Controlled Release as a Strategy to Prevent Solution-Mediated Phase Transformation in Amorphous Solid Dispersions: Effect of Dosage Form Design

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Department of Pharmaceutical Sciences
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Abstract

The purpose of this study was to define the limits of developing a controlled-release amorphous solid dispersion (CRSD) system intended for enhancing the bioavailability of poorly water soluble drugs. Feasibility of multiple solid oral CRSD dosage form designs, such as spray dried powders, coated beads and compressed matrices (dry granulations and tablets) was evaluated. Solid dispersion powders were characterized in terms of ability to establish and maintain amorphicity in the dry form (by DSC and XRD) and ability to circumvent events leading to solution-mediated phase transformation (SMPT), or recrystallization during dissolution. While all dosage forms could successfully be produced with the amorphous dispersion, great differences in dissolution/recrystallization profiles were found, depending on how the controlled release agent was incorporated. These studies reveal that when designing a solid dispersion system, greater benefit can be derived by selecting the appropriate dosage form design, granting the formulator the much sought-after control over the challenge of SMPT.
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List of Abbreviations

API- active pharmaceutical ingredient

ATR- attenuated total reflectance

AUC- area under the curve

BCS- Biopharmaceutic Classification System

$C_{\text{max}}$- maximum concentration, or peak kinetic solubility

CR- controlled release

CRM- controlled release matrix

CRSD- controlled release solid dispersion

DG- dry granulate(d)

D:P ratio- drug:polymer ratio

D:S ratio- dose:solubility ratio

DSC- differential scanning calorimetry

FR (or IR)- fast release (or immediate release)

FTIR- Fourier transform infrared spectroscopy

GIT- gastrointestinal tract

HPMC- hypromellose or hydroxypropylmethylcellulose

ICH- International Conference of Harmonization

MCC- microcrystalline cellulose

MUPS- multi-unit particulate system
NCE- new chemical entity

PCI- polymeric crystallization inhibitor

PM- physical mixture

PVAc- polyvinyl acetate

PVP- polyvinylpyrrolidone

PWSD- poorly water soluble drug

P-XRD- powder x-ray diffraction

SD- solid dispersion

SDDF- solid dispersion dispersible formulation

SMPT- solution-mediated phase transformation (i.e. recrystallization)

SR- slow or sustained release

$T_{\text{max}}$- time to reach peak kinetic solubility

$T_g$- glass transition temperature

USP- United States Pharmacopeia
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Chapter 1

1 Introduction

1.1 Rationale

One of the most prominent challenges that the pharmaceutical industry currently faces is finding superior technologies to formulate and commercialize Biopharmaceutic Classification System (BCS) Class II and Class IV drugs, or those exhibiting dissolution-limited bioavailability for oral delivery. Of the many proposed techniques that are known, solid dispersion remains to be a promising choice since it can be especially effective for candidates with very high dose-solubility (D:S) ratios. In addition, techniques used to produce solid dispersions (SDs), such as spray drying and hot-melting, are commercially scalable and have been well understood for decades. The caveat with solid dispersions however, is the high propensity to lose its solubility advantage by the process of solution-mediated phase transformation (SMPT), or recrystallization upon contact with aqueous media, such as during in-vitro or in-vivo dissolution. That is, as amorphous drug quickly dissolves and supersaturated drug concentrations are allowed to build inside the dosage form and/or in its surrounding bulk solution, the process of solution-mediated phase transformation (SMPT) causes the drug to revert to its less desired, poorly soluble crystalline form. The three stages of SMPT have been described as: (1) dissolution to form a supersaturated solution, (2) nucleation, and (3) crystal growth (Greco & Bogner, 2012). It has also been postulated that the rate of this process is an intrinsic property of the API (Van Eerdenbrugh, Hsieh, Augustijns, & Taylor, 2014).

The conventional approach to address SMPT of amorphous solid dispersions is by careful selection of a polymeric crystallization inhibitor (PCI). Typical candidates are high T_g (glass transition temperature) hydrophilic polymers such as polyvinylpyrrolidone (PVP), hypromellose (HPMC), or polyethylene glycol (PEG) that have the ability to form a hydrogen bonds with the poorly water soluble drug (PWSD) candidate. In effect, mobilization of the amorphous drug is limited and drug-drug interactions are minimized, thus sustaining supersaturation and preventing the events leading to recrystallization. While this strategy is theoretically sound and has been proven to be successful for some drug candidates, it is not always feasible or practical when developing a marketable drug product. Since APIs can differ greatly in their intrinsic properties such as solubility/dissolution, permeability and propensity for recrystallization, there
may be mixed success with developing amorphous SD. Oftentimes the amount of PCI required to sustain supersaturation can be in such large amounts (e.g. >70% in formulation) that the size of the dosage form is no longer practical for human administration once the dose of drug required is considered. Further to this, it has been well reported that spray dried solid dispersion powders often suffer from high cohesivity, very low bulk density, poor flowability and poor compressibility, therefore the end product is highly likely to require other formulation excipients to facilitate the manufacturing process. While the literature in solid dispersion technology is rich with critiques and guidance for selecting PCIs, there is relatively little work conducted on the downward processing stages where SD powders are transformed into fully developed (i.e. formulated and processed) dosage forms. Hence, by solely focusing on the selection of PCI, there may be some important formulation development challenges that are being overlooked. Many current reviews of SD technology have agreed that in order to improve our understanding and advance the development of SD systems, it is essential for the dosage form development aspect to be further explored, which is still vastly lacking in the literature to date (McGinity, et al., 2012; Tran, Tran, Park, & Lee, 2011; Leane, et al., 2013).

In this study, emphasis is placed on solid oral dosage form design during the exploration of an alternative strategy to maximize efficacy and use of drug in SD by involving a controlled release feature. Controlled release (or CR) has established many benefits in drug delivery, such that plasma concentration levels can be better targeted and maintained for longer periods, thus maximizing efficacy, minimizing side effects, and enabling less frequent dosing schedules, hence increasing patient compliance. Typically, these benefits can only be reaped by the more soluble BCS Class I drug candidates, as release retardation effects are not easily afforded by PWSD candidates whose bioavailability is already dissolution rate-limited. Therefore, if CR can indeed be achieved while simultaneously enhancing solubility by the SD technique, a controlled release solid dispersion system (CRSD) would prove to have enormous utility. However, in terms of the strategic approach highlighted in this thesis title, the idea of pairing a CR feature with SD into a CRSD stems from the realization that the success of SD systems can be highly rate-dependent. For example, if dissolution rate of the drug in SD form is so high that it exceeds the rate that drug can be removed from the gastro-intestinal tract (GIT) (i.e. rate of permeation), these areas of supersaturation may trigger the onset of nucleation and crystal growth, causing amount of solubilized drug to plummet. Depending on the intrinsic propensity of recrystallization for the particular drug candidate, the rate of this plummet may also vary.
Therefore, the concept of the proposed CRSD strategy is to tailor release rate so that dissolved drug concentrations in any given compartment (e.g. GIT) can be maintained well below a certain threshold concentration, such that the rate of dissolution matches rate of absorption and onset of SMPT can be avoided. A secondary benefit of a successful CRSD system would also include feasibility of extending CR benefits to PWSD (while elevating solubility), a feature not typically achievable for these types of drug candidates. For these two reasons, CRSD has become the primary direction for this research.

With regards to our focus on dosage form design, the dosage form, which is the vehicle used to deliver the required dose of the drug in the intended manner (e.g. place, time, duration), can be a critical factor itself, when determining how viable a drug candidate may be for oral delivery, especially in the case of CR systems. As is well known, once a CR feature is introduced, design options are almost endless. Given the wide variety of formulation excipients, processing methods and equipment, there may be a multitude of ways to develop a single drug product. Our fundamental knowledge of CR systems tell us that release mechanism and release kinetics can greatly depend on geometry (e.g. cylinder, sphere, slab), method of incorporating the retarding agent (e.g. applied as membrane vs. matrix former), unit design (e.g multi-unit vs. single unit) and on how much of each material is used. The combination of these factors may ultimately affect porosity, tortuosity and permeability, which in turn affect release kinetics and release mechanism. Therefore, in search of the protective mechanisms coming from CRSDs, dosage from design as a factor, should not be ignored.

The model PWSD selected for this study was celecoxib, whose high D:S ratio dictates that advanced formulation techniques are required in order to use the drug more effectively. Albeit, the currently marketed product, Celebrex®, is a capsule filled with a simple crystalline formulation, which barely demonstrates significant improvements in dissolution compared to the unformulated bulk powder, yet has risen to achieve blockbuster status due the compound’s exceptional clinical benefits over other drugs in its therapeutic class. With an expected patent expiration in 2015, much research has been dedicated to finding superior techniques to formulate celecoxib in a more efficient and therapeutically effective way, specifically by targeting its dissolution-limited bioavailability.

For the CRSD systems investigated, Kollidon® SR (polyvinyl acetate-PVP) was the polymer selected to impart the CR feature. Due to its relatively newer introduction to CR applications in
pharmaceutics compared to other commercialized functional polymers, there have been fewer reports, hence limited knowledge gained of its behaviour in CR (not to mention, CRSD) systems. Since Kollidon® SR is available in both an aqueous dispersion form convenient for coating, and in a dry powder form possessing exceptional qualities for direct compression (e.g. excellent flowability, compressibility and compactibility), this further permitted the exploration of a wider scope of dosage form designs.

1.2 Hypothesis
Manipulation of dosage form design can be employed as a useful strategy to explore potential improvements in drug delivery from amorphous spray dried solid dispersion powders. By varying unit design and method of incorporation of a CR agent (Kollidon® SR), a range of fast release (FR) to sustained release (SR) CRSD systems can be developed, functioning to maximize the extent of dissolution by minimizing the phenomena of solution-mediated phase transformation.

1.3 Objectives

1. To explore a comprehensive range of dosage forms varying in unit design (e.g. multi-particulates vs. single unit tablets), and method of CR agent incorporation (e.g. matrix vs. membrane) using Kollidon® SR to gain an understanding of its feasibility, strengths and limitations in CRSD systems.

2. To investigate the utility of CR in preventing SMPT of drug in amorphous solid dispersions. Demonstrate greater efficacy and efficiency of drug use in CRSD formulations compared to conventional SDs and crystalline forms by minimizing internal (within the dosage form) and external (bulk solution) SMPT.

1.4 Scope
The scope of this research was to investigate the effects of manipulating solid oral dosage form design of spray dried SDs and CRSDs prepared from a single model drug candidate (celecoxib) and a single selected CR agent (Kollidon® SR), as assessed by in-vitro dissolution testing. Results from this study could be used to strengthen our general understanding of the behavior of amorphous solid dispersions in various dosage form designs, and to provide a framework for investigating other drug candidates that could potentially benefit from CRSD strategies.
Chapter 2

2 Background and Literature Review

2.1 Solid Dispersions

2.1.1 Applications of Solid Dispersions

Solid dispersions were first developed by Sekiguchi and Obi (1961) by creating eutectic mixtures of crystalline drug and carrier, in attempt to enable solubility enhancement of poorly water-soluble drugs (Serajuddin, 1999; Acevez, Cruz, & Hernandez, 2000; Vasconcelos, Sarmento, & Costa, 2007). In the later 60’s, others evolved SD formulations to include amorphous polymeric carriers, or polymeric crystallization inhibitors (PCIs) where the drug could be rendered in amorphous form, exhibiting an even higher solubility, and maintaining supersaturation levels for longer periods of time (Vasconcelos et al., 2007). Simply put, SDs are pharmaceutical forms in which the drug is dispersed at the molecular or nanoparticle level in a biologically inert solid matrix, with the primary purpose of enhancing solubility of PWSDs. For decades, this strategy has attracted many to conduct further research, unravelling a wider range of SD manufacturing methods, components for use, and elucidating critical factors such as solvent selection, polymer-drug interactions, spray drying parameters, etc. (Bikiaris, 2011). Since the advent of high-throughput screening (HTS), where the striking majority of NCEs are emerging as poorly water soluble, there is a renewed and perhaps greater interest in amorphous solid dispersions for solubility enhancement in order to find better means to formulate these NCEs.

Interestingly, in recent years there have also been attempts to use the solid dispersion technique as a method to manufacture microparticulate controlled release systems using water soluble drugs (Iqbal, Babar, & Ashraf, 2002; Mundargi, Rangaswamy, & Aminabhavi, 2009; Oth & Moes, 1989; Palmieri, Bonacucina, Di Martino, & Martelli, 2001). In a similar manner, the development of polymer-lipid nanoparticles, which render the drug in amorphous form reveal great benefits (Li, Taulier, Rauth, & Wu, 2006; Li, Wong, Shuhendler, Rauth, & Wu, 2008). Highlighted for the ability to create CR matrices on a much smaller scale where polymer and drug may be combined on a smaller scale (e.g. nanoparticle level), this strategy is welcomed to
the existing repertoire of methods (e.g. traditional matrix, membrane-reservoir, osmotic pressure controlled, etc.) offering greater options and flexibility to the formulator. In these systems however, a great majority have only focused on water soluble drug candidates, despite the fact that the benefits of CR systems such as less frequent dosing regimen, less experienced side effects, and overall better therapeutic efficacy and efficiency, are equally sought for PWSD candidates. It has also been noted that more needs to be understood regarding the application and limits for these types of systems (Palmieri et al. 2001).

2.1.2 Methods of Manufacturing Solid Dispersions

Various methods exist to produce amorphous solid dispersions. Common to all, is the requirement that the highly ordered crystal lattice be somehow disrupted and exchanged for the randomly-ordered amorphous form, and that the amorphous drug be dispersed in some inert carrier (typically a polymer). The most frequently cited methods in literature are thermal methods (e.g. fusion, hot melting) and solvent evaporation (e.g. spray drying), as they are the most transferable to commercial scale. However, other methods involving lyophilization, supercritical fluid and grinding have also been explored (Bikiaris, 2011; Caron, Tajber, Corrigan, & Healy, 2011). Below, the two favoured methods based on the thermal and solvent approach are discussed.

**Thermal methods**

Thermal methods entail dissolving (or dispersing) the drug in a molten carrier, transforming it from crystal to amorphous phase upon cooling and solidification (Hancock & Zografi, 2007). Typically, these carriers are thermoplastic matrix forming binders, with the criteria of being thermostable at least 20-30°C lower than the melting point of the API (Djuris, Nikolakakis, Ibric, Djuric, & Kachrimanis, 2013). The crude thermal SD method most suitable for bench-top experiments, is known as simple fusion, where the solidified mass is subsequently milled and sieved to powder. Final product texture however, tends to be hard and difficult to decrease in size (Srinarong, de Waard, Frijlink, & Hinrichs, 2011). Hot-Melt Extrusion (HME) is the commercially relevant thermal method. With HME, molten mass passes through a temperature-controlled cylinder fitted with a die plate and rotating screws so that cooled extrudates can be formed upon exiting. Extrudates can be milled, cut, or spheronized to achieve desired size and shape. Due to its advantage of being a solvent-less, dust-free, continuous process, HME is gaining popularity commercially, and has already benefitted some companies such as Abbott,
who has developed several hot-melt SD products on the market (Kaletra™, Isoptin SR-E, and Norvir). The major drawback of thermal methods, however, is that there is limited applicability to thermolabile API and excipients, and that bench-top experiments such as simple fusion, are not usually transferrable to the larger scale HME method, thus requiring larger amounts of starting material.

*Solvent Evaporation Methods*

Solvent evaporation methods on the other hand, have little restrictions regarding temperature sensitivity of API. In this technique, a solvent or a solvent system is used to dissolve (or disperse) API and polymeric carriers, and subsequently evaporated to yield dry powder. Amorphous forms can be obtained upon rapid drying. Crude bench-top methods may include solvent-casting (or film-casting), where a thin layer of the solution is allowed to dry at room temperature or oven, and the solid mass is milled and sieved. Alternatively a rotary evaporator may be used to improve drying efficiency. While other methods such as super-critical fluid (SCF) drying and freeze drying have also been pursued, the most commercially relevant method that is recognized is spray drying.

