however, not apparent for $\Delta G_c$ calculated based on Equation 3.11. Since the nucleation rate becomes very slow above ~26 °C (see Figure 3.3), it would be expected that $\Delta G_c$ might undergo another sharp increase at this temperature as indicated by the dashed line in Figure 3.9, although the crystallization experiment might take too long timewise to be practical.

The differences between the two sets of values for $\Delta G_c$ appear to result from the different ways the data are processed by these two methods. The first method, which is based on Equation 3.11 for a supercooled melt, calculates $\Delta G_c$ by first correlating the induction times with temperatures for systems at specific weight fractions of LC. By contrast, the second method, which is based on Equation 3.12 for a supersaturated solution, correlates induction times with the degrees of saturation (or the weight fractions of LC in the systems) at a specific temperature. Unfortunately, neither method completely defines the values of $\Delta G_c$. Therefore, it may be more reliable to apply both methods to
calculate \( \Delta G_c \). A conclusion may be reached if a common trend exists in the data
calculated from both methods. Otherwise, caution should be exercised when the data
calculated from these two methods are not consistent.

### 3.3.3 Analysis by Avrami kinetics

While crystallization from supersaturated systems is a two-step process, including
nucleation and crystal growth, a general approach, the Avrami relation, is applicable in
describing the overall kinetics of crystallization processes. Developed independently by
several researchers in the 1940s, the Avrami equation, also called the “Johnson-Mehl-
Avrami-Komogorov equation”, is concerned with the overall crystallization process,
including nucleation and crystal growth.\(^{137-139}\) A brief description of Avrami theory follows.

Assuming conditions of isothermal crystallization, spatially random nucleation,
and linear nucleation and growth kinetics, e.g., constant rates of nucleation and crystal
growth throughout the process, the number of nuclei generated during a time period \( dt \) is
\( J V dt \) and the weight of spherical crystals (from three-dimensional growth) produced is
(according to Reference 132):

\[
dW = J V dt \cdot \frac{4}{3} \pi (G \cdot t)^3 \rho_s \tag{3.14}
\]
where \( J \) is the rate of nucleation, the number of nuclei formed per unit time per unit volume, which is assumed to be constant throughout the process; \( V \) is the total volume of the melt or system; \( \rho \), the density of the crystal; \( G \) the linear crystal growth rate along one dimension, which is assumed to be constant; and \( 4/3\pi \) is the shape factor of a three dimensional spherulitic crystal.

Assuming that at the initial stage of crystallization the weight of crystal produced, \( W \), is negligible relative to the total weight of crystal that will be eventually produced, \( W_T \), then, \( W - W \approx W_T \), and,

\[
dW/W_T (1 - W/W_T) = 4\pi J V\rho_s G^3 t^3 dt / 3W_T \tag{3.15}
\]

Integration of Equation 3.15 from \( t = 0 \) to \( t = t \) yields:

\[
ln (1 - W/W_T) = - \left( \frac{\pi J V\rho_s G^3}{3W_T} \right) t^4 \tag{3.16}
\]

Assuming \( \alpha = W/W_T \), and \( k = \pi J V\rho_s G^3/3W_T \), the equation above then becomes:

\[
ln (1 - \alpha) = - k t^n \tag{3.17}
\]

where \( \alpha \) is the fraction of crystal transformed at time \( t \); \( k \) the crystallization rate constant, which depends primarily on crystallization temperature; and \( n \), the Avrami exponent, is a constant relating to the dimensionality of crystal growth. As shown from Equations 3.14
to 3.17, three-dimensional growth results in $n = 4$. Through a similar derivation, it has been shown that $n$ is equal to the number of dimensions of growth plus 1. In addition, $n$ is also related to the details of the nucleation mechanisms. For example, instantaneous nucleation, where the nuclei appear all at once at the beginning of a process, may reduce the $n$ of three-dimensional growth from 4 to 3. On the other hand, sporadic nucleation, where the number of nuclei increases linearly with time, may keep $n$ at 4 as indicated above (see Equations 3.14-3.17). Table 3.5 shows the values of $n$ in relation to the type of nucleation.

Typically, the value of $n$ is found to be constant over a substantial range of temperature. Therefore, according to Equation 3.17, a plot of $\ln (-\ln (1 - \alpha))$ vs. time $t$ will result in a series of parallel straight lines for each temperature with slopes equal to the value of $n$.

The crystallization rate constant, $k$, according to Equations 3.16 and 3.17, is a combination of the rate constants for nucleation and crystal growth. This rate constant is a function of temperature, which can be described by the Arrhenius equation. The value of $k$ is also directly related to the half-time of crystallization, $t_{1/2}$, by the following equation:

\[
(t_{1/2})^n = \frac{0.693}{k}
\] (3.18)

Therefore, the overall crystallization rate is reflected in the value of $k$. 

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Table 3.5 Values for the Avrami exponent, $n$, for different types of crystal nucleation and growth (from Reference 123).

<table>
<thead>
<tr>
<th>$n$</th>
<th>Type of crystal growth and nucleation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Spherulitic growth from sporadic nuclei</td>
</tr>
<tr>
<td>3</td>
<td>Spherulitic growth from instantaneous nuclei</td>
</tr>
<tr>
<td>3</td>
<td>Disc-like growth from sporadic nuclei</td>
</tr>
<tr>
<td>2</td>
<td>Disc-like growth from instantaneous nuclei</td>
</tr>
<tr>
<td>2</td>
<td>Rod-like growth from sporadic nuclei</td>
</tr>
<tr>
<td>1</td>
<td>Rod-like growth from instantaneous nuclei</td>
</tr>
</tbody>
</table>
The Avrami equation has been widely used to analyze the kinetics of isothermal crystallization of various types of materials including metals, polymers, glass-forming solids, and fats.\textsuperscript{123-126} In combination with thermal analysis methods, the isothermal crystallization kinetics in relation to time and temperature can then be evaluated.\textsuperscript{123,127} According to Equation 3.17, a plot of $\ln (-\ln (1-\alpha))$ vs. time $t$ will yield the values of $k$ and $n$. The temperature dependence of $k$ can be evaluated through the Arrhenius equation and the rate of crystallization rate determined from Equation 3.18. From the value of $n$, the mechanisms of nucleation and crystallization were determined based on Table 3.5 and will be discussed later in this section.

