ENABLING DIRECT COMPRESSION TABLET DEVELOPMENT OF
CELECOXIB THROUGH SOLID STATE ENGINEERING

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To my parents and my love
Abstract

Tablets are the most desirable solid oral dosage form for patients. Direct compression (DC) tablet formulation is the most economical, robust and efficient way of tablet manufacture. Being sensitive to properties of the Active Pharmaceutical Ingredient (API), direct compression tablet formulation is not available for the high dose non-steroidal anti-inflammatory drug, celecoxib (CEL) due to the undesirable properties of the commercial solid form of CEL, including low bulk density, poor flowability and tablet lamination issues.

The solid form used in commercially available CEL capsules is a polymorph of CEL, Form III. Form III CEL is a needle shaped crystal, which is exceptionally elastic. This high elasticity, verified by nanoindentation and three-point bending tests, is unfavorable for good tablet quality and performance during high speed tableting. Through understanding the molecular interactions by analyzing the CEL crystal structure, a structural model for high elasticity is built and validated by Raman spectroscopy. Interlocked molecular packing without slip plane and the presence of isotropic hydrogen bond network are major structural features responsible for both the exceptional elastic flexibility and high stiffness of the CEL crystal.

CEL Form III exhibits unsatisfactory flowability and tablet lamination issues for DC tablet manufacturing. Pharmaceutically acceptable solvates of CEL offer better flow, compaction and dissolution properties than CEL Form III. Two stoichiometric solvates of CEL and N-methyl-2-pyrrolidone (NMP) are extensively characterized and examined, which establishes a clear crystal structure-property relationship essential for crystal
engineering of CEL. Through crystal engineering, a DC tablet formulation of CEL is successfully developed using the dimethyl sulfoxide (DMSO) solvate of CEL. This pharmaceutically acceptable solvate is highly stable and also exhibited much improved manufacturability compared to CEL Form III, including better flowability, lower elasticity and bulk density (superior tablet quality) as well as better dissolution performance.

As a Class II drug in the biopharmaceutics classification system with low solubility and high permeability, the high dose of CEL is partially attributed to its limited solubility. Amorphous CEL, although providing solubility advantages as the thermodynamically high energy state, is unstable and prone to crystallization. The study of crystal growth of amorphous CEL reveals a fast glass-to-crystal growth mode at room temperature with a surface-enhanced mechanism. This paves the way for future development of a stable amorphous solid dispersion tablet product of CEL with improved dissolution performance and tablet manufacturability.

In summary, by understanding the structural origin of undesired properties of CEL, successful development of the most patient-compliant tablet dosage form by direct compression can be achieved. This sets an excellent example of utilizing a solid state engineering approach to effectively overcome challenges encountered in direct compression tablet development.
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<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ASD</td>
<td>Amorphous Solid Dispersion</td>
</tr>
<tr>
<td>BCS</td>
<td>Biopharmaceutics Classification System</td>
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<td>Cambridge Crystallographic Data Centre</td>
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<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>DMA</td>
<td>Dimethyl Acetamide</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethyl Formamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N, N’-Dimethylpropyleneurea</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl Sulfoxide</td>
</tr>
<tr>
<td>DPCP</td>
<td>1,2- diphenylcyclopentene</td>
</tr>
<tr>
<td>DPCH</td>
<td>1,2-diphenylcyclohexene</td>
</tr>
<tr>
<td>DSC</td>
<td>Differential Scanning Calorimetry</td>
</tr>
<tr>
<td>FBRM</td>
<td>Focused Beam Reflectance Measurements</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier Transform Infrared Spectroscopy</td>
</tr>
<tr>
<td>GC</td>
<td>Glass-to-Crystal</td>
</tr>
<tr>
<td>GSF</td>
<td>Griseofulvin</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>HPC</td>
<td>Hydroxypropyl Cellulose</td>
</tr>
<tr>
<td>HPMC-AS</td>
<td>Hydroxypropyl Methylcellulose – Acetate Succinate</td>
</tr>
<tr>
<td>HSM</td>
<td>Hot Stage Microscopy</td>
</tr>
<tr>
<td>ICH</td>
<td>International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>IDR</td>
<td>Intrinsic Dissolution Rate</td>
</tr>
<tr>
<td>IMC</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>IPB</td>
<td>Isopropylbenzene</td>
</tr>
<tr>
<td>MCC</td>
<td>Microcrystalline Cellulose</td>
</tr>
<tr>
<td>MgSt</td>
<td>Magnesium Stearate</td>
</tr>
<tr>
<td>MST</td>
<td>Materials Science Tetrahedron</td>
</tr>
<tr>
<td>NIF</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>NMP</td>
<td>N-Methyl-2-Pyrrolidone</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal Anti-inflammatory Drug</td>
</tr>
<tr>
<td>OTP</td>
<td>O-terphenyl</td>
</tr>
<tr>
<td>PAT</td>
<td>Process Analytical Technology</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene Glycol</td>
</tr>
<tr>
<td>PG</td>
<td>Propylene Glycol</td>
</tr>
<tr>
<td>PLM</td>
<td>Polarized Light Microscope</td>
</tr>
<tr>
<td>PXRD</td>
<td>Powder X-ray Diffraction</td>
</tr>
<tr>
<td>QbD</td>
<td>Quality by Design</td>
</tr>
<tr>
<td>RH</td>
<td>Relative Humidity</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>ROY</td>
<td>5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile</td>
</tr>
<tr>
<td>SCXRD</td>
<td>Single Crystal X-Ray Diffraction</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscope</td>
</tr>
<tr>
<td>SLS</td>
<td>Sodium Lauryl Sulphate</td>
</tr>
<tr>
<td>TGA</td>
<td>Thermogravimetric Analysis</td>
</tr>
<tr>
<td>TMU</td>
<td>Tetramethyl Urea</td>
</tr>
<tr>
<td>TNB</td>
<td>Tris-naphthyl Benzene</td>
</tr>
<tr>
<td>TP</td>
<td>Testosterone Propionate</td>
</tr>
<tr>
<td>TPGS</td>
<td>D-(\alpha)-Tocopherol Polyethylene Glycol 1000 Succinate</td>
</tr>
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</table>
Chapter 1.

Introduction
1.1 General Introduction

Among all dosage forms, tablets are the most widely produced dosage form and are more advantageous than other forms in many ways: 1) elegancy in terms of different shapes/sizes and high patient compliance; 2) precisely controlled dosing for patients; 3) good physical and chemical stability; 4) faster and easier production and transportation and 5) more straightforward and economical manufacturing processes. Although tablet formulation is most desirable for both patients and pharmaceutical companies, it is not always easy to successfully develop a tablet formulation. A balance among aspects of preformulation and formulation, including physical and chemical stability, solubility, powder flow properties, tablet friability and tensile strength, must be achieved during tablet formulation design.

To attain the desired characteristics of the optimal formulation, multiple approaches can be employed. Solid-state properties of active pharmaceutical ingredients (APIs) can be engineered by screening for different solid forms, such as amorphous solid, polymorph/cocrystal/salt/solvate and hydrate. For a given API solid form, particle and powder properties can be engineered by particle size reduction, dry and wet granulation. Lastly, fine-tuning tablet performance can be achieved by altering the formulation compositions. For drugs that are less potent or of low solubility, high doses are usually required for the tablet to demonstrate the desired therapeutic effect. For these types of drugs, the final property of the formulation is highly dependent on the API properties, and the space for manipulating drug product performance through formulation design is limited. In this case, although high drug loading can be achieved by wet granulation and dry
granulation to uniformly disperse the API and densify the powder blend, \(^2\) the granulation process is often costly and requires extra steps and more strict process controls. In comparison, direct compression is the more desirable way for tablet manufacturing. Out of all these possible solid-state engineering methods, API engineering to improve the properties is the most effective.

In this work, a non-steroidal anti-inflammatory drug for treating pain and arthritis, celecoxib (CEL), is used as an example of high dose drug that is challenging for direct compression (DC) tablet formulation development. The marketed CEL product is in form of capsules, Celebrex\textsuperscript{®}, which are usually prescribed in high doses of 200 mg or 400 mg. The marketed product contains the most stable polymorph, Form III of CEL, which has undesired properties for DC tablets. \(^3\) \(^4\) Wet granulation was employed in the original Celebrex\textsuperscript{®} capsules to improve the poor flow properties of API for capsule filling. \(^4\) However, this process is complex, costly and possess risks of overgranulation and chemical and physical stability. \(^5\) In addition, these capsules are of relatively large sizes and thus lower patient compliance than tablets. In addition, the lag time before releasing the drug from capsules is unfavorable for pain medications like CEL, which is preferred to have faster action. To develop a DC tablet formulation of CEL, the unwanted properties of Form III CEL needs to be overcome. This includes poor flow properties, low bulk density and tablet lamination issue during high speed direct compression. \(^4\)

Here we aim to improve CEL properties through solid-state engineering to enable the development of a suitable DC tablet. This is achieved using a combined crystal engineering and Quality by Design (\textit{QbD}) approach. The guiding principles behind this
work is the materials science tetrahedron (MST), which describes the relationship between material structure, properties, processing and performance. 

1.2 Literature Review

1.2.1 Tablet Dosage Form - Prevalence and Advantages

Solid oral dosage forms have been the most widely used for both patient compliance and physical stability. Among solid oral dosage forms, tablets have been the most widely produced and prescribed drug among all dosage forms. For patients, solid oral dosages forms are usually taken without complications, have accurate dosing, easy to store, and can be taken without pain and extra dedication. Tablets stands out among all oral solid dosages forms due to its elegance, which can be made into different shapes, colors, and tastes. In addition, a tablet can also be significantly smaller than capsules with the same amount of drug content. To the pharmaceutical industry, the manufacturing of tablets is more robust, time-saving and economical.

There are many types of tablets for different functions, routes of administration, and release profiles. Tablets categorized for special function include chewable tablets, lozenges, bilayer tablets, orally disintegrating tablets and effervescent tablets. Buccal tablets are administered with slightly different routes of administration. Film coated tablets are often made for ease of swallowing or for an extended release profile.

Depending on the purpose of development, tablet formulations can be altered to attain improving specific properties. For drug product quality control, many important aspects of tablet performance need to be assessed for all kinds of tablets, including
bioavailability, stability, manufacturability, safety and efficacy. According to MST, the performance of a drug product is closely related to materials structure, properties and processing (Figure 1–1). These key attributes will be reviewed in detail in the next section.

![The materials science tetrahedron (MST)](image)

**Figure 1–1.** The materials science tetrahedron (MST)

### 1.2.2 Critical Attributes of a Successful Tablet Formulation

A successful tablet formulation should satisfy the criteria for content uniformity, tablet weight, tablet hardness, tablet friability, disintegration time and dissolution performance. Such performance of a tablet product stems from its properties, the process for manufacturing during drug product, and the structure of materials.

Here, the material properties include the physicochemical properties (solubility of API, thermal properties, hygroscopicity, etc.), micromeritics, powder flow properties and mechanical properties (elasticity and plasticity, brittleness, tabletability, compressibility and compactibility) of to both the API and the excipients. They are closely related to the
material ‘structure’, which include the crystal structure, granule structure, and tablet structure (e.g., porosity and compositions).  

A tablet formulation consists of both the API and other inactive ingredients. Once the drug molecular structure is selected, the different solid forms of the API affect its properties and thus performance of the drug product. The inactive ingredient, commonly called excipients, can play different roles in a tablet formulation. A diluent or filler is used to provide bulk volume, which can also aid in achieving content uniformity of mixtures or modify tableting properties of tablets. The binder is used for increasing particle bonding strength or as the granulation facilitator. A tablet disintegrant is important for immediate release formulations for breaking up the tablets or granules when it is in contact with water, achieving faster API release. A lubricant is used to reduce the friction between powder mixture and the equipment surfaces and thus alleviate sticking and heat generation. A glidant is sometimes used to reduce adhesion between particles and thus improving flowability. Other components, including flavor or colorant for taste masking and appearance, respectively, and surface coating are sometimes used for specific purposes, like taste masking of bitter-tasting drugs. The selected excipients must also be chemically compatible with the API to minimize any possible degradation of the API. Knowing the different properties of the API solid forms and functional excipients is useful for developing a tablet product that best serves the patients’ need.

The ‘processing’ category of MST, including the key parameters of operations during manufacturing, is another degree of freedom during product development that connects the ‘structure’ of API and excipients with their ‘properties’ to achieve optimal
performance. Examples of processing are milling to change primary particle size; dry and wet granulation process for altering particle properties; powder blending time and sequence; and tableting speed and pressure.

A successful tablet product development requires a deep understanding of the material and processing attributes as outlined by the MST. Only with these in mind, can a formulation be truly designed using Quality by Design (QbD) approach.  

1.2.3 Materials Engineering for Drug Product Development

1.2.3.1 Preformulation and Process Chemistry

The impact of pharmaceutical materials engineering spans a wide range from structure, properties and processing to the final drug product performance. Materials engineering includes two categories: preformulation (realized through process chemistry) and formulation (realized through manufacturing process control). The hierarchical organization and details of materials engineering approaches for each step is summarized in Figure 1–2.

Solid form selection is of paramount importance during drug product development, laying a foundation for attaining critical attributes of the drug product, including stability, dissolution performance, manufacturability and tablet quality. 21-25 One of the most popular solid-state engineering approaches is utilizing amorphous solids to increase solubility and bioavailability of drugs. Amorphous solids, do not have long-range order of molecules and tend to convert to their crystalline counterparts because they have higher thermodynamic free energy. 26 To attain sufficient physical stability and high dissolution rates, APIs are
Figure 1–2. Materials engineering activities involved in development of tablets
often molecularly dispersed in polymeric matrices to form amorphous solid dispersions (ASDs).²⁷ ASDs are of increasing interest to the pharmaceutical industry due to the need to improve the solubility of increasing numbers of emerging new drugs belonging to the Biopharmaceutics Classification System (BCS) classes II and IV.²⁸ Some drug products enabled by ASDs include Noxafil, Novir, Kaletra, Onmel, and Sporanox, etc. Among 24 marketed ASD products, 20 of them are made into tablets.²⁹

Developing an amorphous solid dispersion requires careful selection of polymers and the method of generating ASD product. Hot-melt extrusion, spray drying, coprecipitation are the main scalable manufacturing methods for ASDs, while film casting, rotary evaporation and melt-quenching are often used in laboratory scale to screen ASDs.²⁹ The choice of polymer and manufacturing process for ASD is based on its performance, i.e. stability, drug-polymer miscibility, in vitro dissolution performance and in vivo bioavailability.³⁰,³¹ Understanding the crystallization mechanisms and kinetics of pure amorphous API is of fundamental significance for polymer screening and processing conditions,³²,³³ since crystallization negates the solubility advantages of amorphous drug products.³⁴

A crystalline form of drug substances has been traditionally utilized in developing tablet products due to their better physical stability. For drugs in the Biopharmaceutics Classification System (BCS) classes I and III,³⁵ the crystalline state of APIs is preferred due to its robustness in stability and flexibility with processing and formulation. Different crystalline forms of an API molecule include polymorphs, salts, hydrates, solvates and cocrystals (Figure 1–3). Crystal engineering is a way of materials engineering to obtain
desired solid-state properties of API by manipulating crystal structure. The drug solid form also has to be chemically compatible with the excipients used and physically stable during manufacturing and administration. For example, salt disproportionation is sometimes encountered if formulated with specific excipients like dicalcium phosphate dihydrate (DCPD). \(^{20,36}\)

**Figure 1–3. Illustration of common crystalline forms of APIs used in crystal engineering**

After the lead solid form of API is chosen, particle engineering is sometimes utilized to modify the crystal shape and size, which also have practical implications on performance of the final tablet product. For different crystal shapes, the surface area of specific crystal faces vary, and may exhibit distinct properties. Celecoxib plate shaped crystals exhibit higher intrinsic dissolution rate and better wettability than needle shaped crystals of similar size, attributing to the favorable exposure of hydrophilic facets of plate crystals. \(^{37}\) Crystal shape can also affect the flow properties, \(^{38}\) tableting performance \(^{39}\) and punch sticking propensities. \(^{40,41}\)
Particle size is also an essential aspect of particle engineering. Decreasing API particle size by as micronization or nanosizing has been a ubiquitous method of improving the dissolution performance of drug product and thus its bioavailability. \(^{42-44}\) Smaller particle size is also favorable for higher tablet tensile strength as it provides more surface area available for bonding. \(^{45, 46}\) However, smaller particles also exhibit deteriorated powder flowability due to increased cohesion. \(^{47}\) The balance between detrimental effect of small particle size on poor flow and the beneficial effect on tablet tensile strength and dissolution performance needs to be balanced during the tablet product development process.

The different crystal shape and particle size distribution can be achieved by controlling process parameters of crystallization and / or milling. Jet milling, ball milling, wet milling, high pressure homogenization and cryogenic milling are common types of milling methods used in industry. \(^{48}\) Recently, extensive efforts have been made at the drug substance/drug product interface for simultaneously controlling the API morphology and size for better manufacturability with the aid of co-processed excipients for direct compression in continuous manufacturing settings. \(^{49, 50}\)

### 1.2.3.2 Formulation and Process Development

Formulation and process development come after the lead API and particle attributes have been determined. The main purpose of this stage is to select the best route to formulate the API to attain properties suitable for high speed tableting, preferably using DC process. There could be more or fewer steps required to optimize the powder blend for satisfactory critical attributes required for DC. Depending on the dose, API and particulate
properties, project timeline, patient demographics and availability of technologies and platforms, different formulation strategies can be employed to make the final blend for tableting.

The tablet manufacturing of a direct compression formulation requires only excipient selection and proper mixing. Aside from the tableting parameters, including tableting speed, compaction pressure and selection of tooling, which needs to be considered for all tablet formulations, direct compression only requires the assessment of excipient functionalities and blending intensities. Selection of functional excipients helps to build a successful formulation by addressing issues, such as flowability and content uniformity of the blend. Dry nanocoating efficiently improves the flow. Poloxamers can serve as lubricants to reduce the ejection force without sacrificing dissolution. This development process is simple, economical and robust for most APIs. However, for potent drugs with very low doses, content uniformity may be an issue if prepared only by simple mixing. For high dose drugs, on the other hand, the properties and performance are highly dependent on the API itself if direct compression is employed. When the API solid form is fixed, other formulation strategies may be pursued to solve problems in either manufacturability or dissolution performance caused by undesirable properties.

Granulation is the most used technique other than DC. The most widely used granulation techniques are wet granulation, dry granulation and melt granulation (Figure 1–2). Melt-granulation is sometimes categorized as wet-granulation due to somewhat similar processes, where the liquid binder in wet granulation is substituted with a low-melting point solid. A variety of equipment are also available for granulation, which is
sometimes incorporated as one important component in the continuous manufacturing line of pharmaceuticals, such as twin screw wet granulation. \(^{60}\) Granulation is a complicated process, which involves optimization of many critical parameters and characterization techniques are needed to obtain the desired product performance.

Wet granulation has gained great prevalence in formulation and processing of APIs. \(^{5, 61, 62}\) There are many aspects in wet granulation that needs to be evaluated for ideal granule performance. First of all, high-shear wet granulations, fluid bed granulation, spray-drying granulation and twin screw granulation are all wet granulation techniques with different operating principles. \(^5\) Take high shear wet granulation as an example, the operating conditions of the high shear wet granulator critically affects the properties of granules and thus the quality of tablets. The water level, impeller speed, viscosity of binder solution all influence the granule properties and thus tablet quality. \(^{63-69}\) Wet granulation also mandates stable solid forms, since phase changes are more likely to take place during granulation and drying processes. Many process analytical technologies (PAT) have been developed for on-line or in-line monitoring of the granulation process for potential phase changes, particle size distribution, etc. These include near infra-red spectroscopy (Near-IR, Raman spectroscopy, focused beam reflectance measurements (FBRM) and powder X-ray diffraction (PXRD). \(^{62, 70-73}\) To sum up, wet granulation is complicated, time-consuming and requires delicate control. Nevertheless, it is available for APIs with certain properties and the when choice of solvent/binder is appropriate to avoid solid form changes during granulation and drying.
Dry granulation is another route for improving particle properties for tablet compression.\textsuperscript{74-76} For APIs that are unstable for wet granulation processes, dry granulation may be a viable method to improve particulate properties. Just like wet granulation, dry granulation also has several process parameters that needs to be optimized for desired granule properties. The type of roller compaction equipment (roll gap, roll diameter, roll width, roll surface texture, feeding and de-aeration), processing parameters (roll speed, feeding speed, compaction pressure) and formulation variables all impact the granule properties.\textsuperscript{75, 77-81} However, cautions need to be taken for the deterioration in tabletability of granules after dry granulation.\textsuperscript{82}

Melt-granulation is utilized in some pharmaceutical formulations to incorporate low melting point excipients as granulating liquid by heating the granulation vessel to above its melting temperature.\textsuperscript{83-85} In addition to parameters similar to wet granulation, the melt granulation involves processing conditions optimized to melt the solid binder. To sum up, there are many factors to be considered in either wet granulation or dry granulation processes, making granulation a time-consuming, complex and expansive formulation process. The direct compression is the most preferred way of tablet manufacturing, attributing to its robust, economical and straightforward characteristics. Since direct compression tablet formulations is sensitive to API properties, especially for high dose drugs, ways to alter the API properties in favor of direct compression are of great interest to pharmaceutical industry, especially in early development stages. As an effective way to alter drug properties, advancements in crystal engineering has been proven useful in drug product development.
1.2.4 Crystal Engineering to Optimize API Properties

The field of crystal engineering has significantly advanced in terms of both the understanding of the structure-property relationship between crystal structures and API properties, and enabling $QbD$ design for desired physicochemical properties and manufacturability. Crystal engineering can be crucial to obtaining desired properties in both the preformulation and formulation stages. Crystal engineering can be divided into two parts - the first is understanding the root of the properties that needs to be changed – which is the ‘structure-property relationship’ aspect. The second part is the ‘engineering’ aspect – to obtain the desired properties of API by altering its crystal structure.

