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Itraconazole nanocomposites prepared via rotary evaporator drying of nanomilled suspensions

Alexander Santos Coelho
New Jersey Institute of Technology

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ABSTRACT

ITRACONAZOLE NANOCOMPOSITES PREPARED VIA ROTARY EVAPORATOR DRYING OF NANOMILLED SUSPENSIONS

by
Alexander Santos Coelho

The aim of this study is to explore the feasibility of rotary evaporation for drying wet-milled drug suspensions as a novel approach to produce drug nanocomposites that exhibit fast redispersion and immediate drug release. To this end, the physical stability of the nanomilled itraconazole (drug) suspensions, a.k.a., nanosuspensions, during the milling and storage; the drying of the itraconazole nanosuspensions via the rotary evaporator; and the type/loading of various polymers/surfactants (dispersants) on aqueous redispersion and drug release from the nanocomposites were examined. Our results suggest that smaller drug particle size, owing to nanomilling, and smaller nanocomposite particle size, owing to optimized drying and subsequent mortar–pestle milling, as well as higher concentration of hydrophilic polymers/surfactants enhanced redispersion and drug release. Overall, rotary evaporation of drug nanosuspensions could achieve fast redispersion and immediate release of poorly soluble drugs from these nanocomposites, with less concern over potential flowability issues than spray-dried nanocomposites.

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by
Alexander Santos Coelho

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ITRACONAZOLE NANOCOMPOSITES PREPARED VIA ROTARY EVAPORATOR DRYING OF NANOMILLED SUSPENSIONS

Alexander Santos Coelho

Dr. Ecevit A. Bilgili, Thesis Advisor — Date
Professor of Chemical and Materials Engineering, NJIT

Dr. Kathleen McEnnis, Committee Member — Date
Assistant Professor of Chemical and Materials Engineering, NJIT

Dr. Roman S. Voronov, Committee Member — Date
Associate Professor of Chemical and Materials Engineering, NJIT

BIOGRAPHICAL SKETCH

Author: Alexander Santos Coelho

Degree: Master of Science in Chemical Engineering

Date: December 2021

Undergraduate and Graduate Education:

- Master of Science in Chemical Engineering,
  New Jersey Institute of Technology, Newark, NJ, 2021

- Bachelor of Science in Chemical Engineering,
  New Jersey Institute of Technology, Newark, NJ, 2019

Major: Chemical Engineering

Minor: Applied Mathematics

Presentation and Publications:

Journal Articles:

Rahman, M., Arevalo, F., Coelho, A., & Bilgili, E. (2019). Hybrid nanocrystal–amorphous solid dispersions (HyNASDs) as alternative to ASDs for enhanced release of BCS Class II drugs. *European Journal of Pharmaceutics and Biopharmaceutics*, *145*, 12-26. https://doi.org/https://doi.org/10.1016/j.ejpb.2019.10.002

Rahman, M., Coelho, A., Tarabokija, J., Ahmad, S., Radgman, K., & Bilgili, E. (2020). Synergistic and antagonistic effects of various amphiphilic polymer combinations in enhancing griseofulvin release from ternary amorphous solid dispersions. European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences, 150, 105354. https://doi.org/10.1016/j.ejps.2020.105354

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M. Rahman, A. Coelho, S. Ahmad, J. Tarabokija, S. Bhujbal, K. Radgman, E. Bilgili, Possible Synergistic Effects of Binary Polymers in Enhancing Release of a poorly Soluble Drug from Amorphous Solid Dispersions. AIChE Annual M eeting, 2019,
Orlando, FL

M. Rahman, A. Coelho, S. Bhujbal, E. Bilgili, Spray-dried nanocomposites and amorphous solid dispersions with identical formulation for comparative assessment of drug dissolution enhancement. AIChE Annual Meeting, Pittsburgh, PA

To my mom and dad who have always supported me

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CHAPTER 1

INTRODUCTION

1.1 Motivation

In the pipeline a large percentage, about 40%, of newly developed drugs fall under poorly water-soluble due to high molecular weight and hydrophobicity (Lipinski, 2002). Due to their poor water solubility, a slow dissolution can lead to low bioavailability, which is not conducive to developing effective therapeutic medicines (Fasano, 1998). Widely used methods of combating the slow dissolution rates of these drugs include the implementation of nanoparticle formation, amorphous solid dispersions, changing active particle surface properties, and co-crystals (Anagha Bhakay et al., 2014; Jeong & Park, 2008; Niwa & Danjo, 2013; Serajuddin, 1999; Yadav et al., 2009). These strategies all focused on the enhancement of bioavailability through the manipulation of the drug particle size/surface area or its solid-state. Most notably, the use of nanoparticles generated through wet stirred media milling in the form of nanosuspensions has continued to be a reliable method of increasing the drug dissolution rate to this day with approved FDA drugs (Malamatari et al., 2018). However, as solid dosage forms such as tablets, capsules, etc. are preferred by patients over liquid dosage forms due the convenience of the former, drug nanosuspensions must be dried into nanocomposite powder prior to their incorporation into the solid dosages. To dry these nanoparticle suspensions, techniques such as spray drying (Anagha Bhakay et al., 2014; Bilgili et al., 2018; Rahman et al., 2019), fluidized bed coating (Anagha Bhakay et al., 2014; Chaubal & Popescu, 2008; Vogt et al., 2008), and lyophilization (Kim & Lee, 2010; Tuomela et al., 2015) have been widely used. All

methods aim at evaporation of a solvent from the suspension leaving behind a solid composite. A rotary evaporator that can apply vacuum and heating to a suspension has not been used to prepare nanocomposites from wet media milled drugs before, which is in the scope of this thesis work.

1.1.1 Drug Nanosuspensions

Within the literature, drug nanosuspensions have been a focal point to enhancing the bioavailability of poorly water-soluble drugs (Bhakay, Rahman, et al., 2018). In the pharmaceutical nanotechnology literature, drug nanosuspensions refer to aqueous solution of various dispersants in which insoluble colloidal and truly nanosized particles all having the particle size of less than 1μm in size are suspended. The dispersants such as polymers and surfactants dissolve in water and provide physical stability to the nanocrystals by preventing their aggregation (Junghanns & Muller, 2008). The desire to generate a nanosuspension comes from the dissolution enhancement stemming from the larger surface area of milled particles (Bhakay, Rahman, et al., 2018). The most common and widely used method of milling a suspension is wet stirred media milling (Bhakay, Rahman, et al., 2018; Malamatari et al., 2018; Schenck et al., 2019). This can be seen in Table 1.1 of FDA approved drugs produced by wet stirred media milling. The technique for particle size reduction is beneficial in its ability to have a continuous stirred process that can be cooled with the assistance of a jacket for sensitive drug compounds compared to that of other techniques (i.e. LabRAM milling) (Bilgili et al., 2018; Li, Zhang, et al., 2016). The wet media milling can be setup in batch mode or in continuous recirculation mode in which the suspension recirculated through the media chamber filled with beads facilitating the breakage of suspended drug particles and a holding tank (A. Bhakay et al., 2014).

Soluble polymers have been widely used as stabilizers in drug nanosuspensions and film formers in drug nanocomposites (Bhakay, Rahman, et al., 2018; Li, Lopez, et al., 2016). The polymer's molecular weight, its adsorption onto drug surfaces, and viscosity could have an impact on the extent of aggregation in drug nanosuspensions (Bilgili et al., 2018; Choi et al., 2008). This impact will also show upon redispersion of nanocomposites in various liquids once nanocomposites are formed (Bhakay et al., 2013). In addition, surfactants could enhance physical stability of the drug nanosuspensions and wettability of the nanocomposites, but its use could pose some challenges during storage (Li, Azad, et al., 2016; Li, Lopez, et al., 2016; Müllertz et al., 2010). This is due to the micellar solubilization of the drug nanoparticles which exists at higher concentrations and leads to Ostwald ripening (Ghosh et al., 2011; Verma et al., 2011). Although the benefits of surfactant use in formulations are present, its use should be minimized to reduce the instability during long term storage and the Ostwald ripening which could occur during storage and processing of composites.

Table 1.1 Media Milled FDA Approved Drugs

Trade name	Company	Active substance	Indication	Particle Size Reduction Method	Route	Dosage Form	Year approved
Avinza[b]	King Pharma	Morphine sulfate	Pain medication	WMM	Oral	Capsule	2002
Emend[a]	Merck	Aprepitant	Antiemetic	WMM	Oral	Capsule	2003
Focalin XR[b]	Novartis	Dexmethylphenidate HCl	ADHD	WMM	Oral	Capsule	2001
Megace ES[a]	Par Pharmaceutical	Megestrol acetate	Appetite stimulant	WMM	Oral	Suspension	2005
Rapamune[a]	Wyeth	Sirolimus (rapamycin)	Immunosuppressant	WMM	Oral	Suspension, Tablet	2000
Ritalin La[b]	Novartis	Methylphenidate HCl	ADHD	WMM	Oral	Capsule	2002
Tricor[a]	Abbott	Fenofibrate	Hypercholesterolemia	WMM	Oral	Tablet	2004
Zanaflex[b]	Acorda	Tizanidine HCl	Muscle relaxant	WMM	Oral	Capsule	2002

[a]Based on (Verma & Burgess, 2009).
[b]Based on (Shegokar & Müller, 2010).

1.1.2 Drug Nanocomposites

Despite the simplicity of generating a nanosuspension, generating a nanocomposite becomes a much more difficult task. The milled nanoparticles within the suspension will tend to aggregate if they are not stabilized with the appropriate dispersants either immediately, after milling, or during storage (Li, Zhang, et al., 2016). This is due to the Brownian motion that will cause nearby particles to aggregate together within a suspension (Lee, 2003). These forces are typically at play when the suspension is in storage, where nanoparticles could settle and collide with one another leading to aggregation dictated by van der Waals forces (Napper, 1970). Additional phenomena such as Ostwald ripening could also occur when the differences in drug solubility of differently sized particles could cause the dissolved drug to deposit onto larger drug particles causing growth over time (Verma et al., 2011). Due to these competing forces during the storage of the suspension, the importance of stabilizing dispersants and the proper downstream processing are required. As importantly, oral solid dosage forms of a drug are a preferred delivery over that of suspensions. That requires the wet media milled nanosuspensions to be dried into composites which will ultimately be used within a solid dosage unit. This can be performed using spray drying (Anagha Bhakay et al., 2014; Bilgili et al., 2018; Rahman et al., 2019), fluidized bed coating (Anagha Bhakay et al., 2014; Chaubal & Popescu, 2008; Vogt et al., 2008), spray-freeze drying (Niwa & Danjo, 2013), freeze drying (Kim & Lee, 2010; Tuomela et al., 2015) and vacuum drying (Choi et al., 2008; Kim & Lee, 2010). Each drying method has its own pros/cons and poses unique challenges when generating drug nanocomposites.

Furthermore, it should be mentioned that not only do the dispersants affect physical stability of the nanosuspensions, but also they affect the redispersibility of the nanocomposites and drug release from them when they are dissolved *in vivo* or *in vitro* (A. Bhakay et al., 2014; Bhakay et al., 2013; Bilgili et al., 2018; Li, Lopez, et al., 2016). The redispersibility of drug nanocomposites, referring to their ability to release drug nanoparticles, could be an important metric in the development of drug nanocomposites (Bhakay et al., 2013; Bilgili et al., 2018) besides the widely used dissolution tests. It is hypothesized that nanocomposite particle size and type/loading of the dispersants could affect the redispersion as well as drug release during *in vitro* dissolution tests. This led to the investigation of different polymer and surfactant combinations to discover the impact on nanoparticle recovery (Bhakay et al., 2013).

1.2 Background and Challenges

1.2.1 Impact of Dispersants on Nanosuspension Stability

Although nanoparticle suspensions from wet media milling have shown to be effective in dissolution enhancement of poorly water-soluble drugs (Azad et al., 2016; Anagha Bhakay et al., 2014; Bilgili et al., 2018; Norbert Rasenack, 2002), aggregation and physical stability need to be addressed for a proper nanosuspension to be made. To that end, dispersants such as polymers, surfactants, sugars, and other stabilizers are used in nanosuspensions (Azad et al., 2016; Anagha Bhakay et al., 2014; Bilgili et al., 2018; Choi et al., 2008; Ghosh et al., 2011; Van Eerdenbrugh et al., 2008). Unfortunately, the concentration required to achieve the desired stability can negatively affect the total drug concentration within a given formulation leading to low drug formulations and larger tablet sizes (Bilgili et al.,

2018). Furthermore, despite the required stability while as a suspension, during drying aggregation can also occur compromising the composite and leading to poor redispersion and dissolution (A. Bhakay et al., 2014; Bhakay, Rahman, et al., 2018).

One class of dispersants, surfactants, have been widely used throughout literature to enhance drug wettability and provide electrostatic stabilization (Bhakay, Rahman, et al., 2018; Bilgili et al., 2018; Li, Lopez, et al., 2016). Although they are great stabilizers they are not without faults, in that suspensions with surfactants are susceptible to growth from Ostwald ripening during milling and extended storage (Verma et al., 2011). To combat this phenomenon, a combination of polymers and surfactants can be used to mitigate the issues associated with a surfactant only formulation while retaining some beneficial properties of a formulation containing a surfactant (Bilgili et al., 2018; Li, Lopez, et al., 2016; Müllertz et al., 2010).

Another method of achieving a stable nanosuspension would be with the use of surfactant-free formulations (Anagha Bhakay et al., 2014), where water soluble polymers would make up the complete stability of the nanosuspension without the increased risk of Ostwald ripening from surfactant. Examples of water-soluble polymers range from hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), Kollidon VA 64 (VA 64), and Pluronic which have been used without the addition of surfactants to stabilize nanosuspensions (Anagha Bhakay et al., 2014; Bilgili et al., 2018; Fu et al., 2013). The addition of these polymers to stabilize nanosuspensions has been studied by individuals using drying techniques such as spray drying (Bilgili et al., 2018), fluidized bed coating (Anagha Bhakay et al., 2014), and freeze drying (Fu et al., 2013), but none utilizing a rotary evaporator, which will require further investigation into the ability

of polymers to stabilize the nanosuspension through the drying process as that poses a risk to aggregated composites which will disperse and dissolve very poorly.