Spray drying has had numerous applications within the pharmaceutical industry (e.g. excipient manufacturing, powders for respiratory route of administration) for decades, which have benefitted from its ability to tune desired product properties by manipulation of a wide range of operating and processing parameters (Caron, Tajber, Corrigan, & Healy, 2011). Yet despite its sophistication, it is a relatively simple, continuous process that can easily be scaled from mg amounts to several tonnes (Srinarong et al. 2011). Due to these reasons, spray drying is a commercially viable method to produce solid dispersions, as evidenced by some of the marketed spray-dried SD products of Janssen (Intalence ™, Sporanox ™), and Novartis (Zortress ™).

2.1.3 Limitations of Solid Dispersion Systems

To date however, there are still relatively few products on the market benefitting from the amorphous solid dispersion strategy, considering the number of studies pursued in literature and the recognized potential that it offers in solubility enhancement (Shimpi, Mahadik, & Paradkar, 2009; McGinity, et al., 2012; Tran, Tran, Park, & Lee, 2011). Solubility is improved by several mechanisms: decreased particle size, improved wettability, and most importantly, transformation of the crystal lattice form to randomly-ordered amorphous form. By
transformation to amorphous form, which entails higher surface area and higher free-energy, PWSDs may experience a 10 to 1600-fold increase in solubility (Bikiaris, 2011). At times, however, SD particles may be prone to high cohesion, poor flowability, or may be sticky, tacky, possess low bulk density, or have poor compactibility and compressibility (Serajuddin, 1999; Gil, 2011). Therefore, transforming solid dispersions into solid oral dosage forms (i.e. tablets, powder-filled capsules), could be a challenging task.

The most critical challenge however, is the ability of the system to maintain the drug in a physically stable amorphous form, especially during dissolution. While the amorphous state is the critical advantage of the SD, it may also be its critical liability, as it is more thermodynamically unstable compared to its crystalline counterpart. Having a higher free energy and lack of crystal lattice, exposure to elements of heat and moisture (i.e. during processing, storage, and dissolution in the GIT) where plasticization and mobility are highest, make the amorphous form highly susceptible to recrystallization. As a consequence, drug is reverted to a form where dissolution is hindered, and the SD loses the benefit of solubility enhancement. It is this persistent phenomenon of SMPT that prevents many drug candidates from utilizing the solid dispersion technique. Therefore strategies to prevent or minimize this occurrence are obviously of critical importance. It is cautioned, however, that different crystallization inhibition mechanisms may vary with the amount of water in the system, hence recrystallization events occurring within the confines of the dosage form may need to be distinguished from those occurring in its surrounding dissolution media (Ohara, Kitamura, Kitagawa, & Terada, 2005; Zhang & Zhou, 2009; Alonzo, Zhang, Zhou, & Gao, 2010).

2.1.4 Critical Factors in Designing Dolid Dispersion Systems

Although all factors are still not completely understood, decades of research have provided some insightful guidelines on how to design physically stable SD systems. Illustrated in Figure 1, are some important stages along SD product development with their respective contributing factors/effects that have been identified as critical in the achievement of physically stable amorphous SD systems by the spray drying method. Each of these factors is subsequently described in further detail.
Figure 1: Stages and Factors Contributing to the Successful Development of Stable Amorphous Solid Dispersion Systems.
**Polymer Carrier Selection**

The role of polymer carrier in conventional SD systems is already widely regarded as a critical factor in stabilizing the amorphous form; namely in its role as a polymeric crystallization inhibitor (PCI) (Gao, 2008). Some have described the stabilization technique of PCIs as the *spring and parachute effect*, where the PCI decreases the rate of decline after the amorphous drug has rapidly peaked, hence prolonging supersaturation (Brouwers, Brewster, & Augustijns, 2009). It is well referenced that the capability of PCIs strongly depends on the degree of interaction between the drug and polymer, and more specifically, ability to form hydrogen bonds (Zhang & Zhou, 2009; Huang, Wignet, & Schwartz, 2008; Al-Obadi, Brocchini, & Buckton, 2009; Ozeki, Yuasa, & Kanaya, 1997). Proposed mechanisms of crystallization inhibition due to drug-polymer interactions include: reduction in molecular mobility, long polymeric chains sterically hindering association between API molecules, creation of a kinetic energy barrier to nucleation, and an overall decreased free energy of the system (Tran, Tran, Park, & Lee, 2011; Zhang & Zhou, 2009; Yang, Grey, & Doney, 2010). Other polymer properties that have been noted for significance include high Tg and viscosity for their ability to decrease plasticity and molecular mobility, although studies have suggested that they are less reliable predictors for stability (Al-Obadi, Brocchini, & Buckton, 2009; Zhang & Zhou, 2009; Yang, Grey, & Doney, 2010).

**Solvent Selection**

During selection of polymer, a solvent or a solvent system should be selected such that both polymer and API can adequately be dissolved. A good solvent system will also allow for a swelled and extended conformation of polymer so that maximum interaction may occur (Al-Obadi et al., 2009). Also, it has been claimed that maximum conversion to amorphous form can only be achieved when drug is dispersed homogenously, or at best, at the molecular level (Paudel, Van Humbeeck, & Van den Mooter, 2010; Rizi, Green, Donaldson, & Williams, 2011). The minimum solubility of components is suggested to be 50 mg/ml, but ideally 100 mg/ml (Gil, 2011). Finding a common solvent has shown to be a great challenge in many conventional SD systems, due to the fact that conventional PCIs are hydrophilic and the API under development is hydrophobic (Serajuddin, 1999; Gil, 2011). In these cases, bi- or tri-solvent systems, metastable solutions, or suspension compositions may be the alternate choice (Ohara, Kitamura, Kitagawa, & Terada, 2005; Janssens, Anné, Rombaut, & Van den Mooter, 2009).
Other desirable attributes would be low boiling point and low viscosity (in solution with components) to ease evaporation at lower temperatures, and low toxicity (Gil, 2011).

**Drug Loading**

Maximum threshold values are often reported for API in amorphous SD systems. Logically, the higher the drug load, or percentage in the formulation, the shorter the distance between drug molecules, hence increased chances for nucleation and crystal growth. Also, API may contribute a plasticizing effect, posing greater interference between neighboring polymer molecules and preventing them from holding the SD matrix in a rigid state, thus minimizing the intended effect of the polymer. It is especially important that the ratio of API to polymer is balanced so that maximum molecular interaction can occur. As such, most studies will report using drug:polymer ratios (D:P ratios) skewed towards lower drug content (Maulvi, et al., 2011; Beaka & Kim, 2012). However, if the required D:P ratio is too low or if higher doses of drug are required, this may have impractical implications on the size of dosage form (Serajuddin, 1999).

**Spray Drying Parameters**

The spray drying system offers a multitude of parameter combinations, which must carefully be chosen according to the desired properties of the final SD, and to the properties of polymer and API. Microparticle size, regulated by spraying air flow, feed rate and feed concentration, may have influence on rate of dissolution and flow properties. Parameters influencing solvent evaporation rate, such as inlet temperature, feed concentration, and feed rate may be especially important for regulating the resultant density of the SD (Durrigl, 2011), as well as the percent conversion of drug from crystalline to amorphous form. The spray drying process is highly effective in producing amorphous solid forms largely due to its ability to remove solvent at such a high rate from the atomized droplets, thus minimizing time for crystal lattices to be arranged during drying of the solids. On the other hand, solvent-casting or use of a rotary evaporator, commonly used as the ‘solvent evaporation method’ in many bench-top studies, removes solvent at a markedly slower rate, so should be critically evaluated. Resultant SD properties may differ greatly from those produced from spray drying (e.g larger grain size, less homogeneity, lower Tg), and there is typically an underestimation of ability of the system to
convert to amorphous form (Janssens, Anné, Rombaut, & Van den Mooter, 2009; Dahlberg, Millqvist-Fureby, Schuleit, & Furó, 2010).

**Dosage Form Design**

Solid oral dosage form, usually in the form of tablets, is undoubtedly the most preferred dosage form as they comprise approximately 80% of those on market. However, incorporation of SD into a final dosage form seems to be a factor that is grossly underemphasized in studies on SDs, which tend to focus solely on the performance and attributes of the SD particulates itself (Serajuddin et al., 1999; McGinity et al., 2012; Palmieri et al., 2001). While this may be appropriate for our general understanding of SD development and selection of PCIs, it is short-sighted and insufficient, as downward processing will inevitably be required (e.g. encapsulation, tabletting). As mentioned earlier, SD traits such as low bulk density, high cohesivity, tackiness, poor plastic deformation, or poor flow, may pose challenges in the manufacture of tablets (e.g. uniformly filling die cavities of a tablet press, picking and sticking, ability to form strong compacts), or even during simple filling of capsules (e.g. lack of space due to low bulk density). Tablets have many advantages over capsules, such as use of a wider range of functional excipients (e.g. binder, disintegrant, retarding agents), and higher versatility in design (e.g. direct compression vs. granulation, IR vs. delayed release vs. sustained release, CR matrix vs. CR membrane-reservoir), where distribution of drug and excipients, and modulation of drug release can be customized. Furthermore, by simple virtue of compression, tablets have the ability to accommodate a higher amount of material, and modulate tablet density/porosity and hardness. In turn, resultant properties of tablets, such as porosity, may strongly influence water penetration and disintegration rate (i.e. rate of exposure of amorphous drug to water), revealing significantly different behaviour from intermediate SD powder forms (Palmieri et al., 2011).

Multi-unit particulate systems (MUPS), on the other hand, have gained much attention in more recent drug development, due to several advantages over single unit forms. First, distribution of a MUPS is predicted to be higher along the GI lining, minimizing local irritation, enabling higher surface area of drug to contact a greater surface are of the membrane, facilitating absorption. This type of spreading may also lead to less inter-patient variability due to less variation in gastric emptying and motility along the GI tract. For CR membrane-reservoir systems, there is also less risk of dose dumping from coated pellets versus a single coated
tablets. Finally, method of incorporation of active components, SD, or formulation excipients may also have significant effects on the performance of a product, therefore studies should not be limited to varying formulation composition alone (Weuts, 2011). Due to all these abovementioned variables, dosage form design is a major factor that has yet to be fully explored for SD systems.

Storage Conditions

While it is emphasized that the product itself should be designed for resilience against recrystallization, it is also important that storage conditions be selected to maximize its effect. Annealing temperatures of ~50°C below the T_g of the system is suggested in order to reduce molecular mobility to zero. However, since storage is most ideal at room temperature (25°C) this may not always be a practical approach unless T_g can be significantly raised (Caron, Tajber, Corrigan, & Healy, 2011; Vehring, 2008), and likewise if the API has a low melting point (Yang et al. 2010). In order to address effects from humidity, desiccators, moisture scavengers, or moisture barrier film coatings may be considered (Vehring et al. 2008).
2.2 Controlled Release Solid Dispersion (CRSD) Systems: An Alternative Approach to Overcome SMPT

Controlled release solid dispersions (CRSDs) for PWSD may be an attractive form from several perspectives. First, poor solubility is addressed by the SD technique, increasing the efficiency of drug used, giving higher extent of dissolution. Secondly, by incorporation of a CR feature, the widely desired benefits such as less side effects, improved regimen, greater bioavailability, etc. can be sought. In conventional SD systems, resultant *in-vivo* profiles can exhibit high peak plasma concentrations, short $T_{\text{max}}$ and short duration of effective concentration levels, which may be perfectly acceptable for an IR product where a short onset on action and duration is desired. By nature, for amorphous SD forms however, a high $C_{\text{max}}$ within such a short time span translates to a rapid accumulation of dissolved drug (potentially at both the surface of the dosage form and in bulk solution of GIT), which may be especially detrimental since nucleation rate is dependent on concentration (Hajime Konno, 2008). Therefore, by virtue of imparting a CR characteristic to an SD system where concentration of dissolved drug may be kept below a critical threshold concentration at which recrystallization rate predominates (Yang, Grey, & Doney, 2010; Tanaka N., 2006) by gradual imbibement of water and/or gradual drug release, a protective mechanism against recrystallization may potentially be induced. This latter point emphasizes a third attractive benefit of designing a CRSD for PWSD.

Designing an SD system paired with a CR feature may be perceived as an unorthodox approach since it entails prolonging the exposure of the amorphous drug form to a warmer, moist environment where it is least physically stable (Konno, Handa, Alonzo, & Taylor, 2008). Others may view the combination of a Class II drug with insoluble controlled release agents to be contradictory to the goal of solubility enhancement. Hence there is an apparent hesitance for further exploration in this field, as only a few studies can be found for CRSDs for PWSDs, not to mention, the absence of any CRSD on market. Notwithstanding, many have recognized the main attractiveness of these systems, which is the dual ability to tackle solubility enhancement and controlled-release of PWSDs in a single product (Oth & Moes, 1989; Tran, Tran, Park, & Lee, 2011; Tanaka N., 2006; Li, Wang, & Liu, 2008; Rathinaraj, Choudhury, Sheshrao, & Shinde, 2010). As such, there are some relevant case examples to be discussed.
2.2.1 Examples from Literature

Non-traditional manufacturing methods have been used by the following authors to achieve CRSDs for PWSD. Sun et al. (2012) loaded insoluble cross-linked PHEMA hydrogel matrix beads with PWSD, indomethacin, whose concentration versus time profile exhibited gradual increase over 24hrs, unlike the characteristic burst and decline from conventional SD systems containing HPMCAS or PVP. Improved profiles were attributed to a feedback-controlled diffusion mechanism occurring in the hydrogel layer, such that supersaturation within such a short period of time could be prevented, thus avoiding the trigger for nucleation. It was determined that if longer periods of solubility enhancement are required, slower release may be beneficial in subduing recrystallization events (Sun, Ju, & Lee, 2012). Tanaka et al. (2005) developed a novel disintegration controlled matrix tablet (DCMT), containing disintegrant and SD granules coated with hydrogenated soybean oil (HSO), where the HSO formed a waxy moisture barrier for the SDs in the matrix upon compression (Tanaka N., 2005). Full and prolonged drug release was established by keeping tablet core dry (thus preventing recrystallization within the tablet) and by only allowing surface granules to separate and dissolve (thus minimizing supersaturation at the surroundings of the tablet). Drug was released in a slower, more controlled manner, up to 6 hours. In this case example, where the granules are able to distribute dissolved drug over a wider area in the bulk volume, an advantage of a multi-unit particulate system (MUPS) was also inferred. Cui et al. (2003) used a quasi-emulsion diffusion method to produce SD of nitredipine, employing hydroxypropylmethylcellulose phthalate (HPMCP-55) as a conventional PCI, Eudragit® RS (ammonium methacrylate copolymer) or ethylcellulose as a retarding agent, along with Aerosil® (colloidal silicon dioxide) as a dispersing agent. It was found that in-vitro release could successfully be modulated by varying ratios of retarding and dispersing agents, and that in-vivo, greater bioavailability could be established compared to the marketed IR product, Baypress™ (Cui, Yanga, Jianga, Cuna, & Lina, 2003).