Many efforts has been made to understand the molecular origins of mechanical properties of molecular crystals. Panda et al. described the molecular origin of the plastic behavior of bendable hexachlorobenzene molecular crystals. It was argued that upon stress, layers of molecules slide against each other with restorative Cl···Cl interactions, which act cohesively to recover the adhesion between the layers. These studies expand the understanding of molecular origins of mechanical properties of solids, e.g. elasticity and plasticity, and lay the foundation for the design of solid forms with desired properties.

Many researchers have also made efforts to design for wanted drug mechanical properties with crystal engineering. The Reddy research group has successfully induced plasticity of molecular single crystals by introducing plastically active slip planes in the structure via carefully placing selected noninterfering van der Waals, π-stacking, and hydrogen bonding groups, on different compounds. While it is imperative to engineer
the mechanical properties of molecular crystals, more efforts have been made on using
crystal engineering to improve the solubility and dissolution rates of pharmaceutical APIs.
As detailed in Figure 1–3, polymorphs, solvates/hydrates, cocrystals and salts are all
commonly used to improve solubility and dissolution rates in pharmaceutical materials. 87, 95, 96
Cocrystallization of APIs has been shown to improve the solubility of many drugs -
for example, mebendazole 97, ketoconazole 98 and posaconazole 99. Solvates of some APIs
are also found to increase the dissolution rate of many drugs, 100 e.g. rifampicin 101,
olanzapine 102 and spironolactone 103. Screening, selection or synthesis of polymorphs, 104
hydrates 106 and salts 98, 107, 108 are all successful crystal engineering methods for
solubility and dissolution enhancement during drug development. Some work has also
shown improvement in the stability of an API through hydration 109 or salt formation 110.

The manufacturability aspect of crystal engineering is less well explored compared
to the single crystal mechanical properties and solubility. Previous work done in our lab
surveyed crystal engineering approaches to overcome a variety of manufacturability
challenges. For example, poor tablet mechanical properties has been a challenge for many
APIs, preventing them to be made into tablet dosage form via direct compression. Caffeine
is such an example. To overcome this challenge, the caffeine – methyl gallate cocrystal
was developed and was shown to improve mechanical properties, with tabletabilities better
than caffeine and methyl gallate. 111 Cocrystallization of ibuprofen and flurbiprofen with
nicotinamide also exhibited improved tabletability, along with other simultaneously
improved properties like hygroscopicity, and dissolution performance. 112 A high dose
tablet formulation of 5-fluorocytosine was successfully developed into a tablet by salt
formation with oxalate acid. Karki et al. were also able to make intact tablets of a drug with high capping tendency, paracetamol, through cocrystallization.

The flow properties, an important parameter during high speed tablet manufacturing, can also be improved by crystal engineering. The flow properties of a cohesive powder, citric acid, was greatly improved by hydrate formation. Punch sticking, another practical problem encountered during tablet compression, can also be addressed via crystal engineering. The high sticking propensity of acesulfame free acid was pronouncedly alleviated by forming a potassium salt, the mechanism of which was explained by surface chemistry and reduction in plasticity. Cocrystallization of celecoxib and proline have also been proven to greatly reduce the sticking of celecoxib to the punch surface by similar mechanisms.

As a summary, the crystal form of API is crucial developing a direct compression tablet formulation. Crystal engineering is an effective way to improve API properties not only at preformulation stage for properties like stability and solubility, but also for manufacturability and processing during formulation development. According to the MST (Figure 1–1), through understanding of the structural landscape of different crystal forms and their relationships to properties and performance, one can use crystal engineering methods to obtain the desired API properties to enable the tablet manufacture using the direct compression process.
1.2.5 Celecoxib

1.2.5.1 Background of Celecoxib

Celecoxib (Figure 1–4) is a widely prescribed nonsteroidal anti-inflammatory drug (NSAID) developed by Pfizer to treat arthritis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute pain, with also analgesic and antipyretic characteristics. Celecoxib (CEL) is a cyclo-oxygenase (COX) inhibitor that selectively inhibits COX-2 over COX-1 both in vitro and ex vivo. CEL is commercially available as capsules, with available doses of 100 mg, 200 mg and 400 mg. CEL is a class II compound in the Biopharmaceutics Classification System (BCS), having high permeability and low solubility. The absolute oral bioavailability of CEL in dogs was 64-88 % if given as solution and 22-40 % if given as capsule. The absolute bioavailability of CEL in human was not studied due to its low water solubility.

![Molecular structure of celecoxib, MW=381.373 g/mol](image)

**Figure 1–4.** Molecular structure of celecoxib, MW=381.373 g/mol

Celecoxib was developed as a first-in-class COX-2 inhibitor, approved for its role in treating osteoarthritis and rheumatoid arthritis, with potential in treating acute pain. It soon became a blockbuster drug and widely prescribed by doctors. All dosages (100 to
400 mg twice daily) has clinically shown similar efficacy to conventional NSAIDs (e.g. 500 mg naproxen) in pain relief and improvement in functionality. Meanwhile, CEL has a much safer gastrointestinal profile and is well tolerated by patients. \textsuperscript{118} The recommended dose of CEL is 200 mg/day for osteoarthritis, and 100 to 200 mg twice daily for rheumatoid arthritis in adults. No significant food effect was observed in healthy human subjects. \textsuperscript{121}

\subsection*{1.2.5.2 Challenges for Direct Compression Tablet Manufacture}

The marketed Celebrex\textsuperscript{®} capsules utilized the most thermodynamically stable - Form III as the API solid form of CEL. \textsuperscript{3, 4} Aside from the Celebrex\textsuperscript{®} capsules which are of relatively large sizes, only a fixed dose combination named CONSENSI\textsuperscript{®} (amlodipine and celecoxib) was approved by the FDA in 2018, but no tablet containing only CEL is available. Although direct compression is the most simple and efficient way of tablet manufacture, several problems need to be solved to successfully produce CEL tablets.

From the manufacturability perspective, CEL form III has very low bulk density \textsuperscript{123} and thus very poor flow properties. \textsuperscript{124} This is problematic for effective mixing, successful die filling during high speed tableting. CEL Form III also exhibits severe punch sticking problems during tableting. \textsuperscript{115} Lamination is also a prominent issue related to CEL tablets at high tableting speeds. In addition, the high dose (200 mg) required to elicit a therapeutic benefit makes the tablet formulation highly sensitive to the CEL solid form properties in terms of manufacturability. Since CEL absorption is limited by solubility, its dose could be further decreased if its solubility is increased, leaving more room for functional excipients to attain desired properties of the tablet formulation.
Much effort has been focused on increasing the solubility and thus the bioavailability of CEL. Guzmán et al. have used high throughput screening methods to screen for the excipients that can delay the precipitation of a high kinetic solubility sodium salt form of CEL. It was shown that the CEL sodium salt formulation with TPGS/HPC and Pluronic F127/HPC exhibits complete absorption (100% oral bioavailability) in dogs at 5mg/kg dose, whereas the Celebrex® only achieved 40% bioavailability at the same dose. Other efforts have been made to develop amorphous solid dispersions to increase its bioavailability. Much work has been focusing on identifying a polymer that could effectively inhibit the nucleation of CEL during dissolution. Others have explored the effect of surfactants on the crystallization and dissolution performance of CEL amorphous solid dispersions (ASDs) as spray-dried particles or hot-melt extrudates. A ternary solid dispersion of CEL has also been proposed for both quick drug release and nucleation inhibition. Other techniques explored for enhancing CEL solubility and dissolution rate include a solid phospholipid nanoparticle dispersion via freeze-drying or spray-drying; nanoparticles generated by antisolvent precipitation and high pressure homogenization techniques; CEL glass solutions produced by hot-melt extrusion and supercritical carbon dioxide.

Some research has touched on solving problems related to the manufacturability of CEL. For punch sticking of CEL Form III, Wang et al. utilized a cocrystallization method to overcome this challenge; Chen et al. employed spherical crystallization with a polymer as a way to alleviate sticking. The compaction of amorphous and crystalline CEL, and CEL ternary ASD were compared, and the compression-induced destabilization in melt-quenched CEL was examined by low-frequency Raman
Spectroscopy. The mechanical properties of a CEL glass were studied by nanoindentation for effect of drug loading and RH.

So far, little attention was focused on the processability and manufacturability of CEL solid forms for tablet compression. No efforts were made to evaluate and understand the solid forms of CEL for the purpose of developing the direct compression tablets. As a high dose drug, CEL formulation is sensitive to the API properties. Therefore, overcoming the poor tablet quality (lamination) problem and poor flow of CEL Form III by crystal engineering is of practical interest. Per the crystal engineering principle, the design is achieved by first understanding the molecular origin of the properties of CEL, which is then followed by rational proposal and engineer for the desired crystal properties. By employing amorphous solids as the API solid form, the potential dose needed to exhibit adequate therapeutic effects would be lowered. Thus, the stability and crystallization mechanisms of amorphous CEL are critical to such designs for direct compression tablet manufacture. The stability of amorphous CEL and its crystal growth mechanism in its solid state have not been studied before.

1.3 Objectives and Hypotheses

The main goal of this thesis is to use solid state engineering methods to solve the issues associated with the existing commercial Form III of celecoxib that hinder the development of a direct compression tablet formulation. The guiding hypothesis of this thesis is that solid-state engineering is effective in overcoming deficient properties of CEL and enables the successful development of a direct compression tablet formulation. In testing this hypothesis, it is necessary to characterize the solid-state properties of various
novel solid forms of CEL, including the crystal growth mechanism and kinetics of amorphous CEL and structure-property relationships of new crystal forms of CEL.

The objectives of this thesis are:

1. To understand the structural origin of the exceptional elasticity of CEL Form III crystals from a molecular perspective. Its rarely seen high elasticity is unfavorable for good tablet quality and performance during high speed tableting.

2. To screen for a pharmaceutically acceptable solvate with better flow, compaction and dissolution properties that can be employed to develop a DC tablet formulation. The first step of this exercise is to gain a clear understanding of the relationship between crystal structure and solid-state properties and mechanical properties of these new crystal forms. New insights into the structure-property relationship lay a foundation for future crystal engineering.

3. To develop and comprehensively characterize a direct compression tablet formulation, a suitable solid form with improved manufacturability.

4. To prepare and understand the physical stability of amorphous CEL by studying the crystal growth mechanism and role of polymorphism to lay a foundation for future development of CEL ASDs for direct compression tablets. The enhanced solubility of amorphous CEL is expected to reduce dose and hence, leaving more room of using functional excipients for developing a tablet formulation of high performance.
1.4 Research Plan and Thesis Organization

In Chapter 2, the structural origin of the exceptionally high elastic flexibility of CEL Form III crystals is explained at the molecular level. The high elasticity is illustrated by both qualitative three point bending and quantitative nanoindentation tests. A structural model is developed to explain the highly restorative forces among the CEL molecules in Form III needle crystals of CEL. This model is verified by observing changes in micro-Raman spectra of different regions of the bent crystal. The understanding derived from this work can be used to design crystals with desired elasticity and, thus, better compaction properties during high speed tableting.

In Chapter 3, two newly discovered stoichiometric solvates of CEL with N-Methyl-2-Pyrrolidone are characterized. A complex and intriguing conversion from CEL-NMP disolvate to monosolvate is carefully studied. The drastically different stabilities of CEL-NMP disolvate and monosolvate is evaluated and analyzed from their crystal structures. The established structure-property relationship aids the future development of a stable solvate that is suitable for direct tablet compression.

In Chapter 4, a pharmaceutically acceptable dimethyl sulfoxide (DMSO) solvate of CEL, CEL-DMSO is characterized in terms of crystal structure, stability, physicochemical properties, flow properties, compaction properties and dissolution. Then, CEL-DMSO is used to enable the development of a direct compression tablet formulation. The CEL-DMSO formulation exhibits superior flow properties, easy die-filling and satisfactory tablet quality. The CEL-DMSO tablets show faster disintegration and release than the
commercial capsules, which successfully demonstrates the potential of the rarely explored pharmaceutical solvates in solving formulation problems.

In Chapter 5, the amorphous CEL is studied. The amorphous CEL is prepared by melt-quenching, and its stability is assessed by monitoring its crystal growth rate at different temperatures. The results show that below the glass transition temperature of amorphous CEL, the crystal growth rate increase abruptly by activating a new mechanism called Glass-to-Crystal growth mechanism. The surface-enhanced crystal growth indicates that elimination of free surface can stabilize amorphous CEL. Different polymorphs of CEL also exhibited different the crystal growth profile. The results from this study lay a foundation for the future development of direct compression tablets based on ASD of CEL.
Chapter 2.

Exceptionally Elastic Crystals of Celecoxib Form III

This chapter has been published as an ACS Editors’ Choice research article in Chemistry of Materials.

2.1 Synopsis

We report here the structural origins of the elastically bendable single component pharmaceutical crystal, celecoxib Form III. Interlocked molecular packing without slip plane and the presence of isotropic hydrogen bond network are major structural features responsible for both the exceptional elastic flexibility and high stiffness of the celecoxib crystal revealed by bending and nanomechanical studies. The molecular model of the exceptional elasticity is rationalized by the inhomogeneous spatial separations of molecules in the bent crystal, which is further confirmed by micro-Raman spectroscopy. Celecoxib crystal, exhibiting both therapeutic effects and elastic mechanical behavior, could be used to manufacture functional micro-devices with novel medical applications.

![Figure 2–1. Synopsis figure of elastic CEL crystal](image-url)
2.2 Introduction

Molecular crystals with exceptional mechanical properties have gained prominent attention due to the wide range of potential applications, such as pharmaceuticals, explosives, flexible optoelectronics, bioinspired natural fibers, food and fine chemicals. The mechanical behavior of molecular crystals depends on the types of the atoms, ions or molecules, molecular arrangement, and strength of intermolecular interactions. Property engineering in molecular crystals is the main objective of the third-generation crystal engineering, which is accomplished via the modulation of the underlying structure. Crystal engineering is also widely used in designing active pharmaceutical ingredients (APIs) with optimum physicochemical properties, such as solubility, dissolution rate, bioavailability, and mechanical properties. Understanding the mechanical behavior of pharmaceutical crystals in the context of crystal packing, slip planes, and crystal defects is of significant importance both scientifically and practically. For instance, the success in the processes of milling and tableting of an API depends, to a large extent, on its mechanical properties. A key to effective design of pharmaceutical crystals with optimum mechanical properties is the establishment of an appropriate structure-mechanical property relationship.

Mechanical plasticity in most molecular crystals can be rationalized based on crystal packing anisotropy and the presence of slip systems. Hand-twisted helical crystals have also been recently designed by introducing two-dimensional plasticity with a fair degree of isotropic crystal packing. In contrast, elasticity predominately depends on the isotropy of both crystal packing and strength of intermolecular interactions.
Examples of elastic behavior of molecular crystals and co-crystals have been reported and rationalized. Elastic crystals of drugs with therapeutic characteristics could be a class of materials with novel mechano-pharmaceutical applications. For example, a pharmaceutical crystal with combined elasticity and optical fluorescent properties could be exploited for medical and diagnostic imaging in biomedical applications. Despite the appealing aspects of elastically bending crystals with biopharmaceutical activities, their design is extremely difficult due to a lack of clear understanding of the structure-elasticity relationship at the molecular level.

So far, the known elastic pharmaceutical crystals are all multi-component, e.g., cocrystal, solvate, and salt. The first reported elastic molecular crystal was a caffeine cocrystal solvate. Subsequently, an elastic biocrystal of clofazimine hydrochloride salt was discovered. In both cases, the solvent and chloride anion play an integral role in the structural stability and elasticity during bending. Recently, a cocrystal of 4,4'-azopyridine and probenecid, a uricosuric agent, was shown to exhibit unique elastic behavior under external stimuli of heat, light, or mechanical load. However, an elastic pharmaceutical single component crystal remains to be discovered. Herein, we report the first elastic crystal of a blockbuster drug, celecoxib Form III (CEL, Figure 2–2). CEL is a COX-2 selective nonsteroidal anti-inflammatory drug for treating pain and inflammation associated with osteoarthritis or rheumatoid arthritis, and other acute pain in adults. Although no extraneous molecules are present in the crystal lattice, CEL still exhibits surprisingly elastic bending behavior. We conducted bending and indentation experiments
to quantify the elastic properties of the CEL crystal and identified responsible features in the crystal structure and key intermolecular interactions.

![Molecular packing in CEL viewed into (01-1), (001) and (100) faces.](image)

**Figure 2–2.** Molecular packing in CEL viewed into (01-1), (001) and (100) faces.

### 2.3 Materials and Methods

#### 2.3.1 Materials

Celecoxib (CEL) was purchased from Aarti Drugs Pvt Ltd. (Mumbai, India), and used as received. The solid-state polymorphic form of as-received CEL was confirmed by powder X-ray diffraction to be form III.

#### 2.3.1.1 Single Crystal Preparation of Elastic Crystals of CEL Form III

200 mg of Form III as-received Celecoxib was dissolved in 10 mL methanol. The methanol solution of CEL was allowed to slowly evaporate in the chemical hood until dryness. Very long needles were crystallized from the solution and used in looping, bending and single crystal X-ray diffraction experiments.
2.3.2 Methods

2.3.2.1 Single Crystal X-ray Diffraction Experiment

Single crystal X-ray diffraction (SCXRD) of form III CEL was performed on a Bruker D8 Venture diffractometer (Bruker AXS Inc., Madison, Wisconsin) equipped with a Bruker PHOTON-II CMOS detector. The data collection was done at 100 (2) K with a MoK$_\alpha$ radiation source (IμS 3.0 microfocus tube). Data integration was performed with the SAINT program, the SADABS program was used for scaling and absorption correction purposes and XPREP was used for space group determination and data merging. The crystal structure was solved and refined using the ShelXle program (a graphical user interface for SHELXL$^{174}$). The crystal structure was solved using SHELXT (Intrinsic Phasing) methods. The hydrogen atoms were either placed geometrically from the difference Fourier map or allowed to ride on their parent atoms in the refinement cycles. All non-hydrogen atoms were refined with anisotropic displacement parameters. CCDC 1875184 contains the supplementary crystallographic data for CEL form III for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

2.3.2.2 Face Index of CEL Form III

Face indexing of needle–shaped CEL form III crystals was done on a Bruker D8 Venture diffractometer (Bruker AXS Inc., Madison, Wisconsin) equipped with a Bruker PHOTON-II CMOS detector. The major face is (001) along the $c$ axis; the minor faces along $c$ axis are (011) or (011) face. Another minor face is (100).
2.3.2.3 Three-point Bending and Looping Tests of CEL Crystals

The three-point bending, and looping tests were carried out using metallic needle and forceps on the major face (001) of CEL needled crystals. The video was recorded on screen using a Polarized Light Microscope (Leica M165C, Leica Microsystems Inc., Buffalo Grove, IL). Thickness and radius of the bent CEL crystal was measured from video screenshots by Image J program. 175

For deflections of a beam in pure bending, i.e. shear component is not included, the Euler-Bernoulli beam theory is used for strain calculation upon bending. 176

\[ \varepsilon_x = \frac{y}{R} \times 100\% \quad \text{Eqn. 2–1} \]

Here \( \varepsilon_x \) is the normal strain, \( y \) is the distance between the plane of interest to the neutral plane (whose length and location does not change during bending), and \( R \) is the radius of curvature of the neutral plane. Since the side view cross-section of the needle-shaped CEL crystal beam is a rectangle (01\( \overline{1} \) or 0\( \overline{1} \) face), the neutral plane is therefore the central plane, parallel to the bending plane (001). Thus, the maximum bending strains are exerted to the innermost and outermost planes of this crystal, with the innermost plane being compressed (shortened) and the outermost plane being stretched (elongated). Regardless of sign conventions for shortening (negative) and elongation (positive), the numerical values of \( \varepsilon_x \) for the innermost and outermost plane are the same. If the measured thickness of CEL crystal is represented by \( t \), and the measured diameter of curvature is \( d \), the absolute value for \( \varepsilon_x \) is thus:
\[ \epsilon_x = \frac{t/2}{R/2} \times 100\% \quad \text{Eqn. 2–2} \]

2.3.2.4 Nanoindentation

The TI 980 Triboindenter (Hysitron Inc., Minneapolis, MN, USA) system was used to perform nanoindentation experiments. A standard Berkovich diamond indenter tip was employed. Indentations were performed on the (001) face (bending face) of CEL form III crystal under force control mode, with 5 mN/s loading and unloading rate and a peak load of 5 mN held for 20 s. A total of 15 valid indentations were used to calculate Elastic Modulus \((E)\) and Hardness \((H)\) using Oliver-Pharr method.\(^{177}\) The 20\(\mu m\) \(\times\) 20\(\mu m\) area containing the indentation mark was scanned for visualization of surface topology.

2.3.2.5 Raman Spectroscopy

Bent crystals for Raman spectroscopy were prepared by gluing two ends of an elastic CEL crystal onto a glass slide, preventing it from recovering to the normal straight configuration. Raman spectra of straight and bent CEL crystals were collected using a confocal Raman microscope (Witec alpha 300R, WITec, Ulm, Germany), equipped with a CCD detector. CEL straight and bent crystal samples were excited using a 532 nm Omnichrome Argon ion laser. For straight CEL crystal, the 10× lens was used, and a 5-second integration time with 20 accumulations was utilized for spectra collection. For the bent CEL crystal, both the inner part and outer part of the curve were tested using a 100× lens, which provides a laser beam size of 2 \(\mu m\) in diameter. For the inner and outer points on the bent crystal, the spectral acquisition integration time was 5 seconds and the average of 10 spectrum accumulations was obtained. The vibrational computations of CEL was calculated by using Becke-3-Lee Yang Parr (B3LYP) density functional theory (DFT)
method with 6-31G* basis set in ground state using Gaussian-09 program to assign the relevant bands in the experimental spectra. \(^{178}\) The positive value of the calculated vibrational wavenumbers show that the optimized molecular structure is stable.