The crystal fractions, $\alpha$, as functions of time were given in Figure 3.2. The crystallization kinetic data was fitted to the Avrami equation by linear regression, an example of which, Figure 3.10 shows the fitting for 50\% (w/w) LC/DT2287 systems. It can be seen that between 0-17 °C the regression lines are almost parallel, indicating that the values of $n$ are almost constant over this range of temperature, which is consistent with that predicted by the Avrami theory.\textsuperscript{138,139} On the other hand, at temperatures above 17-19 °C, the slopes of the regression lines change significantly, indicating that the $n$ values have sharply increased. Similar results were obtained for other LC/DT2287 systems with weight fractions of LC ranging between 40\%~70\% w/w. The numerical values of these parameters from linear regression are given in Table 3.6. The equation fitted the data well over the entire range of fractional crystallization with correlation coefficients above 0.97. It appears that the Avrami equation fitted the data best for
Figure 3.10 Avrami plots for the isothermal crystallization of LC from 50% w/w LC/DT2287 systems.
<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>$\ln k$</th>
<th>$t_{1/2}$ (min)</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>40% w/w LC/DT2287</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-14.4± 3.2</td>
<td>128± 14</td>
<td>2.90± 0.45</td>
</tr>
<tr>
<td>5</td>
<td>-16.0± 1.3</td>
<td>97.4± 3.2</td>
<td>3.41± 0.68</td>
</tr>
<tr>
<td>10</td>
<td>-11.7± 3.3</td>
<td>64.2± 4.9</td>
<td>2.72± 0.39</td>
</tr>
<tr>
<td>15</td>
<td>-11.1± 5.6</td>
<td>36.9± 1.9</td>
<td>2.98± 0.85</td>
</tr>
<tr>
<td>17</td>
<td>-56.9± 20</td>
<td>137± 24</td>
<td>11.5± 3.2</td>
</tr>
<tr>
<td><strong>50% w/w LC/DT2287</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-7.24± 2.0</td>
<td>8.53± 1.1</td>
<td>3.21± 0.93</td>
</tr>
<tr>
<td>5</td>
<td>-8.84± 0.83</td>
<td>10.4± 0.76</td>
<td>3.62± 0.40</td>
</tr>
<tr>
<td>10</td>
<td>-9.55± 1.2</td>
<td>12.2± 0.53</td>
<td>3.67± 0.33</td>
</tr>
<tr>
<td>15</td>
<td>-9.67± 3.4</td>
<td>11.8± 0.87</td>
<td>3.77± 0.83</td>
</tr>
<tr>
<td>17</td>
<td>-11.0± 3.7</td>
<td>12.0± 1.8</td>
<td>4.26± 0.73</td>
</tr>
<tr>
<td>18</td>
<td>-67.5± 19</td>
<td>49.7± 16</td>
<td>17.2± 5.2</td>
</tr>
<tr>
<td>19</td>
<td>-123± 45</td>
<td>88.6± 29</td>
<td>27.3± 8.0</td>
</tr>
<tr>
<td><strong>60% w/w LC/DT2287</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>-3.87± 0.78</td>
<td>1.69± 0.65</td>
<td>5.27± 0.87</td>
</tr>
<tr>
<td>15</td>
<td>-5.02± 1.5</td>
<td>2.64± 0.83</td>
<td>4.80± 1.1</td>
</tr>
<tr>
<td>20</td>
<td>-5.49± 1.7</td>
<td>3.84± 1.2</td>
<td>3.81± 0.67</td>
</tr>
<tr>
<td>22</td>
<td>-5.07± 2.2</td>
<td>4.25± 2.3</td>
<td>3.25± 0.54</td>
</tr>
<tr>
<td>23</td>
<td>-10.2± 3.7</td>
<td>6.81± 2.4</td>
<td>5.14± 0.16</td>
</tr>
<tr>
<td>24</td>
<td>-38.6± 15</td>
<td>18.4± 6.2</td>
<td>13.1± 3.3</td>
</tr>
<tr>
<td>25</td>
<td>-244± 110</td>
<td>70.1± 33</td>
<td>57.3± 24</td>
</tr>
<tr>
<td><strong>70% w/w LC/DT2287</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>-3.46± 0.33</td>
<td>2.04± 0.43</td>
<td>4.34± 0.51</td>
</tr>
<tr>
<td>17</td>
<td>-4.13± 0.77</td>
<td>2.18± 0.74</td>
<td>4.83± 0.37</td>
</tr>
<tr>
<td>18</td>
<td>-2.28± 0.59</td>
<td>1.53± 0.86</td>
<td>4.46± 0.36</td>
</tr>
<tr>
<td>22</td>
<td>-4.57± 0.96</td>
<td>2.06± 0.54</td>
<td>5.82± 1.3</td>
</tr>
<tr>
<td>23</td>
<td>-10.3± 3.5</td>
<td>2.63± 0.48</td>
<td>10.2± 4.4</td>
</tr>
<tr>
<td>24</td>
<td>-36.3± 8.9</td>
<td>7.20± 2.9</td>
<td>18.2± 4.6</td>
</tr>
<tr>
<td>25</td>
<td>-59.5± 23</td>
<td>11.3± 4.7</td>
<td>24.4± 9.3</td>
</tr>
</tbody>
</table>

Table 3.6 Avrami constants, $k$, and Avrami exponents, $n$, and calculated half-times of crystallization, $t_{1/2}$, as functions of temperature for LC/DT2287 systems.
systems with lower weight fractions of drug (40% and 50% w/w) and over the lower temperature range, where the $r^2$ values were above 0.99. The temperature dependence of the Avrami constants $k$ and exponents $n$ as functions of composition of the LC/DT2287 systems are given in Figures 3.11 and 3.12, respectively. From Table 3.6 and Figure 3.11 it can be seen that $k$ decreases as temperature increases. At the low temperatures the $k$ values are nearly constant, while as temperature increases $k$ sharply decreases. The divisions between these two regions are 15, 18, 23 and 23 °C for the 40%, 50%, 60% and 70% (w/w) LC/DT2287 systems, respectively. It can be noted from Table 3.6 that over the low temperature range the values of $k$ increase as the weight fraction of LC increases although the differences are relatively small (statistically significant differences were found at the 95% confidence interval except for the comparison between 60% and 70% w/w LC/DT2287).

Table 3.6 and Figure 3.12 give the Avrami exponents $n$ as functions of temperature and composition of the systems. Two features are worth noting. First, the temperature dependence of $n$ also displays two-phase behavior, which parallels the temperature dependence of $k$. At the lower temperatures, $n$ is constant, while at high temperatures it sharply increases with temperature. Over the low temperature range, $n$ varies from 3~3.5 for the 40% and 50% to 4~4.5 for the 60% and 70% w/w LC/DT2287 systems. According to Table 3.5, this might indicate that crystals are formed by two-dimensional disc-like growth from sporadic nuclei in the 40% and 50% w/w systems and by three-dimensional spherulitic growth from sporadic nuclei in the 60% and 70% w/w systems. The composition dependence at low temperatures, namely that the system with
Figure 3.11 Temperature dependence of the Avrami constant $k$. 
Figure 3.12 Temperature dependence of the Avrami exponent $n$. 
the higher weight fraction of LC and thus the higher melting temperature tends to have a
higher value for \( n \), is opposite to what has been reported for certain fats and
polymers.\textsuperscript{127,141} Therefore, this behavior can not be explained by the theory that the
higher nucleation density of a system with a higher weight fraction of LC may generate
too many nuclei within a unit volume of the system and thereby inhibit nuclei growth into
large spherulitic crystals, and will give a relatively lower value for \( n \).\textsuperscript{141}

Another peculiarity is that over the higher temperature range the value of \( n \)
increases with temperature and can be greater than 4, which is the highest value of \( n \) that
can be predicted by the Avrami theory. This occurred for all four systems over the range
of 40% ~ 70% w/w LC/DT2287, with the highest \( n \) measured being \(~57\) (see Table 3.6).
Apparently, such high values of \( n \) cannot be explained by conventional Avrami theory, in
which the value of \( n \) basically reflects the number of dimensions of crystal growth. This
suggests that one or more of the assumptions on which the Avrami theory is based may
not be applicable to the LC/DT2287 systems at the higher temperatures, which will be
discussed later in this section.

Although this exception has been rarely reported, it has been suggested that a
value of \( n \) larger than 4 may indicate that the nucleation rate \( J \) increases with time,\textsuperscript{142,143}
which means that the assumption of linear nucleation kinetics, e.g., a constant nucleation
rate throughout the process, may not be valid. Another explanation is that the density of
the growing crystal bodies \( \rho_s \) may be time dependent due to the different degrees of
crystal packing on the outside and inside of the growing crystal bodies.\textsuperscript{141} However, this
second explanation may not be applicable to LC/DT2287 systems since the densities of

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these two components are rather close: 1.04 g cm\(^{-3}\) for LC\(^{119}\) and 0.979 g cm\(^{-3}\) for DT2287\(^{120}\), respectively. Therefore, a significant variation of densities of the crystal growing bodies may not occur over time. On the other hand, the time dependence of the nucleation rate \(J\) may be worth noting. Assuming that the time dependence of the nucleation rate can be expressed in a form similar to that of crystal size \(\Phi(G \cdot t)^n\), where \(\Phi\) is the shape factor and \(n\) is the number of dimensions of crystal growth (see Equation 3.14), then,

\[
J = (J_0 \cdot t)^m \tag{3.19}
\]

where \(J_0\) and \(m\) are constants, and \(t\) is time.

Substitution of Equation 3.16 with 3.19, yields:

\[
\ln (1 - W/W_T) = - \left(\pi J_0^m V \rho_s G^3/3W_T\right) t^{m+4} \tag{3.20}
\]

If \(\alpha = W/W_T\), then:

\[
\ln (1 - \alpha) = - k t^n \tag{3.21}
\]

with \(k = \left(\pi V \rho_s G^3/3W_T\right) J_0^m \tag{3.22}\)

and \(n = m+4 \tag{3.23}\)

Substitution of Equation 3.22 with 3.23, yields:
\[ \ln k = n \ln J_0 - 4 \ln J_0 + A \]  
(3.24)

where \( A = \pi V p_s G^2 / 3 W_r \), and is constant if the linear crystal growth rate \( G \) remains constant.