Traditional solvent evaporation methods (albeit, mostly crude methods versus spray drying), have been used by these following studies to achieve CRSDs for PWSD. Kim et al. (2011) demonstrated the feasibility of various polymers (Eudragit® RL, RS, HPMC, Kollidon® SR) to form CRSD for PWSD when combined with conventional PCI, PVP to form miscible blends. Although dissolution tests were limited to testing loose SD powder forms, a fair degree of
prolonged release was still achieved for all polymers (Kim, Lee, Lim, & Kim, 2011). Ohara et al. (2005) investigated the effect of using suspension versus solutions to prepare CRSDs composed of indomethacin with a combination of hydrophobic ethylcellulose, and hydrophilic HPMC. SEM of the internal structure of the matrices revealed a finer, micro-porous matrix structure from SDs prepared from the homogenous condition (solution), compared to those from heterogeneous condition (suspension) yielding greater controlled release. The authors also attributed better control and stability to the hydrophobic attraction between indomethacin and ethylcellulose (Ohara, Kitamura, Kitagawa, & Terada, 2005).

A final study worth mentioning is the formulation of misoprostol, a difficult to formulate, water-labile drug, into a CRSD with Eudragit RL and RS. Rather than use SD as a means to produce amorphous dispersions, Chen et al. (2000) (37) aimed to trap the drug in an insoluble matrix as to prevent its dehydration by limiting its exposure to water. Impressively, compressed tablets of the SD system were able to sustain drug release for 24hrs, releasing close to 100% (Chen, Tsay, Lin, Chen, & Chao, 2000). In addition, there have been considerable successful reports with CRSDs for water-soluble drug candidates, which have also helped to elucidate many of the formulation and processing factors specific to the CR feature that should be addressed (Iqbal, Babar, & Ashraf, 2002; Ammar & Khalil, 1997; Durrigl, 2011; Al-Zoubi, 2008; Sahoo J., Murthy, Biswal, Sahoo, & Mahapatra, 2008; Sahoo J., Murthy, Biswal, & Manik, 2009). With these few recent examples, it has become apparent that there is a trend towards discovering and challenging a controlled release feature paired with solid dispersion.

2.2.2 Critical Factors in Designing Controlled Release Solid Dispersion Systems

While the emphasis remains high for successful drug-polymer interactions (e.g. miscibility, hydrogen bonding), and other factors already discussed in Figure 1 (e.g. good solvation of components) in order to achieve stable amorphous SDs, the CR feature is expected to satisfy some additional roles: (i) high drug entrapment in polymer, (ii) lower ingress of water to the core, and (iii) gradual drug release to keep below critical nucleation concentration (CNC). Therefore in developing a CRSD product, a new set of factors should also be considered.

With regards to polymer candidate selection, type (e.g. hydrophobicity, plasticity), and level (i.e. polymer load) would be important factors to address. Properties of the polymer should complement the chosen processing method. For example, for highly plastic material, the process
of compression may be quite significant, allowing further densification of SDs in a tablet matrix, enabling neighboring polymer particles to bind, and encouraging formation of a stronger, more continuous barrier between water and amorphous drug (Durrigl, 2011; Tanaka N., 2006).

Processing parameters for spray drying could place stronger emphasis on densification of SD, such that porosity (i.e. potential channels for water to imbibe) is minimized. The effect of dosage form design becomes more heavily weighted when choosing to use a CR polymer as a functional excipient. Designs have the freedom to be complex, so factors such as method of incorporation of the CR polymer (e.g. intra- or extra-SD, matrix vs. membrane) and unit structure (e.g. single-unit tablet vs. MUPS) may become more significant. MUPS in general are beneficial for CR systems due to reduced chances of dose dumping and better distribution of drug in the GIT (Oth & Moes, 1989), but for CRSDs, an additional benefit of dispersing the dissolved drug may be the ability to prevent supersaturation in the microenvironment surrounding the dosage form and avoid nucleation.

With the successes of previous studies in mind, further research on CRSDs for PWSD may enable their evolution into commercially viable options. To date, there are only a handful of retarding agents identified and studied, and a greater understanding of the protective mechanisms is sought. Further, many studies have only focused on the characteristics and behaviour of CRSDs from their intermediate SD powder form, rather than demonstrate its success from the final oral dosage form (e.g. capsule or tablet).

Therefore in order to contribute greater insight into this field, I propose to investigate the breadth of functionality of the less-studied commercial polymer, Kollidon® SR, both as a retarding agent and PCI for the application of spray-dried CRSD dosage forms. More specifically, functionality of the product will be evaluated with respect to dosage form design and method of incorporation of Kollidon® SR.

2.3 Materials Selection for CRSD Systems

2.3.1 Selection of Controlled Release Agent: Kollidon® SR

To impart the ‘controlled release’ feature of the CRSD, the retarding agent, Kollidon® SR was selected (BASF, 2003). Recently introduced to the market by BASF, it joins the repertoire of commercial CR excipients such as Surelease® or Aquacoat® (cellulose based) and some
Eudragit® (acrylate based) grades (e.g. RLPO, RSPO), all of which are non-lipid based polymers used to form hydrophobic CR matrices or coating membranes. Kollidon® SR is a spray-dried physical mixture composed of polyvinyl acetate (PVAc) (80%), polyvinylpyrrolidone (PVP) (19%), and stabilizers, sodium lauryl sulfate (SLS) (0.8%) and silica (0.2%). Its main component, polyvinyl acetate, is insoluble and is responsible for maintaining the rigid mesh-type structure or skeleton matrix of the dosage form throughout dissolution. PVP on the other hand, is highly water soluble, so as it dissolves and leaches out, drug dissolution follows and is released by diffusion. This type of CR polymer, characterized by its role in the formation of an insoluble skeleton matrix, may be referred to as plastic matrix systems, in contrast to other classes such as hydrophobic, water-insoluble, potentially erodible materials (e.g. waxes) and those which are classified as forming hydrophilic, swellable, potentially erodible CR matrices (e.g. HPMC, alginates, methacrylic acid copolymers) (Reza & Haider, 2003). Available in its dry powder form, benefits of Kollidon® SR include: pH-independence, high compressibility and compactibility and excellent flowability, which make it amenable for direct compression. Further, it offers flexibility in use as an aqueous dispersion form (Kollicoat® SR30D) for coating or wet granulation purposes. It can be noted however, that the composition of this 30% w/w aqueous dispersion differs from the powder form such that PVAc, PVP and the stabilizers account for 90%, 9%, and 1%, respectively of the solids content, which can be kept in mind for the co-spray dried and coated bead formulations discussed in sections 3.1.3 and 3.1.4. Due to the practical benefits mentioned above, Kollidon® SR was chosen for this study as these features would appear to aid in the development of spray dried solid dispersion powders, which are known for their high cohesivity, poor compressibility, high elasticity and poor flow. Furthermore, due to its relatively newer introduction to the market and limited data generated in SD systems, deriving greater knowledge using this polymer in CR and CRSD applications could prove to be beneficial in future formulation development.
### Table 1: Molecular Structure and Properties of Kollidon® SR and PVP K30

<table>
<thead>
<tr>
<th>Polymer</th>
<th>MW</th>
<th>K value</th>
<th>Solubility</th>
<th>T&lt;sub&gt;g&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® SR</td>
<td>500,000</td>
<td>60-65</td>
<td>Insoluble in ethanol--soluble in methanol, acetone, N-mp</td>
<td>28-31°C, 152°C</td>
</tr>
<tr>
<td>PVP K30</td>
<td>50,000</td>
<td>28-32</td>
<td>&gt;10% in water and ethanol (freely soluble) Slightly soluble in acetone (1-2%)</td>
<td>149°C, 168°C</td>
</tr>
</tbody>
</table>

2.3.2 Selection of API Candidate: Celecoxib

To select an appropriate model API candidate, several factors were considered. Intrinsic properties of the drug such as: solubility in water and organic solvent, intrinsic dissolution, intrinsic rate of recrystallization, compatibility and interaction with polymer carrier were reviewed. Other practical considerations such as: toxicity, solubility in less toxic solvents (ICH Class 3), material cost and potential market demand as a CR product were also used to short-list candidates. The selection process is described in this section.

*Intrinsic Rate of Recrystallization*

According to a series of studies conducted by Taylor et al. (2010 a, 2010b; 2014) where the crystallization tendencies of a large sample of API were evaluated under conditions of rapid solidification (i.e. hot melting and rapid solvent evaporation), API can be classified into three categories: rapid (Class I), intermediate (Class II) and slow (Class III) rate of crystallization (Van Eerdenbrugh, Baird, & Taylor, 2010; Baird, Van Eerdenbrugh, & Taylor, 2010; Van Eerdenbrugh, Hsieh, Augustijns, & Taylor, 2014). It has been proposed that such a classification system would enable better prediction of viable API candidates for SD systems. Namely, it was suggested that Class I compounds would be poor candidates for SDs and perhaps be best avoided, and that it may be more appropriate to work with Class II and Class III candidates, which would yield higher chances of sustaining supersaturation during the timescale relevant for in-vivo transit and drug delivery. To sum, it was emphasized that intrinsic rate of recrystallization is a useful property to consider when designing SD systems. As a starting
point, the model drug candidate was selected by referring to a set of tabulated results from these studies, categorizing the amorphous drugs prepared from ethanol, DCM or a mixture of both into their respective classes. Our selections were limited to those API belonging to Class II and III.

*Compatibility with Polymer and Solvent*

As decades of research suggest, one of the most important decisions is selecting the appropriate polymer carrier or PCI for the SD system. While creation of pure amorphous drug (without polymer) can be achieved by hot melting or solvent evaporation, process yield of amorphous material may be lower (i.e. resulting in partially crystalline material) and viability of the amorphous form may rapidly be compromised with the slightest of exposure to moisture and heat, therefore rendering the material highly unstable for downward processing. Therefore there is consensus that utility of amorphous drug forms requires a minimum amount of PCI during its development.

As mentioned earlier, it is highly advantageous that both API and polymer carrier have good solubility in the feed solvent during spray drying so that maximum interaction (i.e. at a molecular level) can occur and produce a higher yield of amorphous drug. More specifically, the interaction predicted to favour the formation of stable SDs is hydrogen bonding. Polyvinylpyrrolidone (PVP K30) was chosen for this study as it is a commonly used PCI used for spray dried SDs, possessing a high $T_g$ of 149°C, high solubility in both water and ethanol and also has two potential hydrogen bond acceptor sites. Its success in spray dried SDs has also been attributed to high wettability, good solubility in a wide variety of organic solvents, low toxicity and appropriate viscosity in solution (for spray drying feed) (Leuner & Dressman, 2000).

With regards to safety and environmental concerns (which can tend to be overlooked in many academic studies), ethanol has become a preferred choice as a processing aid among others that are listed on the ICH Guidelines for Class 3 Solvents (International Conference of Harmonization, 1997). While solvent recovery systems exist, there is added diligence required when using solvents belonging to the more toxic Class 1 and 2 categories, both during processing for the safety of the operator and during drying of the finished product so that residual levels meet the FDA requirements for safety of the patient. With these factors in mind,
a shortlist of candidates (ethanol soluble and possession of hydrogen bond donor sites) can be derived from those found as Class II or III API in the classification system developed by Taylor et al. (2010), disregarding drug candidates studied with ICH Class 1 solvent, dichloromethane (DCM). Structures, potential hydrogen bonding sites and other properties are summarized in Table 2 and Table 3.

### Table 2- Structures and Potential Hydrogen Bonding Sites for Selected Ethanol-Soluble API Candidates with Class III Crystallization Tendency

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Polymer Molecular Structure</th>
<th>H-bond acceptors</th>
<th>H-bond donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinylpyrrolidone (PVP)</td>
<td><img src="image" alt="Polymer Structure" /></td>
<td>C=O (on PVP)</td>
<td>Total=4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-N (on PVP)</td>
<td>Total=0</td>
</tr>
<tr>
<td>Drug</td>
<td>Drug Molecular Structure</td>
<td>H-bond acceptors</td>
<td>H-bond donors</td>
</tr>
<tr>
<td>Celecoxib</td>
<td><img src="image" alt="Drug Structure" /></td>
<td>CF₃ (3)</td>
<td>Total= 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S=O</td>
<td>Total= 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S=O</td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td><img src="image" alt="Drug Structure" /></td>
<td>-O</td>
<td>Total= 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=O</td>
<td>Total= 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C=O</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-O</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-NH</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td><img src="image" alt="Drug Structure" /></td>
<td>-C=O</td>
<td>Total= 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-C=O</td>
<td>Total= 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-OH</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Properties of Selected Ethanol-Soluble API Candidates with Class III Crystallization Tendency

<table>
<thead>
<tr>
<th>Drug</th>
<th>MW</th>
<th>LogP</th>
<th>Solubility</th>
<th>MP</th>
<th>#RB</th>
<th>LogP</th>
<th>pKa</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>381.37</td>
<td>2.593</td>
<td>3.3 µg/mL in water</td>
<td>157-158</td>
<td>3</td>
<td>4.3</td>
<td>11.1</td>
<td>(1) (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Soluble in acetone and ethanol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>254.28</td>
<td>2.91</td>
<td>0.5mg/ml in water</td>
<td>94-97</td>
<td>4</td>
<td>2.9</td>
<td>4.5</td>
<td>(3) (4) (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Freely soluble in ethanol, acetone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td>384.26</td>
<td>4.76</td>
<td>6 mg/ml in water</td>
<td>144</td>
<td>6</td>
<td>3.9</td>
<td>5.4</td>
<td>(6) (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Freely soluble in acetone and ethanol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References: (1) (Fouad, et al., 2011); (2) (Thimmasetty, Subrahmanyam, Vishwanath, & Babu, 2009); (3) (Crowley, et al., 2004); (4) (Di Martinoa, et al., 2004); (5) (Yadav, Kumar, Singh, Bhat, & Mazumder, 2013); (6) (Konno, Handa, Alonzo, & Taylor, 2008); (7) (Karavas, Ktistis, Xenakis, & Georgarakis, 2005)

**Final Selection of Celecoxib as Model API Drug Candidate**

Based on the abovementioned considerations and literature review, celecoxib was selected as a model drug candidate (Aatri Drugs Ltd., India). Considering its molecular structure which contains two potential hydrogen bond donors on its amine group, it was predicted that it would indeed form the necessary hydrogen bond interaction with PVP.

Besides the chemical compatibility of celecoxib with the selected polymer carrier and desired attributes for our investigation, additional motivation for its selection was fueled by the market demand of this drug. Currently, celecoxib is the only selective cyclooxygenase II (COX-2) inhibitor on the US/Canadian market, better known as the blockbuster drug, Celebrex® (Pfizer) (Li J. J., 2014). Like other non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, naproxen, or ibuprofen, it is indicated for anti-inflammatory, antipyretic and analgesic treatment, particularly with osteoarthritis and rheumatoid arthritis. However, unlike celecoxib, these classical NSAIDs are non-selective in their inhibition of COX enzymes, so are frequently associated with the adverse effect of peptic ulcers. Of the COX enzymes, COX-1 is responsible for maintenance of the gastric mucosa, while COX-2 is primarily responsible for inflammation and pain. Therefore, since celecoxib selectively targets COX-2, it has become a preferred method of treatment among the NSAIDs for chronic use. For patients who require ongoing
daily treatment of celecoxib, doses are administered twice-daily in the form of 100 to 200 mg capsules. Due to this frequent, ongoing dosing schedule and preference over other forms of drugs in its class, Pfizer has reaped much success since the launch of Celebrex®. To put its market value into perspective, peak sales were generated in 2004 at an astounding $3.3 billion (Stempel, 2013). While this high number in sales was partially due to the withdrawal of a competing COX-2 inhibitor, rofecoxib, or Vioxx® (Merck), due to cardiovascular complications in 2004, successive years have also sustained much success, as sales for 2012 were reported at $2.72 billion. Patent expiry of Celebrex® is expected in December 2015 (Stempel, 2013).