### 2.4 Results and Discussion

Acicular shaped CEL crystals, 3 to 5 mm in length and 0.05-0.1 mm in width, were obtained by slow evaporation of a methanol solution at room temperature. The previously reported crystal structure of CEL was of insufficient quality (R factor = 8.8\%).\(^{172}\) For accurate structural analysis, we solved CEL crystal structure with a higher quality (R factor = 4\%) (Table 2–1). The two dominant faces of CEL crystals were (001)/(00-1) and (01-1)/(0-11), and the end faces of the crystals were (100)/(-100), identified from a face indexing experiment using Single Crystal X-ray Diffraction (SCXRD) (Figure 2–2 & Figure 2–3).
Table 2–1. Crystallographic information for CEL Form III crystals

<p>| | |</p>
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</table>

Figure 2–3. Face index of needle-shaped CEL form III crystal

A crystal structure analysis of CEL shows that the 4-methylphenyl and trifluoromethyl-1H-pyrazol rings are approximately in plane (18°) and are each approximately perpendicular (89.56° and 83.78°, respectively) to the benzenesulfonamide
ring (Figure 2–4). The -NH₂ group of benzenesulfonamide of each CEL molecule is bonded with N of the pyrazol ring to another CEL molecule (N–H···N, D, d, θ: 3.038 Å, 2.19 Å, 159°) to form a hydrogen bonded dimer (Figure 2–5). The dimer extends along the a-axis to form a 1-dimensional (1D) chain fortified by N–H···O (2.922 Å, 2.09 Å, 166°), C–H···N (3.517 Å, 2.740 Å, 139.79°), C–H···π (3.869 Å, 2.966 Å, 159.98°), and C–H···π (3.805 Å, 2.976 Å, 143.97°) hydrogen bonds (Figure 2–5b and Figure 2–6a). Neighboring 1D chains are connected by various weak intermolecular interactions, i.e., C–H···F dimer (3.516 Å, 2.59 Å, 165.2°), C–H···F linear (3.578 Å, 2.696 Å, 149.95°), and C–H···π dimer (3.936 Å, 2.971 Å, 168.4°). CEL dimers from neighboring 1D chains are offset by 4.896 Å along the direction of chain. The connection of dimers via C–H···π dimer (3.936 Å, 2.971 Å, 168.4°) hydrogen bond leads to corrugated layers parallel to the (100) plane (Figure 2–6 b). Each corrugated layer is connected by bifurcated C–H···O dimer (3.255 Å, 2.56 Å, 129°; 3.358 Å, 2.819 Å, 116.82°), C–H···F dimer (3.516 Å, 2.59 Å, 165.2°) and, C–H···F linear (3.578 Å, 2.696 Å, 149.95°) to form interlocked packing along (001) plane (Figure 2–5 and Figure 2–6). Overall, the structural features of CEL satisfy the essential criteria for elastic crystals with a specific bendable face: 1) interlocked isotropic packing without any slip planes, which prevents long-range molecular movement to avoid plastic deformation during flexing; and 2) presence of multiple dispersive interactions in orthogonal directions, which leads to “structural buffering” to allow reversibly stretched intermolecular interactions during elastic bending.¹⁵⁷, ¹⁵⁸, ¹⁶⁶
Figure 2–4. Molecular conformation of CEL represented by perpendicular planes

Figure 2–5. Intermolecular interactions pattern from two different orientations (a) and (b). Interaction within the dimer is highlighted in the gray color.
Figure 2–6. (a) 1-dimensional chain along $a$-axis. (b) Corrugated layered structure of CEL molecule, with yellow color for C-H···π interactions connecting the dimers.

An acicular CEL crystal could be easily and repeatedly bent (Figure 2–7a-i), when a load was applied to the major crystal face, (001)/(00-1), by a metallic needle. An arc was formed without crystal breakage (Figure 2–7b), which was rapidly reversed upon withdrawal of the applied load (Figure 2–7c). This elastic bending phenomenon was highly reversible, as it could be performed multiple times without any sign of fatigue. However, when the load was applied to the minor face (0-11) / (01-1) of the same crystal, the crystal broke before appreciable strain could be developed (See Figure 2–8). Therefore, the CEL crystal is a 1D elastic crystal, since elastic deformation occurs at only one face. In addition, CEL is a rare example of single component elastic crystal without halogen bonds. Thus, unlike what was thought before, the presence of halogen bonds is not a prerequisite for elastic organic crystals. 31
Figure 2–7. Screenshots of bending tests on the bendable face (001) / (00-1) of a CEL single crystal using forceps and a needle, showing four repeated cycles of bending and elastic recovery(a) – (i).

Figure 2–8. Screen shots of bending on CEL crystal minor and major faces – when bent on major (001) face, crystal is elastic; when bent on minor (01̅1) or (011) face, the CEL crystal is brittle.
The CEL crystal could be elastically bent to make a closed loop (Figure 2–9). The complete shape recovery from the loop reflects remarkable elastic flexibility. The elastic strain of the looped crystal, calculated using the Euler–Bernoulli beam-bending theory, is about 3.56% (Figure 2–10). This is significantly higher than the maximum elastic strain (< 0.5%) of most crystalline materials. The highest reported value of maximum elastic strain for known elastic polyhalogenated based molecular crystals is 2% for 2,3-Dichlorobenzylidine-4-chloroaniline. Thus, the elastic strain of CEL crystal is at least 78% higher than the previously known most elastically flexible organic crystal.

Figure 2–9. (a) - (c). Looping of elastic CEL crystal and its complete recovery.

Figure 2–10. Radius of curvature for maximally bent loop of CEL
The mechanical properties of the bendable major face, (001)/(00-1), of CEL crystals were characterized using nanoindentation (Figure 2–11), which provided a highly accurate measurement of the mechanical properties of molecular crystals by examining an essentially defect-free area of a sample.89, 138, 153-156, 182-185 The elastic modulus ($E$) and hardness ($H$) were 16.27 ± 0.43 GPa and 0.45 ± 0.02 GPa, respectively. This $E$ value is significantly higher (28%) than the highest $E$ reported for elastically bendable organic crystal ($N$-2,5-dichlorobenzylidine-4-iodo aniline).166 This is attributed to the presence of a large number of relatively weak hydrogen bonds (C–H⋯π, C–H⋯F, C–H⋯O, and C–H⋯N) between CEL dimers, which are fortified by strong N–H⋯N and N–H⋯O hydrogen bonds, in the CEL crystal compared to those in $N$-2,5-dichlorobenzylidine-4-iodo aniline, where only weak hydrogen bonds (C–H⋯Cl) and halogen bond (type I Cl⋯I) are present. Thus, incorporating both strong and weak intermolecular interactions in the crystal structure may be an effective strategy for designing highly elastic crystals with high stiffness.

![Figure 2–11. Nanoindentation characterization of the CEL crystal. a) Force-depth curve and b) 3D scan of indented area.](image)
All proposed qualitative mechanistic models predict an inhomogeneous molecular distribution in the lattice of bent elastic crystals.\textsuperscript{157, 158} The splaying of molecules and sliding of the molecular layers in the elastically deformed crystal affect the intermolecular interactions in the three domains, i.e., outer, inner, and central arc (\textbf{Figure 2–12}).\textsuperscript{186} In the outer arc, the pronounced weakening of the intermolecular interactions is expected due to the larger intermolecular separations due to tensile strain. However, intermolecular interactions are stronger in the inner arc due to the closer proximity among molecules resulting from the compressive strain, which may even introduce new intermolecular interactions. The structural arrangement in the neutral axis (middle part) of the bent crystal is the same as the straight crystal. Such inhomogeneous interactions in a bent crystal can be experimentally characterized by in-situ micro-Raman spectroscopy, which can measure the structural inhomogeneity in the elastically bent CEL crystal (\textbf{Figure 2–13}).\textsuperscript{186}

\textbf{Figure 2–12}. Schematic representation of the molecular rearrangement in the elastic crystal during the bending state.
Careful inspection of the Raman spectra in the three domains reveals broadening and shifting in bending modes of lattice vibration and aromatic C-H bonds.\textsuperscript{187} Thus, the crucial role of aromatic C-H bonds in the elasticity of CEL crystal (Figure 2–5) is confirmed. The 102.84 cm\textsuperscript{-1} band (Figure 2–14a) of a straight crystal corresponds to the strong lattice vibrations of CEL. Therefore, the changes in the peak indicate the prominence of the strong lattice vibration in strained domains. Strengthening the intermolecular interactions and the formation of multiple, new hydrogen bonds due to closer proximity of molecules in the compressed inner arc result in a significant broadening of the 102.84 cm\textsuperscript{-1} band. However, the same 102.84 cm\textsuperscript{-1} band in the outer arc shows a blue shift with broadening up to 113 cm\textsuperscript{-1} due to the fewer and weaker intermolecular interactions as the
molecules are farther apart. The aromatic C–H group of 4-methylphenyl and pyrazol ring of CEL are involved in the formation of several weak interactions, such as C–H⋯F, C–H⋯O, and C–H⋯N, which act as a structural buffer during elastic bending.

**Figure 2–14.** Raman spectra corresponding to the bent and straight crystals of CEL, with red and blue circles indicate the point of data collection (inner arc and outer arc respectively) a) lattice vibration, and b) aromatic symmetric in-plane bending δ(C–H) modes of inner and outer arc of a bent CEL single crystal, as well as in the non-strained straight state.

The bands at 1596 cm⁻¹ and 1613 cm⁻¹ of unbent crystal correspond to the symmetric in-plane bending δ(C–H) modes of aromatic C–H group (Figure 2–14b). The 1596 cm⁻¹ band shows broadening with increased intensity in the compressed inner arc due to the formation of multiple hydrogen bonds involving the aromatic C–H groups. However, the same band in the outer arc became sharper and blue-shifted due to weakening of the intermolecular interactions as well as strengthening of the C–H bonds. The band at 1613
cm\(^{-1}\) shows significant broadening in the compressed inner arc, which is expected due to strengthening of the interactions involving aromatic C-H group. The intensity of the 1613 cm\(^{-1}\) band is diminished with broadening in the outer arc. This effect is expected for structural modifications due to induced maximum strain and, hence, longer hydrogen bonds present in the outer arc. These observations validate the mechanistic bending model of elastic CEL crystal shown in Figure 2–12 and confirm the inhomogeneous spatial separations of molecules during elastic bending.

2.5 Conclusion

In summary, we report the first elastically bendable single component pharmaceutical crystal. Two major structural features responsible for the superior elasticity in CEL are: (1) Corrugated structure with criss-cross interlocked packing without slip planes, and (2) numerous weak and a few strong dispersive interactions in orthogonal directions. An interlocked packing without slip planes restricts long range molecular movement away from the equilibrium positions during elastic bending. Furthermore, the bending and nanoindentation experiments revealed a new strategy for designing highly elastic crystals by incorporating both strong and weak intermolecular interactions. The structural perturbations model was validated by a Raman spectroscopic analysis, which confirmed the inhomogeneous spatial separation of molecules corresponding to the expected changes in distances among molecules in different domains of bent crystal. A structural understanding of the mechanical elasticity in this single component pharmaceutical crystal can guide future designs of molecules for mechano-pharmaceutical
applications, including low-cost flexible smart functional microdevices for biomedical applications with advantageous mechanical properties.\textsuperscript{188}
Chapter 3.

Structural Insights into the Distinct Solid-state Properties and Interconversion of Celecoxib N-Methyl-2-Pyrrolidone Solvates

This chapter has been submitted as research article to Crystal Growth and Design.

3.1 Synopsis

In an effort to develop a tablet product of celecoxib by overcoming its poor physicochemical properties using a pharmaceutically acceptable solvate, we isolated two stoichiometric N-Methyl-2-Pyrrolidone (NMP) solvates of CEL, mono-NMP and di-NMP solvates. Here, we report the preparation, characterization, and structural origin of different properties of the two solvates, including a rare and complex heating induced phase transformation from di-NMP to mono-NMP solvate.
3.2 Introduction

Celecoxib (CEL, Figure 3–1, C₁₇H₁₄F₃N₃O₂S) is a non-steroidal anti-inflammatory drug that selectively inhibits COX-2 for the treatment of pain and inflammation associated with a number diseases, such as arthritis and osteoarthritis.¹¹⁹ As a BCS class II drug, the poor solubility of CEL in aqueous media leads to slow dissolution and, thus, delayed onset of action for pain relief. CEL is marketed as capsules, available in 100, 200 and 400 mg strengths, under the brand of Celebrex®. An issue with capsules is the larger size when compared to tablets of the same content, which leads to lower patient compliance because of the difficulty with swallowing. An improved drug product of celecoxib would be one that can release CEL more rapidly and in smaller size.

Among available options, crystal engineering is a promising approach to simultaneously improve solubility, dissolution, and tablet manufacturability.¹⁸⁹,¹⁹⁰ The most commonly employed crystal engineering techniques are cocrystallization,⁹⁶,¹¹¹ salt formation,¹⁰⁷ and hydrate formation.³⁸,¹⁹¹ A less well explored but still effective approach is the use of a pharmaceutically acceptable solvate.¹⁹² Organic solvents that can potentially be used for this approach include ethanol, dimethyl sulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP), propylene glycol (PG), ethanol and polyethylene glycol (PEG), as long as the consumed amount of the solvent accompanying the therapeutic dose of the drug remains safe.¹⁹³ An example of this approach is Crixivan, which is marketed as indinavir sulphate - ethanolate.¹⁹⁴ In addition to being a potential API solid form candidate, solvates are frequently used as intermediate crystalline forms during API synthesis for impurity rejection via crystallization.¹⁹²,¹⁹⁵
Known solid forms of CEL include polymorphs I, II, III, and IV, an amorphous form, sodium salt hydrates, some solvates, and various cocrystals with common cocrystal formers or other drugs such as venlafaxine and tramadol hydrochloride. The room temperature thermodynamically most stable Form III is used to manufacture commercial CEL capsules. The choice of capsule dosage form was partially attributed to its very poor flowability and high punch sticking propensity, which make the commercial manufacturing of tablet products challenging. In an effort to simultaneously solve these problems using an alternative solid form to enable the development of a CEL tablet formulation, we explored possible pharmaceutical solvates of CEL. The focus of this work was to characterize CEL mono-NMP and di-NMP solvates and provide molecular level understanding of their distinct properties based on an analysis of their crystal structures. An intriguing series of phase changes of the di-NMP solvate upon heating was captured and explained.

![Chemical structure](image)

**Figure 3–1.** Chemical structure of a) celecoxib (MW = 381.37) and b) NMP (MW = 99.13)
3.3 Materials and Methods

3.3.1 Materials

Celecoxib (Figure 3–1) was purchased from Aarti Drugs Pvt Ltd. (Mumbai, India). N-methyl-2-pyrrolidone (NMP, Figure 3–1, Pharmasolve™) was obtained from Ashland Global Specialty Chemicals Inc (Covington, Kentucky, USA). All materials were used as received.

3.3.2 Methods

3.3.2.1 Single Crystal X-ray Crystallography

Single crystals of CEL mono-NMP solvate were prepared from a saturated solution of CEL in NMP via slow evaporation at room temperature. Single crystals for structural determination of CEL di-NMP solvate were prepared by cooling a solution of 2.8 g of CEL in 5 mL of NMP from 60 °C to 3 °C.

Single crystal X-ray diffraction (SCXRD) of both CEL-NMP solvates was performed on a Bruker D8 Venture diffractometer (Bruker AXS Inc., Madison, Wisconsin) equipped with a Bruker PHOTON-II CMOS detector. Data collections were done at both 298 K and 100 K for di-NMP solvate with a MoKα radiation source (IμS 3.0 micro focus tube). Data integration was performed with the SAINT program, the SADABS program was used for scaling and absorption correction, and XPREP was used for space group determination and data merging. The crystal structure was solved using SHELXT-16 (Intrinsic Phasing) and refined using SHELXL-16, which were executed from the ShelXle graphical user interface. Hydrogen atoms were either placed geometrically from the
difference Fourier map or allowed to ride on their parent atoms in the refinement cycles. The disordered CF$_3$ group of CEL in the CEL-NMP 1:2 structure at 298 K was modeled, where two sets of three F atoms’ site-occupancy factors were constrained to add up to unity. To ensure a reasonable geometry, the C-F distances and the F-F distances were restrained to a common refined value of 1.33 Å and 2.14 Å, respectively. All F atoms were refined with anisotropic displacement parameters. The anisotropic displacement parameters in both disordered parts are modeled to be equivalent.

3.3.2.2 Preparation of NMP Solvate Bulk Powders

A slurry was prepared by suspending an excess amount of CEL solid (~ 2.5 g) in NMP (~ 5 mL) in a 20 mL scintillation vial for at least 10 min by a magnetic stirrer at a temperature of interest ranging from 3 °C to 45 °C. A 1:1 (w : w) seed mixture of the two solvates was then added. The desired temperature was maintained by means of a water-jacketed beaker connected to a temperature-controlled water bath. After at least 3 days, the solid was vacuum filtered in a Buchner funnel for 10 min, and then analyzed for solid forms by powder X-ray diffraction. Preliminary work showed that both solvates remained phase stable after vacuum filtration for 10 min. Such information allowed the determination of the thermodynamic stability of the two solvates in NMP at different temperatures, which was used to bracket the thermodynamic transition temperature between the two solvates.

3.3.2.3 Powder X-ray Diffraction (PXRD)

Powders were scanned over a 2θ range of 5°–35° on a wide-angle X-ray diffractometer (X’Pert PRO; PANalytical Inc., West Borough, MA) using Cu $K_a$ radiation (45 kV and 40 mA) at a step size of 0.0167° and a dwell time of 1.15 s. The simulated
PXRD patterns of CEL Form III, mono-NMP, and di-NMP solvates were calculated from respective 298 K single crystal structures using the Mercury software (v4.3.1 Cambridge Crystallographic Database Centre, Cambridge, UK).

### 3.3.2.4 Thermal Analyses

Thermal behaviors of samples were characterized using a Differential Scanning Calorimeter (DSC, Q1000; TA Instruments, New Castle, DE), heated from room temperature to 180 °C at a rate of 10 °C/min. A sample was placed in an aluminum pan which was then crimped with an aluminum lid. The cell constant for heat flow was calibrated using indium and the cell temperature was calibrated with indium and cyclohexane. The DSC cell was purged with helium gas at 25 mL/min. The maximum temperature used was below the degradation onset temperature of CEL. The DSC sample of each of the two CEL-NMP solvates was a single crystal with surface mother liquor removed using an absorbent tissue (Kimwipe). The weight loss upon heating of different solids was determined on a thermogravimetric analyzer (TGA, Q50, TA Instruments, New Castle, DE). Samples were placed in an open aluminum pan and heated to 300 °C at a rate of 10 °C/min under 60 mL/min nitrogen purge.

### 3.3.2.5 Hot Stage Microscopy (HSM)

Both NMP solvates were observed under a polarized light microscope (PLM) (Nikon Eclipse E200, Nikon, Tokyo, Japan) equipped with a DS-Fi1 microscope digital camera for capturing images and videos. Most crystal samples were dispersed in silicone oil between a glass slide and a cover glass; oil and cover glass were not used in few tests of di-NMP crystals. The samples were heated on a temperature stage (Linkam LTS 420,
Linkam Scientific Instruments, Ltd., Waterfield, U.K.) from room temperature to 180 °C at a rate of 10 °C/min and observed under PLM for on-line monitoring of thermo events.

### 3.3.2.6 Fourier Transform Infrared Spectroscopy (FTIR)

IR spectra of the powder samples were collected using a high resolution FT-IR spectrometer, equipped with a built-in iS50 diamond attenuated total reflection (ATR) component (Nicolet iS50; Thermo Scientific, Waltham, MA) and a DLaTGS detector. A total of 32 scans were collected and averaged for each spectrum. The range of IR spectra collected was 400-4000 cm\(^{-1}\) at a resolution of 2 cm\(^{-1}\). IR data were processed using OMNIC software (v9.2, Thermo Scientific, Waltham, MA).

### 3.3.2.7 Energy Framework Calculations

The pairwise intermolecular interaction energy was estimated using CrystalExplorer\(^{210}\) and Gaussian09\(^{178}\) with experimental geometry of CEL mono-NMP and di-NMP solvates.\(^{211}\) The hydrogen positions were normalized to standard neutron diffraction values before energy calculation using the CE-B3LYP electron densities model. The total intermolecular interaction energy between a given molecular pair was the sum of the electrostatic, polarization, dispersion, and exchange-repulsion components with scale factors of 1.057, 0.740, 0.871, and 0.618, respectively. Intermolecular interactions between two molecules with the closest inter-atomic distance of more than 3.8 Å were ignored. The interaction energies were graphically presented as a framework by connecting centers of mass of molecules with cylinders, with the radii proportional to the total inter-molecular interaction energies. The crystal packing topology was analyzed using a Python program.\(^{212}\)
3.4 Results and Discussion

3.4.1 Crystal Structures of CEL-NMP Solvates

Three methods were used to prepare solvate crystals during initial solvate screening for CEL solvates: slurry at room temperature, cooling from 60 °C to 3 °C and slow evaporation of saturated CEL solutions in NMP at room temperature. The powder X-ray diffraction (PXRD) patterns of the solids obtained from cooling and slurry methods were identical, which were different from the pattern of the solids prepared by slow evaporation (Figure 3–2). Since both PXRD patterns were different from the known CEL polymorphs, the formation of two new solid forms of CEL was indicated.

