Pharmaceutical Research, Vol. 25, No. 10, October 2008 (© 2008)
DOI: 10.1007/s11095-008-9625-0

Research Paper

Conversion of Nanosuspensions into Dry Powders by Spray Drying: A Case Study

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Received March 5, 2008; accepted May 5, 2008; published online May 29, 2008

Purpose. Drying of nanosuspensions can cause destabilization of the particles, leading to irreversible aggregation. In order to prepare an effective solid dosage form for a nanosuspension, it is imperative that the spray-dried nanoparticles should go back to their original particle size when reconstituted in an aqueous system. This case study examines impact of various formulation and processing parameters on redispersibility of the spray dried nanoparticles.
Methods. Nanosuspensions were prepared using the microprecipitation–homogenization process. Spray drying of nanosuspensions was achieved using a lab-scale Buchi spray dryer.
Results. Formulation components appeared to have the most significant impact on redispersibility of spray dried particles. Absence of surface charge led to particles that could not be redispersed. On the other hand, charged particles stabilized with an appropriate sugar led to spray dried powders that were flowable and easily redispersible. Dissolution testing showed the presence of two phases—a lag phase that represented dispersion of the loose aggregates, and dissolution of the dispersed nanoparticles.
Conclusions. Nanosuspensions of a poorly soluble drug could be spray dried to obtain flowable powders that could be easily redispersed. These optimized powders also showed significantly improved dissolution rates as compared to the micronized drug, or unoptimized nanosuspensions.

KEY WORDS: dissolution; nanoparticles; nanosuspension; spray drying.

INTRODUCTION

In recent years there has been a consistent trend in drug discovery towards identification of poorly soluble molecules as lead candidates for development (1). Formulation of such molecules can be challenging (2) and may require the use of novel technologies (3). A number of drug delivery technologies such as solid dispersions, cyclodextrins, and nanoparticles have received significant interest. Nanoparticles have an advantage for oral drug delivery since they can be formulated as solid dosage forms for the general population, or as suspensions for pediatric or geriatric patients. Furthermore, nanoparticle technologies typically enhance the bioavailability of poorly soluble drugs, lead to a reduction in fed-fasted variability, and also provide some inherent taste masking. Due to these benefits, this technology has been quickly adopted by the industry, and a number of oral nanoparticulate products are now commercially available.

Nanoparticle technologies can be classified into various sub-categories such as crystalline nanoparticles, solid lipid nanoparticles, polymeric nanospheres, based on the morphology and nature of the particles. While all of the different nanoparticle technologies are actively pursued in a research setting, crystalline nanoparticles have advanced rapidly to a commercial stage. This is due to the added benefit of higher drug loading (and thereby reduced excipient load), easy scale-down for early formulation screening, and scale-up for large-scale production. A number of nanoparticles based products are now available commercially, including Rapamune (nanoparticulate formulation of rapamycin), Emend (nanoparticulate formulation of aprepitant), Tricor (nanoparticulate formulation of fenofibrate), and Megace ES (nanoparticulate formulation of megasterol acetate). Of these, Rapamune, Emend, and Tricor are formulated as a solid dosage form, whereas Megace ES is an oral suspension.

Crystalline nanoparticles can be prepared by precipitation, milling, high-pressure homogenization, or combination of technologies such as microprecipitation–homogenization. The submicron particles thus formed have a high surface area and are coated with surfactants or phospholipids to avoid aggregation. The reduced particle size and higher surface area allows for increased dissolution rates of the particles and thus can lead to enhanced bioavailability (4). For this reason, formation of irreversible aggregates is undesirable. In order to prepare solid dosage forms out of nanoparticles, the nanosuspension has to be dried and then processed further (into tablets or capsules) (5). Drying of nanoparticles can create stress on the particles that can cause aggregation. For example, if the nanoparticles are coated with polymeric surfactants such as poloxamers, drying may lead to crystalli-

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zation of the polymer, thereby compromising their ability to prevent aggregation. Drying can also create additional thermal stresses (due to heat for spray drying or freezing for lyophilization) that may destabilize the particles. Due to these considerations, understanding the process and the critical parameters that have a strong impact on the redispersibility of the dry powders is important. There are a number of published references that discuss the use of freeze-drying for nanoparticles (6–9). However, research literature that discusses the use of spray drying for nanoparticles is limited.