Notwithstanding, the formulation of commercially available celecoxib has yet to be optimized in order to most effectively use the drug. Peak concentrations achieved from Celebrex® are achieved quite late (~600-900 ng/mL in 3 hours post dose) given its indication for pain (Searle, 1998). It would also be beneficial to deliver a single dose capable of sustaining therapeutic levels for longer duration so that a second daily dose could be avoided, while preventing the drug from climbing to toxic concentrations. Therefore, according to the market demand, frequent, ongoing dosing schedule and sub-optimal pharmacokinetics, it is foreseen that advanced techniques to improve future dosage forms of celecoxib, including controlled release, is highly warranted.
Chapter 3

3 Study of Dosage Form Design on Controlled Release Solid Dispersions: Methods and Materials

3.1 Formulation and Dosage Form Design of SD and CRSD Systems

3.1.1 Spray-Dried Powder Formulations

The first formulation task was to develop a conventional-type spray-dried solid dispersion powder composed of celecoxib (Aarti Drugs Ltd., Mumbai, India) and hydrophilic polymer, PVPK30 (BASF, Ludwigshafen, Germany), which could be used as a control or base comparison for CRSD formulations and additionally, as a component of the various dosage form designs under study.

Spray-Dried SD Powder

Celecoxib was co-dissolved with PVP in ethanol using various drug-polymer ratios (9:1, 7:3, 1:1) at solids concentrations between 10-16% w/w and spray dried using a Buchi B-190 mini spray dryer (Buchi, Flawil, Switzerland). Spray drying parameters were set and maintained as follows: inlet air temperature - 70-80°C, outlet temperature - 30°C, aspirator - 100%, feed rate - 5 g/min. Spray-dried powders were evaluated for amorphicity/crystallinity, bulk powder properties such as bulk and tapped density, Carr’s Index (CI) and particle size, and for performance during in-vitro dissolution testing.

Encapsulated Physical Mixtures

As a simple design approach, resultant spray-dried SD powders were used in physical mixture formulations, where powders were manually dry blended with excipients and tested in loose powder form and after filling into hard gelatin capsules (Coni-snap, Medisca Pharmaceutique Inc., St-Laurent, QC). By simple dry blending with excipients, such as lactose monohydrate (Flolac 100, Meggle, Wasserburg, Germany) and microcrystalline cellulose (Avicel PH101, FMC) effect of dispersibility, or dilution of SD in a powder matrix and effect of excipients in the absence of compression could be examined. SD powder blends were also reserved for use in dry-granulated multi-particulates and tablet matrix formulations.
3.1.2 Compressed Matrices

The effect of compression was predicted to be a significant factor when creating diffusion matrices capable of sustaining release with Kollidon® SR. Recalling the release mechanism indicated for Kollidon® SR, polyvinyl acetate forms a coherent mesh-type insoluble matrix with the drug and water-soluble PVP. It is the dissolution and leaching of the PVP that creates pores from which the drug may diffuse out. Therefore, creation of a well-defined diffusion matrix relies on a minimal packing density so that porosity or free volume can be adequately controlled. In the systems described in this section, compression was used to increase the packing density of the matrix.

*SD and CRSD Tablet Matrices*

Second to physically-mixed dry blends filled into capsules, dry blends compressed into tablets were another simplified approach to combine SD powders with excipients in a solid oral dosage form. Excipients were selected due to amenable compressibility/compactibility characteristics and ability to improve flow of the blend. Tablets containing powder equivalent to 100 mg of drug (425 mg of powder blend) were compressed using a 13.8 mm flat cylindrical die on a Carver laboratory press (Summit, NJ, USA) at 3500 lbs to yield hardness values between 130-140 N.

*Multi-Unit Particulate System (MUPS) Matrices*

To impart higher dispersibility of a compressed system, MUPS matrices were developed by the dry granulation method of slugging. Dry blends comparable to those used for CRSD tablets were compressed using ~500 mg of material in a 13.8 mm die using the Carver press, subsequently crushed with mortar and pestle and sieved. Dry granules were passed through US Std. Sieve #14 (1.5 mm) and fractions were collected on Mesh #20 (850 µm) and #40 (425 µm).

3.1.3 Co-Spray Dried CRSD Powder

An alternate approach of combining the retarding agent with conventional SD formulation was by the process of co-spray drying. In contrast to the SD spray drying method where a true solution is required, for this formulation a suspension containing the aqueous dispersion of Kollidon® SR (known as Kollicoat® SR 30 D) was combined with the ethanolic solution containing celecoxib and PVP (as described above), and subsequently spray dried while stirring.
Solid weight ratios of CEL:PVP SD to Kollidon® SR examined were 7:3 and 1:1. Solid content of the suspension was 15% w/w and spray drying parameters were maintained as follows: inlet air temperature- 90-100°C, outlet temperature- 35°C, aspirator- 100%, feed rate- 2.5 g/min

3.1.4 Drug-layered/SR-Coated Beads

An alternative method to prepare an amorphous SD was explored via drug layering by fluid bed coating non-pareil beads. As the mechanism of forming an amorphous SD relies on rapid solidification of drug from the dissolved state (i.e. rapid cooling of hot melts, rapid solvent evaporation from solution), the same concept involved in spray drying was applied to the fluid bed process, but rather than drying as discrete powder particles, SD solution was applied and allowed to dry onto the surface of the beads in the coating chamber. To prepare a CR membrane-reservoir design for the study, non-pareil sugar beads with diameter of 710-850 µm (Suglets® Mesh 20/25, Colorcon, Bazainville, France) were used as MUPS substrates for drug layering and subsequent SR coating. For SD/drug layering, a 15% w/w solution of celecoxib:PVP (7:3) in ethanol, identical to the SD solution composition for spray drying, was used to apply the SD layer onto the beads. Following drug layering, SR coating was applied using the suspension formulation on Table 4 and sprayed under continuous stirring. Coating excipients listed (except Kollidon® SR 30 D, courtesy of BASF, Germany) were provided by Medisca (St.Laurent, QC, Canada). Drug layering and SR coating processes were performed using a fluid bed machine assembled with a bottom-spray Wurster apparatus (Pro-C-cept 4M8 Fluid Bed, Zelzate, Belgium). Coating parameters were set and maintained according to Table 5: Fluid Bed Coating Parameters.

Table 4: SR Coating Formulation for CRSD Beads

<table>
<thead>
<tr>
<th>Component</th>
<th>g per batch</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymer Suspension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kollidon SR 30D</td>
<td>249.55</td>
<td>49.56</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>7.71</td>
<td>1.531</td>
</tr>
<tr>
<td>Water</td>
<td>174.65</td>
<td>34.68</td>
</tr>
<tr>
<td><strong>Pigment Suspension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>19.95</td>
<td>3.962</td>
</tr>
<tr>
<td>FD&amp;C Yellow #6</td>
<td>0.50</td>
<td>0.099</td>
</tr>
<tr>
<td>Water</td>
<td>51.19</td>
<td>10.17</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>503.55</td>
<td>100</td>
</tr>
<tr>
<td><strong>Solids</strong></td>
<td>103.03</td>
<td>20.5%</td>
</tr>
</tbody>
</table>

26
Table 5: Fluid Bed Coating Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beads Load</td>
<td>400-500 g</td>
</tr>
<tr>
<td>Pump Speed</td>
<td>2-5 ml/min</td>
</tr>
<tr>
<td>Inlet Temp</td>
<td>60°C</td>
</tr>
<tr>
<td>Outlet Temp</td>
<td>37-45°C</td>
</tr>
<tr>
<td>Nozzle Size</td>
<td>0.8 mm</td>
</tr>
<tr>
<td>Atomization Pressure</td>
<td>0.75-1 atm</td>
</tr>
<tr>
<td>Inlet Air Volume</td>
<td>0.8-1.5 m³/min</td>
</tr>
</tbody>
</table>

3.2 Characterization of SDs

3.2.1 Bulk Powder Characteristics

*Particle Size and Morphology*

Particle size was estimated and morphology was characterized using optical light microscopy imaging (EVOS®, Westover Scientific). Morphology was described in terms of surface roughness and shape.

*Bulk and Tapped Density*

Bulk and tapped density was determined by the method of filling and mechanical tapping of a 25 mL graduated cylinder. Carr’s Consolidation Index (CI) was calculated (Equation 1) in order to comment on flowability of powder samples.

\[
CI = 100 \times \left(1 - \frac{\rho_t}{\rho_b}\right)
\]

Equation 1- Carr’s Compressibility Index. CI<15 indicates good flow, CI>20 indicates poor flow

3.2.2 Structural Analysis- FTIR

FTIR analysis was performed to detect potential (hydrogen bonding OR physicochemical interactions) between celecoxib and PVP on a Spectrum 100 (Perkin-Elmer, MA, USA) with a Universal ATR Sampling Accessory (Perkin-Elmer, MA, USA). A diamond coated ZnSe crystal plate was used. Powder samples of celecoxib, PVP, dry blended PM and spray dried SD were
gently ground with mortar and pestle and vacuum dried prior to testing. Samples were scanned over the spectra range of 4000 to 550 cm\(^{-1}\).

3.2.3 Powder XRD

XRD was also used to characterize crystallinity/amorphicity of powder samples. XRD patterns were collected on a Bruker AXS D2 Phaser diffractometer (Karlsruhe, Germany). High resolution CuK\(\alpha\) source was used operating at 30 kV and 10 mA. The system was equipped with Ni-filter for elimination of CuK\(\beta\) peaks and a solid state Lynexeye XE detector. Obtained diffraction patterns were processed by Diffrac \textit{Plus} \texttrademark Ev\textit{a}\textsuperscript{TM} 8.0 software.

3.2.4 Thermal Analysis- DSC

Thermal analysis was used to confirm crystallinity/amorphicity and was performed by differential scanning calorimetry (DSC) (2010 DSC, TA Instruments, Delaware, USA). Samples between 5-10 mg were sealed in aluminum pans and heated at a rate of 10\(^\circ\)C/min over a temperature range of 25-200\(^\circ\)C.

3.3 Dissolution/Recrystallization Studies

Dissolution testing for all test articles containing 100 mg of drug was conducted using a VanKel Dissolution System (VK 7000 Edison, NJ, USA) using 900 mL water or 0.04 M tribasic sodium phosphate at 37 \(\pm\) 0.5 \(^\circ\)C (n=3). Depending on the dosage form, USP Apparatus I at 100 rpm or Apparatus II at 50 or 75 rpm was used (specified in results section). Absorbance of samples were measured online at 255 nm using a multi-cell UV spectrophotometer (Agilent 8453, Waldbronn, Germany) fitted with flow-through cuvettes and a multi-channel peristaltic pump (Ismatec ISM 931A, Idex, Oak Harbor, WA).
Chapter 4

4 Results and Discussion

By studying the concentration versus time profiles obtained from dissolution experiments, various important effects of dosage form design were elucidated. In general, designs that imparted higher dispersibility of the drug in SD (dispersible PM formulations, co-spray dried powders, matrix MUPS), the higher the dissolution rate and peaks in concentration. However, this was also accompanied by higher rates of recrystallization in the bulk media, as evidenced by sharp declines after reaching peak concentrations, limiting its clinical use to fast-acting applications (e.g. IR for immediate analgesic effects). On the other hand, designs which were able to limit surface exposure of SD to the media (e.g. coated beads, tablet matrices), revealed potential for SR applications, where slower rate of release and more prolonged drug activity is desired. In this section, results for each design investigated are discussed along with effects that were discovered.

4.1 Development of Conventional Spray Dried SD Powders

4.1.1 Screening for Drug-Polymer Ratio: Effect of PVP Concentration

As a conventional polymeric crystallization inhibitor (PCI), PVP K30 was selected for celecoxib SD powders. Due to its hydrophilicity, amorphicity, high Tg of 149°C and potential for hydrogen bonding with celecoxib, others have reported its success in stabilizing the amorphous form of many drugs in SD. However, oftentimes the amount of polymer required for stabilization exceeds 50%, sometimes even reaching up to 90% of the SD composition, thus limiting the space available for other formulation excipients, not to mention, the required dose of drug in a single dosage form (Zhao, Barker, Belton, McGregor, & Craig, 2012; Curatolo, Nightingale, & Herbig, 2009). To illustrate this dependency, several SD products on the market such as Kaletra® (Abbott) or Sporanox® (Janssen) have required administration of multiple units (e.g. 2-6 capsules), multiple times daily, which is not always well-accepted by patients who require ongoing treatment. Advanced drug delivery techniques should therefore address this issue and consider more space and material-conserving methods to produce stable SD systems.

To challenge the lower spectrum of polymer concentrations using CRSD strategy, three drug-polymer ratios of Cel:PVP for SD composition (9:1, 7:3 and 1:1) were examined in this study.
Using USP Apparatus II at 50 rpm in sink conditions, SD powder equivalent to 100 mg of celecoxib was introduced to 900 mL of pH 12 aqueous media (pH 12, 0.04M tribasic sodium phosphate) and the following profiles were obtained:

![Dissolution of Celecoxib SD Powders of Various D:P ratios under sink conditions (Apparatus II, 50 rpm, 900 mL pH12)](image)

**Figure 2: Effect of Polymer Concentration in SD Compositions Under Sink Conditions (900 mL pH 12 tribasic sodium phosphate, 37°C, Apparatus II, 50 rpm).** Higher levels of polymer in SD corresponded to faster rate and higher extent of dissolution. Each vessels contained powder equivalent to 100 mg celecoxib, thus peak concentrations for all formulations corresponded to near complete dissolution at 111 ppm.

In 900 mL of pH 12, sink condition was well established for celecoxib, which is a weak acid with pKa of 11.1. Within 5 minutes, peak concentration is achieved for the SD formulation containing the highest amount of PVP (50%), which corresponded to near complete dissolution, while the SD formulation containing the least amount of PVP (10%) exhibits a markedly slower rate of dissolution, reaching its peak after 2 hours. The formulation containing 30% PVP demonstrates an intermediate rate of dissolution, reaching its peak after 1 hour.

Under non-sink conditions, method was repeated using 100 mg dose, except 900 mL water was used instead of pH 12. The following profiles were obtained for SD containing D:P (1:1) and (7:3), compared with the crystalline formulation of Celebrex capsules:
Figure 3: Effect of Polymer Concentration in SD Compositions in Non-Sink Conditions (900 mL deionized water, 37°C, Apparatus II, 50 rpm). Higher levels of polymer in SD corresponded to faster rate and higher extent of dissolution, with a longer peak duration.

Conducting the test in non-sink conditions enables the progression of recrystallization events in the bulk solution (SMPT), as characterized by the declines in concentration following the peak. While these conditions are likely to overestimate the severity of SMPT that may actually occur in-vivo, this method allows for better screening of SD formulations in the formulation development stage. Compared to previous testing in sink conditions, both SD formulations exhibit slower rate of dissolution and lower extent of dissolution as less than 30% of highest expected drug concentration is measured in the bulk solution. The SD formulation containing 50% PVP evidently prolongs supersaturation longer than the formulation containing 30% PVP, which declines close to the peak of crystalline celecoxib (~5 ppm) at a much faster rate. However, it should be noted that both SD formulations demonstrate at least a ten-fold solubility improvement compared to the commercial crystalline product, Celebrex, and that despite the declines due to SMPT, 7 hours later, the plateau concentrations of the solid dispersions are still considerably higher.
Although this experiment highlighted higher potential for the Cel:PVP (1:1) SD formulation in terms of stability, our study objective was to challenge a conventional SD system more prone to SMPT, which could be representative of drug candidates with slower rates of permeability and/or higher rates of intrinsic recrystallization. By using the drug:polymer ratio exhibiting the more classic peak and decline profile, it would be more feasible to make comparisons with the CRSD designs and help us determine if the CRSD strategy could be used to further enhance solubility stabilization. Hence, Cel:PVP (7:3) was chosen as the base formulation of conventional SD powder.

4.1.2 Characterization of Conventional SD Powders- Cel:PVP (7:3)

To further confirm suitability of D:P ratio of 7:3, structural analysis and crystallinity studies were performed using FTIR, DSC and P-XRD. The objective was to ascertain maximal transformation of celecoxib from the crystalline to amorphous form by using the prescribed spray drying process. Bulk powder properties such as particle size, surface morphology, density and powder flow were also evaluated.