![Figure 3–2. PXRD of CEL-NMP solvates prepared using different methods, as compared to patterns of CEL-NMP mono- and di-solvates and Form III CEL calculated from corresponding single crystal structures](image)

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The solved single crystal structures (Figure 3–3) revealed the two forms are NMP solvates with CEL:NMP ratios of 1:1 (mono-NMP) and 1:2 (di-NMP). PXRD patterns of the powders from slow evaporation matched well with the calculated PXRD pattern of the mono-NMP solvate, while the crystals from cooling and slurry methods matched well with the calculated PXRD pattern of the di-NMP solvate (Figure 3–2).

**Figure 3–3.** ORTEP drawings of a) mono-NMP and b) di-NMP solvate structures collected at room temperature (298 (2) K). The CF$_3$ in both solvates and the NMP molecule in mono-NMP are disordered.

In the mono-NMP solvate crystal, two NMP molecules and two CEL molecules form a tetramer, which is stabilized by strong hydrogen bonds ($R_4^2(8)$, Figure 3–4) and serves as a building block for the CEL mono-NMP crystal. All NMP molecules are bonded with CEL via strong hydrogen bonds (Table 3–1), marked a1, a2, a1’, and a2’, where a1’ and a2’ are symmetrically equivalent to a1 & a2 in the tetramer (Figure 3–4a). In the di-NMP crystal, however, only half of the NMP molecules are strongly bonded with CEL to also form the tetramer through strong hydrogen bonds ($R_4^2(8)$, Table 3–1), marked b1, b2, b1’ and b2’ (Figure 3–4b). The other NMP molecules fill in space between the tetramers and do not form any strong hydrogen bonds with either CEL or other NMP molecules. It is noteworthy that this tetramer synthon is preserved in both mono-NMP and the di-NMP
solvate structures (Figure 3–4). The tetr...structu...NMP and di-NMP crystals are similar in terms of both molecular positions and strengths of hydrogen bonds (Figure 3–4 and Table 3–1). There is no significant difference in the conformation of CEL molecules. However, although the orientations of NMP molecules in the two tetr...forwards, the carbonyl oxygen on NMP is pinned to the same location in both structures (Figure 3–5) to act as the acceptor of the strong N-H⋯O hydrogen bond within the tetramer. Thus, the change in NMP orientation only influences the weak intermolecular interactions but does not affect the hydrogen bonding patterns of the tetramer. The hydrogen bond connectivity of the tetramer remains unchanged (Table 3–1).

Figure 3–4. Tetramer with strong hydrogen bonded CEL and NMP molecules in a) CEL mono-NMP solvate and b) CEL di-NMP solvate. Light blue dashed lines are strong hydrogen bonds labeled as 1, 2, 1’ and 2’ in both structures.
Table 3–1. Strong hydrogen bonds that stabilize the tetramer in mono-NMP and di-NMP solvate crystal structures.

<table>
<thead>
<tr>
<th></th>
<th>D-H⋯A (N-H⋯O)</th>
<th>d (H⋯A) (Å)</th>
<th>d (D⋯A) (Å)</th>
<th>∠(DHA) (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mono-NMP</td>
<td>a1, a1’</td>
<td>2.026</td>
<td>2.889</td>
<td>167.98</td>
</tr>
<tr>
<td></td>
<td>a2, a2’</td>
<td>2.043</td>
<td>2.883</td>
<td>161.48</td>
</tr>
<tr>
<td>di-NMP</td>
<td>b1, b1’</td>
<td>2.129</td>
<td>2.963</td>
<td>162.79</td>
</tr>
<tr>
<td></td>
<td>b2, b2’</td>
<td>1.973</td>
<td>2.889</td>
<td>165.18</td>
</tr>
</tbody>
</table>

Figure 3–5. Overlay of CEL mono-NMP solvate (red) and di-NMP solvate (light blue). The conformation of CEL is the same in the two structures, although the NMP in the tetramers adopted flipped orientations (black arrows). N-H⋯O hydrogen bonds between NH₂ of CEL and the carbonyl O atom of NMP molecules are retained.

3.4.2 Solid-state Properties of the Two CEL-NMP Solvates

The CEL-NMP monosolvate crystals obtained from slow evaporation were blocks, while that of the di-NMP solvate crystals from cooling were blocks with higher aspect ratios (Figure 3–6).
The mono-NMP solvate had a single endothermic event in DSC at a peak temperature of 141 °C, which is much lower than the peak melting temperature of Form III CEL (163 °C) (Figure 3–7a). Hot stage microscopy (HSM) data confirmed this thermal event as melting (Figure 3–8). No weight loss was recorded by TGA until the temperature reached ~120 °C (Figure 3–7b), which corresponds to the onset of mono-NMP solvate melting (Figure 3–7a). Therefore, the NMP molecules are tightly bound and could not escape the mono-NMP crystal before the melting occurs. The total weight loss did not reach the theoretical NMP content in mono-NMP crystals (20.64 wt %) until approximately 250 °C, which is more than 30 °C higher than the boiling point of NMP (202 °C). Since pure CEL liquid starts to evaporate at temperatures above 200 °C (Figure 3–7b), a part of the weight loss of mono-NMP solvate at 250 °C may be attributed to CEL. This means that NMP was not completely removed from the CEL mono-NMP melt at 250 °C. This is possible if NMP and CEL form an azeotrope in liquid phase because of the four strong N-H···O hydrogen bonds that stabilize the tetramers (Figure 3–4, Table 3–1).
Figure 3–7. Thermal properties of CEL Form III (black), CEL mono-NMP (red), and CEL di-NMP (blue). (a) DSC and (b) TGA (Dashed lines represent first derivative of TGA traces of the three solid forms).

Figure 3–8. CEL mono-NMP solvate heated using HSM without silicone oil at a rate of 10 °C/min.

The DSC thermogram of the di-NMP solvate shows two separate endothermic events. The first sharper endotherm corresponds to a step weight loss of about 10.33 %, corresponding to about 0.6 mol of NMP, up to ~110 °C. We attribute this to the removal of the more loosely bound NMP molecules from the di-NMP solvate lattice (Figure 3–4b) to form mono-NMP crystals (Figure 3–4a). The loss of approximately 0.6, instead of 1,
stoichiometric NMP gravimetrically (Figure 3–7b) happened because part of the NMP removed from the di-NMP crystals remained as liquid at temperatures below the boiling point of NMP (202 ºC). The liquid NMP dissolved some amount of CEL di-NMP and mono-NMP crystals. The dissolution process of mono-NMP is reflected by the curved baseline immediately following the first endothermic peak (Figure 3–7a), which would have been flat had dissolution not occurred. The second endotherm, which corresponds to the melting of mono-NMP, is about 10 ºC below the melting point of neat mono-NMP crystals. This observation is consistent with the depression of the melting point of mono-NMP by the presence of liquid NMP in the hermetically sealed DSC pan. Meanwhile, the shape of TGA curve above 120 ºC is similar to that of mono-NMP (Figure 3–7b), which is attributed to the evaporation of NMP followed by simultaneous evaporation of CEL and NMP above 200 ºC.

3.4.3 Phase Transformation of di-NMP upon Heating

To better understand and simulate the crimped DSC pan environment, the crystals used in the HSM study were covered with silicone oil when observed between the glass slip and the cover glass. Corresponding to the first endothermic peak for desolvation (50.9-70.2 ºC) in the DSC thermogram of the CEL di-NMP solvate, simultaneous crystal dissolution was seen because di-NMP crystals shrunk in size upon heating (Figure 3–9 b-g.). This is possible because, after leaving the di-NMP crystals at a temperature below its boiling point (202 ºC), NMP exists as a liquid and is in intimate contact with the remaining di-NMP crystals and sealed by silicone oil. As the temperature rises, the desolvation and dissolution processes occur simultaneously (Figure 3–9 b-g). The dissolution of di-NMP
crystals cannot be seen from the DSC curve because it coincided with desolvation of di-NMP (Figure 3–7a). To decouple the desolvation from the dissolution processes, we heated up the di-NMP crystals in HSM without submerging them in silicone oil, allowing evaporation of NMP. Under this condition, di-NMP single crystals converted to polycrystalline mono-NMP crystals in the temperature range of 50 - 70 °C, followed by melting of mono-NMP solvate (Figure 3–10). No dissolution was observed during the entire temperature range. This confirms that the desolvation of di-NMP in this temperature range indeed leads to the mono-NMP solvate, and that the crystal shrinkage of di-NMP in Figure 3–9b-g was due to dissolution in NMP in a sealed pan condition.

Figure 3–9. HSM images as CEL-NMP disolvate was heated at 10 °C/min and undergo a series of events: desolvation, dissolution, and melting.
Figure 3–10. CEL-NMP disolvate heated using HSM at a rate of 10 °C/min, without silicone oil. a) ~ b) no change from room temperature to 50 °C. c) desolvation at 70 °C, forming polycrystalline mono-NMP crystals (the foggy image is a result of the condensation of escaped NMP on the glass window of HSM), d) The mono-NMP remained stable up to at least 108 °C (image was clear again because the condensed NMP evaporated). e) and f) melting of mono-NMP crystals 125 – 133.3 °C.

It is important to point out that, during heating in the 50 - 70 °C temperature range, new mono-NMP crystals grew while the original di-NMP crystals shrunk (dissolved) until completely disappeared (Figure 3–9b-g). This suggests that the mono-NMP solvate has a lower solubility in NMP than di-NMP solvate. Hence, the mono-NMP solvate is thermodynamically more stable than the di-NMP solvate at this temperatures range. In summary, three events are happening within the first endothermic peak in the DSC thermogram of di-NMP solvate (Figure 3–9a) 1) desolvation of CEL di-NMP solvate to form mono-NMP solvate, 2) dissolution of disolvate into NMP, and 3) growth of CEL mono-NMP solvate crystals. With increasing temperatures above 70 °C, (Figure 3–9g, h).
where the CEL concentration in NMP is slightly higher than the saturation solubility CEL-NMP monosolvate, only subtle growth of few CEL-NMP crystals are observed, while the majority of CEL-NMP 1:1 crystals remains unchanged without undergoing melting, dissolution or desolvation. After the temperature reaches 79.5 °C (Figure 3–9h), the solubility of CEL-NMP monosolvate has ramped to the point where the CEL concentration in NMP is below its solubility. Thus, dissolution of the mono-NMP solvate started, Figure 3–9 i-j) where CEL-NMP monosolvate crystals become smaller in size. This dissolution process continues all the way to the onset temperature of CEL-NMP monosolvate melting, which has an onset of and a peak melting temperature of 120.3 °C, and 141.0 °C, respectively, for clean monosolvate (Figure 3–7a, red DSC trace). For disolvate crystals that had undergone desolvation to monosolvate, however, a depressed melting phenomenon prelude. Figure 3–9k) shows the beginning of melting for CEL-NMP monosolvate, which completely melted at 133.4 °C (Figure 3–9l). This depressed peak melting temperature was the result of the presence of NMP liquid surrounding the CEL-NMP monosolvate crystals. To sum up, two events happened from Figure 3–9g) to l): 1) dissolution and 2) melting of CEL mono-NMP solvate crystals. The combination of these two events explained the declining disolvate DSC baseline after the first endotherm (Figure 3–7a), as well as the depressed melting peak following the declining baseline. This is an excellent example that demonstrates the benefit of HSM in aiding the clear interpretation of complex thermal events registered by DSC. The DSC trace marked with thermal events captured by HSM is shown in Figure 3–11.
3.4.4 Thermodynamic Stability Relationship of Two Solvates

The mono-NMP solvate was suggested to be more stable at higher temperatures by the HSM data under a non-equilibrium condition (heated at 10 °C/min). To better understand the thermodynamic stability relationship between the two solvates, we performed competitive slurry experiments, where a mixture of the two crystalline phases was allowed to equilibrate at different temperatures for a period of 72 hours, and the equilibrium solid phases were then harvested and analyzed by powder X-ray diffraction (Figure 3–12. Such data bracketed the transition temperature ($T_t$) between the two solvates.
to be $35.5 \, ^\circ\mathrm{C} < T_t < 36 \, ^\circ\mathrm{C}$. The di-NMP solvate is more stable below $T_t$, while the mono-NMP solvate is more stable above $T_t$ (Figure 3–12).

**Figure 3–12.** PXRD patterns of equilibrium solids obtained from slurry experiments and comparisons with CEL-NMP calculated patterns from room temperature single crystal structures.

### 3.4.5 Physical Stability on Storage

Although the di-NMP solvate is more stable in NMP solution at room temperature (Figure 3–12), CEL di-NMP solvate undergoes partial desolvation to form mono-NMP solvate at room temperature when exposed to open air for 7 days or house vacuum overnight. In contrast, the mono-NMP solvate is stable in open air for up to 12 months. A
clear explanation of the drastically different stability of the two solvates requires an analysis of their crystal structures.

3.4.6 Structural Characteristics of the Two NMP Solvates

In addition to the strong hydrogen bonding interactions within each tetramer building block in both solvates (Table 3–1), there are many weak interactions that help to fortify the tetramer (Figure 3–136a and Figure 3–13a). In the mono-NMP solvate, the tetramers interact with each other only via weak hydrogen bonds in all directions (Figure 3–13). In the di-NMP solvate, a half of the NMP molecules strongly interact with CEL to enable the formation of tetramer synthon; while other NMP molecules interact with the tetramers through weak hydrogen bonds (Figure 3–14). A noticeable common structural feature of both solvates is that the tetramers form a 1-D chain running along the crystallographic b-axis. The stability of NMP molecules in the two solvate crystals is quantitatively assessed using the pair-wise interaction energies graphically presented as the energy frameworks, in which the tetramers are clearly visible as parallelograms in both structures (Figure 3–15). The inter-tetramer interaction strength is weaker than intra-tetramer interactions for both solvate crystals. The energy frameworks of mono-NMP (Figure 3–15a) and di-NMP (Figure 3–15b) solvates match well with the hydrogen bond networks present in the two crystals (Figure 3–13 and Figure 3–14, respectively). There are also some weak interactions along b-axis to stabilize the 1-D chain in both solvates (Figure 3–13a & Figure 3–14b, Figure 3–15). For the mono-NMP solvate, all NMP molecules are part of the rigid tetramers and they are arranged in staggered positions to form an irregular zig-zag solvent spiral running along the b axis (Figure 3–16). The high
energy barrier to removing NMP molecules explains the stability of CEL mono-NMP solvate.

Figure 3–13. Weak interactions in CEL mono-NMP solvate structure: a) intra-tetramer and inter-tetramer to form 1-D chain along b-axis; b) inter-tetramer along a-axis; c) between tetramers along c-axis. d) viewed into a-axis.
Figure 3–14. Weak interactions in CEL di-NMP solvate a) Intra-tetramer along c-axis; b) along b-axis; c) along a-axis; and d) view down a-axis.

Figure 3–15. Energy framework of (a) mono-NMP viewed down a axis and (b) di-NMP viewed down b axis. The pink parallelograms highlight a tetramer in each of the frameworks.
Figure 3–16. Mono-NMP solvate crystal structure viewed along (a) $b$ axis and (b) $a$ axis, (c)–(e) zig-zag void channels housing the strongly-bound NMP molecules

In the di-NMP solvate crystals, consistent with the weak hydrogen bonding network of di-NMP solvates (Figure 3–14d), the NMP molecules outside of the tetramers fill channels along the $b$-axis with weak interactions among each other (Figure 3–15b) and the 1-D chain of tetramers. These weak interactions correspond to weak overall interaction energy (Figure 3–15b). The loosely bound NMP molecules in di-NMP solvate structure form channels along both the crystallographic $a$ and $b$ axes (Figure 3–17), which allows the weakly interacting NMPs to escape easily. This accounts for the instability of di-NMP solvate crystals in air, vacuum, and under heat. This distinct interaction strengths of the tightly bound and loosely bound NMP also explain the observation that the di-NMP solvate
always desolvate to form the mono-NMP solvate instead of CEL under different conditions, unlike in some other disolvates and dihydrates.\textsuperscript{214, 215}

**Figure 3–17.** Packing of di-NMP solvate crystal a) down the $b$-axis and b) down the $a$-axis. In the top row, NMP molecules as part of the framework are colored blue, blue and red rectangles/circles highlight the channels along the $b$- and $a$-axis, respectively; loosely bound NMP molecules are colored red. In the bottom row, the loosely bound NMP molecules are deleted to show the channels.

The structure and energy framework of the di-NMP solvate also explains the ease of transformation from di-NMP to crystalline mono-NMP solvates without sacrificing crystallinity (**Figure 3–9, Figure 3–10**), since the escape of the loosely bound NMP from the channels does not affect the strongly bound 1-D chains of tetramers along the $b$-axis (**Figure 3–17 and Figure 3–18**). Compared to the mono-NMP solvate, the unit cell of the di-NMP solvate has a significantly decreased $\beta$ angle, an expanded $c$-axis, and a larger unit cell volume (**Figure 3–18, Table 3–2**), as a result of inserting loosely-bound NMP molecules in between the rigid tetramers to fill the channels.
**Figure 3–18.** Comparison of unit cell parameters and packing for a) CEL mono-NMP solvate and b) di-NMP solvate (loosely bound NMP molecules removed) down the $b$-axis.

**Table 3–2.** Crystallographic information of CEL mono-NMP and di-NMP solvates

<table>
<thead>
<tr>
<th></th>
<th>Mono-NMP solvate</th>
<th>Di-NMP solvate*</th>
<th>Di-NMP solvate*</th>
</tr>
</thead>
<tbody>
<tr>
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<td>298K</td>
<td>100K</td>
</tr>
<tr>
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<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
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<td>$P_2_1/c$</td>
<td>$P_2_1/c$</td>
</tr>
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<td></td>
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<td>11.8677(5)</td>
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<tr>
<td>$b$ (Å)</td>
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<td>8.5932(7)</td>
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<tr>
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<td>$\gamma$ (°)</td>
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<td><strong>R</strong></td>
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<td>0.0738</td>
<td>0.0527</td>
</tr>
</tbody>
</table>

*Note that the unit cell parameters for both 298K and 100K di-NMP solvate structures were transformed to the non-standard setting of monoclinic $P_2_1/c$ space group for the ease of crystal structure comparison with the mono-NMP solvate. However, their CIFs are reported in the standard unit cell settings.*
3.4.6.1 Spectroscopic Evidence for the Structural Differences Between Two CEL-NMP Solvates

The different hydrogen bonding scenarios of the two groups of NMPs in CEL di-NMP solvate are also revealed by the infrared (IR) spectra (Figure 3–19). The IR spectra of Form III and the two NMP solvates have peaks at 1154, 1234 and 1344 cm\(^{-1}\) in common, which correspond to stretching of functional groups of characteristic of CEL molecule, i.e., O=S=O asymmetric stretch, the CF\(_3\) group stretch, and the O=S=O symmetric stretch, respectively. Compared to the IR spectra of two solvates, the main difference of CEL Form III is the peak broadening of O=S=O asymmetric stretch at 1154 cm\(^{-1}\). This is attributed to the existence of both strong and weak hydrogen bonds with the O=S=O oxygen in Form III as a proton acceptor,\(^{216}\) while the same oxygen atoms only involve weak hydrogen bonds in both NMP solvates. The signature peak for NMP molecule in both mono-NMP and di-NMP solvates is at 1650 cm\(^{-1}\), representing the associated carbonyl (C=O) group of NMP, which is absent in the CEL form III spectrum (Figure 3–19, box in gray). The O atom on this C=O group is the acceptor for the strong N-H⋯O hydrogen bond which is required to form the tetramer. Since this tetramer is present in both mono-NMP and di-NMP structures but not in Form III, the peak at 1650 cm\(^{-1}\) is present in spectra of the two solvates but not of Form III. The peak unique to the di-NMP solvate resides at 1679 cm\(^{-1}\) (Figure 3–19). This corresponds to the stretching motion of unbound carbonyl (C=O) group, in contrast to the 1650 cm\(^{-1}\) peak for the bound carbonyl group. This is consistent with the fact that, in addition to the strongly hydrogen bonded NMP molecules in the mono-NMP solvate, weakly hydrogen bonded, channel-filling NMP molecules also exist as another type of NMP in di-NMP solvate crystals (Figure 3–4, Figure 3–15). Thus, the
FTIR spectrum analysis corroborates the analysis of intermolecular interactions based on crystal structure visualization and energy framework.

Figure 3–19. FTIR spectra of CEL Form III, CEL mono-NMP solvate and di-NMP solvate crystals

3.5 Conclusions

In this study, two stoichiometric (1:1 and 1:2) NMP solvates of CEL were prepared and fully characterized. The di-NMP solvate undergoes a complex phase transformation process when heated, including desolvation, dissolution of the di-NMP solvate, and growth, dissolution and melting of the mono-NMP solvate. This is explained clearly based on complementary thermal analytical techniques. The different stability and interconversion of mono- and di-NMP solvates of CEL were understood based on their crystal structures. The understanding of very different roles of solvent molecules in the two NMP solvates of CEL serves as a good example of characterizing pharmaceutical solvates.
and hydrates using complementary techniques to fully understand their structure-property relationship, which is important for successful drug development where such solid forms are pertinent.
Chapter 4.

Direct Compression Tablet Formulation of Celecoxib Enabled by A Pharmaceutical Solvate

This chapter is in preparation as research article.