Itraconazole (ITZ), a model antifungal drug, has been used to model BCS Class II drugs that have characteristic high permeability, but poor water solubility 0.002µg/ml (Ghazal et al., 2009). Multiple research groups have investigated nanoparticle suspensions of ITZ and their progression through a variety of drying studies including fluidized bed coating, freeze drying, and spray drying, respectively (Azad et al., 2016; Badawi et al., 2011; Bilgili et al., 2018). None has investigated the rotary evaporation of ITZ nanosuspension which will bring its own challenges of suspension aggregation and method development.

1.2.2 Comparison of Different Drying Methods

Drug nanosuspensions are precursors in the preparation of drug nanocomposites; they are dried to form nanocomposites to be integrated into final solid dosage forms that are preferred delivery route for therapeutics (Bhakay, Rahman, et al., 2018; Malamatari et al., 2018; Shegokar & Müller, 2010; Verma & Burgess, 2009). As such, generating these nanocomposites can be done using spray drying (Anagha Bhakay et al., 2014; Bilgili et al., 2018; Rahman et al., 2019), fluidized bed coating (Anagha Bhakay et al., 2014; Chaubal & Popescu, 2008; Vogt et al., 2008), spray-freeze drying (Niwa & Danjo, 2013), freeze drying (Kim & Lee, 2010; Tuomela et al., 2015) and vacuum drying (Choi et al., 2008; Kim & Lee, 2010) to name a few widely used drying techniques. Each has their own pros/cons. For example, the ability to rapidly dry, prevent microbial growth, eliminate degradation of heat-sensitive compounds, and have rapid reconstitution times for parenteral drugs are all characteristic of freeze drying (Khairnar et al., 2012). However, the

method of freeze drying is extremely costly and it is not conducted as a continuous process (Khairnar et al., 2012). With fluidized bed coating, an effective drying with high thermal efficiency and control over temperature makes it ideal for sensitive compounds, but produces composites with low drug loading due to the use of a substrate and does not process unique particles with needle like morphology (Chua & Chou, 2005). Moreover, preparing nanocomposites with high drug loading (>50%) is very time consuming and costly.

Spray drying has many benefits toward drying of suspensions into composites, that includes the cost effective nature of spray drying, the ability to scale from the lab to industrial manufacturing with ease and the wide array of applications that has already been applied using a spray drying as the method of drying composites (A. Bhakay et al., 2014; Bilgili et al., 2018; Chaubal & Popescu, 2008; Jain et al., 2012; Poozesh & Bilgili, 2019; Rahman et al., 2019). The disadvantages of a spray drying approach to drying suspensions results from the relatively low bulk density (due to high Peclet number during evaporation) and poor flowability of the spray-dried powder. Moreover, the particles having an inflated shell morphology can pose a risk to tablet cracking from differential density zones leading to elastic recoil and stress relief (Eiliazadeh et al., 2003; Vehring, 2008).

Thin Film Evaporator (TFE) has recently made its appearance into the pharmaceutical industry to aid in the continuous production of composites (Lee et al., 2020). A TFE is traditionally found within the food industry and is used to concentrate a liquid or suspension stream for use in products such as the dairy industry for skim milk or orange concentrates where a short contact time with a heated surface does not degrade the product being concentrated (Tanguy et al., 2015; Tateo, 1990). The TFE contains a rotating

assemble within a heated barrel that is under a vacuum to aid in driving off the solvent from the process stream, thus concentrating and drying the incoming solution or suspension (Lee et al., 2020). The “thin film” refers to the thickness of the traveling stream through the unit between the barrel and rotating assemble which is scraped and moved along the barrel to maintain a constant film of about 0.5 mm that will make for higher surface area and easy evaporation of solvent from the stream (Lee et al., 2020). These characteristics of a TFE are great conditions for the concentration of solutions and suspensions, but if taken one step forward under higher temperatures and shorter residence time through the barrel, one can use the TFE to generate dried composites like those produced by a spray dryer. Due to this, the use and application of TFE can be very beneficial in generating composites as an alternative to spray drying as a continuous processing unit.

To study this technology within the lab, a bench scale analogous unit to generate a thin film under vacuum and varying temperature was sought after as an alternative running the TFE at manufacturing scale. The rotary evaporator which consists of a spinning round bottom flask placed in a temperature-controlled bath under vacuum was chosen to simulate the drying kinetics in a TFE. The use of a rotary evaporator creates a thin film within a round bottom flask that is like that of a TFE. In literature, the use of a rotary evaporator has been used on distillation or drying of non-pharmaceutical drugs (Zhong et al., 2016). The implementation of a rotary evaporator has only recently made its way to being used for the drying of pharmaceuticals (Gade et al., 2020; Saboo et al., 2020).

1.2.3 Redispersion and Drug Release from Nanocomposites

Testing of drug nanocomposites must be conducted to establish the impact of formulation–process variables *in vitro* before further studies are conducted *in vivo*. To do so, redispersion and dissolution are traditional methods for testing the effects of formulations before in vivo studies are conducted (A. Bhakay et al., 2014; Anagha Bhakay et al., 2014; Bhakay, Rahman, et al., 2018; Ghazal et al., 2009; Jackson et al., 2016; Li, 2017; Norbert Rasenack, 2002; Van Eerdenbrugh et al., 2008). Bhakay et al. (2018b) demonstrated that redispersion testing could be useful for the characterization of nanocomposites ability to disperse nanoparticles into an aqueous media (A. Bhakay et al., 2014; Bhakay, Rahman, et al., 2018). Multiple groups conducted studies involving dissolution testing as the method of characterizing the differences in formulations and their performance on enhancing the therapeutic delivery (Azad et al., 2016; Anagha Bhakay et al., 2014; Bilgili et al., 2018; Jackson et al., 2016; Norbert Rasenack, 2002; Van Eerdenbrugh et al., 2008). Although dissolution testing is a staple of understanding the performance of a formulation, it does not predict the *in vivo* performance. Hence, the use of redispersion testing could complement our understanding of nanocomposites; which may be more discerning than traditional dissolution tests and more representative of the *in vivo* conditions (A. Bhakay et al., 2014; Bhakay et al., 2013).

1.3 Objectives

The specific objectives of this research are to:

1. Develop an understanding of the impacts of the polymers on the particle size and stability of wet-milled drug suspensions and prepare a suitable precursor drug nanosuspension for use in the rotary evaporation studies.
2. Examine the effects of varying drying conditions on the preparation of rotary evaporated nanocomposites.
3. Investigate different processing methods to generate repeatable and consistent nanocomposites.
4. Discern the impact of different polymers/surfactants on the reconstitution of nanoparticles from nanocomposites (redispersion).
5. Analyze the effect of polymers/surfactants on drug release from the rotary evaporated nanocomposites vs. spray-dried nanocomposites

1.4 Thesis Outline

This thesis has been structured into the following chapters. Chapter 2 examines the milling of itraconazole, and the impact different polymers have on the stability of suspension. The use of different polymers to improve on formulation stability and assist with aggregation was demonstrated in this chapter. In Chapter 3, the drying of nanosuspensions using a rotary evaporator will continue to evaluate formulations and use of polymers to prevent aggregation in the transition from a suspension to a powder. The processing conditions and the addition of post processing homogenization was explored in Chapter 3. For Chapter 4, an emphasis on the redispersion was conducted to study the recovery of nanoparticles from

generated nanocomposites produced by the rotary evaporator and supporting dissolution data was generated to show the relationship of redispersion to that of dissolution. Finally, Chapter 5 will provide the summary from this body of work as well as the recommendations and thoughts for future work that will build off this thesis.

CHAPTER 2

NANOSUSPENSIONS PREPARATION AND CHARACTERIZATION

We investigate the impact of different polymers on the preparation of wet-milled suspensions of itraconazole (ITZ). Suspensions were milled using a Netzsch Minicer wet media mill to prepare ITZ nanosuspensions. Different classes of polymers were added to an existing stable drug nanosuspension to assist in downstream processing. The use of hydroxypropyl cellulose SL grade, polyvinylpyrrolidone K30, polyethylene glycol 3350, Kollidon VA64, and Pluronic F-127 were all explored as water-soluble polymers to aid in processing of nanosuspensions. These polymers all contributed to different characteristics of the suspension and changed the properties of downstream nanocomposites that will be discussed in the subsequent chapters. In this chapter, a focus on the preparation of stable ITZ nanosuspension and formulation will be done.

2.1 Materials and Methods

2.1.1 Materials

Itraconazole (ITZ) was purchased from Green Chempharm Inc. (Bardonia, NY, USA). Solubility of ITZ in deionized water is 0.002 µg/ml (Ghazal et al., 2009), which makes it a model Biopharmaceutical Classification System (BCS) Class II drug. Hydroxypropyl cellulose SL grade (HPC SL) with a molecular weight of 100 kg/mol was obtained from Nisso America Inc. (New York, NY, USA). Sodium dodecyl sulfate (SDS) was purchased from Sigma-Aldrich (Milwaukee, WI, USA). Polyvinylpyrrolidone K30 (PVP K30) with a molecular weight of 50 kg/mol was purchased from AppliChem GmbHP (Darmstadt,

Germany). Polyethylene Glycol 3350 (PEG 3350) with a molecular weight of 3350 g/mol was obtained from Spectrum Chemical MFG Corp. (Gardena, CA, USA). Kollidon VA64 (VA64) with an average molecular weight of 57,500 g/mol was purchased from BASF (Lampertheim, Germany). Pluronic F-127 (F-127) was purchased from Sigma-Aldrich (Milwaukee, WI, USA). Yttrium-stabilized zirconia, which is highly wear resistant, with a nominal size of 400 μm was purchased from Norstone Inc. (Bridgeport, PA, USA).

2.1.2 Formulations and Wet Stirred Media Milling

All formulations used in the study for the preparation of suspensions are presented in Table 2.1. The percentages of dispersants within each formulation are on a w/w basis with respect to the total weight of deionized water (300 g). In each formulation, an ITZ percentage was kept at 10%. The basis for all formulations stems from a known effective suspension composition of 10% ITZ–2.5% HPC-SL–0.2% SDS, which has been shown to produce nanocomposites and stabilize ITZ after milling (Bilgili et al., 2018).

Table 2.1 Formulations of the Milled Suspensions

Polymer type/grade	MW[a] (g/mol)	Suspension content	
		Polymer (% w/w)[b]	SDS (% w/w)[b]
HPC SL	100,000	2.5	0.2
HPC SL	100,000	5	0.2
HPC SL	100,000	7.5	0.2
HPC SL	100,000	10	0.2
HPC SL/PVP K30 (1:1)	100,000/ 65,000	5	0.2
HPC SL/PVP K30 (1:2)	100,000/ 65,000	7.5	0.2
HPC SL/PVP K30 (1:3)	100,000/ 65,000	10	0.2
HPC SL/PEG 3350 (1:1)	100,000/ 3,350	5	0.2
HPC SL/PEG 3350 (1:2)	100,000/ 3,350	7.5	0.2
HPC SL/PEG 3350 (1:3)	100,000/ 3,350	10	0.2
HPC SL/ VA64(1:1)	100,000/ 57,500	5	0.2
HPC SL/VA64 (1:2)	100,000/ 57,500	7.5	0.2
HPC SL/VA64 (1:3)	100,000/ 57,500	10	0.2
HPC SL/F-127 (3.6:1)	100,000/ 12,600	3.2	0.2
HPC SL/F-127 (1:1)	100,000/ 12,600	5	0.2
HPC SL/F-127 (1:2)	100,000/ 12,600	7.5	0.2

[a] MW is Molecular Weight of the polymers.
[b] All suspensions have 10% ITZ. %w/w is with respect to the weight of deionized water (300 g).

An overhead mixer (Chemglass, CG-2051-020, Vineland, NJ) was setup over an 800 ml beaker to disperse the ITZ particles and other excipients. The suspension was then transferred over to a holding tank on the Netzsch wet stirred media mill (Minicer, Netzsch, Selb, Germany) (Figure 2.1). Milling conditions were adapted from previous milling study using the Netzsch Microcer conditions of 196 g bead loading and 126 ml/min recirculation rate (Bilgili et al., 2018). Milling conditions explored included the 160 ml chamber filled between 343–525 g of 0.4 mm zirconia beads and a screen orientation of 0.15 mm. The suspension was recirculated through the milling chamber at a rate between 189–252 mL/min with a Masterflex L/S peristaltic pump (Radnor, PA, USA) and C-Flex L/S 17 tubing while milled at a rotor speed of 4000 rpm over a time of 65 min. The milling chamber and holding tank were both cooled by a chiller (Huber Unistat 405w, Huber,

Offenburg, Germany) to maintain the temperature of the suspension below 33 ºC. Particle size was taken at various time points to track the progression of milling over time. Suspensions were saved in a fridge at 4.4 ºC before drying.

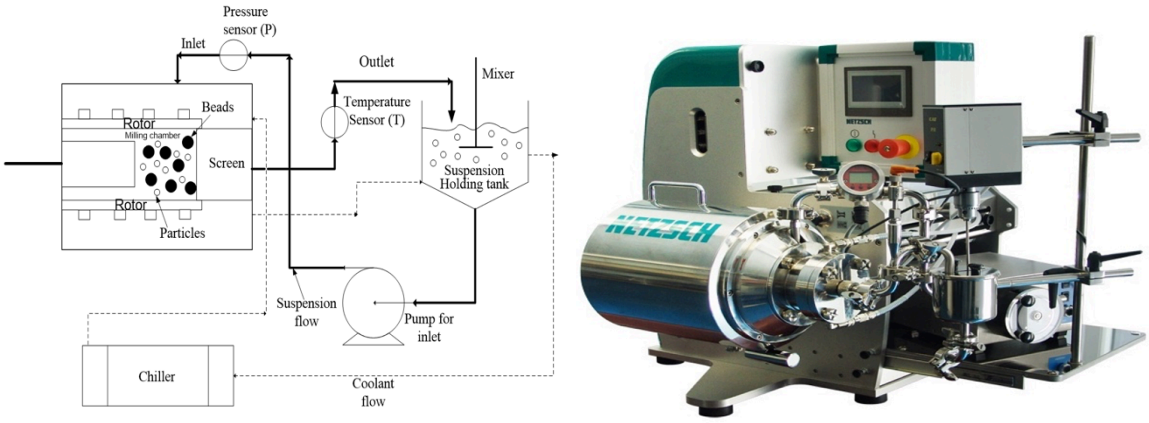

Figure 2.1 Schematic of Netzsch Media mill in the recirculation mode (left) and photograph of the setup in the laboratory (right).