4.1.2.1 Structural Analysis- FTIR

Celecoxib (crystalline bulk material), PVP, dry blended physical mixture (PM) of Cel:PVP (7:3) and spray dried SD were evaluated. Spectra of celecoxib and PVP were consistent with those reported in literature (Lee, Kim, Yoon, & Shim, 2013). In SD, but not PM, there is a disappearance of sulfonamide peaks at 3330 and 3230 cm\(^{-1}\) (N-H), which are prominent in celecoxib bulk material (Figure 4.A). In addition, there is a slight shift in the carbonyl peak of PVP at 1665 to 1657 cm\(^{-1}\) on the SD form (Figure 4.B). The disappearance and shifts of these peaks in the solid dispersion can be interpreted as the formation of hydrogen bonds between the sulfonamide group of celecoxib and carbonyl group of PVP as expected, thus satisfying one of the requirements for our selection of polymeric crystalline inhibitor.
Figure 4: FTIR Spectra of Celecoxib Preparations. From top to bottom- celecoxib (crystalline bulk), PVP K30, Cel-PVP (7:3) PM (physical mixture), Cel-PVP (7:3) SD. Changes in SD spectra compared to PM are reflective of H-bond interactions between celecoxib and PVP in the SD form.
4.1.2.2 Crystallinity Studies- DSC and P-XRD

_DSC Analysis_

Thermal analysis by DSC was performed in order to confirm amorphicity of SD powders composed of Cel:PVP (7:3) and the challenged parameters for the spray drying process (described in Chapter 3). Celecoxib bulk (crystalline), PVP, dry blended physical mixture (PM) and spray dried SD were evaluated by detecting the presence/absence of endothermic melting peaks (Figure 5). The endotherm detected for celecoxib bulk material was confirmed near its known melting point of 165°C, which was also observed in the thermogram for the PM, although slightly depressed. Depression of this peak is attributed to high solubilization capacity of molten PVP during heating to celecoxib. In SD and PVP however, endothermic peaks were completely undetectable, thus confirming amorphicity.

![DSC Thermograms of Celecoxib PM vs SD](image)

*Figure 5: DSC Thermograms for Celecoxib Preparations. From top to bottom- Cel-PVP (7:3) SD, Cel-PVP (7:3) PM, PVP K30, celecoxib bulk (crystalline). Absence of endothermic melting peaks near celecoxib melting point (165°C) for SD sample confirms successful transformation to amorphous form by spray drying.*
Powder XRD Analysis

Diffraction patterns were collected for celecoxib, PVP, dry blended PM and spray dried SD (Figure 6). Celecoxib exhibited the greatest crystallinity, characterized by high-intensity diffraction peaks and minimal background area (representing amorphicity) at the base. Dry blended PM also exhibited high crystallinity but relatively less than celecoxib, as a rise in background level is observed. This detected rise in amorphicity of PM may be attributed to the addition of PVP, whose profile exhibits as completely amorphous. Finally, the spray dried SD powder appears to be completely amorphous as characterized by broad maxima and high degree of scattering, thus supporting results from DSC that the spray drying goal of producing an amorphous SD had been attained.

![P-XRD Patterns of Celecoxib PM vs SD](image)

**Figure 6: Powder XRD Patterns of Celecoxib Preparations.** Broad, diffused peaks of PVP and SD indicate amorphicity, while sharper intense peaks of celecoxib and PM indicate higher crystallinity. Transformation to amorphous form by spray drying is confirmed.

The combined results of FTIR, DSC and P-XRD provide consistent findings that amorphous SD formation can indeed be established using the investigated formulation of Cel:PVP (7:3) and the challenged spray drying process.
4.1.2.3 Bulk Powder Property Evaluation

Particle Size and Surface Morphology

In general, spray dried SD powders exhibited very high cohesivity, as handling and transferring material from one container to another presented challenges of sticking to vessel walls and spatulas. Macroscopic and microscopic imaged presented in Figure 7 reveal formation of agglomerates between approximately 200-500 µm, although individual particles are theoretically between 2-25 µm, according to the spray dryer manufacturer.

Bulk and Tapped Density - Carr’s Index

Density measurements and Carr’s Index were carried out in order to assess the bulk powder characteristics of the SD powders. Consolidation of powder was considerably high, as Carr’s Index was found to be ~40%, corresponding to very poor flowability. This measurement is consistent with observations during handling of the material as powders exhibited high resistance to flow when transferring between containers. Due to the bulk powder properties exhibited, it was determined that further processing or formulation of SD powders was essential.

Table 6: Bulk and Tapped Density Measurements of Cel:PVP (7:3) SD Powder

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bulk Density</strong></td>
<td>0.297 g/mL</td>
</tr>
<tr>
<td><strong>Tapped Density</strong></td>
<td>0.494 g/mL</td>
</tr>
<tr>
<td><strong>Carr’s Index</strong></td>
<td>39.9% (very poor flow)</td>
</tr>
</tbody>
</table>
4.1.3 Performance of Neat SD Powders During Dissolution/Recrystallization Studies

4.1.3.1 Effect of Dose/Level of Sink During Dissolution Testing

While routine dissolution testing is typically performed using sink conditions to mimic the highly efficient absorption of the small intestine, the methodology to evaluate SD systems needs to be approached from a different angle. When evaluating SD systems or other supersaturating delivery systems, testing in non-sink conditions is necessary to subject the system to the extreme conditions encountered in-vivo that may compromise their integrity, and to better screen and challenge formulations most resilient to recrystallization. For example, as a drug product is orally ingested, it momentarily resides in the mouth, followed by transit to the stomach, where it may reside for up to 3 or 4 hours, depending on the physiological state or dietary consumption of the patient. Compared to the small intestine, the bulk volume and absorption in the stomach is reduced, therefore drug must wait for gastric emptying before it can enter a potential area of ‘sink’ conditions. Therefore, it is logical to challenge SD delivery systems under conditions where volumes are minimized/finite for at least ~2-4 hours. In order to determine what level of sink to use throughout our studies, a comparison of varying doses was made using 900 mL of water, Apparatus II, 50 rpm (Figure 8).
Table 1: Summary of Dissolution Data

<table>
<thead>
<tr>
<th></th>
<th>50 mg dose</th>
<th>100 mg dose</th>
<th>200 mg dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD powder amount</td>
<td>71.42 mg</td>
<td>142.85 mg</td>
<td>285.71 mg</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ppm)</td>
<td>11.7±0.7</td>
<td>13.6±0.1</td>
<td>25±2.0</td>
</tr>
<tr>
<td>(% released)</td>
<td>(21.08%)</td>
<td>(12.25%)</td>
<td>(11% release)</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>135 min</td>
<td>115 min</td>
<td>80 min</td>
</tr>
<tr>
<td>AUC (0-120 min)</td>
<td>894.52</td>
<td>1138.80</td>
<td>2313.40</td>
</tr>
<tr>
<td>AUC (0-240 min)</td>
<td>2143.12</td>
<td>2376.10</td>
<td>3977.04</td>
</tr>
<tr>
<td>AUC (0-420 min)</td>
<td>3377.45</td>
<td>3626.78</td>
<td>5356.19</td>
</tr>
</tbody>
</table>

**Figure 8: Effect of Celecoxib Dose (or Level of Sink) During Dissolution (900 mL deionized water, 37°C, Apparatus II, 50 rpm).** Drug is most efficiently used when lower dose (50 mg) is tested, but highest dose (200 mg) is able to reach doubled peak concentration.

First we should recognize that at any given time point, measurements taken in the bulk are a reflection of the net between dissolution and recrystallization. Therefore, the remaining fraction of drug not measurable by the end of the test may be assumed to have undergone SMPT simultaneously during dissolution. While highest bulk concentrations were achieved using the highest dose (SD powder equivalent to 200 mg of celecoxib), it should be noted that drug was least efficiently used in this case, as the peak value corresponded to just 11% relative to the maximum concentration expected. With larger heaps of material at the bottom of the vessel
found for the 200 mg dose, this may be one explanation of why there is less % measured. However, another trend observed was the steeper slope of decline when higher peak concentrations were met, suggesting that concentration may be a prominent driving force for recrystallization. Hence this can also be considered in interpreting the overall lower efficiency of the 200 mg dose. Profiles of 50 mg and 100 mg doses appeared similar, but correcting to percent efficiency, the 50 mg dose was best utilized (21%). This may be explained by considering the greater dispersibility in the vessel volume in the case of when less material is involved. Greater distance between drug molecules can reduce the collisions leading to nucleation and crystal growth, hence reduce the overall rate of bulk concentration decline. Therefore, the 100 mg dose appeared to display a higher degree of SMPT compared to 50 mg since concentration is initially higher, resulting in much lower % efficiency. Also, this dose displays a lower rate and extent of dissolution compared to 200 mg, as it contains comparatively less excess drug in the bulk. This experiment highlights that while increasing dose may have the benefit of reaching higher bulk concentrations, efficient use of drug may be compromised due to more extensive SMPT.

4.1.3.2 Effect of Physical Confinement due to Encapsulation

From a time and cost perspective, the simplest oral dosage form to prepare is undoubtedly the powder-filled hard shell capsule. As determined from tapped density experiments, tapped density of the SD powder composition of Cel:PVP (7:3) was measured as 0.5 mg/mL. Therefore, it was feasible to contain the amount of SD powder equivalent to a 100 mg dose of celecoxib (142.85 mg SD powder) into a single hard gelatin capsule, size #1 (Coni-snap Capsule, Medisca, QC) with volume capacity of 0.5 mL. In order to examine the effect of SD powder confinement and compaction, pure SD powder (neat SD) in the loose form was compared to the capsule-filled form. Dissolution testing was conducted using USP Apparatus I (basket), in order to fully submerge the low-density capsule and powders in the aqueous media. At the end of the test, encapsulated SD powder exhibited tacky, water insoluble agglomerates remaining in the basket, partially in the same shape as the hard gelatin capsule, although the capsule shell had fully dissolved (Figure 9). The loose powder, on the other hand, was observed to disperse more evenly as vessels appeared cloudier during the test and as only few small agglomerates were found remaining in the basket by the end of the test. These observations were consistent with the profiles measured as the rate and extent of dissolution appeared to be impaired for the encapsulated powder compared to the loose powder (Figure 10).
Figure 9: General Appearance of SD Capsules Before (left) and After (right) Dissolution. Formation of tacky, capsule shaped agglomerates were recovered inside the basket apparatus following dissolution testing.

Figure 10: Effect of Confinement by Encapsulation of SD Powder (900 mL deionized water, 37°C, Apparatus I, 100 rpm). Encapsulation appears to hinder dissolution of neat SD powder.

Measured concentrations in the bulk solution for the encapsulated powder are evidently much lower than those measured for the loose powder. Area under the curve (AUC) is almost halved.
by confinement of the material in the capsule shell. From this experiment, it is suggested that confinement in capsules may have a negative effect on drug release. Since only low concentrations could be measured in the bulk solution, it was suspected that recrystallization events may have been promoted by restricting the transient volume to a size amenable for rapid supersaturation. As powders are held immobile in a confined space (i.e. within the capsule shell), it is likely that upon contact with aqueous media, amorphous drug is quickly dissolved and contacted by other neighboring dissolved drug molecules before having the chance to disperse into the bulk solution, crystallizing within the capsule shell. Previous studies have also reported this phenomenon, describing a sticky, non-dispersible plug formation, which may happen as a result of drug-drug interactions, eventually leading to recrystallization (Puri & Dantuluri, 2012). Due to this observation, it was recognized that further formulation (i.e. addition of excipients) and/or processing of the spray dried SD powder would be required in order to consider capsulation as a feasible option to produce a final dosage form. Approaches to overcome this tendency for agglomeration in the capsule are discussed in sections 4.2.1.1 and 4.3.1.

4.1.3.3 Effect of Confinement on Dissolution Kinetics due to Selection of Dissolution Apparatus (Basket vs. Paddle)

![Figure 11: Left- USP Apparatus I (basket), Right- Apparatus II (paddle)](image)

While the basket method (Apparatus I) is suitable for submerging low density test articles such as capsules, beads, or powders to ensure maximal surface area exposure to the media, dispersibility due to hydrodynamics of stirring and physical confinement may differ when compared to the paddle method (Apparatus II). A comparison of the two methods is presented in Figure 12 below.
Figure 12: Effect of Basket (Apparatus I) or Paddle (Apparatus II) on Dissolution of SD Powders. Profile shapes are similar, although extent of dissolution tested by the basket method falls slightly lower compared to the paddle method.

The plots and calculated AUCs reveal that using the basket apparatus for SD powders may hinder the rate and extent of dissolution, potentially promoting the same phenomena described for the encapsulated SD but to a lesser degree. At the end of the test, it was also observed that baskets contained some tacky residue, resembling the remnants of the capsule reported above. Since method of agitation and hydrodynamics is relatively stronger with the paddle and materials are free to expand throughout the volume of the vessel upon immersion, careful consideration should be taken when designing a dissolution test for materials prone to SMPT.
4.2 Performance and Evaluation of Formulated SD Powders

4.2.1 Effect of Dispersibility by Formulation and Dosage Form Design

A prominent feature that was observed for the pure SD powders (neat SD) was propensity to agglomerate during dissolution and form tacky, insoluble residues which trapped/prevented drug from reaching the bulk solution, especially when challenged in restricted volumes, such as the basket apparatus or hard gelatin capsule. Furthermore, during processing (e.g. filling of capsules, transfer from spray drying vessel to container), the cohesive properties such as high electrostatic charge, very small particle size and low bulk density were problematic, causing loss of material during handling. Therefore, it was deemed essential for further formulation and/or process development in order for the SD powder to be transformed into an acceptable final dosage form.

Imparting higher dispersibility was attempted via both formulation and process development aspects. Dispersible formulations incorporated additional excipients that functioned to separate SD (or drug) particles, minimizing contact and interaction during storage and during dissolution. By dosage form design, dispersibility was imparted by investigating multi-unit particulate systems (MUPS), such as beads and granules, which was contrasted with single unit forms that remained relatively more intact during dissolution (i.e. powder filled capsules and tablets).

4.2.1.1 Dispersible SD Formulations

Formulation with MCC and Lactose for Dispersible Capsules and Tablets

Dispersible SD formulations (SDDF) were created by dry blending excipients with SD powder according to the following formulations listed below (Table 7).

<table>
<thead>
<tr>
<th>SDDF Components</th>
<th>Mass per unit (mg)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD Powder-CEL:PVP (7:3)</td>
<td>142.86</td>
<td>34%</td>
</tr>
<tr>
<td>MCC PH101</td>
<td>92.62</td>
<td>22%</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>185.26</td>
<td>44%</td>
</tr>
<tr>
<td>Colloidal silicone dioxide</td>
<td>2.13</td>
<td>1%</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2.13</td>
<td>1%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>425</td>
<td>100%</td>
</tr>
</tbody>
</table>
Neat SD powder (loose) was compared with dry blended powder in encapsulated and tablet form.

\[
\begin{array}{|c|c|c|}
\hline
 & SD Powder (loose) & Capsule SSDF & Tablet SSDF \\
\hline
C_{\text{max}} \text{ (ppm)} & 21.18 \pm 0.61 & 29.57 \pm 1.89 & 26.17 \pm 1.43 \\
AUC (0-120 \text{ min}) & 2183.96 & 2408.57 & 2546.92 \\
AUC (0-240 \text{ min}) & 4067.4 & 4575.52 & 5019.14 \\
\hline
\end{array}
\]

Figure 13: Dissolution of Dispersible SD Formulations in Various Dosage Forms (900 mL deionized water, 37°C, Apparatus II, 50 rpm). Improvements in C_{\text{max}} and AUC are evident when SDDF are used, despite incorporation into capsules and tablets compared to loose neat SD powder.