Equations 3.21 and 3.23 indicate that the Avrami exponent \( n \) is equal to the sum of the crystal growth exponent \( m \) and the number of dimensions of crystal growth. Therefore, \( n \) may be much larger than 4 although in most cases it is \( \leq 4 \). This explains the high values of \( n \) at the higher temperatures. In addition, it is interesting to note that Equation 3.21, which has been derived from the hypothesis that the nucleation rate is time dependent (see Equation 3.19), is still in the form of the conventional Avrami equation (see Equation 3.17) except that the expressions of \( k \) and \( n \) have been changed (see Equations 3.22 and 3.23). This can explain why the crystallization kinetic data have still fitted the Avrami equation at the higher temperatures (see Figure 3.10) despite the fact that the values of \( n \) are much larger than 4.

Although the above hypothesis explains the crystallization behavior of LC in the DT2287 systems at higher temperatures, more experimental evidence is needed to support it. If in Equation 3.19 \( J_0 \) is assumed to be temperature independent and \( m \) is assumed to be temperature dependent, all the effects of temperature on nucleation rate can be ascribed to \( m \). It can then be deduced from Equation 3.24 that plots of \( \ln k \), the logarithm of the Avrami constant, \( v.s. n \), the Avrami exponent, should be linear with a slope equal to \( \ln J_0 \). Figure 3.13 shows the linear correlation, and it appears that \( J_0 \) may be a constant independent of the composition of the systems.
Figure 3.13 Avrami exponents $n$ as functions of Avrami constants $k$. 
Furthermore, it can be seen from Figure 3.13 that \( \ln k \) is inversely proportional to \( n \), which means that the slopes of the plots in Figure 3.13, \( \ln J_0 \), should be negative. Therefore, \( J_0 < 1 \). According to Equation 3.19, the nucleation rate, \( J \), should decrease as temperature increases because \( m \) would increase with temperature and \( J_0 < 1 \). This is also shown in Figure 3.14 by the correlation between the Avrami exponent \( n \) and the crystallization induction time \( \tau \), the latent time before the first crystals can be detected.\(^{121}\)

It can be seen in Figure 3.14 that there is a relationship between these two parameters, and this dependence is significantly influenced by the composition of the LC/DT2287 systems. Similar behavior has been reported for some fats such as cocoa butter and milk fats when \( n \) increases with induction time although the values of \( n \) were still \( \leq 4 \).\(^{127}\) Since the induction time is inversely related to the nucleation rate,\(^{104,121,122}\) it appears therefore that the Avrami exponent \( n \) is not only determined by the number of dimensions of crystal growth, but is also related to nucleation. Since the Avrami exponent \( n \) increases but that the nucleation rate decreases as temperature increases, which conforms to Equation 3.19 when \( J_0 < 1 \), it appears therefore that the nucleation rate of lidocaine increases with time during the crystallization of LC in the LC/DT2287 systems over the high temperature range when \( n > 4 \).

Studies of crystal growth indicated that the linear crystal growth rate \( G \) of LC in the systems was nearly constant during the process, indicating that the nucleation rate may be time dependent. Table 3.7 lists the linear crystal growth rates of LC in each LC/DT2287 system at \( \sim 24 \, ^\circ C \) as determined by microscopy. In general, the linear crystal growth rates are constant during most of the crystal development
Figure 3.14. Avrami exponents as functions of induction times for LC/DT2287 systems.
<table>
<thead>
<tr>
<th>LC (%) w/w</th>
<th>$G$ (mm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>0.122 ± 0.015</td>
</tr>
<tr>
<td>50%</td>
<td>0.218 ± 0.029</td>
</tr>
<tr>
<td>60%</td>
<td>0.722 ± 0.048</td>
</tr>
<tr>
<td>70%</td>
<td>2.40 ± 0.042</td>
</tr>
</tbody>
</table>

Table 3.7  Linear crystal growth rates ($G$) of LC/DT2287 systems at ~24 °C.
process except at the end stage of crystallization, which can be explained by the gradual
depletion of supersaturation at this stage. From Equations 3.16, 3.17 and 3.20, it can be
seen that the value of $n$ can be affected only by the nucleation rate $J$, the crystal growth
rate $G$, and the number of dimensions of crystal growth. Since the number of dimensions
of crystal growth cannot account for values of $n > 4$ and $G$ is constant as shown in Table
3.7, it may be concluded therefore that over the high temperature range the rate of crystal
growth is time independent while the nucleation rate depends exponentially on time.

It is not entirely clear yet why the nucleation rate is time dependent and what
causes the exponent $m$ in Equation 3.19 to increase rapidly with temperature over the
high temperature range. A possible explanation could be related to branching of a crystal
as it grows. In this context, it was observed by microscopy that needle-shaped LC crystals
undergo frequent branching during growth at room temperature (~24 °C), which falls
within the high temperature range (see Figure 3.15). If a branching point can be
considered to be essentially a new nucleus, then the more crystals that are formed, the
more will be the number of nuclei generated. Therefore the nucleation rate can be time
dependent. Presumably, if this is the mechanism of the time dependence of the nucleation
rate, then branching of crystals as they grow should be significantly reduced over the low
temperature range because nucleation rate is time independent at these temperatures, as
shown in Table 3.6 by their values of $n \leq 4$.

Although the hypothesis of the time-dependence of the nucleation rate explains
the rather large value of $n$ over the high temperature range, it does conflict with the
Figure 3.15 Photomicrograph of branching during crystal growth in 60% w/w LC/DT2287 systems at room temperature (~24 °C).
classical theory of nucleation. As shown in Equation 3.2, the classical theory of nucleation expresses nucleation rate in the form of the Arrhenius reaction velocity equation and no time-dependence is involved.\textsuperscript{104,121,122}

To reconcile this difference, it may be that nucleation rate is a two-step process over the higher temperature range. Accordingly, before the nuclei are stable and crystals begin to grow, the nucleation rate may be expressed by the classical theory of nucleation which indicates that the rate of nucleation is controlled by the crystallization temperature and the corresponding activation energies. In this context, a quantitative description of nucleation kinetics can be given by the classical theory of nucleation.\textsuperscript{121} Since this quantitative description was based on the induction time of crystallization as the parameter of nucleation, meaning that no nuclei have been stably formed and therefore no crystals have begun to grow at this stage, it may be possible to separate this stage from the subsequent one where a substantial amount of crystals have appeared and are growing.

On the other hand, after stable nuclei are formed and begin to grow, the time dependence may dominate and the nucleation rate can then be described by Equation 3.19. If branching of the crystals occurs as they grow, and more and more nuclei are produced, it should then be reasonable to assume that differences exist between the nucleation rates before and after crystallization begins.
CHAPTER 4

CHARACTERIZATION OF SUPERSATURATED
LIDOCAINE/POLYACRYLATE PRESSURE SENSITIVE ADHESIVE
SYSTEMS: THERMAL ANALYSIS AND FT-IR

CONCEPT MAP

• Supersaturated LC/PSA systems have been characterized by DSC and FT-IR.

• The composition dependence of the glass transition temperature ($T_g$) was used to qualitatively characterize the thermodynamic state of the supersaturated systems.

• Supersaturated LC/PSA systems undergo significant entropic relaxation upon mixing, and LC functions as a solvent which is absorbed into the polymer network of DT2287.

• The strength of the intermolecular interactions between the two components is in the range of weak to intermediate.

• FT-IR indicated that no specific interactions, such as hydrogen bonding, occur between the two components in the LC/DT2287 mixtures.

• LC molecules are absorbed into the PSA network and are extensively involved in molecular relaxation of the PSA. The PSA molecular network reduces the molecular
mobility of LC by closely involving LC molecules in its relaxation, thereby contributing to inhibition of nucleation of the supersaturated systems.