2.1.3 Particle Size Analysis

Particle size distribution (PSD) of all samples was performed by Mastersizer 3000 laser diffraction particle size analyzer with Hydro MV cell (Malvern Panalytical, United Kingdom) using red and blue light and a detection range of 0.01 µm to 3500 µm (Figure 2.2). Dispersant cell was set at a stir rate of 1500 rpm and sonicated for 30 s at 60% intensity. Mie scattering theory was used to compute the volume-based distribution with a refractive index of 1.68 for ITZ and 1.33 for deionized water (Bilgili et al., 2018). An alignment of the system followed by a background measurement of 10 s for red and 10 s for blue light was taken before each set of readings. Three measurements averaged were taken and reported. Method used was set around repeatable results from measurement to measurement on various samples following ISO model within the Malvern Software. During measurement, the sample was added until obscuration fell between the ranges of 3

to 8%. Suspensions were measured during milling as well as prior to drying to ensure that all suspensions retained their PSD.

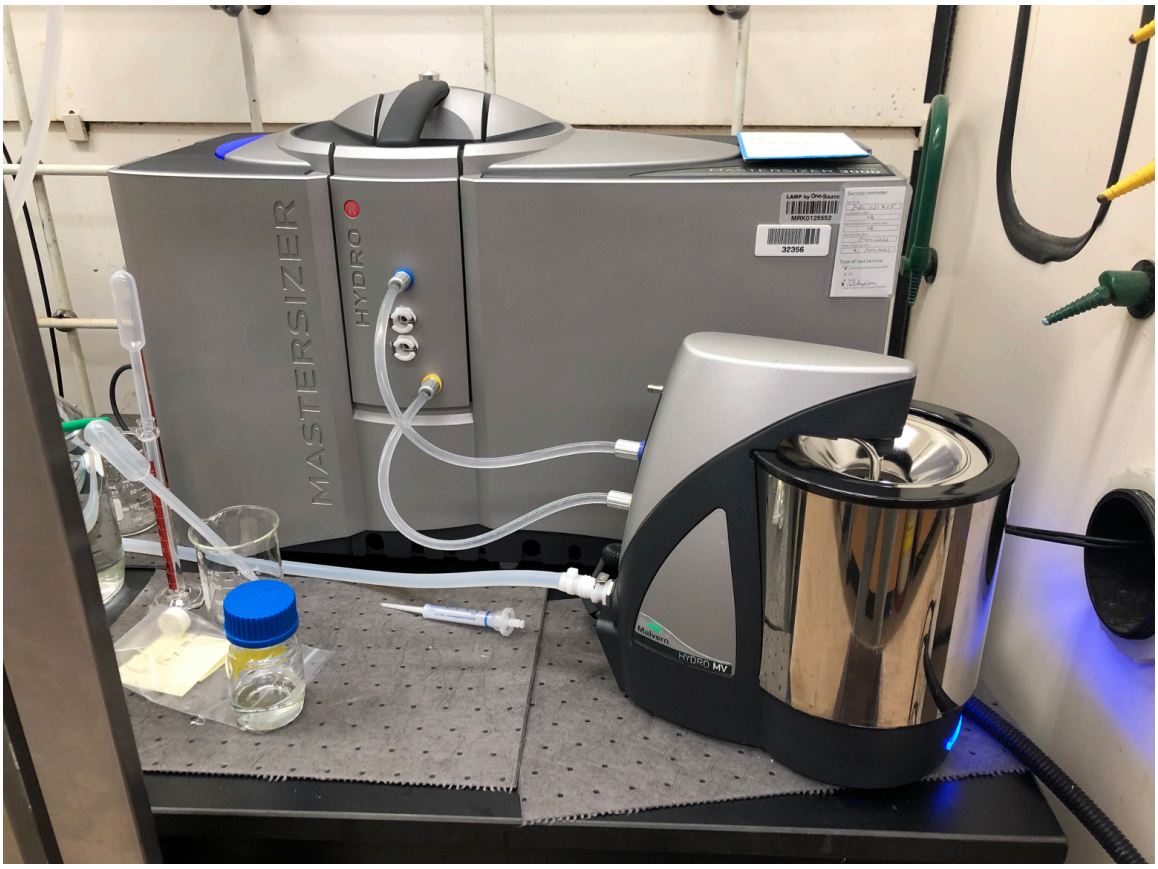

Figure 2.2 Mastersizer 3000 with Hydro MV Dispersion Unit.

2.1.4 Nanosuspensions with Additional Dispersants

The baseline nanosuspension consisted of 10% ITZ, 2.5% HPC-SL, and 0.2% SDS. A third (soluble) dispersant or additional HPC-SL was added to the existing stable nanosuspension to generate more nanosuspensions to test for drying and modulate the redispersibility/drug release from the nanocomposites. The help of a stir bar within a secondary vial was used to mix the nanosuspension with the additional dispersant to completely dissolve it in the nanosuspension. For each formulation above baseline, mentioned in Table 2.1, this was

performed, and the PSD of the following intermediate suspension was also measured by laser diffraction to confirm particle size from the nanosuspension was preserved prior to drying ensuring no aggregation occurred during production and storage. In general, all samples were prepared and dried within 7 days of preparing the suspension to reduce the risk of aggregation over time as previous studies have demonstrated (Bilgili et al., 2018; Rahman et al., 2019).

2.2 Results and Discussion

2.2.1 Particle Breakage During Wet Media Milling

As-received ITZ particles had a median size D_{50} of 15.5 μm and 90% passing size of D_{90} 45.8 μm, as measured via Rodos/Helos laser diffraction system (Bilgili et al., 2018). The suspension with the baseline formulation (10%ITZ, 2.5%HPC-SL, and 0.2%SDS) was milled for a total time of 65 min with the goal to produce a nanosuspension all particles below 1 μm, preferably with a median size below 200 nm, to ensure that significant dissolution enhancement can be achieved from the nanocomposites. Figure 2.3 illustrates the time-wise evolution of characteristic particle sizes, i.e., the median drug particle size D_{50}, 90% passing particle size D_{90}, and the cumulative volume percentage of colloidal/nanoparticles Q (1 μm) for multiple milling runs of which were performed with the same formulation under different conditions. All runs exhibited monotonic decrease in D_{50} and D_{90} and increase in Q (1 μm), which suggests particle breakage is the dominant mechanism, and severe aggregation of the milled particles did not occur, showing the feasibility of the baseline formulation. The sizes tended to approach a D_{50} of ~0.130 μm

and a D_{90} of ~0.330 μm. This corresponds to a remarkable size reduction ratio of ~120 based on D_{50}, which is hard to achieve in any other size reduction equipment.

Although most milling conditions did not show drastic changes in the final milled particle sizes, the total experimental effort/time was affected due to excessive heat generation from the higher bead loading condition and associated multiple shutdowns of the mill to maintain the suspension temperature below 33 ºC set limit. Ultimately, running at a 2x bead loading of 392 g and a 1.5x pump rate of 189 ml/min for the suspension volume of 300 ml were the best conditions for milling with the Minicer chamber. A very similar PSD to that of higher bead loading was achieved as well as a complete nanoparticle suspension which required few shutdowns of the mill and contributed to a great milling experience.

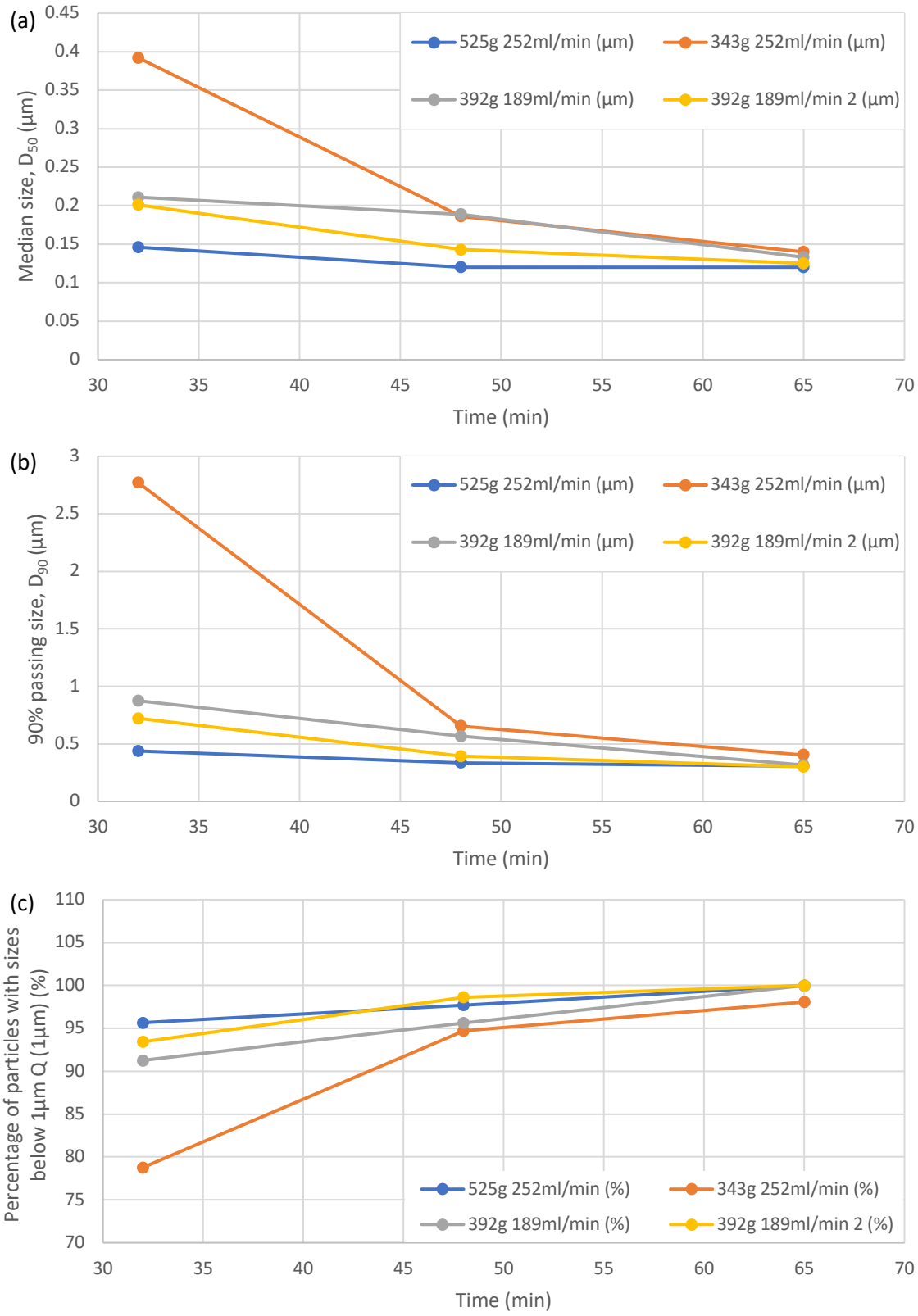

Figure 2.3 Progression of characteristic particle sizes of the nanosuspensions as a function of time under different milling conditions of bead loading and pump rate. All suspensions milled used a stable formulation of 10%ITZ, 2.5%HPC-SL, and 0.2%SDS.

2.2.2 Nanosuspension Stability and Dispersant Analysis

Let us now transition to examination of the impact of additional dispersant. After the preparation of the baseline nanosuspension (10%ITZ, 2.5%HPC-SL, and 0.2%SDS), which is prepared fresh for each final formulation, a third dispersant or additional HPC-SL was dissolved in the nanosuspension to prepare the final makeup of the formulation. Since each additional dispersant was water soluble, little to no change in the particle size of the starting suspension was to be expected. To confirm this hypothesis, the particle sizes of each final suspension was measured again to compare with the particle sizes of the baseline nanosuspension. These values can be seen in Table 2.2 for the particle size of each suspension after milling followed by the measurement after the addition of each dispersant.