Lee discussed the use of spray drying and subsequent compacting of nanoparticles for oral dosage forms (10). While the main focus of the paper is on the characterization of the compacted form, the author does discuss the challenges associated with drying of nanoparticles. Morphology of the dried particles in this study indicated formation of irregular aggregates as well as donut shaped particles. These aggregates disintegrated in water after 24 h. No additional intermediate peaks were seen, indicating that the aggregates disintegrated to the primary particles. Although promising, these results demonstrate the challenge associated with spray drying of nanoparticles. Aggregates formed during spray drying should rapidly disperse so that the original particle size is regained within a short period of time. For oral formulations, the transit time of the particles in the gastrointestinal tract typically ranges from <1 to 8 h, depending on the region of absorption. Hence particle dissolution should occur in a short time frame (on the order of minutes) to facilitate availability of the drug for absorption. Variability in disintegration and dissolution times due to the presence of aggregates can cause unpredictable variations in bioavailability.

Freitas and Muller (11) investigated the use of spray drying for solid lipid nanoparticles. All formulations tested showed the formation of aggregates that could not be disintegrated by simple agitation or shaking. Sonication was required for effective reconstitution of the primary particles. Yin *et al.* (12) described spray drying of poorly soluble drugs, wherein the drug was in a dissolved form prior to spray drying, but formed nanocrystalline domains after spray drying. In this study, Poloxamers were used during spray drying, to form a matrix to encapsulate the nanocrystalline drug domains. Crystallinity was assessed using X-ray diffraction, whereas hot stage microscopy was used to estimate the size of the crystalline domains. It should be noted, however, that no conventional particle size analysis was performed during this study.

The main objective of this article is to provide a case study for preparation of dry powders of crystalline nanoparticles by spray drying. Spray drying is a commonly used process for processing of excipients. Its use in final dosage form processing has been more prevalent in the past decade, with the advent of novel drug delivery technologies. As discussed in a recent review, spray drying can be used to produce particles with complex morphologies that possess specific desired aerodynamic and dissolution properties (13). The process can be modeled using two-phase fluid flow principles and can be scaled-up to industrial scale. A good correlation can been established between small scale and large scale using these principles (14). However, as discussed above, literature for spray drying of nanosuspensions and its subsequent impact on particle dissolution is lacking. As part of this study, critical parameters that should be optimized for spray drying of nanosuspensions so as to produce easily redispersible dry powders have been identified. Itraconazole was chosen as a model drug. Itraconazole is a poorly soluble antifungal agent that has been studied as a candidate for nanosuspensions (15). A crystalline nanosuspension of itraconazole was prepared using a high-pressure homogenization process. Spray drying was conducted using a lab-scale spray dryer. The formulation and the process were optimized to prepare aggregate powders that demonstrate good flowability and yet redisperse back to the original submicron size upon reconstitution in an aqueous buffer.

MATERIALS AND METHODS

Itraconazole was purchased from Wyckoff (South Haven, MI, USA). Poloxamer 188 was purchased from BASF. Sodium lauryl sulfate and *N*-methylpyrrolidone (trade name: Pharmasolve) were purchased from Spectrum Chemicals and ISP, respectively. Lactose was purchased from Mallinkrodt, whereas Sucrose and Mannitol were obtained from J. T. Baker.

Nanosuspensions were prepared by using a tandem microprecipitation–homogenization process as described elsewhere (16). Briefly, the drug was dissolved into *N*-methylpyrrolidone, at a ratio of 1:3 *w*/*v*, drug/solvent. The solution was filtered through a 0.2 μm filter membrane to remove undissolved particulates and then precipitated under controlled conditions into an aqueous solution of surfactants. Typical surfactant concentrations were in the range of 1 to 10 mg/ml. No pH adjustments or buffers were used for the aqueous surfactant solution. Given the poor solubility of Itraconazole, addition of the drug/NMP solution led to instantaneous supersaturation conditions that cause precipitation of the drug. During precipitation, the suspension was mixed using an IKA Ultraturrax rotor-stator mixer (Staufen, Germany) and then homogenized using a high pressure, piston-gap homogenizer, at controlled temperature and pressure settings. The homogenized suspension was then centrifuged at >5,000 relative centrifugal force (RCF) to separate the nanoparticles from the solvent-laden surfactant medium. The aqueous supernatant was replaced with a fresh surfactant solution to remove residual solvent. Alternately, a filtration-based approach was also used for solvent removal. The suspension was then re-processed under milder homogenization conditions (lower pressure) to break the aggregates formed during centrifugation and to obtain a stable nanosuspension. A single 10 l batch was prepared to support all activities in this study. Additional excipients (such as mannitol, sucrose etc.) were added subsequently prior to spray drying. Typical concentrations of sugars used in the suspensions for spray drying were in the range of 2–10% (*w*/*v*).