4.1 Purpose of the studies

In systems consisting of a crystal forming component and an amorphous polymer, crystallization of the crystalline component can be affected by the presence of the amorphous polymer.\textsuperscript{144-147} The impact of the amorphous polymer on crystallization of the crystalline component can be defined in terms of thermodynamic and kinetic effects.\textsuperscript{144} Thermodynamic effects, typically due to intermolecular interactions, can enhance the miscibility of the components and therefore reduce crystallinity in the systems.\textsuperscript{144-146} On the other hand, kinetic effects are caused by hindrance of diffusion and dilution of the viscous amorphous polymer medium.\textsuperscript{146,147} Specific interactions between the components may affect both the thermodynamic effects (miscibility) and kinetic effects (hindrance of diffusion).\textsuperscript{144} While supersaturated drug/PSA systems are intended to enhance drug release, they are challenged by a physical-chemical dilemma: they need a relatively low thermodynamic equilibrium point (miscibility or solubility) to ensure that a high degree of supersaturation can be achieved to enhance drug release, but also need a relatively high kinetic hindrance to maintain good physical stability of the supersaturated systems. Therefore, intermolecular interactions should play an important role in this subtle balance, and should influence the crystallization behavior of LC in the supersaturated systems.
4.2 Theoretical background

One of the methods to characterize intermolecular interactions in a miscible polymer system is to analyze the composition dependence of the glass transition temperatures ($T_g$) of the polymer mixtures. Similar to the transition of “melting” in small molecular weight materials, the glass transition occurs typically in polymers or amorphous materials when they are converted from a glassy state, in which the segmental movements of the polymer chains are exclusively inhibited at a lower temperature, to a plastic state, where the segmental movements are “defrosted” and re-activated by increasing temperature. The temperatures where the glass transitions occur are called the “glass transition temperatures”, at which almost all of the properties of the polymer systems undergo significant changes. This is because segmental movements are the predominant mode of molecular movement of polymers, and therefore profoundly affect the properties of the polymers. Consequently, any change in the glass transition temperatures may indicate changes in polymer properties. The glass transition temperatures are also firmly related to the thermodynamic and molecular environments of the polymer chains because the latter will affect the modes of segmental movements of the polymer chains. Therefore, analysis of the behavior of the glass transition temperatures in relation to composition may provide a potential way to characterize both the physical properties of the polymers and their molecular environments, including intermolecular interactions.
During the latter half of the last century, the composition dependences of the glass transition temperatures ($T_g$) of miscible polymer systems have been studied both empirically and theoretically. Numerous theories and equations have been proposed to describe this relationship, including the equations of Fox, Gordon and Taylor, Kwei, Couchman and Karasz, Kovacs, and Breckner, Schneider and Cantow (BSC equation). Briefly, the general theoretical basis of these equations is the assumption of volume additivity of the polymer segments, which can be described by the Flory-Huggins lattice theory. Based on this general assumption, these equations can be developed for polymer systems with different features. For example, the Fox and Gordon-Taylor equations were derived for systems with weak intermolecular interactions, whereas the Kovacs equation was developed assuming a negligible change of free volume upon mixing of the components. Therefore, the characteristics of a polymer system may be analyzed by comparing the $T_g$-composition dependence of the system with that predicted by these equations. A good fit of the experimental data to a certain equation may suggest that the polymer system possesses features described by that particular equation. An obvious deviation from a certain equation, on the other hand, may indicate that the system does not belong to the particular category where this equation can be applied. In this study, a number of equations were evaluated and those that provided the most relevant and significant information about the LC/PSA systems were selected.

Among these equations, the Couchman-Karasz equation is the most general in nature and is stated as follows.
\[
\ln T_g = \frac{(w_1 \Delta C_{p1} \ln T_{g1} + w_2 \Delta C_{p2} \ln T_{g2})}{(w_1 \Delta C_{p1} + w_2 \Delta C_{p2})}
\] (4.1)

where \(T_g\), \(T_{g1}\), and \(T_{g2}\) are the glass transition temperatures of component 1 and 2 of the polymer mixture, respectively; and \(w_i\) and \(\Delta C_{pi}\) are the weight fractions and heat capacity changes at the glass transitions of the components, respectively.

If the \(\Delta C_p\) values of the two components are approximately equal, the Fox equation can be derived from Equation 4.1:148,152

\[
\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}}
\] (4.2)

Similarly, if \(T_{g1} \approx T_{g2}\), the Gordon-Taylor equation can be obtained:149,152

\[
T_g = \frac{w_1 T_{g1} + K w_2 T_{g2}}{(w_1+K w_2)}
\] (4.3)

where \(K\) is a constant, where \(K = (\rho_1 T_{g1})/(\rho_2 T_{g2})\), which may account for the different thermal expansion coefficients of components. These coefficients are used to define the magnitudes of volume changes of the components at the glass transition temperatures.

All of the above three equations are generally considered to hold for miscible systems in which only very weak intermolecular interactions occur because the
assumption of volume additivity is valid only under ideal conditions where the intermolecular interactions are weak. As a result, the \( T_g \)-composition dependencies predicted by these equations are close to linear.

On the other hand, when there are stronger intermolecular interactions between the components in the system, \( T_g \) may deviate from a nearly linear function of composition. It was suggested therefore that the differences between the observed and the predicted \( T_g \) values may be used as measures to quantitatively evaluate the strength of interactions between the two components. The Kwei equation was therefore proposed:

\[
T_g = w_1 T_{g1} + w_2 T_{g2} + q w_1 w_2
\]  

(4.4)

where the third term \( qw_1w_2 \) represents the effects of intermolecular interactions, and where \( q \) is a measure of the strength of the interactions, which can be used to quantitatively and comparatively evaluate the intermolecular interactions between one specific component and several other components, respectively. In this study, the function of quantitative evaluation of the Kwei equation was not applicable because only a single LC/DT2287 system was involved and no other components were studied. However, the Kwei equation can still be applied to qualitatively evaluate the relative strength of the intermolecular interactions when combined with other equations. This will be discussed later.
Although the Kwei equation has been frequently applied to polymer systems with strong intermolecular interactions,\textsuperscript{155-157} it cannot characterize other important molecular parameters in the system such as chain stiffness,\textsuperscript{158} conformation,\textsuperscript{159} excess volume,\textsuperscript{160} and entropy variation,\textsuperscript{154} which also have significant effects on the thermodynamic and kinetic states of polymer systems. To achieve this goal, Schneider, \textit{et al.} developed a theory which can be used to qualitatively analyze polymer systems in terms of chain stiffness, conformation and entropy variation.\textsuperscript{153, 161-168} Briefly, it is:\textsuperscript{166}

\begin{equation}
T_g = w_{1c}T_{g1} + w_{2c}T_{g2} + k_1 w_{1c} w_{2c} + k_2 w_{1c}^2 w_{2c} + k_3 w_{1c} w_{2c}^2 \quad (4.5)
\end{equation}

where \( w_{1c} \) and \( w_{2c} \) are the corrected weight fractions which may account for the different expansion coefficients of the components, and \( w_{2c} = K w_2 / (w_1 + K w_2) \); where \( K \approx (\rho_1 T_{g1}) / (\rho_2 T_{g2}) \) (see Equation 4.3); and \( w_{1c} + w_{2c} = 1 \). As shown above, the first two terms in the equation reflect volume additivity of the miscible systems, and therefore it is a transformed Gordon-Taylor equation, which is only applicable to polymer systems with weak interactions. The third term, \( k_1 w_{1c} w_{2c} \), characterizes the intermolecular interaction between the components, and therefore it can be transformed into the Kwei equation together with the first two terms. The last two terms, \( k_2 w_{1c}^2 w_{2c} + k_3 w_{1c} w_{2c}^2 \), represent the conformational entropy effects induced by hetero-interactions between the components. Physically, it can be seen from Equation 4.5 that \( k_1 \) accounts for the effect of binary hetero-interactions, whereas \( k_2 \) and \( k_3 \) reflect the effects of binary hetero-
interactions located in a specific neighborhood of either components. Therefore, $k_2$ and $k_3$ actually account for the effects of ternary hetero-interactions. A detailed description of the physical definitions of $k_1$, $k_2$ and $k_3$ can be found in Refs. 163 and 165.