Table 2.2 Nanosuspension PSD After Milling and Formulating: Stability Post Processing

Suspension Formulation[a]	Particle size post milling			Particle size post formulating/stability verification[b]		
	D_{50}±SD (μm)	D_{90}±SD (μm)	Q (1μm) ±SD (%)	D_{50}± SD (μm)	D_{90}±SD (μm)	Q (1μm) ±SD (%)
2.5%HPC-SL	0.132± 0.00	0.316± 0.00	100± 0.00	0.135± 0.00	0.345± 0.00	99.93± 0.00
5%HPC-SL	0.132± 0.00	0.316± 0.00	100± 0.00	0.143± 0.00	0.379± 0.01	98.65± 0.02
7.5%HPC-SL	0.132± 0.00	0.316± 0.00	100± 0.00	0.148± 0.00	0.405± 0.01	99.06± 0.03
10%HPC-SL	0.132± 0.00	0.316± 0.00	100± 0.00	0.152± 0.00	0.414± 0.02	99.63± 0.53
2.5%HPC-SL/ 2.5%PVP K30	0.129± 0.00	0.308± 0.00	100± 0.00	0.133± 0.01	0.328± 0.02	100± 0.00
2.5%HPC-SL/ 5%PVP K30	0.132± 0.00	0.316± 0.00	100± 0.00	0.139± 0.00	0.346± 0.00	100± 0.00
2.5%HPC-SL/ 7.5%PVP K30	0.132± 0.00	0.316± 0.00	100± 0.00	0.145± 0.01	0.383± 0.03	99.16± 0.49
2.5%HPC-SL/ 2.5%PEG 3350	0.129± 0.00	0.308± 0.00	100± 0.00	0.130± 0.00	0.322± 0.01	100± 0.00
2.5%HPC-SL/ 5%PEG 3350	0.132± 0.00	0.316± 0.00	100± 0.00	0.133± 0.00	0.336± 0.00	100± 0.00
2.5%HPC-SL/ 7.5%PEG 3350	0.132± 0.00	0.316± 0.00	100± 0.00	0.146± 0.01	0.379± 0.03	99.29± 0.62
2.5%HPC-SL/ 2.5%VA 64	0.129± 0.00	0.308± 0.00	100± 0.00	0.138± 0.01	0.385± 0.08	98.01± 2.19
2.5%HPC-SL/ 5%VA 64	0.132± 0.00	0.316± 0.00	100± 0.00	0.134± 0.00	0.334± 0.00	100± 0.00
2.5%HPC-SL/ 7.5%VA 64	0.132± 0.00	0.316± 0.00	100± 0.00	0.137± 0.00	0.351± 0.00	99.98± 0.03

2.5%HPC-SL/ 0.7%F-127	0.132± 0.00	0.316± 0.00	100± 0.00	0.137± 0.00	0.342± 0.01	100± 0.00
2.5%HPC-SL/ 2.5%F-127	0.129± 0.00	0.308± 0.00	100± 0.00	0.132± 0.01	0.325± 0.02	100± 0.00
2.5%HPC-SL/ 5%F-127	0.132± 0.00	0.316± 0.00	100± 0.00	0.136± 0.00[c]	0.337± 0.00[c]	100± 0.00[c]

[a]All suspensions have 10% ITZ and 0.2% SDS. %w/w is with respect to the weight of deionized water (300 g).
[b]Intermediate suspensions with additional dispersants were prepared and dried within 7 days of suspension nanomilling.
[c]Particle size measured 12 days after preparation for long term stability.

The first three columns of Table 2.2 show almost identical particle sizes, within a few percent, because they correspond to the freshly prepared nanosuspensions with the baseline formulation, which demonstrates the reproducibility of the wet stirred media milling process. The last three columns correspond to particle sizes of the baseline suspensions after the supplement of a new dispersant or additional HPC-SL. Except for HPC-SL at higher concentrations, the addition of different dispersants led to <10% increase in D_{50} and up to 25% increase in D_{90}. HPC-SL add to highest increase: up to 15% in D_{50} and up to 31% increase in D_{90}. While these increases are statistically significant (due to 0.0% SD of most laser diffraction measurements), the nanosuspensions remained colloidal; all final nanosuspensions had D_{50} below 150 nm and D_{90} below 400 nm, except the 10% HPC-SL nanosuspension.

With formulations containing F-127, a triblock copolymer (a polymeric surfactant), the stability was tested up to 12 days after preparation with 5% concentration. This was done to show stability and investigate Ostwald ripening which can occur at concentrations above the critical micellization concentration (CMC) as is the case with formulations containing more than 0.7% F-127 (Alexandridis et al., 1994; Knieke et al., 2013). Looking

at the particle size of the formulated suspension in Table 2.2, one can see there was no significant growth to the nanoparticles during the extended hold time that would be cause for concern with Ostwald ripening. Overall, each formulation was successful in generating and maintaining a nanosuspension that can and will be used for further downstream processing.

2.3 Conclusions

This study has demonstrated a successful scale-up of wet media milling of ITZ suspensions from the Netzsch Microcer mill to the Netzsch Minicer mill. All the milling conditions tested, from low to high bead loading as well as low to high pump rate showed there was an achievable sweet spot which allowed for similar particle size reduction as compared to that of high bead loading conditions. This allows for reasonable milling times to produce the nanosuspensions without costly time spent on milling. The conditions utilizing a chamber fill of 392 g of beads and a recirculation rate of 189 ml/min returned the best balance of heat generation and total milling time to generate the nanosuspension. The baseline formulation (10% ITZ, 2.5% HPC-SL, and 0.2% SDS) enabled suppression of severe aggregation. Addition of other dispersants or extra HPC did not cause a drastic size increase during the storage (before drying). In most of the formulations, ITZ suspensions with D_{50} below 150 nm and D_{90} below 400 nm were formed. The addition of the polymeric surfactant (Pluronic F-127) above CMC did not impact particle size growth in short term. Overall, all these nanosuspensions can be used in the drying process as precursor to nanocomposites.

CHAPTER 3

NANOCOMPOSITES AND IMPACT OF PROCESSING: A DIFFERENT WAY OF PRODUCING NANOCOMPOSITES

In Chapter 2, itraconazole (ITZ) nanosuspensions with various polymers/surfactants were prepared successfully by a wet stirred media milling process. Here, we prepared drug nanocomposites, using the drug nanosuspensions as precursor, via a new evaporative isolation method of rotary evaporation. These nanocomposites were collected from the round bottom flask in the system and processing via mortar and pestle was performed to homogenize the dried nanocomposites. In addition, different ways of introducing the nanosuspension to the flask were explored to study the impact of a distillation approach compared to that of a feed and bleed with shots of suspension being fed into the round bottom flask while under full vacuum. The combination of different processing methods led to significant insights into the drying of drug nanosuspensions using the rotary evaporator.

3.1 Materials and Methods

3.1.1 Materials

Itraconazole (ITZ) was purchased from Green Chempharm Inc. (Bardonia, NY, USA). Hydroxypropyl cellulose SL grade (HPC SL) with a molecular weight of 100 kg/mol was obtained from Nisso America Inc. (New York, NY, USA). Sodium dodecyl sulfate (SDS) was purchased from Sigma-Aldrich (Milwaukee, WI, USA). Polyvinylpyrrolidone K30 (PVP K30) with a molecular weight of 50 kg/mol was purchased from AppliChem GmbH

(Darmstadt, Germany). Polyethylene Glycol 3350 (PEG 3350) with a molecular weight of 3350 g/mol was obtained from Spectrum Chemical MFG Corp. (Gardena, CA, USA). Kollidon VA64 (VA64) with an average molecular weight of 57,500 g/mol was purchased from BASF (Lampertheim, Germany). Pluronic F-127 (F-127) was purchased from Sigma-Aldrich (Milwaukee, WI, USA).

3.1.2 Formation of Nanocomposites via Rotary Evaporation

The milled prepared ITZ suspensions with added dispersants (refer to Chapter 2) were dried within 7 days of preparation and storage using a Rotavapor R-300 (Buchi, New Castle, DE, USA). The unit was either run in batch distillation mode where suspensions were placed within a round bottom flask and "distilled" dry by having the bath temperature set at 60 ºC and a vacuum below 300 mmHg absolute was pulled until suspension appeared to be dry, evident of no condensation forming on the cold finger of the Rotavapor followed by a 10min hold under 3 mmHg to continue drying the nanocomposite. Alternatively, the Rotavapor was operated in feed and bleed mode where suspension was fed into the round bottom via a tube with a valve while under a vacuum of 3 mmHg absolute and a bath temperature of 90 ºC (Figure 3.1). Bursts of suspension were fed until the entire prepared suspension was processed and condensation stopped followed by additional drying for 10 mins to ensure complete evaporation of water.

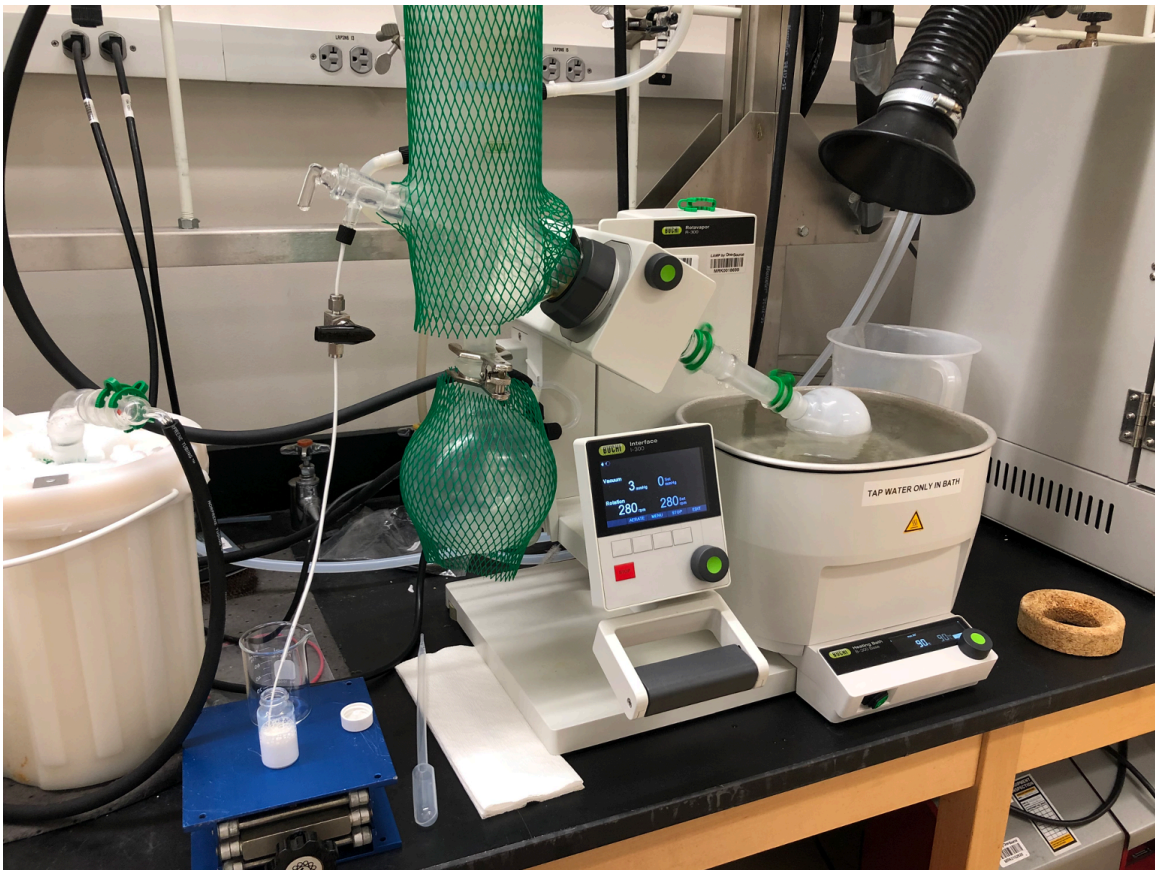

Figure 3.1 Rotavapor setup for drying nanosuspensions using feed and bleed method.

3.1.3 Processing Rotary Evaporated Nanocomposites

Rotary evaporated nanocomposites adhered to the round bottom flasks were scrapped off using a combination of a Chem-spin scraper tool on a handheld drill (Chemglass, Vineland, NJ, USA) and a spatula (Figure 3.2right). The Chem-spin scraper was first used to collect the bulk of solids from within the round bottom flask followed by manual scraping with a spatula for collecting the last bit of solids. The collected nanocomposite samples were then transferred over to a mortar (Figure 3.2right). to be ground with medium to light pressure for 5 min, thus improving the homogeneity of each sample.

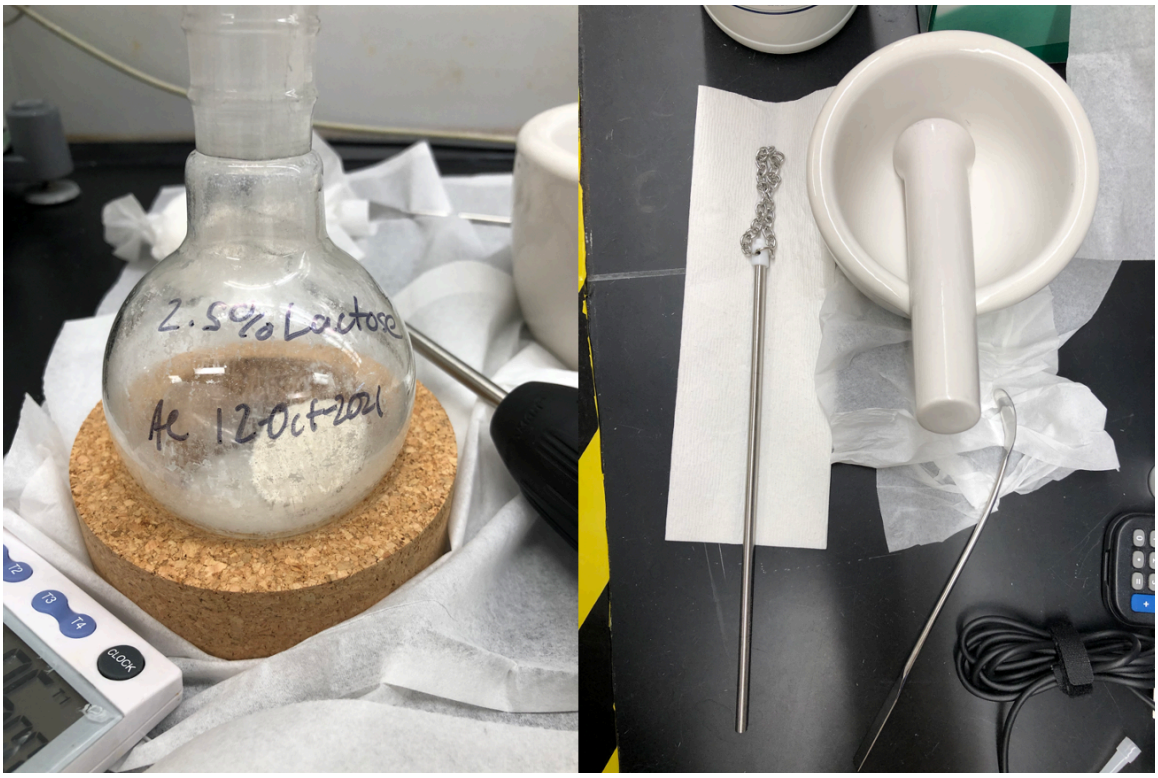

Figure 3.2 Nanocomposite after scraping with Chem-spin and spatula (left). Mortar and Pestle (MP) (top right), Chem-spin (left of MP), and spatula used to scrape round bottom flasks (bottom right) (right).