4.1 Synopsis

Celecoxib, an anti-inflammatory drug for pain and arthritis, is currently only available in capsule form. To reduce the onset time for a faster action and to lower the manufacturing cost, the tablet dosage form is more preferred. However, the commercial celecoxib (Form III) is not suitable for direct compression (DC) tablet manufacture due to its poor flow, low bulk density, and tablet lamination. In this work, we overcome these challenges using a pharmaceutically acceptable dimethyl sulfoxide (DMSO) solvate of celecoxib. Aided with the DMSO solvate, an acceptable DC tablet formulation was successfully developed to manufacture tablets containing 200 mg celecoxib, with satisfactory manufacturability, disintegration, and in vitro dissolution performance.
4.2 Introduction

Celecoxib (CEL, Figure 4–1) is a blockbuster NSAID drug for treating arthritis, available as capsules in the strengths of 100, 200 and 400 mg. The current capsule products on the market contain the most thermodynamically stable form at room temperature, Form III of CEL, which is micronized and wet-granulated with excipients to enhance flow for satisfactory capsule-filling.\(^4\) Compared to capsules, tablets are preferred due to the lower manufacturing cost and short onset time, which is especially important for pain medications, such as CEL. However, although a fixed dose combination product of CEL, Consensi\(^\circledR\) (2.5/5/10 mg amlodipine and 200 mg celecoxib) tablets, was approved by the FDA in 2018, no tablet product of only CEL is available. A tablet formulation containing wet-granulated CEL granules was patented, but never marketed.\(^4\) For tablet manufacturing, the wet granulation process is expensive and inefficient compared to the direct compression (DC) process, which only requires mixing and compression.\(^8, 189\) However, Form III CEL is unfit for the DC process because of its poor powder flowability,\(^124\) low bulk density,\(^123\) poor tablet quality (lamination tendency), and high punch sticking propensity.\(^117, 133, 207\)

![Molecular structures of celecoxib and DMSO](image)

**Figure 4–1.** Molecular structures of celecoxib (MW 381.37) and DMSO (MW 78.13).
Crystal engineering is an effective technique for overcoming problematic physicochemical and mechanical properties of active pharmaceutical ingredients (APIs). Common crystal engineering approaches include cocrystallization, salt formation and hydrate formation. A less well explored crystal engineering approach is the formation of pharmaceutically acceptable solvates. Crixivan (indinavir sulphate - ethanolate) is one of few examples of marketed products using an API solvate crystal form.

CEL has four known polymorphs (Forms I to IV), an amorphous form, sodium salt hydrates, several solvates, and cocrystals with both common cocrystal formers and drugs. In this work, we aimed to develop a DC tablet formulation of CEL by simultaneously improving the flow, bulk density, and mechanical properties of CEL using a pharmaceutically accepted dimethyl sulfoxide (DMSO, Figure 4–1) solvate of CEL (CEL-DMSO) for the following reasons: 1) DMSO is a class 3 solvent categorized by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) with an exposure limit of 50 mg/day, which is higher than the expected DMSO intake of 34 mg/day along with 200 mg of CEL; 2) CEL-DMSO crystalizes in block shape, which is expected to exhibit better flowability, higher bulk powder density, and easier die filling than the needle shaped CEL; 3) DMSO, being a polar solvent commonly used to dissolve hydrophobic drugs, may improve the dissolution rate of CEL; and 4) good physical stability of CEL-DMSO.
4.3 Materials and Methods

4.3.1 Materials

CEL (Form III) was purchased from Aarti Drugs Pvt Ltd. (Mumbai, India) and used as received. DMSO was obtained from Alfa Aesar (Tewksbury, MA, USA). Fused silica (M-5P, Cab-o-sil; CABOT Corporation, Tuscola, IL, USA), microcrystalline cellulose (MCC, Avicel PH102, FMC Biopolymer, Philadelphia, PA), mannitol (Pearitol 100SD, Roquette, Lestrem, France), crospovidone (Kollidon CL-F, BASF, Ludwigshafen, Germany), sodium lauryl sulphate (Kollidon SLS, BASF, Ludwigshafen, Germany) and magnesium stearate (Mg St, Mallinckrodt, St Louis, MO) were obtained from respective suppliers. Cab-o-sil was de-agglomerated by passing through a #30 mesh sieve before use. All other materials were used as received. Celebrex® capsules (200 mg CEL strength) were purchased from Pfizer Pharmaceuticals LLC and used as a reference in dissolution testing.

4.3.2 Methods

4.3.2.1 Single Crystal X-ray Crystallography

Single crystals of CEL-DMSO were obtained from slow evaporation of a saturated solution of CEL in DMSO at room temperature. Single crystal X-ray diffraction (SCXRD) was performed on a Bruker D8 Venture diffractometer (Bruker AXS Inc., Madison, Wisconsin) equipped with a MoKα radiation source (IμS 3.0 micro focus tube) and a Bruker PHOTON-II CMOS detector. Full sets of crystal structure data were collected and solved at both 298 K and 100 K. Data integration was performed with the SAINT program. Scaling and absorption correction was done via the SADABS program, and space group determination and data merging was done with XPREP. The crystal structure was solved.
and refined using SHELXT-16 (Intrinsic Phasing), which was executed through ShelXle graphical user interface. Hydrogen atoms were placed either geometrically from the difference Fourier map or allowed to ride on their parent atoms in the refinement cycles. The CF$_3$ group of CEL and the DMSO molecule in the 298 (K) CEL-DMSO structure were disordered. The CF$_3$ group disorder was modeled as two sets of three F atoms with site-occupancy factors constrained to sum to unity. To ensure a reasonable geometry, the C-F distances were restrained to a common refined value of 1.33 Å. All F atoms were refined with anisotropic displacement parameters, where the anisotropic displacement parameters are modeled to be equivalent in both disordered parts. The disorder of DMSO molecule was modeled as two sets of DMSO molecules, with site-occupancy factors constrained to sum to unity. The anisotropic displacement parameters of the bonds in two sets of DMSO molecules were restrained to be equal.

4.3.2.2 Preparation of Bulk CEL-DMSO Powder

For tablet formulation development, a batch of CEL-DMSO was prepared by a slurry method, i.e., suspending an excess amount of CEL solid (~ 80 g) in DMSO (~ 30 mL) in a 100 mL beaker by a magnetic stirrer at room temperature. After 4 days, the solids were collected via vacuum filtration for 10 min in a Buchner funnel. The surface residual solvent was washed away by briefly spraying deionized water on to the powder in Buchner funnel during vacuum filtration. The powder was then dried in a vacuum oven with air flowing on the top of the powder for 3 days. The washing and drying did not cause detectable phase impurity of CEL-DMSO by powder X-ray diffraction, hot stage polarized light microscope and differential scanning calorimetry.
4.3.2.3 Powder X-ray Diffraction (PXRD)

Powders were scanned over the 2θ range of 5°–35° on a wide-angle X-ray diffractometer (X’Pert PRO; PANalytical Inc., West Borough, MA) equipped with Cu $K_{\alpha}$ radiation (45 kV and 40 mA). A 1/16 ° divergence slit and a 1/8 ° anti-scattering slit were used on the incident beam side. The anti-scattering slit on the diffracted beam side was 5.5 mm (X’ Celerator). Data collection was done at a step size of 0.0167° and a dwell time of 1.15 s. The simulated PXRD patterns of CEL-DMSO and CEL (Form III) were calculated from corresponding single crystal structures solved at 298 K. $^{216}$ using the Mercury software (v4.3.1 Cambridge Crystallographic Database Centre, Cambridge, UK).

4.3.2.4 Thermal Analyses

Thermal behaviors of samples were characterized using Differential Scanning Calorimetry (DSC, Q1000; TA Instruments, New Castle, DE). Samples were placed in aluminum pans and then crimped with aluminum lids. Samples were heated from room temperature to 180 °C, which is below the degradation onset temperature of CEL, $^{32}$ at a rate of 10 °C/min. The cell constant for heat flow was calibrated using indium and the cell temperature was calibrated with indium and cyclohexane. The DSC cell was purged with helium gas at 25 mL/min. For CEL-DMSO, the sample for DSC analysis was a small piece cut from larger single crystals obtained from slow evaporation with surface mother liquor removed using an absorbent tissue (Kimwipe®). The weight loss upon heating of CEL-DMSO was obtained using a thermogravimetric analyzer (TGA, Q50, TA Instruments, New Castle, DE). Samples were placed in an open aluminum pan and heated to 300 °C at a rate of 10 °C/min under 60 mL/min nitrogen purge.
4.3.2.5 **Hot Stage Microscopy (HSM)**

CEL-DMSO crystals were examined using a polarized light microscope (PLM) (Nikon Eclipse E200, Nikon, Tokyo, Japan) equipped with a temperature-controlled sample stage (Linkam LTS 420, Linkam Scientific Instruments, Ltd., Waterfield, U.K.) and a DS-Fi1 microscope digital camera for image-capturing. The crystals were observed while being heated from room temperature to 180 °C at a rate of 10 °C/min without silicone oil.

4.3.2.6 **Nanoindentation of CEL-DMSO Single Crystals**

Nanoindentation experiments were performed on a TI-980 Triboindenter (Hysitron Inc., Minneapolis, MN, USA) system using a standard Berkovich diamond indenter tip. A fused silica sample with known elastic modulus ($E$) of 69.9 GPa and hardness ($H$) of 9.2 GPa was used to calibrate the area function of the Berkovich tip. The crystal was fixed on a glass slide using Super glue (Scotch, 3M, Maplewood, MN), which was then mounted on the sample puck by pulling vacuum. Before each measurement, the crystal surface was scanned to generate the topographical images of 20 × 20 µm size. Only surfaces with an average roughness less than 20 nm were used for indentation. The major crystal face (002) of two CEL-DMSO crystals was indented under force control mode, with 5 mN/s loading and unloading rate. The indenter was held at a peak load of 5 mN for 20 s. A total of 15 indents were made to calculate $E$ and $H$ using the Oliver-Pharr method, assuming a Poisson’s ratio of 0.3. The 20 µm × 20 µm area containing the indentation mark was scanned again after the indentation to gain more information.
4.3.2.7 Nanocoating of Microcrystalline Cellulose

The flow properties of MCC can be profoundly improved by silica nanocoating using a conical mill (Model U3, Quadro Engineering Corp., Waterloo, OT, Canada). Before nanocoating, 0.5 wt% fumed silica was first blended with 50 g MCC with a spatula before the mixture was passed through a #100 mesh sieve (150 μm opening, US Standard Sieve). The mixture was then passed through the comill screen with round 0.995 mm openings (7B039R03125) and a type I impeller (7B16121004, sharp edge forward, corresponding to more scraping motion during milling) at 2200 rpm. A total of 20 comilling cycles were done to ensure uniform coating.

4.3.2.8 Powder Flow Property Assessment

The flow properties of powder with comparable particle sizes were characterized using a shear cell (RST-XS, Dietmar Schulze, Wolfenbüttel, German), with a 10 mL cell at 3kPa preshear normal stress. The normal stresses for shear testing were 230, 1000, 1500, 2000, and 2500 Pa (230 method). Shear failure stress at each normal stress was used to construct a yield locus, from which the unconfined yield strength \(f_c\) and major principal stress \(\sigma_n\) were obtained by drawing Mohr’s circles. Flowability index \(ff_c\) was calculated using Eqn. 4–1. All flow tests were all triplicated, with the relative humidity during measurements ranged 39% ~ 42%.

\[
ff_c = \frac{\sigma_n}{f_c}
\]  
Eqn. 4–1
4.3.2.9 Preparation of Tablet Formulations

All formulation components, except MgSt, were first mixed roughly in an amber glass bottle with spatula, and then using a Turbula mixer (Glen Mills Inc., Clifton, NJ) at 49 rpm for 10 minutes. MgSt, the lubricant, was added only after this for another 5-minute mixing by Turbula at 49 rpm to avoid over-lubrication.

4.3.2.10 Tabletability Profiling

Tablets of each formulation were made on a compaction simulator (Styl’ One Evolution, MedelPharm, Beynost, France), simulating a Korsch XL100 press. To attain the same dose of 200 mg per tablet, tablet weights were 600 mg for CEL-DMSO formulations, and 500 mg for CEL formulations, made using 11.28 mm and 9.53 mm flat face tooling, respectively. Different tooling sizes were used to maintain a suitable diameter to thickness ratio of 2 - 2.32. A dwell time of 30 ms (16,320 tablets/hour) was used to make tablets for expedited friability, disintegration time, and dissolution tests for formulations containing CEL-DMSO. For comparing tabletability profiling, flat face round tooling (8 mm diameter) was used to compress 200 mg tablets using a dwell time of 100 ms, since tablets from the CEL Form III formulation severely laminated at shorter dwell times.

The tabletabilities of the pure CEL Form III and CEL-DMSO were characterized using 8 mm flat face round tooling with external lubrication on a Materials Testing Machine (ZwickRoell 1485, Ulm, Germany). The compaction pressures for tabletability profiles ranged 12 - 370 MPa.
Tablet tensile strength was characterized by breaking the tablets diametrically using a texture analyzer (TA-XT2i, Texture Technology Corps, NY, equipped with a 30 kg load cell, trigger force of 5 g. The test speed was 0.01 mm/s. Tablet tensile strength ($\sigma$) was calculated from breaking force, $F$, tablet diameter, $D$, and thickness, $h$ using Eqn. 4–2.  

$$\sigma = \frac{2F}{\pi Dh}$$  

Eqn. 4–2

4.3.2.11 True Density Determination

Accurate powder true density, $\rho_t$, is crucial for accurate analysis of powder compaction properties. Helium pycnometry is generally used to measure powder $\rho_t$ for anhydrous or non-hygroscopic materials. For formulations containing MCC, $\rho_t$ by helium pycnometry is overestimated because of the release of water in MCC during measurement. Hence, we obtained the true density using the Sun method by non-linear fitting of Eqn. 4–3 to tablet density ($\rho$) versus compaction pressure ($P$) data, Using Origin 2020 (OriginLab Corp, Northampton, MA).

$$P = \frac{1}{C} \left[ (1 - \varepsilon_c) - \frac{\rho}{\rho_t} - \varepsilon_c \ln \left( \frac{1 - \rho}{\rho_t \varepsilon_c} \right) \right]$$  

Eqn. 4–3

Here, $1/C$ is a parameter relating to material plasticity, where the lower $1/C$ value corresponds to higher material plasticity, and $\varepsilon_c$ is the critical porosity at which the powder starts to gain rigidity and mechanical strength.
4.3.2.12 Powder Bulk Density Measurement

Each powder (∼5 mL) was poured in a 10mL graduated cylinder and its weight was recorded. The bulk density is recorded as the weight divided by volume (g/cm³).

4.3.2.13 Compressibility and Compactibility

Compressibility describes the relationship between tablet porosity (ε) and pressure. For individual tablets, ε was calculated from ρ and ρt according to Eqn. 4–4. The ρ was calculated from tablet weight, thickness, and diameter of tablets.

\[ ε = 1 - \frac{ρ_{tablet}}{ρ_{true}} \]  
Eqn. 4–4

Compactibility describes the relationship between σ and ε, which was fitted with equation Eqn. 4–5, when possible. Here, σ₀ is the tensile strength at zero porosity, and b is an empirical constant. σ₀ can be used to describe the bonding strength of materials.

\[ σ = σ₀e^{-bε} \]  
Eqn. 4–5

4.3.2.14 In-die Elastic Recovery

In-die elastic recovery of tablets made with compaction simulator is calculated using Eqn. 4–6, where h and h₀ are tablet thicknesses at maximum and zero compaction pressures, respectively.

\[ ER = 100(h - h₀)/h₀ \]  
Eqn. 4–6
4.3.2.15 Intrinsic Dissolution Rate

The intrinsic dissolution rate (IDR) was determined using the rotating disc method. Powder of CEL or CEL-DMSO were compressed with a 2000-lb force on a Carver Press (Wabash, IN, USA), in a custom-made stainless-steel die and punch for 2 min to obtain a pellet (6.39 mm diameter) for dissolution experiments. This eliminates possible particle size effects that affect powder dissolution. While rotating at 200 rpm, the die and pellet assembly was submerged into a 200 mL of pH 12 dissolution medium of tribasic sodium phosphate buffer containing 1% sodium lauryl sulfate at 23.5 ºC in a water-jacketed beaker. A UV–vis fiber optic probe (Ocean Optics, Dunedin, FL) was used to continuously monitor the UV absorbance of the solution at λ = 252 nm. The concentration-time profiles of Celecoxib were obtained from the absorbance data and a previously established calibration curve. All IDR experiments were triplicated.

4.3.2.16 Tablet Disintegration Time

Three tablets of CEL-DMSO formulation (600 mg) were made at ~7 kN using the Styl’ One compaction simulator at 30 ms dwell time. Tablet disintegration time (DT) was determined using a disintegration tester (DJ-1, Tianjin Guoming Medical Equipment CO., LTD). Tablets were immersed into a beaker containing 800 mL deionized water, with temperature maintained at 37°C by a circulating water bath.

4.3.2.17 Expedited Friability Test

Tablet friability profiles were determined using an expedited friability method. Coded tablets prepared under different compaction forces were weighed and loaded into a friabilator (Model F2, Pharma Alliance Group Inc., Santa Clarita, CA) at 25 rpm for 4 min
(corresponding to 100 drops). The final weight of each tablet was noted, and percentage weight loss of each tablet was plotted against compaction force. The range of compaction force corresponding to less than 1% tablet weight loss was identified from the friability plot.

4.3.2.18 Dissolution of CEL Tablets and Capsules

Dissolution performance of formulated CEL-DMSO tablets and commercial CEL capsules (Celebrex®, 200 mg) was tested in 500 mL of the FDA recommended pH 12 medium of tribasic sodium phosphate buffer with 1% SLS at 37°C in a water-jacketed beaker controlled by water bath with circulating water. An overhead paddle stirrer rotating at 50 rpm was used. The concentration of dissolved CEL was continuously monitored by a UV–vis fiber optic probe (Ocean Optics, Dunedin, FL) at absorbance of $\lambda = 252$ nm. All dissolution experiments were triplicated.

4.4 Results and Discussion

To develop a tablet formulation of CEL with improved manufacturability, the poor flow, low bulk density and high lamination propensity of CEL (Form III) need to be tackled effectively. It was achieved in this work through forming a DMSO solvate of CEL. A batch of CEL-DMSO powder with particle size similar to that of as-received CEL was prepared for use in formulation (Figure 4–2).
Figure 4–2. Particle size of a) CEL-DMSO powder and b) CEL Form III as-received powder. The scale bar is 50 μm in both pictures. Since the shape of CEL Form III and CEL-DMSO crystals are different, while CEL Form III is in needle shape with high aspect ratio, it was made sure that the longest dimension of CEL-DMSO and CEL Form III crystals match.

4.4.1 Physicochemical Properties of CEL-DMSO Solvate

CEL-DMSO is a 1:1 solvate (space group of P2₁/c) that crystallizes into hexagonal block shaped crystals (Figure 4–3). When heated, CEL-DMSO solvate is very stable, which does not undergo desolvation below its melting point. The DSC thermograph (Figure 4–4a) shows a single sharp endothermic peak (onset temperature of 105.4 ± 0.02°C, heat of fusion of 77.06 ± 1.01 J/g, n=3). The endothermic event in DSC were confirmed by hot stage microscopy studies to be melting of crystals ranged 103 °C - 111°C (Figure 4–5), matching well with the range of the endothermic peak in DSC thermogram.
Figure 4–3. a) Block morphology of CEL-DMSO solvate crystals and ORTEP diagrams of CEL-DMSO single crystal structure at b) 298 K and c) 100 K. The DMSO molecule and the CF$_3$ group on CEL are disordered only in 298 K structure.

Figure 4–4. a) DSC and b) TGA thermographs of CEL-DMSO solvate crystals. The dashed lines in b) represents the first derivative of weight signal.
Figure 4–5. Polarized light microscope images of CEL-DMSO single crystal as it is heated using a hotstage

The absence of desolvation before melting suggests a higher stability of CEL-DMSO than many other solvates and hydrates in the literature, which routinely lose solvent molecule before melting. Thus, CEL-DMSO displays adequate physical stability important for pharmaceutical tablet formulation development. The high stability of CEL-DMSO is attributed to the fact that two CEL molecules and two DMSO molecules form a tetramer (Figure 4–6) via very strong hydrogen bonds ($R_4^2(8)$ & Table 4–1). This tetramer is the basic building block of the CEL-DMSO crystal structure. Each tetramer is stabilized by four strong hydrogen bonds, labeled 1, 2, 1’ and 2’, where 1’ and 2’ are symmetrically equivalent to 1 and 2 in the tetramer (Figure 4–6, Table 4–1). The DMSO molecules occupy staggered positions in zig-zag channels of the CEL-DMSO crystal lattice, meanwhile stabilized by strong interactions with CEL molecules (Figure 4–7). These structural features all lay the foundation of the exceptional stability of this CEL-DMSO
solvate. The TGA curve shows that the total weight loss did not reach the theoretical DMSO content in CEL-DMSO crystals (17 wt %) until approximately 230 °C (Figure 4–4b), which is about 40 °C higher than the boiling point of DMSO (189 °C). Since pure CEL liquid starts to evaporate at temperatures above 200 °C (Figure 4–4b), a part of the weight loss of CEL-DMSO solvate around 230 °C may be attributed to CEL. This means that DMSO was not completely removed from the CEL-DMSO melt at 230 °C. This is possible if DMSO and CEL form an azeotrope in liquid phase, because of the stability of tetramers (Figure 4–6). A similar phenomenon was observed in CEL mono-NMP solvate crystals (Chapter 3).