For the purpose of data fitting, Equation 4.5 needs to be transformed to the following form by substituting $(1 - w_{2c})$ for $w_{1c}$, which gives a third order concentration (or weight fraction) power equation for $T_g$:

$$\frac{(T_g - T_{g1})}{(T_{g2} - T_{g1})} = (1+K_1)w_{2c} - (K_1 + K_2)w_{2c}^2 + K_2w_{2c}^3 \quad (4.6)$$

where $K_1$ and $K_2$ are fitting parameters with $K_1 = k_1 + k_2$ and $K_2 = k_2 - k_3$.

Based on Equation 4.6, a non-linear data fitting of experimental $T_g$ values of miscible polymer systems would provide a set of values for $K_1$ and $K_2$. Unfortunately, the values of $k_1$, $k_2$ and $k_3$ in Equation 4.5, which have clear physical meanings, are not obtainable through direct data fitting because the data of $w_{1c}$ and $w_{2c}$ are mutually dependent.\textsuperscript{162-166} To further characterize the polymer systems, it is necessary therefore to qualitatively relate the values of $K_1$ and $K_2$, which are accessible by data fitting, to the physical characteristics of the systems, such as polymer chain conformation and entropy variation.

It has been pointed out that $K_1$ mainly accounts for the differences between the interaction energies of the binary hetero- (between different components) and homo- (between molecules of the same component) interactions, while $K_2$ depends on additional energetic contributions resulting from conformational entropy changes.\textsuperscript{165,166} It should be
noted that intermolecular interactions between the components would promote the enthalpy effects, which may induce two opposite entropic effects to the systems: a decrease of conformational entropy due to increased local chain reorientation and stiffness, or an increase of conformational entropy resulting from increased local conformational rearrangement and relaxation. Positive values of $K_1$ then indicate prevailing enthalpic effects due to strong interactions between the components, which further increase local chain stiffness and reduce conformational entropy. Negative values of $K_1$, on the contrary, indicate dominant entropic effects due to conformational rearrangement and relaxation, resulting from weak interactions between the components.

The parameter $K_2$ reflects only the contributions of entropic changes due to polymer chain conformation orientation caused by the formation of hetero-interactions between the components.\textsuperscript{165,168} $K_2 \rightarrow 0$ when little chain orientation occurs. A positive $K_2$ is related to chain reorientation and reduced conformation flexibility, while a negative $K_2$ indicates chain disorientation and an increase in entropy.\textsuperscript{152} To clarify this, the properties of polymer systems have been placed into five categories according to the values of $K_1$ and $K_2$, and are given in Table 4.1.\textsuperscript{168}

Finally, it is worthwhile noting that the Kovacs equation which was derived on the assumption that the free volume change upon mixing of the components was negligible is as follows:\textsuperscript{169}

\begin{equation}
T_k = T_{g1} + f_{g2} / \alpha_1 (V_1/V_2) \tag{4.7}
\end{equation}
Characteristics of polymer mixtures

<table>
<thead>
<tr>
<th>$K_1$</th>
<th>$K_1 - K_2$</th>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>$&gt; 0$</td>
<td>$&gt; 0$</td>
<td>Prevailing enthalpic effects due to strong interactions.</td>
</tr>
<tr>
<td>$&gt; 0$</td>
<td>$&lt; 0$</td>
<td>$S$-shaped $T_g$ vs. composition curves.</td>
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<td>$</td>
<td>K_1</td>
<td>&lt; 0.5$</td>
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<tr>
<td>$&lt; 0$</td>
<td>$&gt; 0$</td>
<td>$S$-shaped $T_g$ vs. composition curves.</td>
</tr>
<tr>
<td>$&lt; 0$</td>
<td>$&lt; 0$</td>
<td>Prevailing conformational entropic effects due to moderate or weak interactions.</td>
</tr>
</tbody>
</table>

Table 4.1 Characteristics of polymer systems categorized by parameters of the concentration power equation of the glass transition temperature, $T_g$. 

154
where $V_i$ is the volume fractions of the components; $f_{g2}$ is the fractional free volume of component 2 at its $T_g$; and $\alpha_1$ is the thermal expansion coefficient of component 1. According to the free volume theory\(^{170}\), the fractional free volume of polymers, a key parameter that is used to evaluate their molecular mobility, can be approximated to a universal value of \(\sim 0.025\) at their glass transition temperatures. Therefore, the Kovacs equation as indicated by Equation 4.7 actually attributes the changes of $T_g$ of the polymer systems entirely to component 1 rather than to component 2. In other words, the $T_g$ of the polymer systems will be determined totally by dilution of component 1 and will exhibit a straight line relationship to the volume ratio $V_1/V_2$ within a part of or the whole range of compositions if the free volume change resulting from mixing the components is negligible. When this happens, the thermodynamic state of component 1 may be considered to be unchanged upon mixing.

Although the theories described above were developed with regard to random copolymers or compatible polymer-polymer systems, they are also applicable to polymer-plasticizer systems\(^{165,171}\) and to dye-polymer blends\(^{156}\), which consist of polymers and low molecular weight materials. Therefore, the LC/PSA systems, consisting of a polymer mixed with a low molecular weight drug, may also be analyzed based upon these theories. However, an apparent challenge to this assumption, as pointed out by Slark\(^{172}\), is the validity of the concept of a low molecular weight crystalline material such as LC having a glass transition. Experimentally, the amorphous forms of many low molecular weight crystalline materials are not obtainable due to the aggressive crystallization of these materials in cooling or solvent evaporation processes. Consequently, the glass
transitions of these materials are difficult to resolve. In an attempt to solve this problem, annealing and quenching techniques were combined in the present work to create an amorphous form of LC, and the glass transition temperature was measured by differential scanning calorimetry (DSC).

To further clarify the nature of the interactions between the two components, LC/DT2287 systems with different weight fractions of LC were studied by FT-IR, which has been used to characterize specific intermolecular interactions between the components.\textsuperscript{173-176}

4.3 Experimental methods

4.3.1 Sample preparation

A series of LC/DT2287 mixtures with different weight fractions of LC were prepared by dissolving appropriate amounts of both LC and DT2287 in ethyl acetate followed by evaporation of the solvent at room temperature for one month. The samples were then stored in desiccator at room temperature for at least two weeks prior to use.

4.3.2 Measurement of the glass transition temperature ($T_g$) of lidocaine

The $T_g$ of LC was determined by combining annealing and quenching techniques with DSC (Mettler Model TA4300). To do this, an accurately weighed sample (~15 mg)
of LC was placed in an aluminum DSC pan and hermetically sealed. To obtain amorphous LC, the sample in the pan was heated to 100 °C and annealed isothermally at that temperature for an hour to eliminate heterogeneous nuclei in the LC melt before it was quickly quenched in liquid nitrogen for 5 minutes. Subsequently, the aluminum pan containing amorphous LC was quickly transferred to the DSC which had been precooled to –100 °C. During this process it is important to avoid unnecessary exposure of the sample to ambient temperature because temperatures higher than –60 °C will cause the sample to transition from amorphous to crystal form, and the glass transition will no longer be found in subsequent DSC thermograms. The samples were then scanned from –100 to 100 °C at 20 °C/min, and the midpoint of the baseline shift (heat capacity) was taken as the glass transition temperature. All data reported are the average of three independent measurements.

4.3.3 Measurement of the $T_g$ of DT2287 and LC/DT2287 mixtures

Accurately weighed samples (~10 mg) of DT2287 and LC/DT2287 mixtures were placed in aluminum DSC pans and sealed. The lids were vented with a pin hole in the center. To determine the $T_g$ values of LC/DT2287 mixtures with excess LC crystals suspended in saturated solutions of LC in DT2287, labeled as “crystallized” mixtures, the samples were first cooled to –100 °C and then scanned from –100 to 100 °C at 20 °C/min. Following the same procedure, the $T_g$ of DT2287 was measured. To measure the $T_g$ values of LC/DT2287 mixtures supersaturated with LC, which were then considered
as “miscible” systems or “supersaturated” systems, the samples were first heated to 100 °C at 20 °C/min and then annealed for 20 minutes in the DSC oven. They were then quenched to -100 °C at 100 °C/min to create supersaturated solutions of LC in DT2287, and scanned from –100 to 100 °C at 20 °C/min. To ensure miscibility of the two components in the systems after they were quenched to -100 °C, the DSC thermograms of the quenching process were examined to ensure no crystallization exotherm peak appeared. As before, the midpoints of the baseline shifts (heat capacities) were taken as the glass transition temperatures.156 All data reported are the average of three independent experiments.