Particle size analysis of the suspension was conducted using a Horiba (Irvine, CA, USA) LA-920 laser light scattering instrument. Drug suspension was added to the sample cell to obtain transmittance within the 70–95% range. A relative refractive index value of 1.2 was used for particle size analysis. This value was obtained by actually measuring the refractive index of Itraconazole powder using the Becke Line method. Zeta potential was measured using a NanoZS from Malvern Instruments. Residual moisture was measured using an IR-120 infrared moisture analyzer (Denver Instruments, Colorado, USA). A Jeol JSM-6300F scanning electron

Table I. Different Formulations Categories Tested to Understand the Effect of Individual Formulation Components on the Quality of Spray-dried Powders

Formulation category	Polymeric surfactant(s)	Charged surfactant	Sugars
I	Poloxamer 188 Poloxamer 407	–	–
II	Poloxamer 188 Poloxamer 407; HPMC	–	Lactose; mannitol; sucrose
III	Poloxamer 188	Sodium deoxycholate	Lactose; mannitol; sucrose; dextrose

microscope was used for imaging of the dry powders. A Polaron SEM coating system was used to coat immobilized particles with palladium prior to imaging.

Spray drying was conducted using a Buchi B290 lab scale spray-drying unit from Buchi Corporation (Switzerland), equipped with thermocouples for inlet and outlet temperatures, as well as controllers for pump and aspiration rates. The spray dryer was equilibrated with water prior to every run. An integrated nozzle-cleaning device was utilized between runs to prevent clogging of the spray nozzle. Typical batch size for spray drying was around 100 ml (volume of feed). The aqueous suspension was pumped into the spray-drying chamber using a peristaltic pump at a rate of 10–30%. Spray drying was conducted at inlet temperatures in the range between 80°C and 120°C. At higher temperatures, excessive collection of the particles was observed in the spray chamber, whereas lower temperatures led to particles with higher residual moisture content. Inlet temperature of ~90–100°C appeared to be most favorable for spray drying of the Itraconazole particles. Transient exposure to high temperature was expected to provide minimal destabilizing effect on the particles. Furthermore, this temperature range was also below the phase transition temperature of the Poloxamers used in the study, and significantly below the melting point of the drug. Outlet temperature was typically in the range of 40°C to 60°C.

Wetting of dry powders adds an extra variable to *in vitro* dissolution testing. Hence, a two-stage approach was adopted to generate dissolution curves. This approach involves pre-wetting the powders by mixing in a buffer for a fixed time period, prior to charging to the dissolution cell. This approach is similar to that published in the literature for other nanoparticulate formulations (17). Dissolution testing of spray dried powders was conducted by first adding the powder to water and mixing for up to 10 min at 37°C to allow thorough wetting of the particles. It should be noted that although the purpose of the dissolution curves was not to obtain *in vivo* correlation, the wetting process can be considered similar to the initial part of GI transit of the oral solid dosage form, wherein the dosage form (tablet, capsule) disintegrates to allow the particles to come in good contact with the aqueous medium. The suspension thus formed post-wetting was then added to an aqueous surfactant solution maintained at 37°C, and %transmittance through the solution was monitored using a Cary UV–Vis spectrophotometer at a wavelength of 400 nm. Immediately upon addition of the drug suspension, the buffer solution transmittance goes down. As the drug particles dissolve, the %transmittance increases, eventually going back to 100%. Hence a comprehensive dissolution curve is generated. This approach was considered more convenient than the conventional HPLC based dissolution approach, given the difficulties in rapid sample pulls and filtration of the samples to remove undissolved drug particles. It should however be noted that this method was not validated for this application, and further studies would be required to confirm the method's robustness.