3.1.4 Particle Sizing

Particle size of nanocomposites was measured by HELOS/KR laser diffraction sensor in combination with the RODOS dispersion unit (Sympatec, Pennington, NJ, USA) running Fraunhofer theory. Three measurements were averaged to obtain a stable reading. Each sample went onto the vibratory chute set at 65% intensity and a dispersion pressure of 1.0 bar was used. To capture the wide variety of PSDs the R6 lens was used for all measurements which had a measurement range of 9–1750 µm (Figure 3.3).

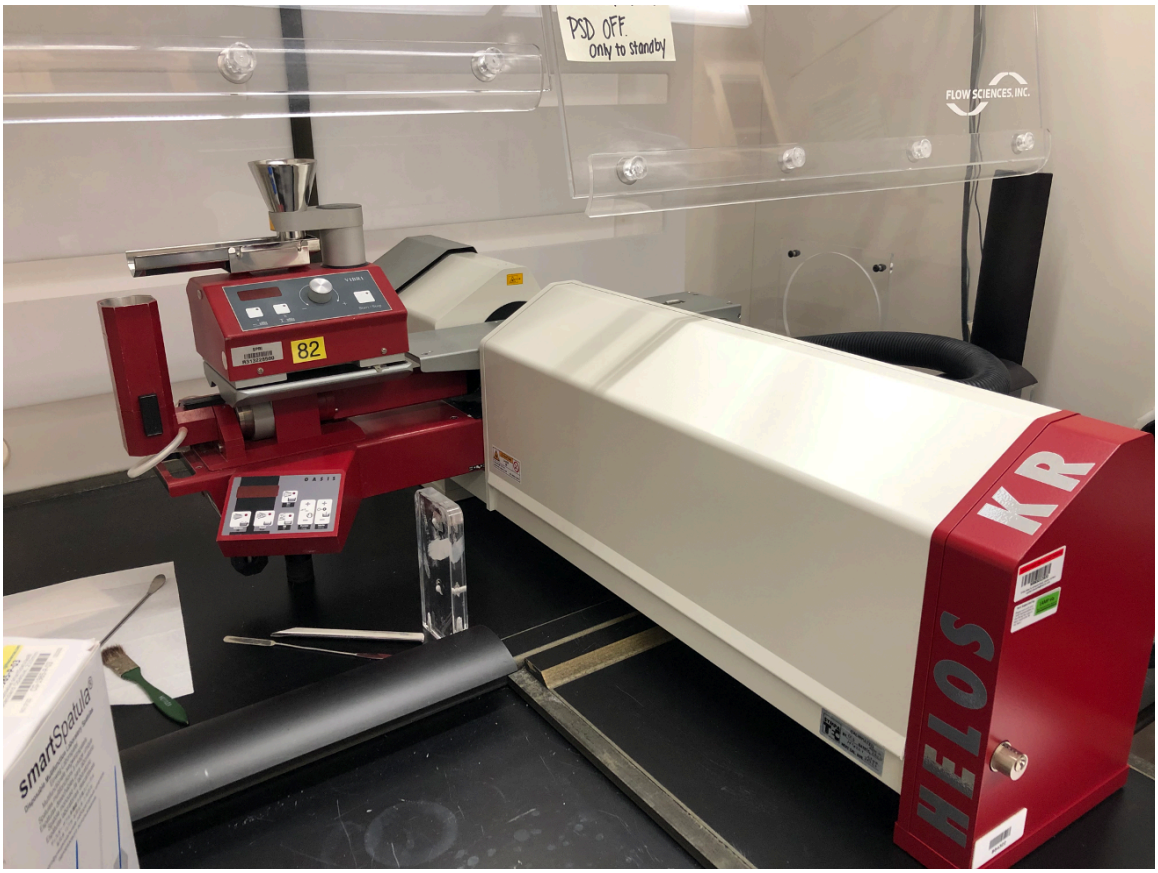

Figure 3.3 HELOS/KR Laser with RODOS Dispersion Unit.

3.2 Results and Discussion

3.2.1 Properties of the Nanocomposites

The previously prepared nanosuspensions from Chapter 2 (Table 2.2) were dried by the Rotavapor to form the nanocomposites. Upon initial investigation of utilizing the equipment, the use of a bath temperature of 60 ºC and a distillation approach was first tested using the baseline formulation of 10%ITZ, 2.5% HPC-SL, and 0.2% SDS. This initial test returned a nanocomposite that was very coarse when scraped off the round bottom flask and posed numerous challenges with generating reproduceable particle size readings as well as gathering further downstream data in other analyses. In Table 3.1, we

can see the clear particle size variation in the samples obtained from scraping the nanocomposites off the round bottom flask.

Table 3.1 Particle Sizes of the Nanocomposites from Rotavapor without Further Downstream Processing

		Nanocomposite Particle Size			
Measurement	Formulation[a]	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Volume Mean Distribution (VMD) (μm)
1	2.5HPC-SL	82.0	240.0	739.0	336.1
2	2.5HPC-SL	97.0	290.2	731.7	356.2
3	2.5HPC-SL	150.5	457.6	1372	614.2
4	2.5HPC-SL	161.4	612.9	1476	747.1
Average		122.7	400.2	1080	513.4
Standard Deviation		33.9	146.9	346.3	173.9

[a]Baseline precursor nanosuspension contained 10% ITZ 2.5% HPC-SL and 0.2% SDS.

The variations illustrated in Table 3.1 must be eliminated or minimized to generate reproduceable and reliable results. As a result, we augmented the use of the Chem-spin as well as a few minutes of mortar and pestle to the post processing of each rotary evaporated sample. Since mortar and pestle was a very strenuous task on one individual, two time points of 5 min and 10 min was explored. The first time point at 5 min of mortar and pestle, returned a much more homogenous nanocomposite which reflected in the SD of the

measurements performed (Table 3.2). With the additional use of mortar and pestle up to 10 min, a slight improvement was seen over the 5min reading with the X_{90} SD (Table 3.2). With this data in mind the decision to use 5min of mortar and pestle was carried out for all experiments since 10 min of mortar and pestle was a physically demanding task to be executed for little to no improvement in the overall sample homogeneity.

Table 3.2 Particle Sizes of Nanocomposites after Mortar and Pestle Milling

Measurement[a]		Nanocomposite Particle Size			
		D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	Volume Mean Distribution (VMD) (µm)
5 min	Average	11.5	91.3	238.0	108.5
	Standard Deviation	0.5	4.7	16.3	5.4
10 min	Average	9.6	72.6	198.0	90.0
	Standard Deviation	0.4	6.0	8.4	5.3

[a]Baseline precursor nanosuspension contained 10% ITZ 2.5% HPC-SL and 0.2% SDS.

3.2.2 Other Drying Challenges

Let us now examine other challenges that were observed with the use of HPC within the formulations. Even after a homogenous nanocomposite generated upon using a mortar and pestle step, there were still issues with downstream testing and release of nanoparticles

from the nanocomposites. HPC has a very low cloud point of ~40 ºC despite its very good solubility at room temperature (Khuman et al., 2014). Hence, the concern for HPC precipitating during the drying of the nanosuspensions was raised when nanoparticle recover was next to nothing. As was shown in a previous study, HPC is crucial to the stability of the nanosuspension (Bilgili et al., 2018). Without it, a nanosuspension cannot be formed or stabilized against the aggregation of ITZ nanoparticles. With the precipitation of HPC at the processing conditions of the Rotavapor, the nanosuspension is allowed to aggregate and show little to no nanoparticle recovery. To this end, a modified approach to drying nanosuspensions was adopted with the prevention of nanoparticle aggregation due to potential HPC precipitation. The goal was to switch from a distillation to one that would not allow the suspension to be dried without heating past the cloud point of HPC. For that to occur, the feed and bleed method was adopted where a tube was passed into the round bottom flask and small bursts of suspension were fed into the flask that was both heated at 90 ºC and under 3 mmHg absolute vacuum. This process allows for instantaneous evaporation of the water from the suspension and drying to generate a nanocomposite that would not see a high temperature with the assistance of evaporative cooling. All proceeding suspensions were processed utilizing this technique for the prevention of HPC precipitation followed by the previously mentioned use of a mortar and pestle step to ensure the uniformity of the nanocomposites. All nanosuspension PSDs followed by their respective nanocomposite particle size can be seen in Table 3.3. Due to different types/molecular weight/loadings of the polymers and surfactants and perhaps their complex interactions, the nanocomposite particle sizes varied considerably. The median size D_{50} ranged from 62 μm to 288 μm, whereas D_{90} ranged from 214 μm to 680 μm. However, the standard

deviation (SD) values in Table 3.3. and the relative standard deviation values (RSD, not shown) were much smaller than that presented in Table 3.1 for the nanocomposite without process optimization. Establishing strong correlations between the nanocomposite particle sizes and polymer properties will likely be difficult. However, in general, addition of a third dispersant (besides HPC-SL and SDS) or additional HPC semes to have resulted in coarser nanocomposite particles although there are trend-breaking formulations.

Table 3.3 Particle Sizes of the Nanosuspensions and the Nanocomposites Prepared via Drying (with Feed and Bleed)/Mortar and Pestle Milling

Suspension Formulation[a]	Particle size post milling			Nanocomposite Particle size		
	D_{50}±SD (μm)	D_{90}±SD (μm)	Q (1μm) ±SD (%)	D_{50}± SD (μm)	D_{90}±SD (μm)	VMD ±SD (μm)
2.5%HPC-SL	0.132± 0.00	0.316± 0.00	100± 0.00	66.5± 4.7	186.9± 18.6	85.6±8 .0
5%HPC-SL	0.132± 0.00	0.316± 0.00	100± 0.00	222.4± 22.8	608.0± 73.2	279.0± 30.9
7.5%HPC-SL	0.132± 0.00	0.316± 0.00	100± 0.00	122.0± 4.1	329.0± 8.2	151.9± 4.1
10%HPC-SL	0.132± 0.00	0.316± 0.00	100± 0.00	287.7± 57.2	679.8± 49.0	335.2± 43.9
2.5%HPC-SL/ 2.5%PVP K30	0.129± 0.00	0.308± 0.00	100± 0.00	122.3± 6.5	355.9± 9.4	157.8± 5.5
2.5%HPC-SL/ 5%PVP K30	0.132± 0.00	0.316± 0.00	100± 0.00	109.6± 12.9	354.3± 30.2	146.5± 10.6
2.5%HPC-SL/ 7.5%PVP K30	0.132± 0.00	0.316± 0.00	100± 0.00	108.7± 2.9	395.0± 9.9	161.3± 1.3
2.5%HPC-SL/ 2.5%PEG 3350	0.129± 0.00	0.308± 0.00	100± 0.00	127.4± 5.7	349.5± 3.7	160.1± 4.1
2.5%HPC-SL/ 5%PEG 3350	0.132± 0.00	0.316± 0.00	100± 0.00	157.1± 10.6	386.8± 30.2	185.4± 13.6
2.5%HPC-SL/ 7.5%PEG 3350	0.132± 0.00	0.316± 0.00	100± 0.00	133.1± 10.5	417.2± 30.6	181.7± 13.6
2.5%HPC-SL/ 2.5%VA 64	0.129± 0.00	0.308± 0.00	100± 0.00	100.4± 14.1	302.2± 20.6	133.1± 12.0
2.5%HPC-SL/ 5%VA 64	0.132± 0.00	0.316± 0.00	100± 0.00	134±6. 6	339±24 .9	167±5. 5

2.5%HPC-SL/ 7.5%VA 64	0.132± 0.00	0.316± 0.00	100± 0.00	87.5±3 .0	304.9± 7.9	126.5± 3.1
2.5%HPC-SL/ 0.7%F-127	0.132± 0.00	0.316± 0.00	100± 0.00	62.0±8 .9	213.9± 28.7	92.0±1 2.7
2.5%HPC-SL/ 2.5%F-127	0.129± 0.00	0.308± 0.00	100± 0.00	136.4± 9.0	375.7± 5.7	172.9± 4.5
2.5%HPC-SL/ 5%F-127	0.132± 0.00	0.316± 0.00	100± 0.00	108.1± 10.4	341.4± 21.7	149.8± 11.4

[a]All suspensions have 10% ITZ and 0.2% SDS. %w/w is with respect to the weight of deionized water (300 g).

3.3 Conclusions

A robust rotary evaporation (drying) process was developed with feed and bleed type introduction of drug nanosuspensions, followed by mortar and pestle milling of the produced nanocomposites. This approach enabled one to prepare a more relatively homogeneous/uniform nanocomposite powder than that without the optimization of the processing steps. In the redispersion and dissolution tests, some confounding impact of the nanocomposite particle size is to be expected.

CHAPTER 4

IMPACT OF DISPERSANTS ON DRUG REDISPERSION AND DISSOLUTION

In this chapter, the impact of formulation and drying conditions on the redispersion and dissolution of the drug nanocomposites prepared by the optimized rotary evaporation process is examined. A detailed analysis of the results will elucidate the roles of various types/loadings of the dispersants on the redispersibility and drug release. Based on *in vitro* drug release profiles, the impact of drug particle size and nanocomposite particle size will be scrutinized. Finally, formulations that lead to fast, immediate drug release (80% release in 20 min) during the *in vitro* dissolution will be identified as lead formulations for bioavailability enhancement. It is critical to mention that all labels for the nanocomposites are based on the composition of the respective precursor drug nanosuspensions. All drug nanosuspensions contain a baseline formulation of 10% ITZ, 2.5% HPC-SL, and 0.2% SDS on a wet basis. Obviously, the "dry" nanocomposites do not contain 10% ITZ, for example. Other precursor nanosuspensions were prepared by adding a third dispersant or extra HPC-SL to the baseline nanosuspension. Since all these nanosuspensions contain 10% ITZ and 0.2% SDS, their labeling will only mention HPC-SL concentration and the third dispersant concentration (PVP K30, PEG 3350, Kollidon VA64, and Pluronic F-127).