The composition dependence of the $T_g$ of miscible LC/DT2287 systems was analyzed by non-linear data fitting using MINITAB 13.1 statistical software. The densities of LC119 and DT2287120, which were used in the Gordon-Taylor (Equation 4.3) and BSC (Equation 4.6) equations, were 1.04 and 0.979 g cm$^{-3}$, respectively.

4.3.4 FT-IR studies

A series of solutions with different concentrations of LC and DT2287 were prepared by dissolving appropriate amounts of both LC and DT2287 in ethyl acetate. The total concentrations of the solutes, including LC and DT2287, in the solutions were set at 5% (g/mL). A volume of ~ 0.5 mL of each solution was spread over a sodium chloride IR crystal window followed by evaporation of the solvent at 50 °C for two hours. The
LC/DT2287 films contained LC ranging from 0-100% w/w. The FT-IR spectra were obtained by scanning the sample films on an IR spectrometer (Protégé 460 E.S.P. spectrometer, Nicolet Corporation).

4.4 Results and discussion

The DSC thermogram of amorphous LC obtained by combining annealing and quenching is shown in Figure 4.1. The thermogram has been enlarged to indicate its important features. It is significantly different from that of LC crystals (see Figure 4.2), in which only a single melting peak at ~67 °C appears. Additionally, it can be seen from Figure 4.1 that the glass transition of amorphous LC occurred at ~-60 °C, followed closely by crystallization of LC at ~ -53 °C, indicating that an amorphous form of LC was obtained by the annealing and quenching treatments. The fact that crystallization of LC occurred at a temperature close to its glass transition temperature suggests that the crystallization process is highly aggressive, which may explain the difficulty of observing the glass transition of LC. Furthermore, the melting peak of LC appeared at ~68 °C (only partly shown in Figure 4.1 due to the enlargement), which is the same as that of untreated LC crystals, indicating a “normal” crystal of LC had been formed after the progressive steps of the glass transition (~ -60 °C), crystallization (~ -53 °C), and the structural redistributions over the range of -10 ~ 35 °C. This latter process is rather complex as indicated in Figure 4.1. It should also be noted that the area of the exotherm
Figure 4.1. DSC thermogram of amorphous lidocaine.
Figure 4.2 DSC thermogram of crystal lidocaine.
(\textasciitilde13 \, \text{J/g}) \) for cold crystallization at \textasciitilde -53 \, \text{\degree C} is smaller than the endotherm of melting at 68 \, \text{\degree C} \, (\textasciitilde63 \, \text{J/g}), which may indicate that only a portion of the LC was converted into its amorphous form by the annealing and quenching treatment.

Figure 4.3 indicates the experimental composition dependence of the glass transition temperatures of LC/DT2287 systems and the predicted \( T_g \)-composition relationships based on the Fox, Gordon-Taylor, and Kwei equations. As the weight fraction of LC increases, the \( T_g \) of crystallized LC/DT2287 systems, as represented by the solid triangles, stays relatively constant after the system reaches saturation at \textasciitilde20\% w/w (see Section 2.2.1) and excess LC forms a separate crystal phase from the saturated LC/PSA medium. This indicates that the \( T_g \) of the LC/DT2287 systems is virtually independent of the presence of an immiscible (heterogeneously dispersed) solid phase. On the other hand, in the miscible systems, which are either subsaturated or supersaturated LC/DT2287 systems, \( T_g \) decreases as the weight fraction of LC increases, indicating that miscibility is crucial to the \( T_g \)-composition dependence. This is understandable because the polymer molecular conformation distribution reflected by \( T_g \) is influenced by hetero-molecular contact and molecular environment changes due to the addition of a miscible material. An immiscible additive, however, may not cause a significant change in the molecular environment of a polymer and thereby its \( T_g \) due to limited molecular contacts across the interface between the immiscible components.

It can be seen also from Figure 4.3 that the predicted \( T_g \)-composition dependences based on the Fox and Gordon-Taylor equations deviate significantly from the experimental data. Since these two equations, as discussed earlier, hold specifically for
Figure 4.3 Composition dependence of the glass transition temperatures ($T_g$) of LC/DT2287 systems. Key: ▲: the experimental $T_g$ values of the LC/DT2287 systems containing crystallized LC in equilibrium with a saturated system; □: the experimental $T_g$ values of the subsaturated and supersaturated (miscible) LC/DT2287 systems; ⋆: data fitted by the Kwei equation; +: data predicted by the Fox equation; ○: data predicted by the Gordon-Taylor equation.
miscible systems with weak intermolecular interactions,\textsuperscript{152} it may be suggested therefore that the intermolecular interactions between LC and DT2287 in the systems are not weak in nature. This suggestion is reinforced by the accordance of the experimental $T_g$ and the predicted result based on the Kwei equation as shown in Figure 4.3, which is generally applied to a system with stronger intermolecular interactions. It should be noted that this conclusion is based on the assumption of Kwei that the deviation of $T_g$ from linearity is due to intermolecular interactions. This may not be correct or sufficient if there are factors other than intermolecular interactions contributing to the deviation of the $T_g$ values. This possibility will be discussed later. Another point is that the glass transitions of the quenched 80\% and 90\% w/w systems were not observed because crystallization of LC from the systems became increasingly fast as the weight fraction of LC increased. Consequently, the quenching process at 100 °C/min (the upper limit of the DSC instrument) cannot create an amorphous form of LC in the 80\% w/w and 90\% w/w mixtures.

The experimental $T_g$-composition dependence of the LC/DT2287 systems and non-linear data fitting based on the BSC equation is given in Figure 4.4. It can be seen that the BSC equation fits well to the experimental data, indicating that it can be used to describe the LC/DT2287 systems. The expression obtained by non-linear data-fitting is:

$$\frac{(T_g - T_{g1})}{(T_{g2} - T_{g1})} = 0.091 \, w_{2c} + 1.17 \, w_{2c}^2 - 0.253 \, w_{2c}^3,$$

which yields, based on Equation 6, $K_1 = -0.909$, $K_2 = -0.253$, and $K_1 - K_2 = -0.656$. As discussed earlier, values of $K_1 < 0$ indicate that the effects of conformational relaxation and entropy increase, while $K_1 > -0.5$ reflects a moderate interaction between the components (see Table 4.1). In
Figure 4.4. $T_g$-composition dependence of supersaturated LC/DT2287 systems.
addition, the negative value of $K_2$ also indicates the occurrence of polymer chain disorientation and an increase in conformation flexibility$^{152}$ According to Table 4.1, LC/DT2287 systems should belong to the last category where $K_1 < 0$ and $K_1 - K_2 < 0$, in which weak or intermediate intermolecular interactions may result in increases in conformational relaxation and entropy. In other words, LC in the supersaturated state may function as a “solvent” in the miscible LC/DT2287 systems; while the PSA may be considered as “dissolved” or “solvated” or “swollen” in the “solvent” of LC. This results in increases in the molecular conformation relaxation and entropy of the PSA. This behavior is significantly different from that of miscible poly(N-vinyl pyrrolidone)/short chain poly(ethylene glycol) systems in which intermolecular interactions resulted in conformational reorientation and immobilization as well as a decrease in entropy$^{152}$ In these systems, the short chain poly(ethylene glycol) may bridge between the poly(N-vinyl pyrrolidone) molecules by hydrogen bonding resulting in immobilization of both molecules$^{152}$.

Conversely, the molecular mobility of LC may be reduced by hindrance of diffusion and intermolecular interactions due to the presence of the PSA. This is supported by the fact that the $T_g$ values of miscible LC/DT2287 systems are higher than that of amorphous LC, which suggests a decrease in molecular mobility of LC. This effect may be thought of as a reduction of the molecular mobility of a solvent as it is absorbed into a swelling polymer. Considering the objectives of these studies, a decrease
in molecular mobility of LC in the supersaturated LC/DT2287 systems may inhibit nucleation and crystal growth processes, thereby promoting the physical stability of the supersaturated systems.