RESULTS AND DISCUSSIONS

Spray Drying

Nanosuspensions of Itraconazole were prepared using different combinations of surfactants and sugars. Stability of the suspensions was determined using a variety of stress tests that were designed to assess the tendency of the suspension to aggregate, cake, or Ostwald ripen over long term storage (18). Ostwald ripening tendency was gauged by exposing the nanosuspension to thermal cycling over a three-day period. Suspensions were observed under a microscope for any crystal growth. Aggregation tendency was gauged by shaking the suspension on an orbital shaker for three days. Early screening studies indicated that a combination of surfactants was required to stabilize Itraconazole nanoparticles. Poloxamer 188 in combination with a neutral surfactant (such as poloxamer 407) or a charged surfactant (such as sodium deoxycholate) stabilized the Itraconazole nanoparticles against aggregation or Ostwald ripening. Presence of sugars during homogenization did not have any effect on stabilization of the particles in the wet suspension stage. Formulations were

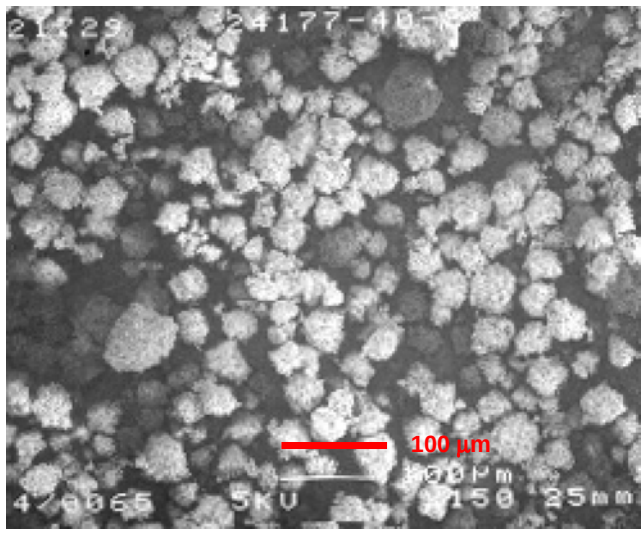

Fig. 1. Scanning electron micrograph of a typical spray dried nanosuspension. The spray-dried aggregates were spherical and devoid of fused or donut shaped particles.

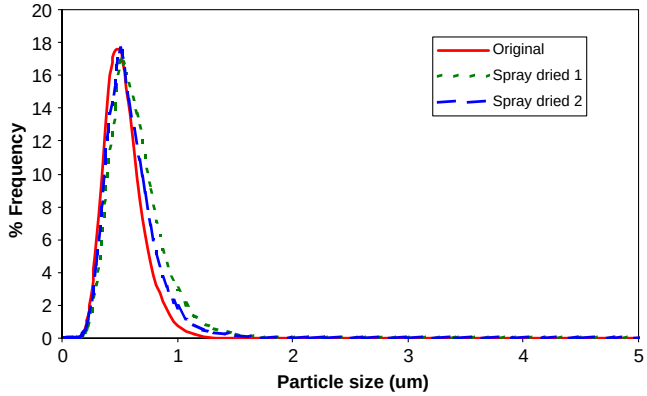

Fig. 2. Particle size frequency distribution plots for the original nanosuspension and the spray dried powders. The similarity of distribution indicated that the spray dried powders redispersed back to the original particle size when reconstituted in water, without any significant external driving force (such as sonication).

developed that fell in one of the three categories listed in Table I. Zeta potential measurements were used to confirm that only formulations in Category III had a net charge on the surface (negative charge due to the presence of charged surfactants). Formulations that failed stress testing were discarded. Stable formulations thus screened were spray dried and the dry powders were tested and characterized. Key process parameters that were investigated during spray drying included inlet temperature, initial suspension concentration, and feed rate.

Figure 1 shows the SEM of a typical batch of spray-dried powder. It was seen that the particles were spherical aggregates of nanoparticles, typically in the range of 10–40 μm, depending on the conditions used for spray drying. Formation of fused or donut shaped particles had been previously reported during spray drying of crystalline nanoparticles (10). Such irregular particles might form because of a loss of structural stability of a droplet in a two-phase flow field caused by very high gas flow rates (19). The inlet gas flow rate and feed temperatures were adjusted to avoid formation of such particles.