Figure 4–6. A tetramer synthon $R_4^2(8)$ comprised of two CEL and two DMSO molecules

Table 4–1. Hydrogen bonds that stabilize the tetramer in the CEL-DMSO structure

<table>
<thead>
<tr>
<th>N-H⋯O bond name</th>
<th>1 &amp; 1’</th>
<th>2 &amp; 2’</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d$ (H⋯A) (Å)</td>
<td>2.071</td>
<td>2.043</td>
</tr>
<tr>
<td>$d$ (D⋯A) (Å)</td>
<td>2.931</td>
<td>2.883</td>
</tr>
<tr>
<td>$\angle$(DHA) (°)</td>
<td>163.34</td>
<td>162.36</td>
</tr>
</tbody>
</table>
Figure 4–7. Packing of CEL-DMSO with removed DMSO molecule to highlight the void space. Hydrogen atoms were removed for simplicity and clarity. a) Viewed down the $b$-axis, the spiral is barely look-through. b) viewed down the $a$-axis, the spiral is obvious and the DMSO occupies staggered positions in the lattice

The high solid-state stability of CEL-DMSO is important for removing the surface residual DMSO without causing desolvation. Phase pure CEL-DMSO powder was obtained by spraying deionized water onto the CEL-DMSO powder during vacuum filtration and then placing the powder in a vacuum oven at room temperature and dried for 3 days with air flowing over the powder. The CEL-DMSO powder was also stable upon storage at ambient conditions for at least 9 months in a closed container. Additionally, the CEL-DMSO was stable against high compaction pressure since the XRD pattern of a tablet (200 mg) compressed at 325 MPa showed no sign of phase conversion when compared to the simulated pattern from room temperature single crystal structure (Figure 4–8). Therefore, no phase stability related issues are expected during API preparation and tablet manufacturing. It is also useful to point out that the DMSO molecules and -CF$_3$ group of CEL in the crystal are disordered over two sites at 298 K, but disorders are absent at 100K (Figure 4–3). Thus, the two disordered sites correspond to slightly different interaction energies, with the energy difference comparable in magnitude to the kinetic energy difference of the molecules between the two temperatures. At 298 K, the disordered DMSO
molecules occupy two positions with 0.84 and 0.16 occupancies with only subtle changes to the position of O atom that forms the tetramer with N-H on sulfonamide of CEL. The disorder at 298 K did not affect the crystal packing much.

**Figure 4–8.** Powder X-ray patterns of CEL-DMSO solids and tablets. The simulated pattern was used as a reference, which was obtained from the room temperature crystal structure.

CEL-DMSO exhibited a higher intrinsic dissolution rate than CEL in deionized water at 25 °C (**Figure 4–9**). However, it is important to point out that conversion of CEL-DMSO to CEL Form III occurred quickly (in 10 – 30 s) during IDR measurements. Therefore, washing CEL-DMSO with water. To remove residual DMSO requires careful monitoring and control during large scale manufacturing.
Figure 4–9. IDR data showing CEL-DMSO tests and CEL Form III tests at 25 °C. Three CEL-DMSO curves showed different extents of supersaturation followed by rapid precipitation and phase conversion to Form III.

4.4.2 Mechanical Properties of CEL-DMSO

The elastic modulus ($E$) and hardness ($H$) are important parameters that could potentially be used to predict tableting performance of APIs.$^{90,237,238}$ CEL Form III crystal is exceptionally elastic,$^{216}$ with an $E$ of $16.27 \pm 0.43$ GPa and an $H$ of $0.45 \pm 0.02$ MPa when the (001) crystal face was indented. Therefore, CEL falls in the category of stiff crystals based on $E$ and intermediate-stiffness based on $H$. $^{239}$ This is consistent with the poor tabletability of CEL since highly elastic materials are generally poorly compressible and tends to form laminated tablets due to high elastic recovery in die. $^{238}$ Compared to CEL, the elasticity of CEL-DMSO is greatly reduced, with an $E$ of to be $5.574 \pm 0.31$ GPa when indented on the major (002) crystal face. This places CEL-DMSO in the category of compliant molecular crystals. $^{239}$ The $H$ of the (002) face of CEL-DMSO ($0.29 \pm 0.02$
MPa) is also much lower than CEL. However, the CEL-DMSO crystal fractured during the nanoindentation test (Figure 4–10), indicating higher brittleness of CEL-DMSO than CEL. This also means that actual $H$ of CEL-DMSO is likely higher had the fracture not taken place.

![Figure 4–10](image)

**Figure 4–10.** Surface scans of indentation imprint after nanoindentation tests for a) CEL Form III on (001) face and b) CEL-DMSO on (002) face. The hairline in b) is a crack in the crystal.

The tabletability plots of CEL-DMSO powder is significantly lower than CEL (Figure 4–11), which may partially be attributed to the brittleness of CEL-DMSO crystals. For example, more brittle materials tend to develop defects in the tablets during decompression, which generally leads to poorer tabletability. Hence, the inclusion of a plastic excipient in the formulation is expected to be critical for tablet formulation of CEL-DMSO to avoid compaction related problems. In this regard, MCC is a good candidate because of its high plasticity and excellent tabletability.  

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Figure 4–11. a) Tabletability profiles and b) flowability of CEL-DMSO solvate, CEL Form III and their Formulations D.

4.4.3 Flowability of CEL-DMSO

Although the longest dimensions were similar (Figure 4–2), the flowability index ($ff_c$) of CEL-DMSO powder ($7.1 \pm 0.2$) was almost two times that of the $ff_c$ of CEL powder ($4.0 \pm 0.3$) (Figure 4–11b). The bulk density was also higher than that of CEL Form III
The improved flowability of CEL-DMSO as attributed to its more equi-dimensional shape, which is more favorable to powder flow than the needle like CEL crystals (Figure 4–2, Figure 4–3). The CEL-DMSO crystals with a lower aspect ratio alleviates the detrimental effect of particle entanglement among needle-shaped crystals on powder flowability. Despite the improvement, the flowability of CEL-DMSO is still poorer than that of Avicel PH 102 ($ff_c = 12.2 \pm 0.8$), which exhibits flowability minimally required for high speed tableting. However, the improvement in flowability by CEL-DMSO is sufficient to enable the development of a DC tablet formulation with the aid of functional excipients.

### 4.4.4 Development of A Direct Compression Tablet Formulation Using CEL-DMSO Solvate

Based on the flowability and tabletability of CEL-DMSO, we designed the first DC tablet formulation (Formulation A) containing 50% CEL-DMSO (Table 4–2). This formulation corresponds to 200 mg CEL when the total tablet weight is 500 mg. Formulation A also has 23% MCC as the plastic binder to enhance tablet strength; mannitol Pearlitol 100SD was used to enhance the flow of the formulation; crospovidone was used as a disintegrant; SLS was added as a dual functionality wetting agent and lubricant and Mg St was used as the internal lubricant. Formulation A ($ff_c = 14.1 \pm 1.6$) exhibited significantly better flowability than both CEL-DMSO alone and Avicel PH102. When CEL-DMSO in Formulation A was replaced by CEL, the flowability profoundly deteriorated ($ff_c = 3.7 \pm 0.1$), to be similar to CEL alone. Thus, at 50% CEL loading, the flowability of the formulation is dominated by CEL. At this drug loading, the use of a better
flowing crystal form, CEL-DMSO in this case, leads to profound improvement in the flowability of the formulation. Additionally, CEL containing Formulation A could not be made into intact tablets at low compaction pressures at a 20 ms dwell time due to severe lamination (Figure 4–12). When CEL-DMSO was used in Formulation A, all tablets were intact below 300 MPa but very mild lamination occurred at higher pressures where hairline cracks on the side of tablets were observed. Since faster compression aggravates tablet capping and lamination, a slower speed (corresponding to a dwell time of 100 ms) was used to make intact tablets for delineating their tabletabilities. At this speed, the tabletabilities of the two formulations were comparable, sufficiently strong tablets (> 2MPa tensile strength) could be made for both formulations (Figure 4–13a). However, the ejection force of CEL-DMSO Formulation A ~ 550 N at 150 MPa compaction pressure, which is higher than the preferred 400 N. Thus, Formulation A requires optimization to be more suitable for commercial manufacturing.

Table 4–2. Summary of tablet formulation compositions and weights. The total amount of CEL in each tablet is 200 mg.

<table>
<thead>
<tr>
<th>Components (%)</th>
<th>Formulation A</th>
<th>Formulation B</th>
<th>Formulation C</th>
<th>Formulation D</th>
</tr>
</thead>
<tbody>
<tr>
<td>API (CEL or CEL-DMSO)</td>
<td>50</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>23</td>
<td>41.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mannitol Pearlitol 100SD</td>
<td>20</td>
<td>11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nanocoated Avicel PH102</td>
<td>-</td>
<td>-</td>
<td>52.5</td>
<td>52.25</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>4.75</td>
<td>4.75</td>
<td>4.75</td>
<td>4.75</td>
</tr>
<tr>
<td>SLS</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MgSt</td>
<td>0.25</td>
<td>0.75</td>
<td>0.75</td>
<td>1</td>
</tr>
<tr>
<td>Tablet weight (CEL)</td>
<td>400 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Tablet weight (CEL-DMSO)</td>
<td>500 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
</tbody>
</table>
Figure 4–12. Severe lamination of tablets made from CEL Form III Formulation A.

Figure 4–13. a) The tabletability and b) the ejection force profiles of CEL-DMSO and CEL Form III formulations who were formulated as listed in Formulation A.

To minimize possible damages of high ejection force to tablets and dies during large scale commercial manufacturing, two changes were made to arrive at Formulation B (Table 4–2), i.e. 1) increasing the amount of MgSt from 0.25 wt % to 0.75 wt % to reduce the ejection force seen in Formulation A; and 2) using more of the plastic MCC to replace some brittle mannitol to mitigate the lamination issue at high compaction pressures. Since CEL-DMSO is also brittle (Figure 4–10), the loading of active crystals was also reduced.
from 50 wt % to 40 wt %. This necessitates a larger tablet (600 mg) to deliver 200 mg of CEL equivalent dose (Table 4–2).

The $ff_c$ of CEL-DMSO containing Formulation B is $14.0 \pm 0.01$, indicating its satisfactory flowability for high speed tableting. However, very light hairline cracks on the side of tablets were still observed only at high compaction pressures. Therefore, the formulation composition changes did alleviate the observed lamination problem, but further formulation optimization is needed to fully eliminate tablet defects. In Formulation C (Table 4–2), all mannitol was removed to further reduce brittleness of the formulation. However, the elimination of freely flowing mannitol also likely deteriorates the flowability of the formulation. Hence, silica nanocoated MCC was used to ensure sufficient flowability for high speed tablet manufacturing. $^{56}$ In fact, the $ff_c$ of CEL-DMSO containing Formulation C ($22.0 \pm 2.7$) indicates excellent flowability. Importantly, defect-free tablets were made in the entire pressure range at 20 ms dwell time. However, the ejection force, ranging from 556 to 725 N, is still slightly too high. To address this problem, we increased the amount of MgSt to 1 wt % in Formulation D (Table 4–2).

As expected, the ejection force profile of Formulation D is much improved compared to Formulation C, with ejection force lower than 400 N in the entire pressure range (Figure 4–14). Thus, the increased level of MgSt is effective in addressing the high ejection force. We then assess Formulation D against other important aspects of tablet manufacturing. As expected from the minor change in formulation, the $ff_c$ of CEL-DMSO containing Formulation D ($19.0 \pm 1.70$), is comparable to that of Formulation C. Its flowability is excellent. The flowability is significantly higher than that of CEL-containing
Formulation D (4.5 ± 0.1). Clearly, the better flowability of CEL-DMSO is translated into better flowability of the DC tablet formulation (Figure 4–11b). The CEL-DMSO containing Formulation D also exhibited adequate tabletability, although it is slightly lower than that of the CEL-containing Formulation D (Figure 4–11a). Similar to flowability, the different tabletability of the two solid forms is translated into different tabletability of Formulation D. This is attributed to the smaller bonding strength between CEL-DMSO formulation than the CEL Form III formulation (Figure 4–15). With the same excipient matrix composition, only the solid form of CEL is different in the two formulations - CEL Form III or CEL-DMSO. Thus, the difference in compaction properties of these formulations are attributed to the properties of different solid forms. The same compressibility of both formulations (Figure 4–15a) indicates the bonding area of both formulations are similar. Whereas the higher $\sigma_0$ of CEL-DMSO formulation D (3.68 MPa) than the $\sigma_0$ of CEL Form III Formulation D (2.99 MPa) indicates that CEL Form III formulations has higher bonding strength (Figure 4–15b). The higher bonding strength overrides the tableting performance of CEL Form III formulation through the bonding area-bonding strength interplay, thus causing the CEL Form III Formulation D to have slightly higher tabletability than CEL-DMSO Formulation D.

So far, Formulation D exhibits excellent flowability, adequate tabletability (with tablets free from lamination), and acceptable ejection force. The much lower bulk density of the CEL-based Formulation D (0.20 g/cm$^3$), compared to the CEL-DMSO formulation (0.48 g/cm$^3$), led to the difficulty of packing 500 mg of powder into the die even at the maximum filling depth (Figure 4–16). The low bulk density along with the poor
flowability ($ff_r = 3.7 \pm 0.1$) made it impossible to prepare tablets with the desired tablet weight using the CEL-containing Formulation D. When 500 mg powder was force-filled into the die, aided by pressing the powder bed with hand to consolidate the powder, no intact tablets could be made at 20 ms dwell time due to severe lamination upon ejection (Figure 4–17 a & b, where pictures of a tablet made at 7 kN using CEL formulation D has exhibited severe lamination). In contrast, intact tablets could be made from the CEL-DMSO based Formulation D under identical compression conditions (Figure 4–17c). Overall, the CEL-DMSO based Formulation D exhibits adequate manufacturability. Hence, it is further examined for friability and dissolution to confirm its suitability for developing a DC tablet formulation of CEL.

![Ejection force of Formulations D for both CEL Form III and CEL-DMSO](image)

**Figure 4–14.** Ejection force of Formulations D for both CEL Form III and CEL-DMSO
Figure 4–15. a) Compressibility and b) compactibility of CEL-DMSO and CEL Form III Formulations D.

Figure 4–16. 500 mg of CEL Form III-containing Formulation D powder cannot be packed into the die, even if it is at the maximum depth of filling. The powder had to be pushed into the die by hand for compaction into tablets.

Figure 4–17. a) Lamination upon ejection of CEL Form III Formulation D tablets made at 7kN. The inset is a close-up of the middle piece of the broken tablet, which is further
laminated into layers. b) Another laminated tablet of CEL Form III Formulation D made at 7 kN. c) Intact tablet of CEL-DMSO Formulation D made at 7 kN.

4.4.5 Expedited Friability of CEL-DMSO Formulation D Tablets

Friability is critical for tablet quality in terms of general handling and shipping, and it determines suitable packaging of the final product. For example, individual blister packaging may be needed for more friable tablets to protect their integrity, while bulk tablets can be put into bottles if they are not friable. Typically, tablet friability should be <1%. However, tablet friability of a given formulation depends on the mechanical strength of the tablets, which is in turn determined by tableting speed, compression force, tooling design, and tablet size. A suitable set of compression conditions can be determined from a friability profile, which can be determined using a material-sparing and expedited method. In this work, the expedited friability test of CEL-DMSO Formulation D tablets compressed at 20 ms dwell time using flat-faced round tooling (Figure 4–18a) suggests that tablets with < 1% friability can be obtained in the compression force range of 4.6 – 21.7 kN. Below 4.6 kN, the tablets are friable because of their low mechanical strength. Above 21.7 kN, tablets are friable likely because of defects introduced into tablets due to higher extent of elastic recovery. This is supported by the coincidence of both rising tablet friability (Figure 4–18a) and the deflection of the in-die elastic recovery profile at 10 kN compression force (Figure 4–18b). The link between elastic recovery and friability is further supported by the effects of tableting speed on friability and elastic recovery. At a slower speed, corresponding to a dwell time of 30 ms, both friability and elastic recovery are overall lower than those at higher speed. (Figure 4–18, open triangles). This is sensible
because longer dwell time allows particles to undergo larger extent of plastic deformation, which both dissipates more elastic energy and increases tablet strength. 53

**Figure 4–18.** a) Friability profiles and b) in-die elastic recovery profiles for the CEL-DMSO Formulation D at 20 ms (solid squares) and 30 ms (open triangles) dwell times. Trend lines are manually added to guide the eye.

With the 30 ms dwell time, the friability and in-die elastic recovery at 7.5 kN is predicted from corresponding profiles to be ~ 0.5% and ~4.6%, respectively (Figure 4–18a). Three tablets made at 7.4 ± 0.1 kN, exhibited a friability of 0.47 % ± 0.09 % and an elastic recovery of 4.5 % ± 0.2 %, supporting the validity of these profiles.

### 4.4.6 Disintegration and Dissolution of CEL-DMSO Formulation D Tablets

Three tablets of the CEL-DMSO Formulation D compressed at 7.70 ± 0.05 kN all disintegrated in less than 15 seconds in deionized water at 37 °C. The fast disintegration of these tablets is advantageous for CEL to exhibit faster onset of action.

Compared to the commercial 200 mg Celebrex® capsules, the release of CEL from the CEL-DMSO Formulation D tablets is much faster, largely because of an absence of the
lag time, corresponding to the very fast tablet disintegration process (Figure 4–19). Although the Celebrex® capsules have a ~2 min lag time before dissolution initiated, it exhibited a relatively fast dissolution rate, likely because of the smaller particle size of the micronized CEL Form III used in the capsules. If needed, the dissolution performance of CEL-DMSO tablet can likely be further improved by using a suitable precipitation inhibitor to slow down or even prevent the crystallization of CEL during the course of dissolution 27, 126, 249.

Figure 4–19. Tablet dissolution tests of CEL-DMSO Formulation D vs. marketed 200 mg CEL capsules.

Aided with CEL-DMSO, we have successfully developed a DC tablet formulation of CEL that can be manufactured on a high speed press with improved dissolution performance compared to marketed capsules. The efficient development of this tablet formulation was facilitated by predictive tools and material-sparing techniques for
characterizing formulations, as repeatedly shown before.\textsuperscript{247, 249-251} The formulation optimization employed a materials science based decision making process, which invariably starts with clear understanding of deficiencies of a prototype formulation, and is followed with changes in formulation to specifically address such deficiencies. This successful example highlights the largely neglected applications of pharmaceutically acceptable solvates in tablet product development. With pharmaceutical solvates added to the toolbox, one has more flexibility in solving formulation problems.

4.5 Conclusion

We have developed a direct compression tablet formulation of CEL using DMSO solvate of CEL, which exhibits improved flowability, manufacturability, tablet quality, and faster dissolution over those of CEL. The formulation development process was efficient because of the employment of predictive techniques for assessing powder flowability and tableting performance. This study is another example that shows the benefits of combining crystal engineering and materials science to enable the development of high quality tablet products efficiently.
Chapter 5.

Crystal Growth of Celecoxib from Amorphous State - Polymorphism, Growth Mechanism, and Kinetics

This chapter has been published as a research article in Crystal Growth and Design.

5.1 Synopsis

The crystal growth kinetics of amorphous celecoxib (CEL), an anti-inflammatory BCS class II drug, was systematically investigated for developing effective stabilization strategies to enhance solubility of CEL. Compared to bulk, the surface crystal growth was much faster, e.g., ~80 fold higher at $T_g + 3 \, ^\circ\text{C}$. Both surface and bulk growth near and below $T_g$ was accelerated over that predicted from diffusion-limited process. Similar to some other organic small molecule glasses, the faster surface and bulk growth near and below $T_g$ are attributed to solid-state crystal growth and Glass-to-Crystal growth mechanisms, respectively. These two solid-state growth modes were disrupted by fluidity differently upon heating, with a much wider transition zone of CEL on the surface compared to the bulk. Interestingly, the surface transition zone is the widest among all systems studied so far. The phenomenon of cross-nucleation was also observed between CEL polymorphs, forms I and III, which also exhibited different crystal growth rates in the diffusion-controlled region both on surface and in bulk.
Figure 5–1. Synopsis figure. Crystallization of celecoxib from amorphous phase exhibits the phenomena of fast surface growth, fast bulk glass-to-crystal growth, and cross-nucleation between two polymorphs. The fast growth mechanisms are disrupted by the onset of fluidity controlled growth at temperatures above $T_g$. 

![Diagram showing growth rate vs. temperature for different forms of celecoxib](image-url)
5.2 Introduction

There is an increasing percentage of poorly soluble compounds, i.e., biopharmaceutical classification system (BCS) classes II and IV compounds, under development in the pharmaceutical industry. For example, approximately 39% of 698 oral immediate release drugs on the market and 60% of 28,912 new chemical entities under development fall in the BCS classes II and IV. Consequently, there has been a rising demand for enabling techniques to improve solubility and/or dissolution of drugs. Common ways to improve solubility and/or dissolution include 1) adoption of a more soluble solid form of a compound, such as salts, co-crystals and amorphous solid; 2) particle size reduction to increase surface area; 3) use of cosolvents, surfactants, lipids, or complexing agents. Among these methods, the use of amorphous solids has gained much interest as a universal solubility enhancing technique, owing to their inherently higher thermodynamic activity than corresponding crystalline counterparts. However, an amorphous drug tends to convert to its thermodynamically more stable crystalline form during storage, which negates its potential solubility advantages. Thus, mechanistic understanding and control of the crystallization behavior of amorphous drugs are of practical importance.

It has been shown that crystal growth from the amorphous state can still be surprisingly fast at the storage condition, which is well below its glass transition temperature, \( T_g \), due to two mechanisms: 1) a solid-state glass-to-crystal (GC) growth in bulk that exceeds the rate of bulk diffusion of molecules; 2) fast surface crystal growth due to the considerably higher molecular mobility on the surface of an organic glass
Among the 15 organic small molecules exhibiting bulk GC growth so far, there are three common features: 1) an abrupt increase in the crystal growth rate near $T_g$, compared to that extrapolated from growth rate data above $T_g$ (attributed to diffusion-controlled growth mechanism); 2) temperature dependent growth morphology of crystals; and 3) lower activation energy ($E_a$) of GC growth than that for diffusion-controlled growth. Several mechanisms have been suggested to explain GC growth, including the homogeneous nucleation-based crystallization model; the tension-induced interfacial mobility; and solid-state growth by local fracture and surface mobility. However, none of these theories could completely explain all features of GC growth. The fast surface molecular diffusion was established by following the surface grating decay of organic glasses. It explains the phenomenon of crystals growing hundreds of nanometers above the surface. This mechanism was further indirectly verified by showing arrested surface crystal growth upon nanocoating the glass surface.