It should be noted that a disparity may exist between these conclusions from analysis of the $T_g$-composition dependence. While analysis based on the Fox, Gordon-Taylor, and Kwei equations suggests relatively strong intermolecular interactions, data fitting based on the BSC equation indicates weak to intermediate interactions. This difference could be due mainly to differences between these theories. According to the BSC equation, the deviation of $T_g$ from linear additivity, which has been used as a measure of intermolecular interactions, and is reflected by the parameter $q$ in the Kwei equation, can be divided into enthalpic and entropic effects. The enthalpic effect, which is indicative of the strength of intermolecular interactions, is reflected by $k_1$; while the entropic effects that do not represent the strength of the intermolecular interactions are assigned values of $k_2$ and $k_3$. Both effects, as shown in Equation 4.5, contribute to the deviation of $T_g$ according to the BSC equation. Therefore, it is possible that a relatively large deviation of $T_g$, which has been attributed to strong intermolecular interactions by analysis based on the Kwei equation, may result from strong entropic effects and relatively weak interactions if the BSC equation is applied instead. The LC/DT2287 systems may be such an example, for which the large deviation of $T_g$ could be attributed to stronger entropic effects and relatively weak enthalpic effects. In addition, this example may also imply that the BSC equation may be more effective in characterizing the nature of a polymer blend than the other equations cited above. On the other hand,
because the entropic effects, such as those due to conformation rearrangement and relaxation, are caused by intermolecular interactions, it may still be true that weak interactions can only generate a nearly linear additivity of $T_g$, but not a considerable deviation in $T_g$. Therefore, it appears that intermolecular interactions of intermediate strength may exist in LC/DT2287 systems.

The experimental data of the $T_g$-composition dependence was also fitted to the Kovacs equation as shown in Figure 4.5. It can be seen that no linearity exists throughout the entire composition range indicating that there are appreciable changes of free volume upon mixing of the two components. Combined with the results obtained from the analysis based on the BSC equation, which indicated that the entropy of the PSA increases upon mixing, the free volume should increase and therefore the molecular mobility would increase. The curved plot indicates that the free volume and entropy of the polymer system are continuously increasing as more LC is added into the system, and therefore no “simple dilution”, in which almost no change of thermodynamic state is observed, occurs throughout the composition range. This suggests that most LC molecules are closely associated with the PSA chains and participate in the molecular movement and conformation relaxation of the PSA either directly or indirectly. Therefore, LC plays a key role in the thermodynamic state of the PSA system despite the intermediate intermolecular interactions between the components. Furthermore, the close compatibility between the two components may indicate a more significant hindrance of diffusion inhibiting crystallization because the amount of “free” LC molecules is reduced.
Figure 4.5 $T_g$-composition dependence of supersaturated LC/DT2287 systems based on the Kovacs equation. Note: $V_1$ and $V_2$ are the volume fractions of the component 1 and 2, respectively.
To further characterize the nature of the interactions between the two components, a FT-IR study was conducted as shown in Figure 4.6. Two shifts of characteristic absorption peaks of LC were observed as the weight fractions of LC increased from 20% to 30% w/w. The amide N-H stretching vibration moved from ~3302 to ~3255 cm\(^{-1}\) and the amide C=O stretching peak shifted from ~1689 to ~1667 cm\(^{-1}\). An association between these two functional groups is indicated by the red shifts, which conform to those reported in Reference 119. This is reinforced by the fact that the shifts were mass related, wherein the group with the higher mass (C=O) exhibits a smaller shift, i.e., ~22 cm\(^{-1}\), relative to that of ~47 cm\(^{-1}\) of the N-H group. Since the solubility of LC in DT2287 is ~20% w/w, these two groups may associate, most likely by hydrogen bonding, when the concentration of LC exceeds this value in DT2287 and undergoes crystallization. X-ray crystallography has indicated that LC molecules are in the trans-amide configuration and thus hydrogen bonding between the N-H and C=O groups on two adjacent molecules would occur when the molecules were packed into crystals.\(^{119}\) However, in solution, e.g., in the 10% and 20% w/w mixtures, the intermolecular hydrogen bonds between LC molecules are disrupted and the vibration peaks of both groups shift to violet. To confirm this, the IR spectra of supersaturated 30% and 40% w/w mixtures were compared with that of crystallized mixtures containing the same weight fractions of drug. As shown in Figure 4.7, the two stretching peaks of LC in the supersaturated state are ~3300 cm\(^{-1}\) for N-H and ~1688 cm\(^{-1}\) for C=O, respectively, which are very close to that of a solution, i.e., the 20% w/w LC/DT2287 mixture, but are significantly different from that in the
Figure 4.6. IR spectra of LC/DT2287 mixtures. The percentages refer to the weight fractions of LC in LC/DT2287 mixtures. Dashed lines indicate the positions of peaks.
Figure 4.7. FT-IR spectra of supersaturated and crystallized LC/DT2287 mixtures. The percentages refer to the weight fractions of LC in the LC/DT2287 mixtures. “Crystallized”, “saturated”, and “supersaturated” refer to the state of LC in the mixtures. Dashed lines indicate the positions of peaks.
crystallized state. It appears therefore that the hydrogen bonds between LC molecules in crystals are disrupted when LC dissolves or supersaturates in DT2287.

Meanwhile, no significant shifts of characteristic absorption peaks of DT2287 were observed in these FT-IR spectra, indicating that the associations which accounts for the peak shifts of LC are not due to LC-DT2287 hetero-interactions, but to LC-LC homo-interactions. To further clarify this, LC solutions in ethyl acetate were analyzed by FT-IR. Ethyl acetate contains an ester group which is also the major functional group of DT2287. The spectra of LC in the ethyl acetate solutions did not change significantly from those in supersaturated LC/DT2287 systems suggesting that no specific interactions occur between LC and DT2287 in the supersaturated state.
GENERAL SUMMARY

Transdermal drug delivery systems (“patches”) consisting of a pressure sensitive adhesive (PSA) supersaturated with drug (“supersaturated patches”) have been studied with the objective of enhancing drug release. Lidocaine (LC), a local anesthetic, was used as the model drug. Several types of PSAs, including polyisobutlenes (PIB), polyvinylpyrrolidone/polyethylene glycol (PVP/PEG) hydrogels, and polyacrylate copolymers were evaluated as the model PSA. A medical grade polyacrylate PSA DuroTak® 87-2287 (DT2287) was selected since it could be supersaturated with LC and have sufficient physical stability. These transdermal systems are of the drug-in-adhesive matrix type.

The solubility of LC in the PSA was measured by differential scanning calorimetry (DSC) and hot stage microscopy. DSC was used to measure the solubility of LC in the PSA at room temperature and at the temperature of the drug release studies (31 °C). The solubilities of LC in the PSA were 20.8% ± 0.43% and 21.3% ± 0.66% (w/w) at room temperature and 31 °C, respectively. In addition, the temperature dependence of the solubility of LC in the PSA was approximated by hot stage microscopy. It was found that crystallization of LC from LC/PSA mixtures over the range of 5~25 °C at low degrees of supersaturation was slow, apparently due to the high
viscosity of the PSA systems. Consequently, the solubility of LC over the range of 5~25 °C could not be measured directly within a reasonable period of time. To solve this problem, the temperature dependence over the range of 26.0~67.5 °C was determined instead and then extrapolated to the range of 5~25 °C. From this, the temperature dependence of LC solubility in the PSA over the temperature range of 5~25 °C could be approximated.