Comparison of the profiles reveal higher extents of release for dispersible formulations versus the loose, neat SD powder, despite their confined design in capsule and tablet form. Tablets and capsules composed of the dispersible powder formulation were observed to disintegrate and disperse within the vessel within a few minutes after introduction into the aqueous media. With dispersible formulation at the current SD loading of 34%, it is also apparent that the effect of
compression during tabletting does not negatively impact release rate, as the profiles and AUCs are comparable.

This findings from this experiment demonstrate the effectiveness of formulation excipients to physically separate SD powder particles and promote dispersibility, despite forces of compression or confinement within capsules. This effect further supports the idea that physical dispersibility of SD powders is necessary in order to maximize extent of dissolution and prevent internal recrystallization.

4.2.1.2 Dispersible Unit Design

Dispersibility was also attempted by varying unit design. Multi-unit particulate systems (MUPS) such as granules, pellets and beads, are known for their benefits of dispersing within the GI tract, while preventing cohesion typically observed in powders. Unlike single-unit forms such as tablets, MUPS carry the benefit of spreading along surfaces of the GI membrane, which may be useful to enhance absorption, minimize local irritation, prevent dose dumping (in the case of membrane-reservoir systems), and also to improve dissolution, since particle size is decreased and volume of surrounding media per solid surface is increased. In the case of an SD system however, a dispersible multi-unit design may specifically be advantageous, preventing SMPT by distributing throughout the entire volume in which it is being dissolved, minimizing areas of high, supersaturatable concentrations. Recalling the inherent nature of SD powder to form agglomerates, the coated beads were predicted to benefit dispersibility by their discrete design.

![Figure 14: General Appearance of Uncoated (left) and SD-Coated (right) Non-Pareil Beads.](image_url)
Drug/SD layered beads were prepared to challenge the dispersible unit design and compared with SD powder and SD dispersible formulation with MCC (SD:MCC, 7:3) (Figure 15).

![Dispersible SD Formulations and Designs (100 mg dose in 900 mL water, Apparatus I, 100 rpm)](image)

<table>
<thead>
<tr>
<th></th>
<th>SD Beads</th>
<th>SD Powder</th>
<th>SD:MCC (7:3) PM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cmax (ppm)</strong></td>
<td>19.25±1.64</td>
<td>18.00±0.23</td>
<td>22.50±1.57</td>
</tr>
<tr>
<td><strong>Tmax (min)</strong></td>
<td>150 min</td>
<td>60 min</td>
<td>80 min</td>
</tr>
<tr>
<td><strong>AUC (0-120 min)</strong></td>
<td>1005.69</td>
<td>1628.70</td>
<td>2195.42</td>
</tr>
<tr>
<td><strong>AUC (0-240 min)</strong></td>
<td>3462.914</td>
<td>2984.13</td>
<td>4039.86</td>
</tr>
</tbody>
</table>

**Figure 15: Effect of Dispersible Unit Design and Formulations (900 mL deionized water, 37°C, Apparatus I, 100 rpm).** Compared to loose SD powder, SD beads and PM have an overall higher extent of dissolution (as per AUC), although rate of dissolution for beads is relatively slower than powder formulations.

SD-coated beads appeared to have a slower release rate compared to both SD powder and the dispersible dry blend powder formulation, despite having a dispersible unit design. This pattern of release could be attributed to the specific surface area of drug exposed to dissolution media. Since the arrangement of drug/SD in the coated bead design exists as a layer over the larger, beads spheres (~750 µm), exposure to media is more lateral compared to smaller powder particulates, where there is more multi-directional contact with aqueous media. Therefore this difference in arrangement might have had an impact on dissolution, such that less surface area of drug was able to contact media, thus exhibiting a slower rate of release. A second interpretation of the slower release from SD beads is the potential for surface SMPT. If
recrystallization is prone to occur over extended time, the layer of precipitate may also contribute to hindered dissolution.

4.3 CRSD Development with Kollidon® SR

When developing controlled release dosage forms, design options have the ability to become more variable and complex compared to simple IR forms. Variables include method of incorporation of the retarding agent (e.g. intra vs extra-granular), unit design (e.g. single unit tablets vs. MUPS), grade, level and combination of formulation excipients (more notably, retarding agent), plus processing or manufacturing considerations such as equipment and method of manufacture (e.g. fluid-bed granulation vs. conventional wet granulation vs. dry granulation). In this section, attempts to develop CRSD systems in various dosage form designs using Kollidon® SR are discussed.

As mentioned earlier, due to its relatively newer introduction to the market for CR systems compared to Eudragit and ethylcellulose products, there is still limited understanding of Kollidon® SR in CR systems, and even less with respect to formulation with solid dispersions. Kollidon® SR was selected as an ideal candidate for this study due to its multi-functionality as a retarding agent for controlled release matrices and membrane-reservoir systems, and for its amenable bulk powder properties such as: high compressibility and compactibility, excellent flowability, pH-independence and availability in an aqueous dispersion for coating (Kollicoat® SR30D). Its versatility was challenged across a broad range of dosage form designs, depicted on Figure 16. Incorporation of Kollidon® SR (and Kollicoat® SR30D) is depicted in the red-circled images. Descriptions of the formulation designs examined are summarized on Table 8. A detailed summary of all designs may also be found in the Appendix.
Table 8: General Description of SD and CRSD Dosage Form Designs Investigated

<table>
<thead>
<tr>
<th>SD Powder Formulations</th>
<th>Composition and Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray Dried SD Powder</td>
<td>Celecoxib and PVP dissolved in ethanol, spray dried using a spray dryer</td>
</tr>
<tr>
<td>Co-Spray Dried SD Powder</td>
<td>Celecoxib and PVP dissolved in ethanol, mixed with Kollicoat® SR 30 D, spray dried</td>
</tr>
<tr>
<td>SD Powder Dry Blended with Excipients (Physical Mixture), filled into Capsules</td>
<td>SD powder dry blended with lactose and/or MCC and/or Kollidon® SR</td>
</tr>
<tr>
<td>Compressed Matrix Formulations</td>
<td>Composition and Process</td>
</tr>
<tr>
<td>SD Tablets (Single Unit SD Matrices)</td>
<td>SD powder blended with excipients (diluent, lubricant) compressed into tablets</td>
</tr>
<tr>
<td>CRSD Tablets (Single Unit CRSD Matrices)</td>
<td>SD powder blended with excipients (diluent, lubricant and/or Kollidon® SR) compressed into tablets</td>
</tr>
<tr>
<td>Dry Granulation of SD Powder (MUPS Matrices)</td>
<td>SD powder blended with excipients (diluent and/or Kollidon SR), compressed into slugs, crushed and sieved (Dry Granulation)</td>
</tr>
<tr>
<td>Coated Bead Formulations</td>
<td>Composition</td>
</tr>
<tr>
<td>SD Coated Beads (MUPS Membrane Systems)</td>
<td>Non-pareil beads coated with ethanol solution of celecoxib and PVP by fluidized bed</td>
</tr>
<tr>
<td>CRSD Coated Beads (MUPS Membrane Systems)</td>
<td>Drug (SD) layered non-pareil beads coated with Kollicoat® SR 30 D by fluidized bed</td>
</tr>
</tbody>
</table>
Figure 16: Process Flow Chart to Produce SD and CRSD Systems Resulting in Various Dosage Form Designs. SD solution (top) is transformed into SD by solvent evaporation methods using a spray dryer (left stream) or fluid bed coater (right stream). Resultant spray dried SD powders are further processed into capsules, tablets and dry granulates. SD coated beads are further coated into SR coated beads. Incorporation of KSR in the various stages are depicted in the red-highlighted circles.

To emphasize the effect of dosage form design on CRSD systems studied, dissolution profiles those designs composed of identical formulations (SD:KSR, 7:3) are presented on Figure 17 to Figure 19.
Figure 17: Compilation of Profiles Obtained for Various CRSD Dosage Form Designs Composed of SD:KSR (7:3) (Note: KSR- Kollidon®SR or Kollicoat®SR 30D, based on solids content)
Figure 18: Fast-Release Dosage Form Designs Composed of SD:KSR (7:3)

Figure 19: Slow-Release Dosage Form Designs Composed of SD:KSR (7:3)
These figures emphasize that despite using similar formulation compositions (i.e. SD:KSR, (7:3)), dissolution and recrystallization rates and extents can greatly differ due to the manipulation of dosage form design. That is, by simply altering the processing method, unit design, or the way in which the retarding agent is introduced, very different profiles can emerge. The spectrum of profiles displayed above ranges from those that have become much faster than the SD powder alone, as well as profiles that have become much slower. Due to the finding that this wide spectrum of profiles could be achieved in a somewhat predictable manner, and that spray dried SD powder could equally benefit from both faster and slower release depending on the clinical application, the general term ‘Controlled Release Solid Dispersion’ or CRSD, was refined to include ‘Fast Release CRSD’ (FR-CRSD) and ‘Slow or Sustained Release CRSD’ (SR-CRSD).

Dispersible designs, or those exhibiting faster release (FR) compared to the SD powder, were created by incorporating Kollidon® SR by the methods of co-spray drying, dry granulation of MUPS, and dry blending in a physical mixture. Slower or sustained release (SR) designs were more difficult to achieve due to higher degree of internal SMPT, but were best explored through bead coating and formation of tablet matrix.

In the remainder of this section, each of the designs will be discussed in further detail.

4.3.1 Dry Blended Dosage Form Designs

*KSR Capsules - Effect of Encapsulation*

The simplest manufacturing method to incorporate a powder blend into solid oral dosage form is filling the powder in a hard gelatin capsule. Therefore, this was the first method investigated to evaluate the incorporation of Kollidon® SR with SD powder. The loose powder form was compared with its encapsulated form, depicted in Figure 21. Evaluations were based on quality of the produced dosage form and feasibility of KSR to impart CR characteristics.
Dissolution of Celecoxib Capsules containing CRSD (SD:KSR, 7:3) vs. SD (100 mg dose in 900 mL)

<table>
<thead>
<tr>
<th></th>
<th>SD Capsules</th>
<th>CRSD Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ppm)</td>
<td>13.5±0.5</td>
<td>17.5±2.1</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (min)</td>
<td>68</td>
<td>14</td>
</tr>
<tr>
<td>AUC (0-120 min)</td>
<td>1226.16</td>
<td>1224.75</td>
</tr>
</tbody>
</table>

Figure 21: Dissolution of Capsules filled with SD vs. CRSD (SD:KSR, 7:3) powder blend (900 mL deionized water, 37°C, Apparatus I, 100 rpm). Incorporation of retarding agent KSR, unexpectedly speeds up dissolution of SD powder instead of sustaining release.

Rather than providing a retarding effect, KSR in the capsule form (filled with dry powder blend, SD:KSR, 7:3) appears to induce the opposite effect. With a $T_{\text{max}}$ of 14 minutes, dispersibility and dissolution seems to improve due to the addition of KSR to the SD formulation. Similar to dry blend excipients used in the SD dispersible formulations (SDDF) discussed earlier, KSR may instead aid in the separation of SD particles, hindering cohesion and nucleation, while
promoting dissolution and release into the bulk media. In the case of loose powder formulations where KSR is not bound to the SD, its hydrophobicity may not be considered an impediment to dissolution, but rather a more effective separation agent, dispersing between the hydrophilic SD particles. From this experiment it was suspected that in order for KSR powder to elicit its SR effect, it may require further densification and compressive force in order for polymer matrix to form. Inclusion of KSR by simple dry blending and encapsulation of the physical mixture is not sufficient. On the other hand, flowability and density improved after dry blending, increasing bulk density from 0.297 g/mL to 0.419 g/mL.

KSR Tablets vs. Capsules

Initially, an identical SD formulation composed of SD:KSR (7:3) was compressed into tablets. The effect of compressing the blend is shown in Figure 22. While composition remained the same as the capsule, there is a great difference in dissolution as a result of compression. Release rate and extent is nearly as low as the crystalline solubility of celecoxib, hence solubility enhancement of the SD cannot be observed. At the end of the test, tablets were crushed and it appeared that the cores remained dry. It is possible that water was unable to penetrate into the compressed matrix during the test time period due to dense mass and small specific surface area as compared to the SD particles in the capsule. It was suspected that due to a large proportion of SD in the tablet (70%), it was possible that surface recrystallization and formation of an insoluble shell surrounding the tablet may have been formed, or that there were insufficient pathways or pores for water to enter the tablet and for drug to leach out.
Figure 22: Dissolution of CRSD Capsules and Tablets containing SD:KSR (7:3) (900 mL deionized water, 37°C, Apparatus I, 100 rpm). Under compression (CRSD tablet), the identical formulation of SD:KSR (7:3) fails to release drug beyond the capabilities of crystalline formulations, emphasizing need to evaluate formulations with respect to dosage form design.

Effect of Tablet Matrix Composition

In order to investigate these ideas, a second CR matrix formulation (CRM-2) was developed (Table 9), which reduced the SD powder to 33% in the formulation and incorporated water soluble lactose as a filler/pore former. Resulting profiles (Figure 23) revealed slightly improved dissolution from CRM-2, however peak concentrations still failed to rise beyond crystalline solubility, thus negating any solubility advantage gained by the SD technique. At the end of the test, it was observed that CRM-2 tablets were soft, swollen, gummy, porous and more thoroughly wetted, unlike the dry, harder cores of CRM-1 (Figure 24). Considering this observation, it was suspected that water was indeed capable of reaching the interior of the tablet core thus providing sufficient media for drug to dissolve, however, drug was prevented from effectively releasing from the core and into bulk solution. Since drug concentrations could not be measured in the bulk solution, yet core appeared wet, it is likely that recrystallization may have predominated within the pores of the tablet, transforming drug to its crystalline form and remaining trapped and insoluble inside the core.
Figure 23: Effect of CR Tablet Matrix Formulation on Dissolution (900 mL deionized water, 37°C, Apparatus II, 50 rpm). Slight improvements were made by incorporating soluble pore-forming components (lactose) into the tablet, although solubility enhancement compared to crystalline formulation is negligible, or even impaired.

Table 9: Controlled Release Matrix Formulations with Kollidon® SR

<table>
<thead>
<tr>
<th>Component</th>
<th>CRM-1</th>
<th>CRM-2</th>
<th>CRM-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cel-PVP (7:3) SD powder</td>
<td>70</td>
<td>33.6</td>
<td>50</td>
</tr>
<tr>
<td>Kollidon SR</td>
<td>30</td>
<td>40.0</td>
<td>50</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>-</td>
<td>25.4</td>
<td>-</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 24: General Appearance of CRSD Tablets (CRM-2) before (left) and after (center and right) dissolution. After dissolution, tablet appeared to be soft, pliable and gummy throughout the surface to the core.
The CRSD tablet matrix formulations, which could be described as single-unit matrix forms, were unsuccessful in providing sufficient drug release, defeating the solubility enhancement effect gained by the solid dispersion technique. Its failure was attributed to severe internal SMPT or recrystallization within the core, as sufficient drug could not be measured in the bulk solution, yet its core appeared fully wetted. To address this phenomenon, a smaller sized, dispersible multi-unit particulate design was investigated. Identical CRM blends for tablet matrices (as listed on Table 9) and a third formulation containing SD:KSR (1:1) (CRM-3) were processed by the slugging dry granulation method to yield dry granulated (DG) MUPS. Blends were compressed into tablets, crushed by mortar and pestle, then sieved and collected in two fractions (Mesh #20- 0.850 to 1.5 mm and Mesh #40- 0.425 to 0.850 mm). Dry blend formulations, CRM-1 and CRM-2 for tablets versus dry granulates collected on Mesh #40 can be contrasted on Figure 26, and also compared with CRM-3 granules and SD powder.
Figure 26: Effect of Dry Granulated MUPS Unit Design (900 mL deionized water, 37°C, Apparatus II, 50 rpm). DG-MUPS design exhibits faster release compared to both tablets of identical formulations and SD powder.