In this study, we used Celecoxib (CEL, Figure 1–4) as a model compound to further probe the prevailing crystallization mechanisms of a pharmaceutical organic glass, both on surface and in bulk. CEL is a widely prescribed nonsteroidal anti-inflammatory drug (NSAID) for treating pain and inflammation. It is a BCS class II compound, exhibiting low solubility and high permeability. The bioavailability of CEL is expected to be improved through solubility enhancement by the use of its amorphous form. A highly stable CEL glass has been prepared before by vapor deposition and its stability was studied at a single temperature. We found that CEL also exhibits fast GC growth in the bulk and fast crystal growth on the surface, near and below its $T_g$. We also observed that
both mechanisms are disrupted by the onset of fluidity as previously observed in other model systems.\textsuperscript{270} The intriguing phenomenon of abrupt increase in growth rate near $T_g$ of amorphous compounds as temperature decreases has been attributed to the activation of diffusionless solid-state growth mechanisms. A unique feature observed in CEL is that it exhibits presently the widest transition zone between solid-state growth and diffusion-controlled growth both on surface and in bulk. This makes CEL a good model system for future studies to further elucidate the molecular mechanism underlying this phenomenon. In addition, we have also observed different growth rates and activation energies of two CEL polymorphs in the diffusion-controlled region, which indicates that crystal structures play a role in crystal growth kinetics. A clear understanding of the kinetics of various crystal growth mechanism is useful to developing effective stabilization strategies of amorphous drugs, such as surface elimination by nanocoating.\textsuperscript{282, 283}

5.3 Materials and Methods

5.3.1 Materials

Form III CEL was purchased from Aarti Drugs Pvt Ltd. (Mumbai, India) and used as received.

5.3.2 Methods

5.3.2.1 Preparation of Amorphous CEL Thin Films

Amorphous CEL thin films were prepared by melt-quenching. Approximately 3~5 mg CEL crystals were sandwiched between a glass slide and a rectangular cover glass orthogonally placed, keeping the overlapping area constant (24mm $\times$ 24mm). The
sandwiched sample was then melted on a hot stage (Linkam LTS 420, Linkam Scientific Instruments, Ltd., Waterfield, UK) at 180 °C and held for 5 min until the molten CEL spread and cover the entire overlapped area. When bulk crystal growth rate was measured, the cover glass was left in place. When surface crystal growth rate was measured, the cover glass was peeled off to expose the free surface after the sample had been quenched to room temperature (Figure 5–2). The thickness of films was estimated to be 3.7 ~ 6.2 μm, based on the total surface area, sample weight, and true density of amorphous CEL (Table 5–1) measured using a helium pycnometer (Ultrapyc 1200e, Quantachrome Instruments, Boynton Beach, Florida). This film thickness was used to avoid the known phenomenon of subsurface nucleation in supercooled liquid, which is about 48.3 ± 7.4 μm for acetaminophen. 287

![Diagram](image)

**Figure 5–2.** Sample configuration of surface and bulk amorphous thin films (top view)

**Table 5–1.** Physical properties of Form III, Form I and amorphous CEL

<table>
<thead>
<tr>
<th>CEL solid form</th>
<th>Melting point or $T_g$ (°C)</th>
<th>Density (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form III</td>
<td>160.80</td>
<td>1.549</td>
</tr>
<tr>
<td>Form I</td>
<td>163.45</td>
<td>-</td>
</tr>
<tr>
<td>Amorphous</td>
<td>51.80</td>
<td>1.392</td>
</tr>
</tbody>
</table>
5.3.2.2 Crystal Growth Rate Measurements

Amorphous CEL samples were kept in Drierite® containing desiccators, which were placed in ovens at temperatures of interest. They were periodically withdrawn and observed under a polarized light microscope (PLM) (Nikon Eclipse E200, Nikon, Tokyo, Japan) equipped with a DS-Fi1 microscope digital camera for capturing digital images to enable crystallite size measurements. Crystal growth in the 100 – 160 °C temperature range was measured from video clips captured during hot stage microscopy experiments because it was too fast to reliably measure by taking still images. The size of a crystal that grew as compact spherulites/polycrystalline circles was evaluated by measuring the orthogonal diameters of the crystal circle and taking the average. The average radii of the crystal spherulites were then plotted as a function of time (Figure 5–3). For crystals that grew as single crystals, the growth rate was taken as the linearly advancing speed of the crystals’ growing front. Each crystal growth rate was calculated by tracking the growth of 3 to 39 different crystals. More crystals were tracked at lower temperatures when parallel samples could be set up.
**Figure 5–3.** a) Growth of bulk Form I crystals at 70 °C over 6 days b) Linear regression on increasing crystal radii over time.

### 5.3.2.3 Arrhenius Analysis of Crystal Growth Rate

Growth rate – temperature data was analyzed using the Arrhenius Eqn. 5–1, where $A$ is a pre-exponential factor, $E_a$ is the activation energy of the crystal growth (kJ/mol), $T$ is the absolute temperature (K), and $R$ is the universal gas constant (8.314 × $10^{-3}$ kJ mol$^{-1}$K$^{-1}$). The slope of a line on a ln($k$) vs. $1/T$ plot yields $-E_a/R$.

$$k = A \times e^{-E_a/(RT)} \quad \text{Eqn. 5–1}$$

### 5.3.2.4 Preparation of Polymorphic Seeds of CEL

Form III CEL seeds were prepared by storing melt-quenched amorphous samples in a 40 °C oven for 1–2 days. Form I CEL seeds were prepared by placing the melt-quenched samples in an 80 °C oven overnight. Samples containing appropriate seeds were then stored at temperatures of interest to determine crystal growth rates.
5.3.2.5  Raman Spectroscopy

Raman spectra of the amorphous and crystallized CEL were collected using a confocal Raman microscope (Witec alpha 300R, WITec, Ulm, Germany), equipped with a CCD detector for identifying solid forms of CEL samples. Surface and bulk thin film samples were excited using a 532 nm Omnichrome Argon ion laser. A 100× lens was used, providing a laser beam size of 2 μm in diameter. For each point tested, the spectral acquisition integration time was 10 s and the average of two spectrum accumulations was obtained. Both line scan and area scan were performed at the interface of two CEL polymorphs, using 5 s and 3 s integration time per point, respectively. For line scan, the scan length was 100 μm with 1 μm resolution (100 points total). For the area image scan, a 100μm × 20 μm strip was scanned with 1 μm resolution. The intensities of the non-overlapping peak ranging from 1113 to 1143 cm⁻¹ representing Form I was measured and is plotted against the relative positions on the sample. In the resulting image of the 2D scan, higher brightness represents higher intensities of this peak.

5.3.2.6  Micro X-ray Diffraction

A wide-angle Bruker-AXS Micro diffractometer (Bruker-AXS, Madison, Wisconsin) with a 2.2 kW sealed Cu X-ray source was utilized to collect X-ray diffraction patterns of crystals grown from melts. A 0.8 mm size collimator was selected for a better resolution. Data were collected using an area detector at room temperature over 5 - 35° 2θ range with a total exposure time of 300 s. The glass slide containing crystals of interest grown from melt was glued to the vertical sample holder. The holder can be moved to allow the X-ray beam to focus on the crystal spherulites of interest.
5.3.2.7 Thermal Analysis

Melting point was determined using a Differential Scanning Calorimeter (DSC, Q1000; TA Instruments, New Castle, DE) at a heating rate of 10 °C/min. Prior to DSC study, the degradation temperature of CEL was determined by thermogravimetric analysis (TGA) (Q50, TA Instruments, New Castle, DE). Maximum temperature used in DSC experiments was kept below the corresponding degradation temperature. The samples for DSC were prepared by scratching off the crystals of interest, which are grown from amorphous CEL.

5.3.2.8 Scanning Electron Microscopy (SEM)

The surface crystals grown from melt at 110 ºC on a glass slide were cut by a tungsten carbide point scriber/etching pen to obtain a small piece of glass containing a complete crystallite to be analyzed. The cut piece of glass sample with surface crystal on top was glued to a carbon tape on the bottom, and then adhered to a SEM stub. The sample surface was coated with platinum coating of approximately 75Å thickness using an ion-beams sputter (IBS/TM200S; VCR Group Inc., San Clemente, CA). The surface textures were analyzed using a JEOL 6500F scanning electron microscope (JEOL Ltd., Tokyo, Japan), operated at SEI mode with an accelerated voltage of 5kV.

5.4 Results and Discussion

5.4.1 Differential Surface and Bulk Crystal Growth Rates

The growth rate profile of CEL is summarized in Figure 5–4, where $T_g$ and $T_m$ represent glass transition temperature of amorphous CEL (51.8 ºC) and melting
temperature of form III CEL (160.8 °C), respectively. Under PLM, the crystals are birefringent and the areas surrounding the crystals are amorphous (Figure 5–5a-b). Both CEL Forms I and III were observed during the course of this study. Form III bulk growth rate data between 60 °C and 100 °C could not be collected because only Form I grew in bulk samples in this temperature range, even when seeded with Form III. The missing data points of surface growth rate for either Form III or Form I crystals at ≥120 °C was due to the difficulty in capturing fast crystal growth into a flowing liquid.

Figure 5–4. Surface and bulk crystal growth rate - temperature profiles of CEL a) Form III CEL. b) Form I. Open symbols indicate growth mechanisms distinct from the diffusion controlled growth (solid symbols).
Figure 5–5. Crystallization of CEL from amorphous phase observed under PLM and Raman Microscope, a) Form III crystals grew on surface at 40 °C, and b) Form I crystal grew in the bulk at 80 °C, c) The two polymorphs under Raman microscope, d) Raman area scan of the boundary between Form I (orange red) and Form III (black).

From the data obtained, the surface growth rates of Form III were 1~2 orders of magnitude higher than those in the bulk below and near $T_g$ of CEL ($T_g = 51.8$ °C) (Figure 5–4a) and the enhancement effect appears to increase with decreasing temperature. This is similar to that observed in several other small organic molecules, where the faster surface crystal growth rate is sustained by the orders of magnitude faster molecular diffusion on the surface than in the bulk, as suggested by the strong positive correlation between the surface crystal growth rate and surface diffusion coefficients of o-terphenyl (OTP), nifedipine (NIF) and indomethacin (IMC). This phenomenon is also responsible for the faster growth along crevices and voids in an amorphous sample. Also
similar to other molecules, the relative difference between the surface and bulk growth rates of CEL decreases with increasing temperature, with a convergence temperature of about 100 °C (Figure 5-4a and b). At and above the convergence temperature, the differences between the surface and bulk growth rates cease to exist because wetting and embedding of surface crystals by surrounding liquid. This was confirmed for CEL Form III surface crystals at 110 °C (Figure 5-6).

**Figure 5-6.** Liquid-embedded crystal in the diffusion-controlled crystal growth region of CEL Form III, taken from 110 ºC sample. Crystal growth direction is indicated with an arrow. a) Top view; b) tilted view in SEM.

### 5.4.2 Temperature-dependent Crystal Growth Mechanisms

With decreasing temperature, CEL Form III crystal growth rate abruptly increased in the 25 – 60 °C range ($T_g$ is 51.8 °C for CEL) for both surface and bulk growth (Figure 5-4a). Similar observations were made in several other organic materials. The abrupt increase in bulk growth rate was attributed to the GC mechanism, while the abrupt increase in the surface growth rate was related to the activation of a solid-state crystal growth mechanism that differs from fluidity-limited growth at higher temperatures.
Both mechanisms are disrupted by the onset of fluidity when the temperature is sufficiently high for the diffusion-controlled process to play a more significant role in crystal growth. The vertex of the transition region, termination temperature ($T_t$), marks the temperature above which the GC growth mode or the solid-state growth mode is disrupted by onset of fluidity-based crystal growth. The temperature range between $T_t$ and onset of the diffusion-controlled growth may be defined as the transition zone. In the transition zone, both the solid-state growth mechanisms and fluidity based mechanism are in play.

Since bulk GC growth mode in the glassy state is a solid-state process due to local molecular mobility rather than the global process, it has been suggested that the much higher mobility near fracture-created surfaces is responsible for the GC growth. In contrast, the $\alpha$ process is more closely related to the diffusion-controlled mode of crystal growth. It was suggested that the crystallization of amorphous CEL above $T_g$ is diffusion-controlled (associated with $\alpha$ relaxation process), whereas the crystallization below $T_g$ is not. To probe the prominence of the $\alpha$ relaxation of CEL in GC growth mode, the number of molecules ($n_\alpha$) being added to the crystalline phase in one structural relaxation time $\tau_\alpha$ was calculated by $n_\alpha = u\tau_\alpha/a$. Taking the estimated molecular diameter, $a$, of 10.29 Å and $\tau_\alpha$ of 100 s at $T_g$, the $n_\alpha$ for CEL is calculated to be 67~5443 in GC growth mode over the range of measured GC growth rate, $u$. The diameter of CEL was estimated by treating CEL molecules as spheres having a packing coefficient of 70%, and solve for $a$, where the sphere volume is the unit cell volume of CEL Form III. This is much greater than the expected $n_\alpha$ ($<1$) if the dominating mechanism were bulk-diffusion-
controlled growth. This calculation further supports that $\alpha$ relaxation is not responsible for GC growth and is consistent with the view that local molecular motions like surface diffusion and $\beta$ relaxation play a role.

The transition from bulk GC growth and surface solid-state growth processes to the fluidity based mechanism also differentiated CEL in two ways. Firstly, the transition zone of CEL Form III crystal from GC or solid-state based growth to diffusion-controlled growth is wider on surface (22 °C) than in bulk (12 °C) (Figure 5–4a and Figure 5–7). Both are substantially wider than all previous reported surface and bulk transition zones of other compounds, e.g., OTP (11°C for surface and 5 °C for bulk) and NIF (13 °C for surface and 3 °C for bulk). For some compounds, e.g., griseofulvin and ROY (YN, R05 and ON polymorphs), the transition zones for the surface crystal growth were not obvious, showing smooth growth rate profiles. Secondly, the surface $T_t$ of Form III (41.4 °C) is lower than that in bulk (44.8 °C). The higher $T_t$ in the bulk suggests that the solid-state growth in the bulk can persist until a higher temperature, indicating possibly different mechanisms by which fluidity affects surface and bulk crystal growth. $T_t$ for both surface and bulk crystal growth of CEL Form I could not be determined due to the lack of data in GC growth region (Figure 5–4b).

As the bulk growth rates for Forms I and III gradually converge with increasing temperature in the diffusion-controlled region (Figure 5–7), a maximum growth rate near the melting point of CEL is observed. The decrease in growth rate when approaching the melting point, despite the higher mobility of CEL molecules, is attributed to the reduction
in thermodynamic driving force for crystallization near the melting point instead of a new
crystal growth mechanism.  

Figure 5–7. Surface and bulk crystal growth rate - temperature profiles of Form I and III of CEL. Characteristic crystal morphologies in different temperature regions are shown. Open symbols indicate growth mechanisms distinct from the diffusion controlled growth (solid symbols). $T_t$ was determined from linear fitting, and the black and purple dashed
d-lines aid visualization of transition zones on surface and in bulk.

5.4.3 Polymorph Cross-nucleation

The Form I and Form III CEL crystallites were easily distinguishable by PLM since they differed in color (when viewed between crossed polarizers) and in texture. Form III
crystallites were composed of fibrous crystals and appeared dark and dense (Figure 5–5a, c). These crystals exhibited micro X-ray diffraction peaks (10.69 °, 12.97 °, 14.80 °, 16.07 °, 17.96 °, 19.6 °, 21.52 °, 22.42 °, 24.60 °, 27.02 °, 27.72 °, 29.56 °, 32.2 °) characteristic of Form III (Figure 5–8). Form I crystallites were composed of plate-like crystals with smoother surfaces (Figure 5–5b, c) and exhibited an X-ray diffraction pattern having peaks (16.4 °, 18.24 °, 19.08 °, 21.96 °, 23.08 °, 25.28 °, 28.72 °) characteristic of the Form I (Figure 5–8). The melting points, determined by DSC of crystallites isolated from the samples also confirmed their Form I and Form III polymorphic identity (Figure 5–9). When characterized by Confocal Raman Spectroscopy, the main difference is that the single peak at 1154 cm⁻¹ for Form III is split into two peaks (1139.83 and 1160 cm⁻¹) for Form I (Figure 5–10). This spectral difference was subsequently used to identify polymorphic nature of crystallites or to map samples by Raman microscopy (Figure 5–5d and Figure 5–11).

Figure 5–8. Characterization of CEL Form I and Form III by powder X-ray diffraction and micro-diffractometer.
Figure 5–9. DSC and TGA curves of Forms I and III of CEL crystallization from melt.

Figure 5–10. Characterization of CEL Form I and Form III by Raman spectroscopy; characteristic peak of Form III is at 1154 cm\(^{-1}\), which split into two peaks for Form I.
Figure 5–11. a) Characteristic peak representing CEL Form I used for Raman mapping and b) Raman 1D line scan result.

Figure 5–10 shows the Raman spectra for amorphous, Form I, and Form III CEL. Forms I and III have many differences in their Raman spectra. The 1154 cm\(^{-1}\) peak for Form III is split into two peaks at 1139 cm\(^{-1}\) and 1160 cm\(^{-1}\). The 1139 cm\(^{-1}\) peak was used for mapping (details in Figure 5–11). Other characteristic peaks are 326 cm\(^{-1}\), 447 cm\(^{-1}\), 760 cm\(^{-1}\), 3118 cm\(^{-1}\), 3230 cm\(^{-1}\), 3338 cm\(^{-1}\), and 3349 cm\(^{-1}\) for Form III; and 1295 cm\(^{-1}\), 1311 cm\(^{-1}\), 1408 cm\(^{-1}\), 3053 cm\(^{-1}\), and 3258 cm\(^{-1}\) for Form I. There are also some minor peak shifts and splitting, e.g., The 409 cm\(^{-1}\) peak in Form I is shifted to 395 cm\(^{-1}\) in Form
III spectrum; and the 1596 cm\(^{-1}\) peak in Form I is shifted to 1574 cm\(^{-1}\) in Form III. The 624 cm\(^{-1}\) peak in Form I is split into 626 cm\(^{-1}\) and 644 cm\(^{-1}\) peaks in Form III.

CEL also exhibited cross-nucleation behavior between Form I and III polymorphs, where heterogeneous nucleation of a crystalline phase is induced by crystals of the same chemical composition but a different phase. During surface growth, Form III nucleated from Form I seeds at temperatures from 25 to 60 °C because only Form III grew from either Form I or Form III seeds. At ≥65 °C, Form I could nucleate on Form III because both polymorphs grew from Form III seeds, but Form III never nucleated on Form I. During the bulk growth of CEL, Form III could nucleate on Form I below 60 °C because only Form III grew regardless of polymorphic nature of seed crystals. Above 60 °C, Form I seeds always led to growth of Form I. Meanwhile, above 60 °C, cross-nucleation on Form III seeds was complex. In the temperature range of 60 °C - 90 °C, Form I always nucleated on Form III so that Form III never grew. However, Form III seeds could either cross-nucleate Form I or grow into larger polycrystalline Form III in temperature range of 100 °C - 140 °C. Cross-nucleation was confirmed by both 1D Raman line scan (Figure 5–11) and 2D Raman mapping (Figure 5–5c & d). It is useful to mention that when cross-nucleation occurred, the fast growing polymorph always nucleated on the slow growing polymorph in the respective temperature ranges.

5.4.4 Relationship between Growth Mechanism and Crystal Morphology

The morphology of crystals grown from melt is highly dependent on the temperature (Figure 5–12), eluding to the different underlying growth mechanisms. The GC growth (30 and 40 °C) of Form III surface and bulk CEL led to compact spherulites,
while Form III crystals grew as fibers at 55 - 60 °C (part of the transition zone). At the beginning of the diffusion-controlled region (70 °C), Form III grew as fibers while Form I grew as polycrystalline crystals with well-defined growth front. As the temperature further entered the diffusion-controlled region (80 - 150 °C), both Form III and Form I grew with polycrystalline texture. At 160 °C (1-2 °C below melting temperature), the CEL crystals grew into single crystals of Form III. Similar trend was also observed in ROY polymorphs. However, some ROY polymorphs grew in the bulk as both fast-growing fibers and slow-growing crystalline spherulites between Tt and 1.15 Tg. Nevertheless, fibrous bulk growth of CEL within the transition zone (44.8 – 56.6 °C) only grew as compact spherulites (Figure 5–12).

**Figure 5–12.** PLM images of CEL crystals grown from amorphous films at different temperatures. B is for bulk and S is for surface samples. Scale bars are all 100 µm.
5.4.5 Effect of Polymorphism on Growth Rate

In the diffusion-controlled region, molecules arriving at the growth front must also take on the correct orientation and conformation before it is accepted into the crystalline phase. Therefore, crystal packing pattern may influence crystal growth rate from the same amorphous material. Comparing crystal growth rates of different polymorphs offers an opportunity to assess the relative contributions of this step relative to diffusion. For CEL, the surface growth rate of Form I was consistently higher (18% - 60%) than that of Form III over the temperature range of 70 - 150 °C (Figure 5–13). Therefore, the step of adjusting molecular conformation and orientation required for Form III crystal noticeably slowed down CEL crystal growth on the surface. Within the temperature range where bulk growth rates of Forms I and III could both be measured (100 - 150 °C), Form I bulk growth rate was about 8 – 43 % higher than that of Form III (Figure 5–14). Thus, the process of molecules adjusting conformation and orientation also played a significant role in crystal growth in the bulk.
Figure 5–13. Growth rate profile of both crystal forms for surface samples of amorphous CEL; the inset represents the growth rates of two polymorphs on linear scale.