4.1 Materials and Methods

4.1.1 Materials

Itraconazole (ITZ) was purchased from Green Chempharm Inc. (Bardonia, NY, USA). Hydroxypropyl cellulose SL grade (HPC SL) with a molecular weight of 100 kg/mol was obtained from Nisso America Inc. (New York, NY, USA). Sodium dodecyl sulfate (SDS) was purchased from Sigma-Aldrich (Milwaukee, WI, USA). Polyvinylpyrrolidone K30 (PVP K30) with a molecular weight of 50 kg/mol was purchased from AppliChem GmbH (Darmstadt, Germany). Polyethylene Glycol 3350 (PEG 3350) with a molecular weight of 3350 g/mol was obtained from Spectrum Chemical MFG Corp. (Gardena, CA, USA). Kollidon VA64 (VA64) with an average molecular weight of 57,500 g/mol was purchased from BASF (Lampertheim, Germany). Pluronic F-127 (F-127) was purchased from Sigma-Aldrich (Milwaukee, WI, USA).

4.1.2 Redispersion of Nanocomposites

The redispersion of nanocomposites produced by rotary evaporation was performed using the method in (Bilgili et al., 2018). A 50 ml beaker with 30 ml of 3.0 g/L SDS solution was placed under an overhead mixer (Chemglass, CG-2051-020, Vineland, NJ) set at a speed of 400 rpm with a 4 blade 25 mm downward pitched impeller on a Mettler Toledo stir shaft (Figure 4.1). Nanocomposite samples containing 0.394 g ITZ basis were mixed with the SDS solution in the beaker at room temperature (see table 4.1 for drug content in each formulation). A 0.5 ml aliquot from the mixed suspension was taken at three different time points of 2 min, 10 min, and 30 min and measured directly by laser diffraction. Two runs were performed for each sample to obtain an average and show reproducibility in the results. With this drug to solution ratio, the dispersants could completely dissolve and

release the ITZ with little ITZ dissolution and no concern with generating a solution concentration close to the CMC of F-127 (Alexandridis et al., 1994; Bilgili et al., 2018).

Figure 4.1 Redispersion apparatus with overhead stirrer.

Table 4.1 Theoretical Drug Loading of Nanocomposites

Polymer type/grade	Nanocomposite Formulation		Theoretical Drug Content (%)
	Polymer (% w/w)[a]	SDS (% w/w)[a]	
HPC SL	2.5	0.2	78.7
HPC SL	5	0.2	65.8
HPC SL	7.5	0.2	56.5
HPC SL	10	0.2	49.5
HPC SL/PVP K30 (1:1)	5	0.2	65.8
HPC SL/PVP K30 (1:2)	7.5	0.2	56.5
HPC SL/PVP K30 (1:3)	10	0.2	49.5
HPC SL/PEG 3350 (1:1)	5	0.2	65.8
HPC SL/PEG 3350 (1:2)	7.5	0.2	56.5
HPC SL/PEG 3350 (1:3)	10	0.2	49.5
HPC SL/ VA64(1:1)	5	0.2	65.8
HPC SL/VA64 (1:2)	7.5	0.2	56.5
HPC SL/VA64 (1:3)	10	0.2	49.5
HPC SL/F-127 (3.6:1)	3.2	0.2	74.6
HPC SL/F-127 (1:1)	5	0.2	65.8
HPC SL/F-127 (1:2)	7.5	0.2	56.5

[a]All suspensions have 10% ITZ. %w/w is with respect to the weight of deionized water (300 g).

4.1.3 Dissolution Testing

Dissolution of ITZ nanocomposites was performed using a Distek 2100C dissolution tester (North Brunswick, NJ, USA) according to the USP II paddle method (Bilgili et al., 2018). The dissolution medium was 1000 mL 3.0 g/L SDS solution to follow the same media as was used within redispersion testing. The medium was maintained at 37 °C and stirred by a paddle at 50 rpm. Nanocomposites, equivalent to a dose of 20 mg of ITZ, were added to the medium, and 4 mL samples were taken manually at 1, 2, 5, 10, 20, 30, and 60 min. The nanocomposite weight was determined by the theoretical drug content for each

formulation. The absorbance of ITZ dissolved in the media was measured via UV-spectroscopy (Agilent, Santa Clara, CA, USA) at 260 nm wavelength. Aliquots of the samples were filtered using a 0.1 μm PVDF membrane type syringe filter to avoid any effect of undissolved drug during UV-spectroscopy. The medium solution without drug was used as the blank. The amount of drug dissolved was measured using a calibration curve generated in (Bilgili et al., 2018), with an $R^2 = 0.9995$. ITZ release was reported as a function of dissolution time for an average of six replicates. >80% drug release in 20 minutes was the criteria for immediate drug release (A. Bhakay et al., 2014; Bilgili et al., 2018). Dissolution profiles of all nanocomposites were statistically compared using difference (f_1) and similarity (f_2) factors (Kassaye & Genete, 2013). f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) suggest statistical similarity of two profiles (Bilgili et al., 2018).

4.1.4 Particle Size of Redispersed Nanocomposites

Particle size distribution (PSD) of all suspensions was measured by Mastersizer 3000 laser diffraction particle size analyzer with Hydro MV cell (Malvern, United Kingdom) using red and blue light and a detection range of 0.01 μm to 3,500 μm. Dispersant cell set at a stir rate of 1,500 rpm, and sonication performed for 30 sec at 60% intensity. Mie scattering theory was used to compute the volume-based distribution with a refractive index of 1.68 for ITZ and 1.33 for deionized water (Bilgili et al., 2018). An alignment of the system followed by a background measurement of 10 sec for red and 10 sec for blue light was taken before each set of readings. Three measurements averaged were taken and reported. Method used was set around repeatable results from measurement to measurement on

various samples following ISO model within the Malvern Software. During measurement, the sample was added until obscuration fell between the ranges of 3 to 8%.

4.2 Results and Discussion

4.2.1 Nanoparticle Recovery via Redispersion

The redispersion particle size distribution from initial nanoparticle recovery can be shown in Table 4.2. The resulting data was obtained from preliminary testing of generating nanocomposite by scrapping off a round bottom flask. This was where a particle size discrepancy was first noticed when a single sample produced in the rotary evaporator could not be reproduced from one run to another. As one can see between the two sets of runs at different polymer loadings, an issue with reproducing a result in redispersion was seen. The issue tracing back to the particle size as discussed in Chapter 3 and can also be seen within the D_{50} and D_{90} of the dispersed composites.

Table 4.2 Nanocomposite Redispersion: Preliminary Testing of Rotary Evaporated Nanocomposites

Formulation[a]	Redispersed Particle Size[b]		
	D_{50}±SD (μm)	D_{90}±SD (μm)	Q (1μm)±SD (%)
2.5%HPC-SL	21.2±1.14	219.0±38.73	0.05±0.03
2.5%HPC-SL	17.87±3.22	235.5±64.78	1.06±0.04
10%HPC-SL	36.18±1.76	226.5±11.77	3.56±0.08
10%HPC-SL	0.16±0.01	8.11±8.01	88.83±3.2

[a]All precursor suspensions of the nanocomposites have 10% ITZ and 0.2% SDS. %w/w is with respect to the weight of deionized water (300 g).

[b]Redispersed particle size was measured at the end of a 30 min run following the procedures outlined in this chapter.

Following the results in Table 4.2, the implementation of a 5 min mortar and pestle step developed in Chapter 3 was used with all samples. This allowed for reproducible runs during the redispersion testing and homogenized all following samples used throughout the rest of the study. Continuing with mortar and pestle samples and running through a few formulations demonstrated there was an issue with nanoparticle recovery that was not captured in previous runs. Although increasing the polymer concentration up to a total of 7.5% HPC-SL was beneficial in the recovery of almost 25% more nanoparticles (Table 4.3), this was still a low recovery of ITZ nanoparticles as previous studies have reported with just 2.5% HPC-SL a nanoparticle recovery close to 90% (Bilgili et al., 2018).

Table 4.3 Mortar and Pestle Processed Composites Redispersion

	Nanocomposite Particle Size		Redispersed Particle Size[b]		
Formulation[a]	D_{50}±SD (μm)	D_{90}±SD (μm)	D_{50}±SD (μm)	D_{90}±SD (μm)	Q (1μm)±SD (%)
2.5%HPC-SL	91.3±4.7	238±16.3	20.9±8.79	205±78.2	0.78±0.22
5%HPC-SL	75.6±1.09	185±5.20	19.3±0.76	74.5±2.66	16.4±1.54
7.5%HPC-SL	134±7.47	382±4.99	17.5±3.15	77.7±10.7	25.0±4.05

[a]All precursor suspensions of the nanocomposites have 10% ITZ and 0.2% SDS. %w/w is with respect to the weight of deionized water (300 g).
[b]Redispersed particle size was measured at the end of a 30 min run following the procedures outlined in this chapter.

With the issue of reproduceable runs resolved, we can transition to investigating issues with polymer solubility. As mentioned in Chapter 3, the solubility of HPC was

challenged at the increased temperature that the composites were initially being produced at. After this processing change the following formulations were explored by redispersion as a comparison to the initial runs. We can see from the initial results in nanoparticle dispersion that this change was very impactful and necessary to the process of generating true nanocomposites (Table 4.4). In addition, the particle size of the generated nanocomposites was not very different between the feed and bleed approach compared to the distillation method. Hence there does not appear to be a nanocomposite particle size effect on the redispersion of nanoparticles from the nanocomposites on this set of data.

Table 4.4 Feed and Bleed Nanocomposite Redispersion

	Nanocomposite Particle Size		Redispersed Particle Size[b]		
Formulation[a]	D_{50}±SD (μm)	D_{90}±SD (μm)	D_{50}±SD (μm)	D_{90}±SD (μm)	Q (1μm)±SD (%)
2.5%HPC-SL	66.5±4.7	187±18.6	5.62±0.67	31.98±1.03	22.91±3.01
5%HPC-SL	222±22.8	608±73.2	0.367±0.00	26.48±1.15	65.99±0.44
7.5%HPC-SL	122±4.1	329±8.2	0.326±0.01	15.32±0.8	68.36±1.34

[a]All precursor suspensions of the nanocomposites have 10% ITZ and 0.2% SDS. %w/w is with respect to the weight of deionized water (300 g).
[b]Redispersed particle size was measured at the end of a 30 min run following the procedures outlined in this chapter.

Continuing with the investigation of polymer impact and loading, in Table 4.5, we can observe the impact that various polymers, at varying loadings, had on the dispersion of nanoparticles.

Table 4.5 Impact of Polymer Type and Loading on Redispersed Particle Size

Formulation[a]	Nanocomposite Particle Size		Redispersed Particle Size[b]		
	D_{50}±SD (μm)	D_{90}±SD (μm)	D_{50}±SD (μm)	D_{90}±SD (μm)	Q (1μm)±SD (%)
2.5%HPC-SL	66.5± 4.7	187±18.6	5.62±0.67	32±1.03	22.9±3.01
5%HPC-SL	222±22.8	608±73.2	0.367±0.00	26.5±1.15	66±0.44
7.5%HPC-SL	122±4.1	329±8.2	0.326±0.01	15.32±0.80	68.4±1.34
10%HPC-SL	288±57.2	680±49.0	0.238±0.01	6.54±0.51	85.92±0.35
2.5%HPC-SL/ 2.5%PVP K30	122±6.5	356±9.4	0.474±0.06	19.07±1.39	58.11±3.15
2.5%HPC-SL/ 5%PVP K30	110±12.9	354±30.2	0.374±0.02	15.27±0.84	63.24±1.84
2.5%HPC-SL/ 7.5%PVP K30	109±2.9	395±9.9	0.323±0.00	14.90±0.45	69.89±0.42
2.5%HPC-SL/ 2.5%PEG 3350	127±5.7	350±3.7	0.812±0.15	17.87±1.34	51.88±1.72
2.5%HPC-SL/ 5%PEG 3350	157±10.6	387±30.2	0.386±0.01	6.31±0.73	74.35±1.53
2.5%HPC-SL/ 7.5%PEG 3350	133±10.5	417±30.6	0.306±0.00	4.33±0.05	81.66±0.14
2.5%HPC-SL/ 2.5%VA 64	100±14.1	302±20.6	2.58±0.09	23.30±4.06	43.05±0.94

2.5%HPC-SL/ 5%VA 64	134±6.6	339±24.9	2.637±0.16	21.10±2.21	40.62±1.52
2.5%HPC-SL/ 7.5%VA 64	87.5±3.0	305±7.9	3.06±0.04	15.73±0.63	33.42±0.50
2.5%HPC-SL/ 0.7%F-127	62.0±8.9	214±28.7	0.259±0.00	4.74±0.13	83.16±0.43
2.5%HPC-SL/ 2.5%F-127	136±9.0	376±5.7	0.141±0.00	0.394±0.02	98.76±0.54
2.5%HPC-SL/ 5%F-127	108±10.4	341±21.7	0.145±0.00	0.393±0.01	98.48±0.07

[a]All precursor suspensions of the nanocomposites have 10% ITZ and 0.2% SDS. %w/w is with respect to the weight of deionized water (300 g).
[b]Redispersed particle size was measured at the end of a 30 min run following the procedures outlined in this chapter.

At first glance, one can see a well-defined correlation of nanoparticle release as the polymer concentration increased for almost all formulations aside from that of VA 64. With VA 64 a plateau of nanoparticle recovery can be seen in which the addition of more VA 64 to the formulation had a hinderance effect on the release of ITZ nanoparticles from the composites. This could be due to the affinity of VA 64 to the ITZ nanoparticles over that of dissolving in water, which would preferentially hinder nanoparticle release as a particle size effect influence could not be seen with this polymer. On the other hand, at a total polymer concentration of 10%, formulations were able to release between ~69 and 86% of nanoparticles as compared to that of ~23% nanoparticle recovery from the baseline formulation of 10%ITZ–2.5HPC-SL–0.2%SDS. Most notably was that of PEG containing formulations, PEG 3350 and F-127, which not only generated a nanocomposite which

dispersed well, but also contained very desirable processing enhancement due to the waxy nature of PEG. As seen below in Figure 4.2 the final scraped round bottom from that of composites containing PEG compared to that of other polymers was very evident in the clarity of the flask.