From the graph, it is obvious that the reduction in matrix dimensions by unit design from tablet to DG-MUPS has the effect of speeding up and increasing extent of dissolution. Removing the physical constraints of a single unit tablet design, the DG-MUPS are able to achieve greater solubility improvement in shorter time period. With a $T_{\text{max}}$ of approximately 30 min, the DG designs even appear to show improvement over to the SD powder form tested at the same conditions, which reach $C_{\text{max}}$ of just ~14 ppm around 120 min. This finding also highlighted the need for better dispersibility of SD powder formulations in order to maximize effective use of
the drug. It was interesting to note that despite undergoing compression and inclusion of a retarding agent (Kollidon® SR) there is a significant fast release (FR) effect of the DG matrices. In this case example, where the profiles of DG-MUPS and tablets differ so drastically, effect of dosage from design highly precedes effect of formulation.

Comparing both DG formulations however, it can be noted that peak of the granules produced from the CRM-1 formulation (with higher proportion of SD powder and less KSR) appears to surge higher than CRM-2. To further investigate whether this difference could be attributed to varying the level of KSR or SD loading, the third formulation of CRM-3 was compared. While its peak and release rate overlaps the granules of CRM-2, its slope of decline closely resembles the decline of CRM-1, albeit slightly slower. It was suspected that the difference in decline might be attributed to the presence/absence of lactose, which may be functioning as a pore former. In CRM-2, as lactose dissolves, this may create larger and more numerous pores, loosening the matrix, thus enabling drug to exit at a faster rate into the bulk solution. With higher concentrations of drug in the bulk in a short time, progression of SMPT is more rapid. This idea was consistent with our observations that shortly after introducing the granules to the dissolution vessels, those containing lactose became very cloudy and formation of precipitates were easily visible (Figure 27).

![Figure 27: General Appearance of Dissolution Vessels during Dissolution of DG-MUPS. CRM-1 (left) and CRM-2 (right) exhibit differences in media clarity and visible formation of precipitates from side and top views of the dissolution vessel.](image)

On the other hand, binary formulations without pore former (CRM-1 and CRM-3), having greater association between SD and KSR, may have a protective effect by maintaining higher
rigidity of the matrix, thus better controlling the rate of collisions between drug molecules as they dissolve in the core and controlling the rate of release into the media. It was also observed that binary CRM formulations maintained the dry granulate structure (shape and dimensions) following dissolution (Figure 28), while those containing lactose did not. With slower release into the media, accumulation in the bulk is not as rapid, slowing down SMPT. Although supersaturation is still ultimately reached and causes concentrations to plummet, it appears that rate of decline can be partly controlled by KSR and whether or not pore-forming excipients are used.

Figure 28: DG-CRM-3 Before (left) and After (right) Dissolution. Following dissolution, shape and dimensions of granules are maintained relatively the same compared to the dry form.
The effect of granule size using CRM-3 was also investigated, depicted on Figure 29.

![Dissolution of Dry Granulations (CRM-3)](image)

**Figure 29: Effect of Granule Size on Dissolution of DG-MUPS.** CRM-3 was used to vary granule size (Mesh #40 vs Mesh #20). Larger particle sized granules (Mesh # 20) exhibited diminished dissolution compared to smaller granules.

<table>
<thead>
<tr>
<th></th>
<th>Mesh #40</th>
<th>Mesh #20</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ppm)</td>
<td>17.5±0.6</td>
<td>13.9±0.7</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>25 min</td>
<td>40 min</td>
</tr>
<tr>
<td>AUC (0-120 min)</td>
<td>1629</td>
<td>1253</td>
</tr>
<tr>
<td>AUC (0-240 min)</td>
<td>2367</td>
<td>1837</td>
</tr>
</tbody>
</table>

The next trend examined with CRM-3 was effects of particle size. As expected with common dissolution theory, rate of dissolution was decreased when particle size was increased from ~0.6 to ~1.1 mm. Typically, this is described in terms of increase/decrease in surface area exposed to media. We can also imagine that as the granule size increases, the complexity of the path that the dissolved drug needs to travel to exit the core and enter bulk solution, also increases. It is this latter point that may also be responsible for the lower extent of dissolution obtained for the larger granule. Perhaps the more tortuous path length creates more resistance for drug to emerge from the core before it begins to contact other drug molecules and undergo SMPT. Therefore,
as with tablet matrix designs, and previous DG-MUPS examples where KSR is increased, there is still some indication that the matrix is prone to internal recrystallization, despite the reduction in unit size or particle size.

DG-MUPS matrix designs may be advantageous for applications requiring fast onset of action, as with the previous SDDF dispersible designs mentioned (SDDF capsules and tablets), with the binary SD:SKR DG-MUPS formulations carrying the added benefit of controlling and decreasing rate of recrystallization, maximizing AUC for the short time period. However, dry granulations prepared from simple dry blends of SD and KSR appear to lack the degree of control required to sustain release for longer acting SR applications and still show evidence of internal SMPT within the matrix.

4.3.2 Co-Spray Dried SD Dosage Form Design with Kollidon® SR

*Co-Spray Dried Powder– Effect of Homogenous Distribution of KSR*

![Figure 30: General Appearance of Co-Spray Dried SD-KSR Powder (top row) versus Spray Dried SD Powder (bottom row). Macroscopic view (left), Microscopic image at 4x magnification (center) and 10x magnification (right). Compared to spray dried SD powder, co-spray dried bulk powder appears to have more discrete, less dense, spherical particles and exhibits less cohesivity.](image-url)
Table 10: Bulk and Tapped Density of Co-Spray Dried Powder

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bulk Density</strong></td>
<td>0.11 g/mL</td>
</tr>
<tr>
<td><strong>Tapped Density</strong></td>
<td>0.15 g/mL</td>
</tr>
<tr>
<td><strong>Carr’s Index</strong></td>
<td>27 (poor flowability)</td>
</tr>
</tbody>
</table>

In attempt to maximize the homogeneity of the SD-KSR matrix at the finest, most intimate physical level, co-spray drying the SD solution with the aqueous polymeric dispersion, Kollicoat® SR30D (PVAc:PVP, 90:9) was performed using the spray dryer. As KSR aqueous dispersion was allowed to combine with drug in its dissolved form in the spray solution, interparticulate (or inter-SD) dispersion of KSR was predicted to be highest. Resultant co-spray dried powders yielded lower bulk density (0.11 mg/mL), with similar CI (27-29%), but demonstrated much greater processing efficiency than the conventional SD powders, as it was observed that less material adhered to the spray drying chamber. Higher flowability may be attributed to the more spherical shape of the particles and less observable fines (Figure 30). Particle size appeared to be approximately ~100μm. DSC thermograms also revealed successful transformation to amorphous form as peaks near celecoxib melting point was not detected (Figure 31).

Figure 31: DSC Thermograms of Co-Spray Dried SD. *From top to bottom- 30% KSR, 5-% KSR, SD, PVP K30, celecoxib (crystalline bulk).* Absence of celecoxib melting peak in co-spray dried SD samples indicates transformation to amorphous form.
The effect of SD to KSR ratio was examined between two levels, 1:1 and 7:3, and subsequently compared with profiles obtained for dry granulated MUPS of the same compositions. As concentration of KSR increased, rate and extent of release during dissolution decreased.

![Graph showing comparison between CRSD dry granules and CRSD co-spray dried powder](image)

**Figure 32:** Effect of Method of Incorporation of KSR- Co-Spray Dried Powder versus Dry Granulated MUPS (900ml deionized water, 37°C, Apparatus II, 50 rpm). Retarding KSR is greater when applied as an aqueous dispersion in co-spray dried powders.

<table>
<thead>
<tr>
<th>Co-Spray Dried SD KSR:SD (7:3)</th>
<th>Co-Spray Dried SD KSR:SD (1:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}}) (ppm)</td>
<td>13.9±1.4</td>
</tr>
<tr>
<td>(T_{\text{max}}) (min)</td>
<td>45 min</td>
</tr>
<tr>
<td>AUC (0-120 min)</td>
<td>1401.92</td>
</tr>
<tr>
<td>AUC (0-240 min)</td>
<td>2172.29</td>
</tr>
<tr>
<td>AUC (0-420 min)</td>
<td>2894.72</td>
</tr>
<tr>
<td>AUC (0-700 min)</td>
<td>3703.75</td>
</tr>
<tr>
<td></td>
<td>78.1±0.5</td>
</tr>
<tr>
<td></td>
<td>25 min</td>
</tr>
<tr>
<td></td>
<td>739.93</td>
</tr>
<tr>
<td></td>
<td>1219.60</td>
</tr>
<tr>
<td></td>
<td>1670.10</td>
</tr>
<tr>
<td></td>
<td>2365.70</td>
</tr>
</tbody>
</table>

An overall trend is similar between Matrix MUPS composed of SD powder dry granulated with Kollidon SR, and CRSD powders as concentration of KSR is varied. Both designs appear to display suppression of release rate and extent when levels of KSR are increased. That is, \(C_{\text{max}}\)
and AUC drops to about half when increasing KSR from 30% to 50%, while $T_{\text{max}}$ remains relatively unchanged (~25 min). However, comparison of the two designs might reveal a difference in effective use of KSR. From the graph, the profile of granules containing 50% KSR is comparable to the CRSD powders containing just 30% KSR. That is, the retarding effect of KSR may appear to be more prominent by the co-spray drying technique, versus the dry blending/dry granulation technique if we consider the difference in particle size. Despite the granules’ larger size (0.425-.850 mm) and involvement of compressive forces to form the matrix, the CRSD powders tested in the loose form exhibited a greater SR effect from KSR. That is, dissolution rate of dry granulated MUPS is much faster than CRSD powders, which are smallest in size. The predicted improvement of homogeneity or finer dispersibility of SD with in KSR could be used to explain these effects, indicating that formation of a coherent matrix could be better achieved by incorporating KSR at the earliest stage of spray drying. Alternatively, it can also be considered that the difference in PVAc:PVP composition in the KSR aqueous dispersion compared to powder form (90:9 vs. 80:19, respectively) may also be responsible for this effect. To elucidate this, concentrations of KSR should be adjusted to match composition of Kollidon®SR powder. With a goal of fast release (FR) in mind, it would also be helpful to challenge lower KSR amounts.
4.3.3 Coated Bead Dosage Form Designs

*KSR Coated Beads- Effect of Applying KSR as a Membrane Film*

A second design that incorporated KSR in the aqueous dispersion form was the SR coated bead. The design of drug-layered/coated beads was worthy of investigation since in theory, there are notable differences compared to matrix or monolithic designs. An important consideration in selecting a membrane-reservoir system design achieved via coating was the potential to provide zero-order release, whereas CR matrix systems usually follow first-order release kinetics. Zero-order kinetics is beneficial as it provides ability to maintain constant drug concentrations in the bulk solution/plasma for longer periods of time. It was anticipated that this feature could be particularly useful in preventing supersaturation in the bulk if rate of release could constantly be controlled to match rate of absorption. Therefore, due to the distinct differences in arrangement of drug and application of CR agent, it was expected that the kinetics of dissolution and recrystallization would differ between the coated beads design versus the monolithic designs, hence warranting comparison between the forms.

---

**Figure 33: General Appearance of KSR Coated Beads.** a) uncoated beads, b) drug/SD-layered beads, c) SR coated beads, d) microscopic image of SR coated beads at 4× magnification.
### Dissolution of SD vs. CRSD Coated Beads

100 mg dose of celecoxib (Apparatus II, 75 rpm, 900 mL deionized water)

<table>
<thead>
<tr>
<th></th>
<th>SD Beads</th>
<th>CRSD Beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ppm)</td>
<td>13.1±0.6</td>
<td>5.4±0.6</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>150 min</td>
<td>720 min (12 hrs)</td>
</tr>
<tr>
<td>AUC (0-120 min)</td>
<td>837.61</td>
<td>96.56</td>
</tr>
<tr>
<td>AUC (0-240 min)</td>
<td>2217.28</td>
<td>328.62</td>
</tr>
<tr>
<td>AUC (0-420 min)</td>
<td>3274.98</td>
<td>942.08</td>
</tr>
<tr>
<td>AUC (0-700 min)</td>
<td>4250.74</td>
<td>2337.54</td>
</tr>
<tr>
<td>AUC (0-1400 min)</td>
<td>6005.53</td>
<td>5367.63</td>
</tr>
</tbody>
</table>

**Figure 34: KSR Incorporation in Membrane-Reservoir Coated Bead Design (900 mL deionized water, 37°C, Apparatus II, 75 rpm).** Zero-order release appears to be feasible up to 12 hours with SR coated beads.

Of all the CR dosage forms prepared with Kollidon® SR, the coated beads demonstrated the highest potential for SR application, although improvements must be made to increase extent of dissolution. Results show that continual increase in concentration in a zero-order release fashion was indeed possible up to 12 hours, although peak concentrations were relatively lower than other SD and CRSD designs. The failure to reach higher concentrations may be partially attributed to ongoing SMPT in the bulk, but also to some internal recrystallization. As the first layer on the bead is composed of just SD (Cel:PVP, 7:3), without any other excipients to separate neighboring molecules, it is probable that SMPT was occurring beneath the SR layer. To rectify this occurrence and facilitate removal of drug from the core, addition of pore formers or other diluents can be considered. As with the co-spray dried powder, it should be noted again...
that KSR was applied in the form of its aqueous dispersion, Kollicoat® SR 30D, which contains relatively less PVAc to PVP (90:9) as compared to Kollidon® SR powder (80:19). Therefore we should consider that reductions in release in these spray forms may also be partially attributed to the lesser degree of PVP, which has potential to function as a pore former and crystallization inhibitor. Notwithstanding, despite the lowered peak concentrations achieved for the CRSD beads, solubility advantage is still ~2-3-fold greater than the crystalline solubility and its zero-order release pattern could serve applications where steady plasma concentrations are desired, as to maintain therapeutic levels and avoid exceeding those that induce toxic side effects. Hence, high potential utility of the coated bead design is warranted.

4.4 Summary of Results

The goal of this work was to discover general trends that can result from the manipulation of dosage form design. A recap of general trends discovered was as follows:

1. Neat SD powder results in formation of insoluble agglomerates during dissolution, especially in cases of increased confinement (capsule, basket apparatus), demonstrating a high potential for internal SMPT. Furthermore, poor bulk powder properties such as high cohesivity, poor flowability and poor compressibility highlight the need for further development to improve manufacturability. SD powder in its pure form, whether in loose powder or encapsulated form, is not appropriate for delivery.

2. Strategies to prevent coagulation of SD particles during dissolution, such as dry blending with water-soluble or water dispersible excipients (e.g. lactose or MCC) improves dissolution rate and extent of SD, which can be further processed by encapsulation or compressed into disintegrating tablets without hindering dissolution.

3. Incorporation of a polyvinyl acetate based retarding agent to an SD system is feasible by two distinct methods. In one, its powder form, Kollidon® SR, may be dry blended with the SD powder, followed by encapsulation of the resultant blend into hard gelatin capsules, compression into tablets, or further processed into dry granulated multi-particulates. Alternatively, the liquid aqueous dispersion form, Kollicoat® SR30D may be added to the SD formulation by means of co-spray drying in a spray dryer, or by layering onto SD loaded beads by fluidized bed coating.
4. Depending on method of incorporation, unit design and CR design, dissolution and recrystallization behavior was presented differently, despite being composed of identical formulations (SD:KSR, 7:3). Dissolution studies revealed a wide spectrum of profiles, encompassing dissolution/recrystallization rates that were relatively faster compared to neat SD powder, to those that were much slower. Given the clinical utility of being able to tailor both faster release and slower release from poorly water soluble drugs, this provoked us to redefine the goals of controlled release to include FR-CRSD and SR-CRSD.