Dry powders were reconstituted in water and the particle size was measured. Formulations in Categories I and II showed significantly higher particle size, which decreased nominally after sonication (data not shown). This data indicates that spray drying of those formulations led to formation of irreversible aggregates. As seen in Fig. 2, the particle size distribution for the spray-dried particles from Category III formulations was similar to the original suspension. A slight shift in the distribution to the higher particle size was observed. The mean particle size of the spray-dried particles was typically 10–20% higher than the mean of the

Table II. Relevant Properties of the Four Sugars Investigated as Carriers for Spray Drying of Itraconazole Nanosuspensions

Sugars	Melting point (°C)	Tg (°C)
Lactose	223	101
Mannitol	165	87
Sucrose	185	62
Dextrose	146	31

Table III. Particle Size and Flowability of Suspensions Made from Category III Formulations

Batch	Particle size (μm)		Particle size ratio $[Mean]_f/[Mean]_i$	Flowability
	Mean	99%		
Original suspension	0.4562	0.881	N/A	N/A
23438-91	0.4957	1.066	1.09	+
23438-95	0.5372	1.147	1.18	+
23438-96	0.5444	1.273	1.19	+

The differences in the different batches are related to the varying process parameters explored. Particle size ratio was calculated as a ratio of the mean particle size of the reconstituted powders post-spray drying, to the mean particle size of the nanosuspension prior to spray drying.

original suspension. It should be noted also, that unlike Category I and II formulations, there was no presence of larger particles aggregates seen in the spray-dried suspensions for Category III formulations. This data indicates that polymeric surfactants and sugars were not sufficient to stabilize the nanoparticles during the spray drying process. An additional charged surfactant was required to prevent irreversible aggregation. This was in contrast to observations made by Layre *et al.* (8) that indicated that poloxamer 188 and sugars alone were sufficient to stabilize nanoparticles during the drying process. It should be noted however that freeze-drying was used in that study (as opposed to spray

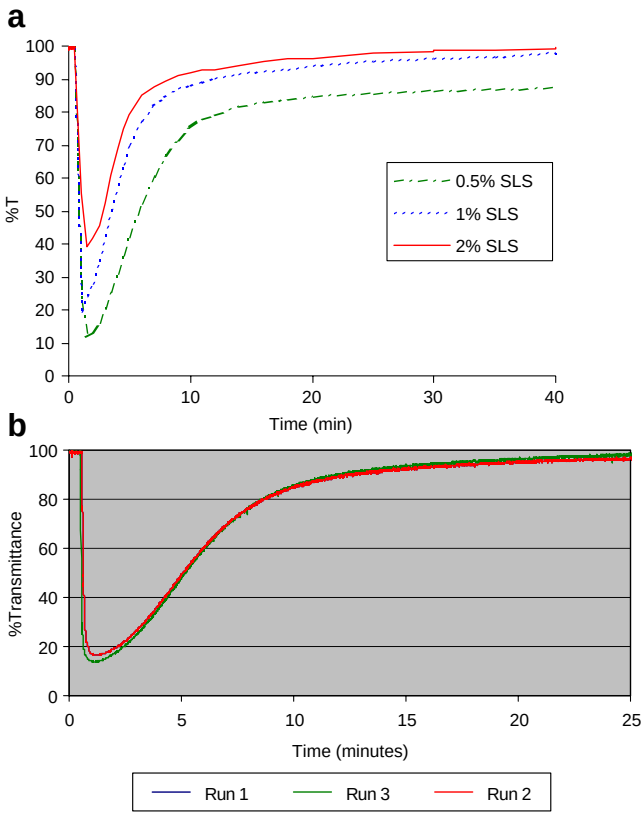

Fig. 3. Dissolution profiles generated using a transmittance based method: **a** effect of varying strength of the dissolution medium on the dissolution profile; **b** reproducibility of the dissolution method.

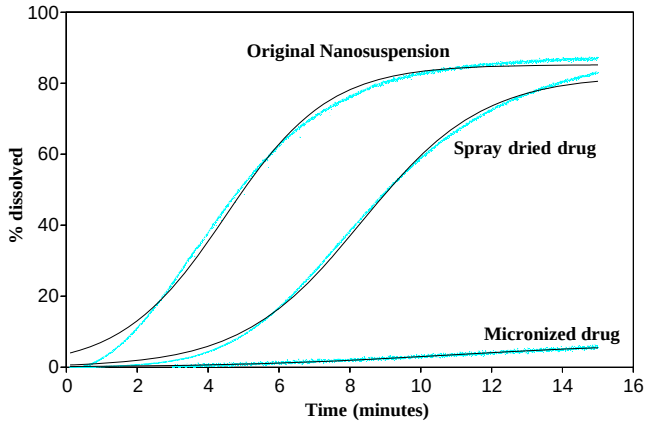

Fig. 4. Dissolution plots generated by deconvoluting the transmittance data, for a coarse microsuspension, the original nanosuspension, and an optimized spray-drying batch. The blue line represents the dissolution curves whereas the solid lines represent the Weibull function dissolution model.