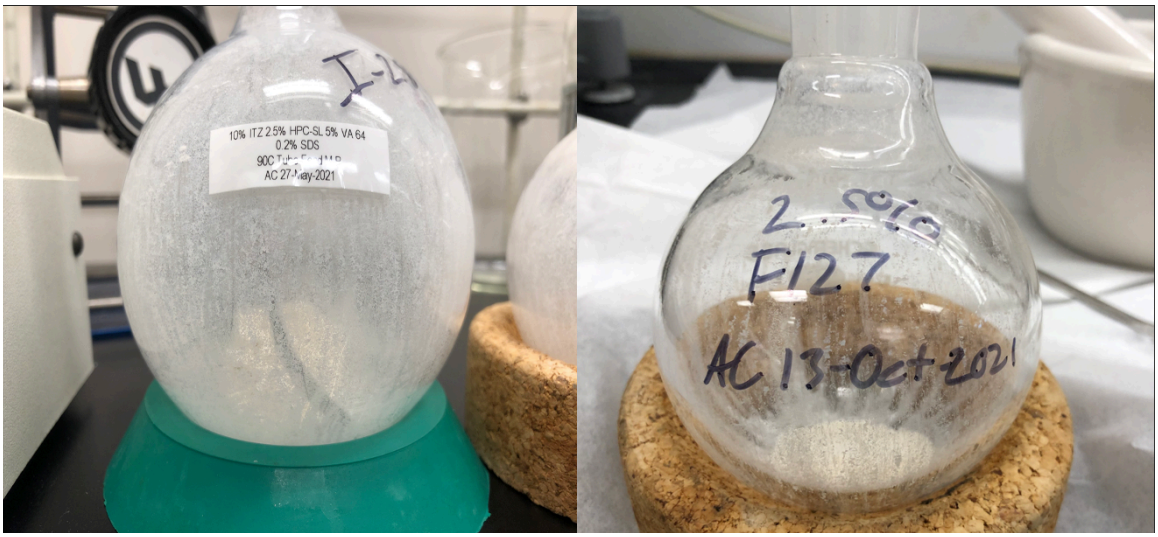

Figure 4.2 Round bottom flasks at the end of scraping. Higher clarity correlated to an easily processed and recovered nanocomposite. Flask on the left formulation with additional 5%VA 64 and flask on the right containing additional 2.5%F-127 a PEG containing triblock copolymer.

A cursory look at F-127 redispersion data in Table 4.5 suggests that the additional 2.5% F-127 was the only additional dispersant that resulted in a Q (1 µm) above 90%. Furthermore, with additional 0.7% F-127, the formulation containing Pluronic was able to obtain a dispersion comparable to that of other polymers which needed 7.5% additional dispersant (Alexandridis et al., 1994). This drastic reduction in the use of additional dispersant is very desirable in final formulations which allows a higher % drug loading (drug payload) in the nanocomposites. F-127 is very desirable in the formation of nanocomposites, having the characteristics of PEG to be processed very efficiently and

enhancing the wettability of the nanocomposites during the redispersion owing to its surfactant-like properties.

4.2.2 Dissolution Enhancement of ITZ

Figure 4.3 presents the dissolution profiles of as-received ITZ (unprocessed ITZ) powder, a nanocomposite powder prepared via rotary drying of the 2.5%HPC-SL–2.5%F-127–0.2% nanosuspension, a microparticle composite (labeled "Unmilled") prepared with the same formulation but using unmilled ITZ suspension, a physical mixture (PM) of as-received ITZ with the formulation but prepared via simple blending, and spray-dried nanocomposite of 10%ITZ–2.5%HPC-SL–0.2%SDS nanosuspension prepared by Bilgili et al. (2018). The as-received ITZ particles dissolved extremely slowly due to its low solubility and their large particle sizes (D_{50} =15.5 μm and D_{90} = 45.8 μm) perhaps presence of aggregates; only 8% of the drug dissolved after 60 min. Presence of the hydrophilic dispersants in a PM had a slight, but almost negligible effect, whereas rotary evaporation of a suspension of the unmilled ITZ with the dispersants (Unmilled) led to a nanocomposite with a more notable increase in drug release (22% at 60 min) due to more intimate contact of the dispersants with ITZ particles. These results suggest that without some alteration of ITZ particle size or solid state of the crystals, it is impossible to achieve immediate ITZ release (80% release within 20 min).

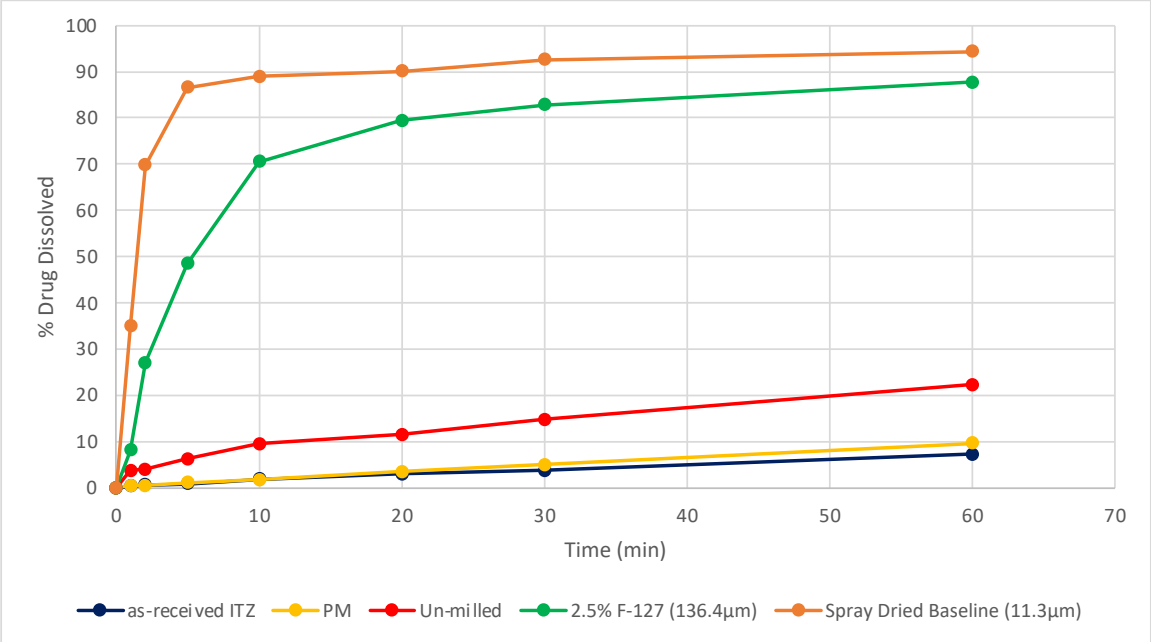

Figure 4.3 ITZ dissolution from nanocomposites compared to physical mixture and rotary evaporated suspension without milling. All formulations are based on having 10%ITZ–2.5%HPC-SL–2.5%F-127–0.2%SDS aside from as-received ITZ and spray-dried nanocomposite which only has 10%ITZ–2.5%HPC-SL–0.2%SDS. PM is a physical mixture. Un-milled was rotary evaporated without milling. Nano-milled was milled and dried on the rotary evaporator. Spray-dried nanocomposite and as-received ITZ data were obtained from (Bilgili et al., 2018).

The 10%ITZ–2.5%HPC-SL–0.2%SDS suspension was wet-milled, 2.5% F-127 was dissolved in it, and the resulting nanosuspension was dried by the rotary evaporator (Figure 4.3). This nanocomposite (2.5%F-127) achieved immediate release. XRPD and DSC studies on nanomilled ITZ (Bilgili et al., 2018) have established that ITZ was largely nanocrystalline. Hence, the observed remarkable increase in the dissolution rate as compared with "PM" and "Unmilled" samples is simply due to the large surface area of the ITZ nanoparticles in the nanocomposites. These nanoparticles were present in the precursor nanosuspension (refer to Table 2.2): D_{50} = 0.132 µm and D_{90} = 0.325 µm. These ITZ nanoparticles has about 117 times larger external surface area than the as-received, unprocessed ITZ particles. Thus, the profiles in Figure 4.3 signify that wet stirred media

milling is the most important processing step that enhances the ITZ dissolution. The calculated difference factor f_1 and the similarity factor f_2 in Table 4.6 suggest that effect of processing with ITZ nanoparticles is statistically different and has the largest impact in comparison to only processing on the rotary evaporator (Table 4.6). A spray-dried nanocomposite even with less dispersant (prepared using a nanosuspension of 10%ITZ–2.5%HPC-SL–0.2%SDS) outperformed all other samples, achieving immediate release within 5 min. The difference between spray-drying and rotary drying will be further scrutinized in Section 4.2.3.

Table 4.6 f_1 and f_2 Statistics for the Dissolution Profiles of Differently Processed ITZ Particles

	Processing Condition/Formulation		
	As Received ITZ[a]	Physical Mixture 10%ITZ 2.5%HPC-SL 2.5%F-127 0.2%SDS	Un-milled Rotary Evaporated Suspension 10%ITZ 2.5%HPC-SL 2.5%F-127 0.2%SDS
f_1[b]	95.68	94.60	82.22
f_2[b]	12.06	12.34	15.27

[a]Dissolution data to calculate statistics was obtained from (Bilgili et al., 2018).
[b]The dissolution profiles were compared to 10%ITZ–2.5%HPC-SL–2.5%F-127–0.2%SDS nanocomposite which was taken as the reference profile.

Let us examine the effects of various polymers on the dissolution performance (see Figure 4.4). Most formulations with the additional 2.5% dispersant as compared to the *baseline* nanocomposite (10%ITZ–2.5%HPC-SL–0.2%SDS) were able to achieve an 80% dissolution within a 20 min time. The dissolution profiles of all rotary dried

nanosuspensions are somewhat constrained within a narrow space, except the baseline nanocomposite and the "low" dissolution profile of the 2.5% HPC-SL nanocomposite (with D_{50} = 222.4 μm particles). The latter nanocomposite had much larger D_{50} than all other nanocomposites; hence, its dissolution took longer despite the presence of additional 2.5% HPC-SL (total of 5% HPC-SL), which clearly demonstrates the importance of nanocomposite particle size besides the itraconazole (drug) particle size. A slight improvement was also observed when 2.5%F-127 nanocomposite nanoparticles (D_{50} = 136.4 μm) was milled in Labram equipment after mortar and pestle milling into the 2.5%F-127 nanocomposite (D_{50} = 28.4 μm). Finally, the superfast dissolution from the spray-dried nanocomposite particles with D_{50} = 11.3 μm (highest profile in Figure 4.4) also validates the positive impact of finer nanocomposite particles on drug release. Unfortunately, for the other nanocomposites, this nanocomposite particle size effect is a confounding factor along with the different polymers used.

In Table 4.7, the f_1 and f_2 statistics show that there is not a significant difference between the different formulations aside from that of 2.5%HPC-SL which does appear to show a slight dissimilarity from the baseline in its poor performance in the dissolution testing.

The f_1 and f_2 statistics from the nanocomposite milled formulation which underwent 50 min of ball milling and contained 2.5% F-127 additional over *baseline* showed no difference, see Table 4.8, from taking the particle size of 136.4 μm D_{50} down to 28.44 μm D_{50} particle size. On the other hand, there was a statistical difference in the dissolution performance of the spray dried nanocomposite from Bilgili et al. (2018), compared to the same formulation that was rotary evaporated having an f_1 of 21.84 and f_2 of 35.62, showing

there is a significant improvement in the dissolution potentially due to the particle size difference in the nanocomposites (Bilgili et al., 2018).

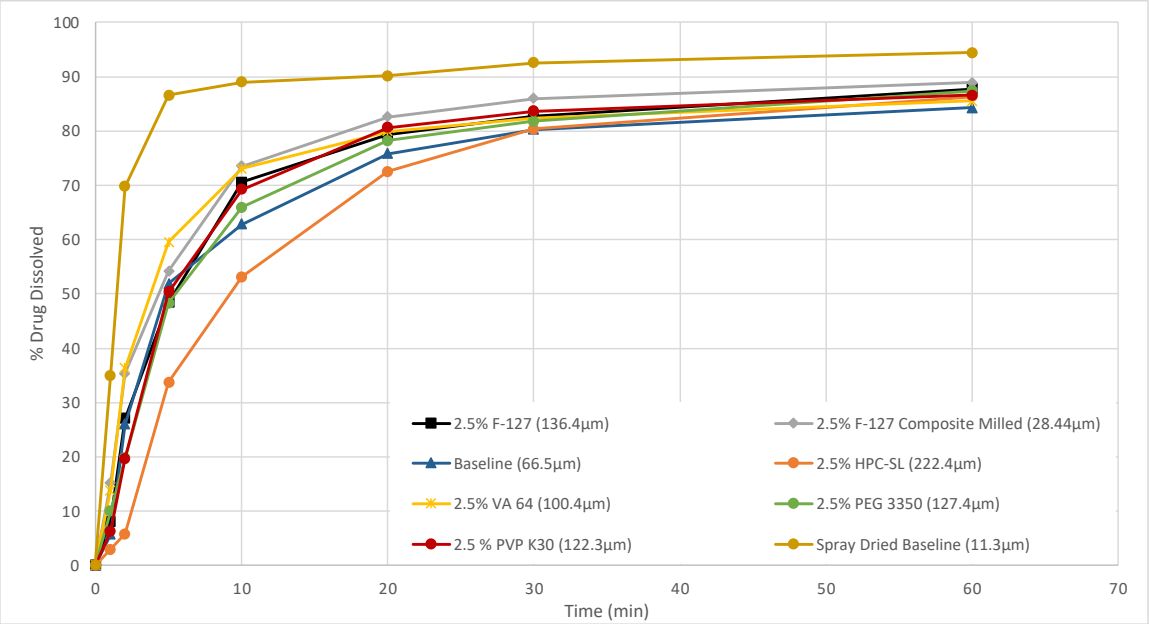

Figure 4.4 Dissolution at 2.5% additional dispersant over baseline formulation 10%ITZ 2.5%HPC-SL 0.2%SDS. Nanocomposite particle size for reference is recorded next to each formulation in the legend. Spray-dried nanocomposite data were taken from (Bilgili et al., 2018). The formulation of the spray-dried nanocomposite was that of the baseline formulation 10%ITZ 2.5%HPC-SL 0.2%SDS.