5. Dissolution of compressed matrices was highly dependent on unit design. Single unit tablets failed at preserving solubility advantage of amorphous drug, as majority of drug was suspected to undergo extensive internal SMPT. This was attributed to the larger, rigid, insoluble, tortuous matrix of the tablets, where drug was challenged to diffuse over a longer distance to reach the bulk solution. Formation of pockets or pores within the tablet may have provided significant areas of supersaturation triggering SMPT prior to reaching the media.

6. Dry granulated MUPS matrices on the other hand, were capable of providing FR, but not SR. This was explained by the lack of complexity in the smaller-sized matrix dimensions, failing to provide a sufficient barrier for gradual water penetration and sufficient tortuosity for drug release. The effect of KSR as a retarding agent in the granules however, was apparent as dissolution profiles were subdued when levels of KSR were increased. Since a decrease was observed not only in the rate, but also in the extent (i.e. peak) of dissolution as KSR was increased, it is theorized that internal SMPT is still at risk whenever using KSR in a matrix form, despite selection of a smaller unit designs.

7. Incorporation of KSR in aqueous dispersion was advantageous in increasing homogeneity or dispersion in SD matrix, as observed with co-spray dried CRSD powders. Co-spray drying may be a useful strategy to incorporate KSR in any of the dosage forms examined, in order to maximize separation or distribution of dissolving SD particles and prevent internal SMPT.
8. Application of KSR as a membrane over coated beads showed highest promise for SR-CRSD application, as it enabled zero-order release up to 12 hours. However, peak concentrations were diminished compared to FR designs and further development would be required to overcome internal SMPT.

9. The designs investigated could be grouped into the following categories, with their release rates respective to neat SD powder:

<table>
<thead>
<tr>
<th>Fast Release (FR) CR Designs</th>
<th>Slow Release (SR) CR Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDDF Capsules, Tablets</td>
<td>KSR Tablet Matrices (failed)</td>
</tr>
<tr>
<td>KSR Dry Granulated MUPS</td>
<td>SD Coated Beads</td>
</tr>
<tr>
<td>KSR Co-Spray Dried Powders</td>
<td>KSR Coated Beads</td>
</tr>
</tbody>
</table>
Chapter 5

5 Conclusions and Future Directions

This work effectively characterized the behavior of spray dried SD and CRSDs over a range of dosage form designs. Limited studies to date have been conducted in this field, where SD is transformed into orally administrable dosage forms, although fortunately, greater research on this topic in the past couple of years has begun to emerge (Leane, et al., 2013; Puri & Dantuluri, 2012; DiNunzio, Schilling, Coney, & McGinity, 2012). Therefore, the results of this study, pooled together with new research on SDs incorporated into dosage forms, can help to improve our general understanding of the strengths and limitations of SDs during formulation development and how utility of the drug can be maximized by rational selection of dosage form design. Furthermore, by examining dosage form design with respect to Kollidon® SR, we may also become more aware and better equipped to tackle the specific challenges entailed when designing CRSD systems.

5.1 SMPT: A Dual-Faceted Phenomenon

Traditional SD studies typically illustrate SMPT as the classic peak and decline on a dissolution profile. However, in this study it was demonstrated that SMPT is a phenomenon that can present itself in two distinct manners, depending on its area of predominance: in bulk solution (external SMPT) or within the dosage form (internal SMPT). A comprehensive review of DFD revealed that neat SD powder (unformulated SD) is inherently prone to both phenomena, thus requiring CR strategies to include both FR and SR in order to maximize drug utility, and to also target desired pharmacokinetics and clinical application. High external SMPT, best exemplified by loose powder or dispersible formulations and designs (FR designs), was characterized by sharp peaks in concentration followed by sharp declines, plateauing close to crystalline solubility (classic SMPT profile). Conversely, in dosage forms where water penetration and/or diffusion of the drug to the bulk was restricted, forcing dissolved drug to reside within smaller confined space for longer time, as with SR coated beads or CRSD tablet matrices (SR designs), internal SMPT became more predominant. This was displayed by slower rates of dissolution, lower peak concentrations and slower declines measured in the bulk solution, which was an occurrence less obvious, until compared over DFDs. Ultimately, it was discovered that if
attempts are to be made in developing a viable CRSD system, attention should be paid to both sides of the spectrum of the SMPT phenomena.

5.2 Co-Spray Drying as Method to Maximize Homogenous SD Distribution in Matrix

Co-spray drying the retarding agent in aqueous dispersion form combined with the SD solution was discovered to be an effective method to maximize homogenous distribution of SD within a matrix, yielding highest peak concentrations and relatively longer peak durations compared to other FR designs. It appears to be especially beneficial in addressing internal SMPT. It seems worthy to investigate whether this strategy could be extended to any of dosage form designs and downward processing (e.g. use co-spray dried powder to produce DG-MSD) and if it can also be performed using other combinations of excipients, where enhanced association between the SD and excipient, or greater separation/prevention of inter-SD interaction is desired. It also seems likely that if homogeneity of the matrix can be improved by co-spray drying (i.e. dispersion of SD on a smaller scale), physical stability during its shelf life is also likely to be extended. A similar concept, explored in recent work with SDs prepared in mesoporous CaCO$_3$, attributed the preservation of amorphous celecoxib to the ability of the nano-scaled pores formed within the CaCO$_3$ matrix to maximize separation of SD particles (Forsgren, Andersson, Nilsson, & Mihranyan, 2013). Therefore, it seems plausible that co-spray dried matrices capable of forming a dispersion on the smallest (e.g. nano) level may possess critical benefits. Furthermore, from a manufacturing perspective, co-spray dried SD powders seemed to possess more amenable bulk powder characteristics, resulting in less losses in material during handling, higher yield from the spray drying process, and fewer manufacturing steps. Therefore, cost of production could be reduced, increasing the attractiveness of this method.

5.3 Developmental Strategies for SR-CRSDs

Challenging SD performance in various dosage form designs in this study highlighted a critical requirement for SR-CRSD development, which is to optimize the sensitive balance between dispersibility and immobilization. While FR systems could be easily be achieved by simple formulation (e.g. dispersible excipients) and manufacturing (e.g. dry granulation, co-spray drying) approaches, sustained release relying on Kollidon® SR alone was found to be more challenging, appearing to require further refinement or alternate approaches in order to
overcome internal SMPT. Majority of work in this field, which has tended to focus on the
development of the SD powders (an intermediate product), underemphasize the occurrence of
internal SMPT, as this seems to be a more significant result of transformation into dosage form
(the final product). Future efforts to improve the viability of SR-CRSD should aggressively
target the prevention of internal SMPT. This may include an investigation of alternate polymer
classes, such as those that are erodible, thus capable of reducing path length (and risk for
internal SMPT) as dissolution progresses, and/or those capable of keeping the core relatively
dry. Taking a further approach, strategies to extend or maintain supersaturation during
dissolution within the core of the SR matrix by addition of other agents could also be sought.

5.4 Bio-Relevant Dissolution and Identifying CR Targets

Since the scope of this project was to extract the general trends of manipulating dosage form
design, levels (i.e. concentration, dose) of drug/SD used in the dissolution studies were arbitrary
and may not necessarily correlate with in-vivo results. However, in order to proceed with more
meaningful conclusions about the behavior of SD and CRSD systems, especially, we must
consider the development of bio-relevant testing. The variables used to design bio-relevant
testing, which would consider those such as gastric and intestinal volumes, gastric emptying
time, fed and fasted states, luminal pH, etc., are especially critical in the development of SD
systems. More specifically, in a closed dissolution system (i.e. closed vessel), where contents
are not removed or replaced, it is difficult to predict how a supersaturating system would behave
in-vivo, where drug is able to permeate through the GI membranes. This is another avenue
relatively unexplored in the field of SD technology, yet is crucial in further pursuit of its
development.

The progression of CRSD development can be envisioned as such, where CR targets could be
defined by the PK of the drug. First, one must determine what the therapeutic range of the drug
must be in order to maximize clinical efficacy. This could be obtained from existing data
derived from clinical studies. Second, a dose adjustment based on the amorphous SD form
should be performed in order to scale down the dose required for development (i.e. determine
what SD dose is required to reach target plasma concentration). For example, peak
concentration for Celebrex® is reported to be 600-900 ng/mL for a 200 mg dose (Searle, 1998).
For a celecoxib SD system, it would be likely that much less than 200 mg of drug could be used to reach similar concentrations. Once the appropriate SD dose is determined, suitable levels and compositions of dissolution media can be configured and formulation development can proceed. Finally, using FR (dispersible) and SR (retarding) techniques, rate of dissolution and recrystallization can be tailored to suit (1) desired onset of action, (2) the half-life of the drug, (3) rate of absorption (to maintain steady concentration levels in GIT) and (4) intrinsic rate of recrystallization of the drug.

5.5 Clinical Significance of SD Technology

The pursuit of greater knowledge in the field of SD technology can potentially have enormous impact on the future healthcare of mankind. With the vast number of poorly soluble NCEs unable to pierce the formulation barriers in order to reach the patient’s bedside, we are losing opportunities to create countless improvements and additions to current therapies. It is our role as drug development scientists to continue to search for solutions and better strategies so that we can make these improvements to healthcare. If this can be done, it is hopeful that many of these BCS Class II and Class IV compounds may finally be put to clinical use. SD technology has made tremendous progress over the past few decades and many would agree that it is one of the most promising strategies to tackle poorly water-soluble drugs. Continuance in this field with a more solid understanding of SD systems, complimented with some creativity, as exemplified by our attempts to challenge CRSDs, may help us to discover alternate ways to tear down the barriers that we have been struggling with. Finally, we should bear in mind that as the feat to develop many poorly water soluble drugs has yet to be conquered, so do the many diseases and conditions that may potentially be treated with these drugs.
References


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Appendix

Appendix: Summary Overview Chart of SD and CRSD Designs
## Appendix: Summary Overview Chart of SD and CRSD Designs

<table>
<thead>
<tr>
<th>SD Powder Formulations</th>
<th>Effect Studied</th>
<th>Factors Investigated</th>
<th>Observations</th>
<th>Conclusions</th>
<th>Best Formulation/Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Spray Dried SD Powder</td>
<td>Effect of D:P ratio (Cel:PVP)</td>
<td>Cel:PVP (9:1) vs. (7:3) vs. (1:1)</td>
<td>Higher crystallinity and lower solubility with (9:1), (1:1) provides prolonged bulk supersaturation</td>
<td>Solubility advantage over crystalline drug is confirmed for all D:P ratios, especially by using higher amounts of PVP as a SD carrier.</td>
<td>To demonstrate effectiveness of CRSD strategy to prevent SMPT, Cel:PVP (7:3) was selected. Neat SD is unsuitable for delivery, must be formulated with excipient/further processed.</td>
</tr>
<tr>
<td></td>
<td>Effect of confinement</td>
<td>App I vs App II Encapsulation</td>
<td>Formation of tacky agglomerates</td>
<td>Confinement in basket (App II) and capsule lead to higher rate of internal/surface SMPT</td>
<td></td>
</tr>
<tr>
<td>2 Co-Spray Dried SD Powder</td>
<td>Effect of SD:KSR ratio</td>
<td>30% KSR 50% KSR</td>
<td>Peak concentrations are reduced with higher amount of KSR. SR effect of KSR is more pronounced compared to DG-MUPS</td>
<td>For FRSD applications, co-spray drying SD solution with KSR is suitable in delivering comparable profiles as dry granulated MUPS, with higher process efficiency (less stages)</td>
<td>For FRSD applications: 30% KSR (Should investigate 10%KSR, or other candidates)</td>
</tr>
<tr>
<td></td>
<td>Spray method of Incorporation to improve KSR dispersion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 SD Powder Dry Blended with Excipients and KSR (Physical Mixture)</td>
<td>Effect of SD dispersible formulations</td>
<td>MCC, lactose as diluent KSR as diluent</td>
<td>SR cannot be achieved in powder PM filled in capsule. Both excipients behave as dispersing agents.</td>
<td>Physically distancing neighbouring SD particles by introduction of excipient results in faster greater dissolution. However, rate of SMPT is also higher.</td>
<td>Dispersibility effect is not specific to KSR, therefore, other excipients should be preferred.</td>
</tr>
<tr>
<td></td>
<td>Determine if SR can be achieved with KSR in PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compressed Matrix Formulations</td>
<td>Effect Studied</td>
<td>Factors Investigated</td>
<td>Observations</td>
<td>Conclusions</td>
<td>Best Formulation/Recommendations</td>
</tr>
<tr>
<td>4 Dry Granulation of SD Powder (DG-MUPS Matrices)</td>
<td>Effect of Particle Size</td>
<td>20 mesh 40 mesh</td>
<td>Larger granules provided slower release and reduced peak</td>
<td>High dispersibility of granule form promotes faster release and higher Cmax.</td>
<td>For FRSD applications: 30% KSR, 40 mesh Best formulation and design to achieve highest AUC &lt;120 min.</td>
</tr>
<tr>
<td></td>
<td>Effect of KSR concentration</td>
<td>30% KSR 40% KSR (25% lac) 50% KSR</td>
<td>Less KSR provided higher peaks at same Tmax Faster decline with lactose</td>
<td>Peaks are momentarily sustained compared to pure SD powder, esp. without lactose Rate and extent of release can be modified by particle size.</td>
<td></td>
</tr>
<tr>
<td>5 SD Tablets (Single Unit SD Matrices)</td>
<td>Determine if compression of SD powder into tablets impairs dissolution.</td>
<td>Use of MCC and lactose as diluents</td>
<td>Compressed tablet exhibited similar profile to uncompressed powder blend filled into capsules.</td>
<td>When formulated with excipients (water soluble or disintegrating), dispersibility is preserved as compression does not affect dissolution.</td>
<td>Suitable for FRSD applications</td>
</tr>
<tr>
<td>6 CRSD Tablets (Single Unit CRSD Matrices)</td>
<td>Effect of KSR concentration -with diluent -without diluent</td>
<td>30% KSR 40% KSR (25% lac)</td>
<td>Concentrations fail to rise above crystalline solubility. Tablet matrix skeletons remain intact after dissolution, cores are wet.</td>
<td>Failure to reach higher concentration in the bulk solution may be attributed to higher degree of SMPT within tablet core (internal SMPT)</td>
<td>Tablet matrix is not recommended for CRSD using the formulations studied</td>
</tr>
<tr>
<td>Coated Bead Formulations</td>
<td>Effect Studied</td>
<td>Factors Investigated</td>
<td>Observations</td>
<td>Conclusions</td>
<td>Best Formulation/Recommendations</td>
</tr>
<tr>
<td>7 SD Coated Beads (MUPS Membrane Systems)</td>
<td>Effect of dispersible (MUPS) design</td>
<td>Compared with SDDF (PM with MCC)</td>
<td>Release rate is slower (Tmax ~150min) compared to other SD PM designs.</td>
<td>Coated bead design lowers surface area for drug dissolution, resulting in slower release (despite absence of KSR)</td>
<td>Coated SD bead design may be useful for slower release &lt;150 min time frame.</td>
</tr>
<tr>
<td>8 CRSD Coated Beads (MUPS Membrane Systems)</td>
<td>Determine if SR can be achieved with KSR as membrane coating</td>
<td>~3% WG</td>
<td>Rate of release is considerably slower, Cmax is follows zero-order for extended duration (&lt;12 hrs)</td>
<td>Coated CRSD system can be used to achieve SR release in zero-order fashion, but current coating level and formulation used provided low (2-3 fold) solubility improvement</td>
<td>Further development could utilize pore formers to increase rate and extent of dissolution.</td>
</tr>
</tbody>
</table>