The supersaturated patches were prepared by an in situ heating/cooling procedure, in which the supersaturated systems were produced by heating the patches that contained excess drug crystals suspended in a saturated solution in the PSA (“crystallized patches”) in an oven at 80 °C for 10 minutes, followed by cooling at room temperature. The physical stability of the supersaturated patches containing 40% w/w LC (degree of saturation ~1.88) was determined to be sufficient for in vitro drug release studies. The in vitro drug release studies were performed using a Franz-type cell. Comparing supersaturated and crystallized patches it was found that drug loading had a significant influence on the accumulated amounts of drug released, especially for the supersaturated systems. For crystallized patches, excess drug crystals suspended in the PSA system function as reservoirs keeping the thermodynamic activity of the drug constant until they are completely dissolved. However, for patches containing a supersaturated solution, the apparent thermodynamic activity of the drug continuously decreases during the release study. To eliminate the effect of drug depletion in these systems, a sufficiently large drug loading (135 mg LC/patch) was used to ensure that the effect of depletion on the rates of release was negligible during the time of the studies. Furthermore, it was found that LC
release across a composite barrier membrane consisting of five layers of cellulose membrane (SpectroPor® 1) and a single silicone membrane was significantly higher from supersaturated 40% w/w LC/PSA systems than from systems in which drug had crystallized. The ratio between the fluxes from the supersaturated and crystallized systems was \( \sim 1.76 \), which is close to the degree of saturation (\( \sim 1.88 \)) of the supersaturated 40% w/w patches. This indicates that PSA patches supersaturated with LC could enhance its \textit{in vitro} release across this composite barrier membrane. Further studies of patches containing different weight fractions of LC and therefore different apparent thermodynamic activities of LC in the PSA systems indicated that LC release across the composite barrier membranes followed Fick’s first law. On the contrary, LC release across the SpectroPor® membrane, a water-permeable cellulose dialysis membrane, was found to be non-Fickian in two ways: 1) supersaturated patches did not show a significantly higher rate of LC release compared to that from the crystallized patches; and 2) LC release was dependent on its weight fraction rather than on its apparent thermodynamic activity in the PSA systems.

Microscopy indicated that appreciable hydration of the DT2287 pressure sensitive adhesive occurred when water was present, e.g., when the barrier consisted only of the water-permeable cellulose membrane. The degree of hydration of the PSA systems was directly related to the weight fraction of LC in the systems, indicating that the presence of LC may enhance hydration of these systems. Hydration of the PSA systems may then provide an alternative pathway with less resistance to drug diffusion than through the viscoelastic PSA medium, and therefore account for the non-Fickian release of LC across
the water permeable membranes. Furthermore, microscopy also indicated that slow crystallization of LC may be induced by hydration of the supersaturated LC/PSA systems. This slow crystallization was observed between 7 to 16 hours after the drug release experiments began, which may account for the decrease in the rate of LC release across the cellulose membranes from supersaturated LC/PSA patches because crystallization may significantly decrease free drug concentration in the PSA.

Considering that transdermal delivery patches are hydrophobic and usually block water evaporation from the skin, it can be assumed that hydration of polyacrylate PSA in a transdermal system would also occur in the patient-use setting. Such hydration could change the release profile as well as the physical stability of these delivery systems.

To understand the mechanism of the physical stability of supersaturated drug/PSA systems and the factors that may affect it, crystallization of drug from these systems was evaluated kinetically and thermodynamically. DSC was used to characterize the isothermal crystallization of LC from these systems at different temperatures, which was then analyzed by theories of nucleation, e.g., the Fisher-Turnbull equation; and phase transformation, e.g., the Avrami equation. Kinetic analysis based on the classical theory of nucleation indicated that the activation energies of drug diffusion in the PSA were larger than that of crystallization. This indicates that nucleation is a diffusion-controlled process, which is therefore highly dependent on the viscoelastic properties of the PSA medium. In addition, nucleation rather than crystal growth appears to govern the crystallization of LC from the supersaturated LC/PSA systems. A critical temperature $T_{crit}$ for crystallization of LC in LC/DT2287 systems was found to be $\sim 26^\circ C$, above
which the crystallization process became slow. The lack of dependence of \( T_{crit} \) on the composition of the mixtures indicates that thermodynamic parameters of the crystallization of LC in drug/PSA systems, i.e., \( T_{crit} \), were retained from crystalline LC, and that the presence of the PSA affected the kinetics (diffusion) rather than the thermodynamics of the nucleation process. A critical degree of saturation \( S_{crit} \) of \( \sim 4 \) was also found, above which the nucleation rate sharply increased. This is a critical parameter which can be used to evaluate the potential of using these supersaturated systems for enhancing drug release. It was also found that the activation energy for nucleation had a two-phase dependence on temperature, suggesting that the mechanism of crystallization may change at the transition temperatures. Minimal values of the activation energy of crystallization, \( \Delta G_{c} \), were found at \( \sim 15 \) °C for LC/PSA mixtures, showing that the rate of nucleation is maximal at this temperature.

Kinetic analysis based on the Avrami theory of phase transformation showed that crystallization of LC in supersaturated LC/DT2287 systems can be described by the Avrami equation. Similar to the activation energy for nucleation, some other key kinetic parameters, such as the Avrami exponent \( n \) and the Avrami constant \( k \), also exhibited a two-phase temperature dependence, again suggesting that the mechanism of crystallization might change with temperature. Over the low temperature range, both \( k \) and \( n \) are nearly constant, while over the high temperature range, they undergo sharp changes as temperature increases. The transition points between the low and high temperature ranges are related to the composition of the LC/DT2287 mixtures. Additionally, over the low temperature range, the values of \( n \) indicate that crystals are
formed by two-dimensional disc-like growth from sporadic nuclei in the 40% and 50% w/w mixtures, and by three-dimensional spherulitic growth from sporadic nuclei in the 60% and 70% w/w mixtures. Both types of crystallization can be described by the Avrami equation and the classical theory of nucleation. Over the high temperature range, however, the Avrami exponent $n$ is high and cannot be explained by conventional Avrami theory although the data fitted the Avrami equation. In this context, a hypothesis can be proposed that the nucleation rate increases exponentially with time. Theoretical analysis based on this hypothesis could explain the crystallization behavior of LC over the high temperature range. Crystal growth rate was found to be nearly constant throughout the crystallization process, which indirectly indicates that nucleation was time dependent. To reconcile the apparent differences between the classical theory of nucleation in which nucleation is time independent and the proposed hypothesis of time-dependent nucleation, nucleation may actually be a two-step process. Before nuclei are stably formed, the nucleation rate may be expressed by the classical theory of nucleation, which indicates that the nucleation rate is determined by the crystallization temperature and the corresponding activation energy of nucleation, and is therefore time independent. However, after the nuclei are stable the nucleation rate increases exponentially with time (the second step of the process). It also appears that frequent branching that occurs as crystals grow may account for the time dependence of the nucleation rate because the branching points may be considered as nuclei and their numbers will increase exponentially with time after nuclei are formed.
To further explore the mechanisms of crystallization in the supersaturated LC/PSA systems, the physical and chemical properties of LC/PSA systems, especially with regard to intermolecular interactions between the two components, were characterized by DSC and FT-IR. The composition dependence of the glass transition temperature ($T_g$) was used to qualitatively characterize the physical and thermodynamic states of the supersaturated systems. It was found that supersaturated LC/DT2287 systems underwent significant entropic relaxation upon mixing although the strength of the intermolecular interactions between the two components is in the range of weak to intermediate. LC in the miscible mixtures may function as a “solvent” or “plastizer” which was absorbed into and caused swelling of the polymer network of DT2287. Consequently, LC exhibited reduced molecular mobility due to the localization effect of the DT2287 polymer network, while DT2287 in the mixtures behaves as a solvated polymer subject to prevailing molecular conformation relaxation and increased molecular flexibility. Although no specific interactions, such as hydrogen bonding, were found by FT-IR between the two components in the mixtures, it can be assumed that most LC molecules were closely associated with the PSA chains and extensively participated in the molecular movement and relaxation of the PSA. Therefore, no simple dilution effect could be observed throughout the composition range studied. This may contribute to the physical stability of the supersaturated LC/DT2287 systems because the amount of free LC in the systems was reduced by association with the PSA molecular network, thereby reducing their molecular mobility.
In conclusion, transdermal delivery systems containing a PSA supersaturated with LC can enhance its \textit{in vitro} release. The physical stability of the supersaturated LC/PSA systems can be affected by several factors such as hydration, temperature, and degree of saturation. The hindrance of diffusion due to the viscoelastic PSA medium plays an important role in enhancing the physical stability of the supersaturated systems. This hindrance of diffusion apparently results from an association between LC and the PSA molecules which reduces the molecular mobility of LC in the systems.
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