Table 4.7 f_1 and f_2 Statistics for Polymer Type

	Processing Condition/Formulation[a]					
	2.5% F-127[b]	2.5% F-127 Composite Milled[b]	2.5% HPC-SL[b]	2.5% VA 64[b]	2.5% PEG 3350[b]	2.5% PVP K30[b]
f_1[c]	6.24	12.6	14.5	11.3	6.25	6.52
f_2[c]	70.8	57.4	49.2	58.5	72.1	69.6

[a]All nanocomposites have 10% ITZ 2.5%HPC-SL 0.2% SDS (baseline). Additional dispersants were shows in the table%w/w is with respect to the weight of deionized water (300 g).
[b]Each formulation composition is that of additional dispersant added in addition to baseline nanocomposite.
[c]The dissolution profiles were compared to 10%ITZ–2.5%HPC-SL–0.2%SDS nanocomposite which was taken as the reference profile.

4.2.3 Spray Drying vs. Rotary Evaporator Drying

The dissolution performance of rotary evaporated nanocomposites and that of spray-dried nanocomposites was compared in Figure 4.5. The initial impression that can be seen from the figure is a slight increase in the dissolution performance as an additional 2.5% of F-127 was added to the formulation. In addition to the polymer effect, the particle size of the nanocomposites was of great interest due to the variety that can be seen in Table 3.3. The smaller nanocomposites in theory would have higher surface area and assist with the dissolution and redispersion performance. As one can see from the dissolution results below looking at the reduction of particle size, we can see that there is a slight assistance from having a smaller nanocomposite particle size. To quantify the statistical significance of these differences, f_1 and f_2 factors were calculated on the formulations in Figure 4.5 (see Table 4.8).

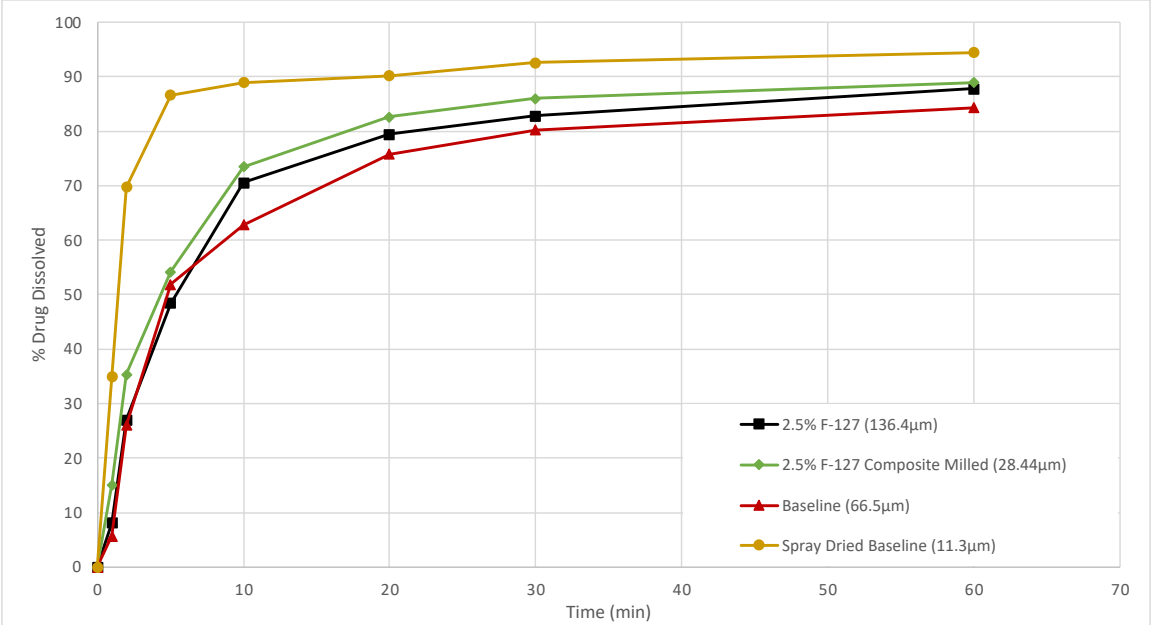

Figure 4.5 Dissolution comparison of spray-dried vs. rotary evaporated nanocomposites. Nanocomposite particle size for reference is recorded next to each formulation in the legend. Spray-dried nanocomposite data were taken from (Bilgili et al., 2018). The formulation of the spray-dried nanocomposite was that of the baseline formulation 10%ITZ 2.5%HPC-SL 0.2%SDS and other contained an additional 2.5% of their respective dispersant.

The f_1 and f_2 statistics for all formulations compared to the spray dried were statistically different based on the values reported within Table 4.8. A particle size effect from the spray dried nanocomposites being the smallest could be the driving factor in the significant improvement which spray dried composites have over that of rotary evaporated composites. In addition, the effect of milling the 2.5% F-127 sample from a particle size of 136.4 µm down to 28.44 µm was not statistically different as evident in the f_1 and f_2 values in Table 4.8.

Table 4.8 f_1 and f_2 Statistics for Dissolution of Rotary Evaporated and Spray-Dried Nanocomposites

	Processing Condition/Formulation[a]		
	Baseline	2.5% F-127 Composite Milled[b]	Spray-Dried Baseline
f_1[c]	5.97	7.82	38.0
f_2[c]	70.8	65.6	31.0

[a]All nanocomposites have 10% ITZ 2.5%HPC-SL 0.2% SDS. %w/w is with respect to the weight of deionized water (300 g).
[b]Each formulation composition is that of additional dispersant added in addition to baseline nanocomposite.
[c]The dissolution profiles were compared to 10%ITZ–2.5%HPC-SL–2.5%F-127–0.2%SDS nanocomposite which was taken as the reference profile.

To conclude, the particle size effect from the rotary evaporated nanocomposites at 28.44 μm down to 11.3 μm of the spray-dried nanocomposites was a statistical and visual improvement into the dissolution performance of the composites. On the other hand, the particle size reduction from that of the same two rotary evaporated nanocomposites from 136.4 μm down to 28.44 μm was not statistically different and did not show a great improvement in the dissolution. This suggests that there may be a sweet spot in the nanocomposite particle size that will allow for great improvement in dissolution without compromising powder properties (e.g. deteriorated flowability) associated with particles sizes below a D_{50} of 50 μm.

Interestingly, the impact of polymer type/loading on the nanocomposite redispersion was notable and significant; however, their impact on the dissolution was somewhat less remarkable. To put it another way, our dissolution test protocol has less discriminatory power than the dissolution test. This could be due to the use of 3 g/L SDS concentration as opposed to a 0.1 N HCl redispersion/dissolution media, which could have

improved the discriminatory power of the dissolution testing. Also, there was no significant correlation between the redispersion test and the dissolution test. In general, a significant correlation between these two different tests is not expected as they measure fundamentally different, but interconnected phenomena. The hydrodynamics in the redispersion vessel and the dissolution vessel are different. The large volume of aqueous media allows for dissolution of the drug particles, thus facilitating redispersion; whereas drug cannot dissolve in the redispersion test. In other words, the redispersion during the dissolution test is expected to be faster than that in the redispersion test. Interestingly, for the fluidized-bed coated/dried nanocomposites of griseofulvin (another BCS Class II drug), Bhakay et al. (2018a) established a correlation between the redispersion test and the dissolution test (Bhakay, Davé, et al., 2018). Nevertheless, they used deionized water as the medium in both tests, which enabled excellent discrimination power for different formulations. We could not use water here as ITZ solubility would be undetectable by UV spectroscopy.

4.3 Conclusions

The redispersion and dissolution data presented in this manuscript has shown great insight into nanocomposites and their performance when dried using a rotary evaporator. The dissolution data showed that wet stirred media milling was required to achieve a significant increase in ITZ release rate. In general, with respect to the effect of different polymers on the dissolution performance, there was no statistical difference among all formulated nanocomposites provided they do not have a median size above ~150 μm. On the other hand, the redispersion tests told a different story. Across the same polymer concentration, each polymer affected the dispersion of nanoparticles from the nanocomposite affecting

the percentage of nanoparticles that were able to be recovered within the testing period. Out of all formulations in this test, the samples containing F-127 had the most significant impact on the reconstitution of nanoparticles achieving complete dispersion with just 2.5% additional dispersant. This was the only formulation to completely disperse nanocomposites back to a nanoparticle suspension. At just 0.7% additional F-127, the polymer was able to disperse an equivalent percentage compared to that of other formulations containing 7.5% additional polymer in the formulation. This drastic difference in use of polymer makes for a large difference in the overall assay of the nanocomposites that is beneficial when looking at downstream tablet formulation. However, both tests agreed on the fact that additional 2.5% dispersant led to higher extent of nanoparticle recovery and faster dissolution; however, the dissolution tests were less discerning than the redispersion tests.

CHAPTER 5

CONCLUSION AND FUTURE WORK

5.1 Conclusions

This research has established the feasibility of rotary evaporation drying of wet-milled itraconazole nanosuspensions and examined the impact of various polymers/surfactants on the redispersion and drug release from the nanocomposites. Overall, rotary evaporation of drug nanosuspensions could yield drug nanocomposites with high drug loading (~67%), fast redispersion, and immediate release of poorly soluble drugs, with less concern over potential flowability issues than spray-dried nanocomposites.

Wet stirred media milling plays the most important role in enhancing the drug dissolution as it increased the drug surface area by ~100-folds. The presence of hydrophilic water-soluble polymers helped to enhance the wettability and enabled film formation during the nanocomposite formation. The neutral polymeric surfactant (Pluronic F-127) and the anionic surfactant (SDS) also helped to improve the wettability of the nanocomposites; while SDS also contributed to the physical stability of the precursor suspensions. The impact of various polymers was more apparent in the redispersion tests than in the dissolution tests due to the lower discrimination power of the latter. Provided that the nanocomposites had a median size less than ~150 μm, the nanocomposites with 1:2 dispersant:polymer ratio enabled immediate ITZ release from the nanocomposites during the *in vitro* dissolution tests.

In rotary evaporation drying, a feed and bleed approach proved to be the best method of generating nanocomposites when studying the redispersion of nanoparticles

from certain formulations. Mortar and pestle milling of the dried nanocomposite particles enabled us to produce a relatively homogeneous powder with all particles less than 1 mm and reduced standard deviation in measured particle sizes. In larger scales, mortar and pestle milling could be replaced by continuous conical-screen milling. Besides reducing the particle size range, mortar and pestle milling reduced the particle sizes, thus enabling faster redispersion and dissolution.

While the spray-drying led to finer nanocomposites with the median sizes (10–30 μm) with faster drug release, such small particles are associated with poor flowability. The nanocomposites prepared via rotary evaporator drying followed by mortar and pestle milling have coarser particles (median size ranging from ~50–150 μm), which are expected to have more favorable flowability. Therefore, when optimized, the wet stirred media milling followed by rotary evaporation and a size-determining milling step could help formulators to design ideal nanocomposites for effective delivery of poorly soluble drugs.

5.2 Future Work

5.2.1 Use of Other Dispersants for Dissolution Enhancement

Some categories of dispersants and their potential effect on redispersion and dissolution were not considered in this work. The need for dispersant optimization using colloidal superdisintegrants (a novel dispersant), sugars, sugar alcohols, and other polymers/surfactants is obvious. The optimization of these various dispersant would take a variety of experiments to understand the complete impact of these dispersants on the formulations generated from rotary evaporation.

5.2.2 Flowability and Tabletability Assessment of Nanocomposites

The nanocomposite powders are ultimately integrated into various solid oral dosages such as oral capsules and tablets for final consumption and use by the patient. To create tablets, flowability, compactability, and compressibility characteristics of the nanocomposites either directly or after addition of excipients such as functional fillers and lubricants. The use of an FT-4 to measure the resistance of a powder to flow and the stress on a nanocomposite would better help to understand what powder properties are desired for tableting. In addition, the use of bulk and tapped density would also show which formulations are more desirable as powders that have the least difference in bulk and tapped density tend to tablet much better without the need for additional dispersants to bulk up the tablet for desirable properties.

5.2.3 Pharmacokinetics Studies

In this study, we were able to demonstrate a sensitive method of characterizing nanocomposites dried with a rotary evaporator using redispersion. In addition, the use of dissolution was also studied with less discrimination between the different formulations. To understand the full impact on polymers on these nanocomposites, the use of pharmacokinetic studies would need to be conducted to see if the differences in redispersed nanoparticles will translate into greater systemic absorption by the body by having a constant reservoir of nanoparticles that can dissolve as the body is absorbing the drug. These studies should be able to show if the results from *in vitro* redispersion or dissolution are translated into absorption or if the results seen in the dissolution test hold true and no difference is seen between the formulations regardless of the polymers used to generate

nanocomposites. Therefore, pharmacokinetic studies are essential to understand the full extent of differences in formulating nanocomposites produced from rotary evaporation.

5.2.4 Thin Film Evaporation (TFE): Drying of Nanosuspensions

A rotary evaporation technique was developed in this study for lab scale understanding of drying nanocomposites. This lab scale unit is meant to be analogous representation of the TFE and the properties of nanocomposites that can be dried using this technique. To completely understand if the rotary evaporator was a correct choice for the lab scale performance of drying drug nanosuspensions, running scale up runs on the TFE and comparing the dried nanocomposites using the same gauntlet of tests, redispersion and dissolution, to that of rotary evaporated nanocomposites is a must to close the gap in this understanding of nanocomposite formation. This would be done for a similar set of formulations as was used in the dissolution testing to understand the particle size, polymer type, and overall characteristics of both TFE nanocomposites and those produced from rotary evaporation.

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