Figure 5–14. Growth rate profile of both crystal forms for bulk samples of amorphous CEL; the inset in the growth rates of two polymorphs in linear scale.
The slightly higher percent increase in growth rate of Form I over Form III on the surface (18% - 60%) than that in the bulk (8% - 43%) (Figure 5–13 and Figure 5–14) may be simply because of the different temperature regions over which both polymorphs can grow, i.e., 70 - 150 °C for surface growth and 100 - 160 °C for bulk growth. The relative difference became smaller at higher temperatures because molecules can rotate, re-orientate, or undergo conformational changes more rapidly. Thus, its effect on the time taken for the different polymorphs to grow is reduced with temperature. This is supported by the fact that, below and near corresponding \( T_g \), differences in growth rates between \( \alpha \) and \( \gamma \) polymorphs of IMC (70 - 570 %) and Forms I and IV polymorphs of carbamazepine (440 – 600 %) were significantly larger than that between CEL Forms I and III at temperatures significantly above \( T_g \).  

5.4.6 Arrhenius Growth Kinetics of CEL Crystals

To gain more insight into the kinetics of the crystal growth process, the surface and bulk growth rate data for Forms I and III were fitted to the Arrhenius equation (Eqn. 5–1) to obtain the corresponding activation energies, \( E_a \) (Table 5–2). Both diffusion-controlled and GC growth kinetics follow the Arrhenius relationship, as shown by the linear dependence of \( \ln(k) \) on \( 1/T \) (Figure 5–15). However, the points started to digress from linearity above 120 °C and was therefore not included for fitting. This digression could be attributed to the more prominent role of the reduced free energy difference between crystal and the melt when approaching melting point (zero at the melting point). In both surface and bulk crystallization, the \( E_a \) is significantly lower for solid-state growth/GC growth than for diffusion-controlled growth. This is aligned with the fact that GC growth requires only
minor local molecular mobility (e.g., β process), which is easier than global mobility of molecules (e.g., α process) in the diffusion-controlled growth region.  

In the solid-state growth and GC growth region, the $E_a$ for CEL Form III surface growth (68 kJ/mol) is lower than that for bulk growth (91 kJ/mol). Both activation energies for surface and bulk lie in the middle of the range of $E_a$ in systems studied for GC growth so far (30 – 185 kJ/mol) (Table 5–2). Since the surface crystal growth has been correlated with surface diffusion coefficient, and both surface and bulk diffusion coefficients follow Arrhenius relationship, $E_a$ based on diffusion coefficients is expected to be comparable to that based on growth rate. In fact, the $E_a$ of surface diffusion coefficient (146 kJ/mol) is lower than that of the bulk diffusion coefficient (368 kJ/mol) for tris-naphthyl benzene (TNB). This is consistent with the observed lower $E_a$ for the surface growth than the bulk growth of CEL.

Another observation is that $E_a$ values of both CEL polymorphs in the diffusion-controlled regions, both on surface and in the bulk, are higher than those in the solid-state growth/GC growth region. This is consistent with the fact that below $T_i$, the solid-state growth mechanisms dominate over diffusion mechanism. In addition, most of previous work on growth kinetics only included the bulk crystal growth process. As a result, the different $E_a$ values between surface and bulk crystallization processes have not been established. The lower surface $E_a$ than that of bulk $E_a$ (~25% for Form III CEL) in solid-state growth region, and ~42% for Form I CEL in diffusion-controlled region) is reported here for the first time.
Table 5–2. Kinetic parameters of CEL bulk and surface processes compared to known examples of GC crystal growth in bulk glasses

<table>
<thead>
<tr>
<th>Systems</th>
<th>Growth mode</th>
<th>$T_g$, K</th>
<th>$T_f$, K</th>
<th>$\log u$ at $T_f$, m/s</th>
<th>$E_a$, kJ/mol</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROY-YT04</td>
<td>bulk GC</td>
<td>260</td>
<td>269</td>
<td>-7.2</td>
<td>83</td>
<td>272</td>
</tr>
<tr>
<td>ROY-Y</td>
<td>bulk GC</td>
<td>260</td>
<td>265</td>
<td>-7.4</td>
<td>76</td>
<td>272</td>
</tr>
<tr>
<td>ROY-OP</td>
<td>bulk GC</td>
<td>260</td>
<td>265</td>
<td>-7.5</td>
<td>88</td>
<td>272</td>
</tr>
<tr>
<td>ROY-R</td>
<td>bulk GC</td>
<td>260</td>
<td>261</td>
<td>-8.2</td>
<td>71</td>
<td>272</td>
</tr>
<tr>
<td>TP (TPm)</td>
<td>bulk GC</td>
<td>272</td>
<td>280</td>
<td>-6.1</td>
<td>127</td>
<td>273</td>
</tr>
<tr>
<td>NIF (β)</td>
<td>bulk GC</td>
<td>315</td>
<td>316</td>
<td>-8.5</td>
<td>126</td>
<td>271</td>
</tr>
<tr>
<td>IMC (γ)</td>
<td>bulk GC</td>
<td>315</td>
<td>306</td>
<td>-10.4</td>
<td>131</td>
<td>270</td>
</tr>
<tr>
<td>OTP</td>
<td>bulk GC</td>
<td>246</td>
<td>249</td>
<td>-7.8</td>
<td>65</td>
<td>276</td>
</tr>
<tr>
<td>DPCP</td>
<td>bulk GC</td>
<td>222</td>
<td>225</td>
<td>-7.8</td>
<td>30</td>
<td>274</td>
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<tr>
<td>DPCH</td>
<td>bulk GC</td>
<td>230</td>
<td>233</td>
<td>-8.1</td>
<td>45</td>
<td>274</td>
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<tr>
<td>salol</td>
<td>bulk GC</td>
<td>222</td>
<td>226</td>
<td>-7.1</td>
<td>57</td>
<td>272</td>
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<tr>
<td>IPB</td>
<td>bulk GC</td>
<td>129</td>
<td>127</td>
<td>-9.5</td>
<td>-</td>
<td>299</td>
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<tr>
<td>toluene</td>
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<td>118</td>
<td>116</td>
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<td>50</td>
<td>272</td>
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<tr>
<td>GSF</td>
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<td>360</td>
<td>-8.5</td>
<td>185</td>
<td>268</td>
</tr>
<tr>
<td>CEL (III)</td>
<td>bulk GC</td>
<td>325</td>
<td>317</td>
<td>-9.5</td>
<td>91</td>
<td>This work</td>
</tr>
<tr>
<td>CEL (III)</td>
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<td>325</td>
<td>315</td>
<td>-9.1</td>
<td>68</td>
<td>This work</td>
</tr>
</tbody>
</table>
Figure 5–15. Arrhenius relationship of CEL growth rate a) on the surface and b) in bulk.
In the diffusion-controlled regions (≥ 63.3 °C on the surface and ≥ 56.6 °C for bulk), Forms I and III have similar $E_a$ on the surface, being 186 kJ/mol and 185 kJ/mol, respectively. The bulk growth of Form I has a significantly higher $E_a$ (265 kJ/mol) than that on the surface. The bulk $E_a$ of CEL Form I in the diffusion-controlled regions is the highest in all systems reported so far (Griseofulvin had $E_a$ of 236 kJ/mol in diffusion-controlled region). The Form III doesn’t have enough data for obtaining bulk $E_a$ in this temperature range, but similar observation to the Form I growth is expected.

The crystal growth rates at $T_i$ normalized by $T_g$, i.e., $T_i/T_g$, for small organic molecules studied so far follow a common trend (Figure 5–16). This trend is upheld when bulk crystal growth of CEL is added, which suggests a universal physical mechanism for the GC crystal growth model among these investigated compounds. In more than half of these systems, faster GC growth can persist up to a temperature above $T_g$ (Figure 5–16). The $T_i/T_g$ for CEL GC growth in bulk is among the lowest (comparable to that of γ-IMC), compared to other compounds studied. Therefore, the $T_i$ is lower than the $T_g$ of bulk CEL, indicating an earlier disruption by the onset of diffusion-controlled growth mechanism than other systems.
Figure 5–16. Growth rate $u$, at $T_i$ as a function of $T_i / T_g$ of several small organic molecules studied for GC growth mode. The black star represents CEL.

5.5 Conclusions

We have systematically studied the crystal growth kinetics of amorphous CEL both on the surface and in bulk. Upon cooling, the crystal growth rates near and below $T_g$ (51.8°C) for both surface and bulk Form III CEL abruptly increased from those predicted from diffusion-controlled crystal growth mechanism, agreeing with the known solid-state and GC growth mechanism. The nearly 80-fold increase in the surface growth rate of CEL Form III crystal over bulk growth in the glassy region is attributed to the fast molecular surface diffusion. These two fast crystal growth mechanisms are influenced by the onset of fluidity differently, showing higher $T_i$ and a wider transition zone on the surface. The transitions zones of both surface and bulk growth of CEL are the widest among all known
small organic molecules exhibiting GC growth. CEL also exhibited cross-nucleation phenomenon, which has been characterized by micro-Raman mapping. Form I exhibited faster growth rate than Form III in all crystal growth processes, where both followed the Arrhenius relationship. The activation energies for diffusion controlled mechanisms are higher than surface solid-state growth/bulk GC growth mechanisms. In summary, CEL exhibits several intriguing phenomena in crystal growth from the amorphous state, including fast surface growth, GC-growth, cross-nucleation, and growth mechanism dependent crystallite morphologies. Compared to other molecules investigated for growth mechanisms, two unique features with CEL include: 1) the widest transition zone between surface solid-state growth/bulk GC growth and diffusion-controlled growth, and 2) the highest activation energy in the diffusion controlled growth in the bulk. Data presented here can also help the development and stabilization of amorphous based tablet products of CEL with improvement in solubility and dissolution properties.
Chapter 6.

Research Summary and Future Work
Research Summary

Celecoxib (CEL) is a non-steroidal anti-inflammatory drug (NSAID) that is widely prescribed for treating arthritis, osteoarthritis and rheumatoid arthritis associated pain and inflammation. It is a high dose drug only available as capsules, and not in the most patient-compliant tablet dosage form. The low bulk density, high elasticity and poor flowability of commercial CEL Form III makes it difficult to be formulated into tablets suitable for high speed direct compression tablet manufacture. In this thesis, the shortcomings of the current Form III of CEL are overcome by solid state engineering, and a direct compression tablet formulation is successfully developed via crystal engineering.

Understanding the molecular origin of the properties of CEL Form III that challenge direct compression tablet manufacturing is the first step of developing strategies to mitigate these problems via Quality by Design (QbD) approach. In Chapter 2, the exceptionally high elasticity of CEL is examined using analytical techniques – micro-Raman spectroscopy and nanoindentation, and understood on a molecular level. A large needle-shaped single crystal of CEL Form III is grown, which is quantitatively bent for a high elastic strain of 3.65%; after which the crystal recovered to straight conformation. Nanoindentation suggested a high Elastic Modulus ($E$) of 16.27 ± 0.43 GPa. A model is proposed based on analysis of key intermolecular interactions within CEL Form III crystals, which is then confirmed by micro-Raman spectroscopy. The results suggest numerous weak and a few strong intermolecular interactions establish the high elasticity on the major (001) face of CEL crystals. This implicates that future crystal engineering approach to modify elasticity could aim at the intermolecular interactions within the crystal structure.
In search of alternative solid forms of CEL, pharmaceutically acceptable solvates of CEL are screened as an alternative way to improve the tablet manufacturability of CEL through crystal engineering. During the screening of CEL solvates, two stoichiometric solvates of CEL and N-methyl-2-pyrrolidone (NMP) are discovered with stoichiometric ratios of 1:1 and 1:2 CEL:NMP. The two solvates have distinct crystal structures and physicochemical properties. An intriguing conversion from CEL di-NMP solvate to mono-NMP solvate as CEL di-NMP solvate is heated up is captured using Differential Scanning Calorimetry (DSC). A hot stage combined with polarized microscopy (HSM) reveals a series of events including desolvation, dissolution of di-NMP solvate, crystal growth, dissolution and melting of mono-NMP solvate, which match with each step in the DSC curve. The mono-NMP solvate of CEL is stable at room temperature while di-NMP solvate easily converts to mono-NMP solvate at ambient conditions. Crystal structure analysis and the energy framework reveal the tightly bound NMP in mono-NMP crystal structure. Channels of loosely bound NMP molecules corresponding to 1 stoichiometric NMP in di-NMP structure are found, in addition to the tightly bound NMP molecules that have very similar packing as mono-NMP solvates. These structural features contribute to the ultra-stability of mono-NMP solvate and the easy conversion form di-NMP to mono-NMP solvate without sacrificing crystallinity. Infrared spectroscopy further confirmed the two interaction states of NMP molecules in the di-NMP solvate structure. This study details the structure-property relationship of the two CEL-NMP solvates and their interconversions, and illustrates the importance of using orthogonal analytical techniques to characterize solid state properties of drugs (Chapter 3).
To develop a direct compression (DC) tablet formulation for CEL, a pharmaceutically acceptable solvate - celecoxib dimethyl sulfoxide (DMSO) solvate is characterized and selected as suitable for DC tablet of better manufacturability and dissolution performance. The challenges facing commercial Form III powder for developing a DC formulation include low bulk density, poor flowability and tablet lamination issues. Through crystal engineering, we utilize the DMSO solvate of CEL to greatly improve the bulk density by 6 fold, and the flow factor ($ff_c$) by 2 fold. By reducing the elastic modulus ($E$) of CEL Form III by 1/3, CEL-DMSO tablets exhibit less in-die elastic recovery, and thus much alleviated lamination problem. The lamination of CEL-DMSO tablets are completely eliminated by developing a DC table formulation, which is a result of step-by-step data-oriented decision making process. Through optimization of formulations by evaluating the tablet quality, friability, ejection force, tabletability and dissolution performance, a DC tablet formulation is successfully developed. This is an example of combining a crystal engineering approach and guiding principles of the material science tetrahedron (MST) to develop a successful tablet formulation of a high dose drug (Chapter 4).

As a biopharmaceutics classification system (BCS) class II drug, CEL dissolution is limited by solubility. Thus, high doses of CEL are required to elicit a therapeutic benefit. To increase the solubility and thus the bioavailability of CEL, its amorphous form is studied for potential development as a candidate for tablet formulation. With the increased bioavailability, the dose can be potentially lowered, leaving more room for excipients to fine-tune the formulation performance as a DC tablet formulation. One problem about amorphous solids is its instability and tendency to convert to it crystalline counterpart. In
Chapter 5, the stability of amorphous CEL is evaluated through monitoring the crystal growth rate of melt-quenched amorphous CEL at a range of temperatures. The mechanism of crystal growth is found to be different on the free surface and in bulk of melt. Faster surface crystal growth than bulk is found across all temperature ranges. Below the glass transition temperature $T_g$ of CEL, the glass-to-crystal (GC) growth mode is activated, resulting in fast crystal growth rates at pharmaceutically relevant temperatures. Cross-nucleation between CEL Forms I and III is also observed, which play a role in the crystal growth profiles. The crystal growth rate follows Arrhenius kinetics, with the activation energy of surface crystal growth lower than in the bulk. This study systematically studied the crystal growth kinetics of amorphous CEL. It lays the foundation for future development of amorphous solid dispersion (ASD) based tablet products with improvement in solubility and dissolution properties.
Future Work

This thesis has taken celecoxib (CEL) as a model drug and delved into utilizing solid state engineering strategies to obtain the desired properties suitable for direct compression (DC) tablet manufacturing. Guided by Quality by Design ($QbD$) principles and Material Science Tetrahedron (MST), the physicochemical properties and tablet manufacturability of celecoxib have been greatly improved, with a viable DC tablet formulation successfully developed.

Solid-state engineering stems from understanding of molecular origins of properties. From the verified model of highly elastic CEL Form III crystals (Chapter 2), the high elasticity of (001) face of CEL is well understood. However, the minor ($0\bar{1}1$)/($01\bar{1}$) faces of CEL needle crystals exhibits brittle fracture when subjected to 3-point bending experiments. When subjected to an external force, the changes in molecular interactions of minor ($0\bar{1}1$)/($01\bar{1}$) faces are different from the major (001) face, which may lead to drastically different properties. The size of crystals faces also leads to different mechanical behavior. This exploitation can be achieved by growing larger single crystals of needle-shaped CEL Form III crystals, for which the nanoindentation could be performed on minor faces of the crystal. The different mechanical behavior on different faces of CEL contribute to the mechanical performance during tableting to different extents. If a crystal is highly anisotropic, the effect of major crystal faces may dominate the tablet behavior of the crystal; conversely, the tableting properties can be equally influenced by every face of an isotropic crystal. The details of correlating anisotropic mechanical properties of crystals with the tableting performance requires further studies with selective model compounds.
The insights obtained from this research will enrich the landscape of ‘structure-property-performance’ within MST, especially in connection to tableting behaviors of pharmaceutical materials.

During solvate screening of CEL, 6 solvates were discovered and characterized. The 6 solvent molecules involved are dimethyl acetamide (DMA), dimethyl formamide (DMF), N-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO), tetramethyl urea (TMU) and N, N′-Dimethylpropyleneurea (DMPU). The mechanical properties (E and H) of the 6 solvates are characterized by nanoindentation. All six solvates are highly stable solvates having high melting points below which no desolvation occurs. One commonality of the mechanical properties among the 6 solvates are their fracture tendency after nanoindentation tests (e.g. CEL-DMSO solvate fracture, Figure 4–10). Another similarity is that all 6 solvates had lower E and H on their major face (002) than CEL Form III on (001) face. The tendency to fracture of CEL solvate crystals indicate that they are more brittle than CEL Form III. The fracture mechanism, fracture plane, and fracture toughness remained unexplored. Further studies of fracture behavior will gain structural insights into the mechanisms of fracture. The fracture toughness has also been correlated with milling behavior in molecular crystals. The detailed study of fracture toughness of the 6 CEL solvates will also have indications on their susceptibility to milling and size reduction, as well as the milling induced disorder and instability, which are important process parameters during drug product development.

A direct compression tablet formulation is successfully developed in Chapter 4 through crystal engineering methods by utilizing a stable and pharmaceutically stable
solvate – CEL-DMSO solvate. The CEL-DMSO tablet exhibits better dissolution profile with faster onset than Celebrex® capsules. However, the intrinsic dissolution rate (IDR) study of pure CEL-DMSO solvate crystals reveals the fast conversion and precipitation to thermodynamically stable Form III upon contact with dissolution medium. This suggests a much higher thermodynamic solubility of CEL-DMSO than CEL Form III, leading to fast supersaturation generation followed by rapid precipitation due to instability in solution. Maintaining the supersaturation after CEL-DMSO is in contact with water and thus maintaining its solubility advantage, will effectively increase the bioavailability of CEL. Selection of polymer inhibitors to be added into the tablet formulation will be an effective measure to solve this problem. The dose of CEL can also be lowered potentially through this measure. Polymer screening can be done through monitoring the nucleation induction times of CEL crystals under presence of different types of polymers in saturated CEL solution. The longer nucleation induction time corresponds to better ability of the polymeric material to stabilize CEL in dissolution media, forming the ‘spring and parachute’ curve to sustain high CEL concentrations.

In Chapter 5, the stability of amorphous CEL is evaluated by understanding the crystal growth mechanisms of amorphous CEL at a range of temperatures. The fast glass-to-crystal growth below its glass transition temperature $T_g$, especially on the surface, indicates its instability as amorphous state. To stabilize the amorphous CEL, an amorphous solid dispersion (ASD) of CEL needs to be developed. First, the polymer type and grade needs selected to be miscible with CEL without phase separation; it also needs to stabilize amorphous CEL and prevents crystallization from happening both in solid state. Lastly, this polymer should also be a good stabilizer when the ASD is being dissolve in dissolution
media. In addition to the enhancement in solubility and dissolution, the manufacturability of ASD also needs to be evaluated. For a direct compression tablet formulation, the flow properties, punch sticking propensities and tabletability should be considered. Preliminary studies have shown that the CEL and HPMC-AS ASD prepared by fast solvent evaporation exhibited much less punch sticking propensity compared to CEL Form III. This is another example of using solid-state engineering method to overcome manufacturability challenges. The flow and tabletability of this ASD remain to be evaluated. However, the different processing conditions and particle engineering techniques can be employed in the DC tablet formulation design of CEL ASDs under the MST landscape.

Finally, a successful direct compression tablet formulation of CEL with improved stability, dissolution performance and excellent manufacturability can be successfully developed via solid-state engineering strategies.


(accessed August 11, 2020).


47. Hou, H.; Sun, C. C., Quantifying effects of particulate properties on powder flow properties using a ring shear tester. *J. Pharm. Sci.* **2008**, *97* (9), 4030-9.


58. Sun, W. J.; Aburub, A.; Sun, C. C., A mesoporous silica based platform to enable tablet formulations of low dose drugs by direct compression. *Int. J. Pharm.* **2018**, *539* (1-2), 184-189.


64. Shi, L.; Feng, Y.; Sun, C. C., Roles of granule size in over-granulation during high shear wet granulation. *J. Pharm. Sci.* **2010**, *99* (8), 3322-5.


80. Sun, W. J.; Sun, C. C., Ribbon thickness influences fine generation during dry granulation. *Int. J. Pharm.* **2017**, *529* (1-2), 87-88.


125. Guzman, H. R.; Tawa, M.; Zhang, Z.; Ratanabanangkoon, P.; Shaw, P.; Gardner, C. R.; Chen, H.; Moreau, J. P.; Almarsson, O.; Remenar, J. F., Combined use of


142. Cao, Y.; Li, H., Engineered elastomeric proteins with dual elasticity can be controlled by a molecular regulator. *Nat. Nanotechnol.* **2008**, *3* (8), 512-6.


Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision E.01; Gaussian, Inc.: Wallingford, CT, 2009.


https://www.fda.gov/drugs/guidances-drugs/international-council-harmonisation-quality

Accessed June 11, 2020


204. Almarsson, Ö.; Hickey, M. B.; Peterson, M.; J, Z. M.; Moulton, B.; Rodriguez-Hornedo, N., Pharmaceutical co-crystal compositions of drugs such as carbamazepine,


239. Wang, C.; Sun, C. C., The landscape of mechanical properties of molecular crystals. 


Appendix

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