drying). Furthermore the polymer nanoparticles in that study had an intrinsic negative surface charge as seen from the negative zeta potentials. For the Itraconazole nanoparticles used in our study, the drug itself is a neutral molecule and therefore does not provide an ionic charge. Hence there is a need for a charged surfactant that provides electrostatic stabilization of the particles during drying. Formulations from all three categories had provided stable suspensions. Hence although polymeric surfactants can stabilize nanoparticles in an aqueous environment, their stabilization ability is compromised in the dehydrated state.

Table II lists the sugars that were used as excipients in our studies to facilitate redispersion of the spray-dried powders (20). The flowability of the powders was dependent on the type of sugar used. Although all of the sugars had high melting point (>140°C), sugars with lower glass transition temperatures resulted in sticky powders (e.g. dextrose and sucrose). Lactose and mannitol (Tg>80°C) on the other hand provided easily flowable powders. Hence, glass transition temperature rather than melting point was a better predictor for spray drying performance. Residual moisture was tested for lactose and mannitol-based formulations. Spray dried powders containing lactose typically had 4–6% moisture content, whereas mannitol-based formulations contained less than 2%. The high moisture content for the lactose-based formulations may be due to the conversion of the lactose to its monohydrate form. Based on the ease of flowability as well as moisture removal, mannitol was found to be the most favorable carrier for spray drying of the nanoparticles. Table III lists the results from three spray-dried Itraconazole batches utilizing mannitol as the sugar of choice. All batches resulted in good flowability. Differences in particle size ratio (final particle size mean: original particle size mean) was attributed to differences in spray drying parameters.

Dissolution

Particle size reduction leads to enhancement in dissolution rates in accordance with the Noyes–Whitney equation:

$$\frac{dQ}{dt} = \frac{D}{h} S(C_s - C_g) \quad (1)$$

where the rate of dissolution (dQ/dt) is directly proportional to the diffusion coefficient of the drug (D), the available surface area (S), and the difference between saturation solubility of the drug in the boundary layer (C_s) and concentration of drug in the bulk fluid (C_g). Therefore as particle size decreases, surface area increases, thereby leading to improved dissolution rates. However, if nanoparticles form fused aggregates, the overall surface area would increase and the dissolution rate would be negatively impacted.

Dissolution testing was carried out using %transmittance as described in the section above. The first step to developing a dissolution test for the spray-dried powders was to identify an appropriate buffer system. Solutions with various concentrations of sodium lauryl sulfate (SLS) were explored. As seen in Fig. 3a, at higher levels of SLS, dissolution was rapid (and non-discriminating). Decreasing the SLS concentration led to a progressively lower transmittance level upon addition of the drug suspension. A 0.5% SLS solution gave good and consistent dissolution curves (as shown in Fig. 3b), and hence was chosen as the dissolution medium for subsequent studies. Dissolution was performed in triplicates to ensure that a consistent curve is obtained from the method.

Figure 4 shows dissolution curves obtained for a suspension of the micronized drug, spray dried drug powder (Formulation Category III), and the original drug nanosuspension. The dissolution curves were obtained by deconvolution of the transmittance data. As can be seen in the figure, the micronized drug showed the least favorable drug dissolution profile. The nanosuspension showed the most rapid dissolution profile. The spray dried nanosuspension showed a slight delay (2–4 min), after which dissolution progressed, with a profile similar to the original nanosuspension. This delay in dissolution profile may be related to hydration as well as disintegration of drug aggregates. As was mentioned by Lee, drug nanoparticles disintegrate from aggregate form to their original nanosuspension form (10).

Table IV. Impact of Spray Drying on the Dissolution Rate of Reconstituted Suspensions

Batch	Surfactants	Additional Excipients	Condition	Dissolution rate (min^{-1})
Microsuspension	Poloxamer 188, sodium deoxycholate	None	Microsuspension	0.55
Nanosuspension	Poloxamer 188, sodium deoxycholate	None	Nanosuspension	12.95
Spray drying—Unoptimized	Poloxamer 188 Poloxamer 407	5% (*w/v*) Mannitol	Nanosuspension	0.98
Spray drying—Optimized 1	Poloxamer 188, sodium deoxycholate	2.5% (*w/v*) Mannitol	T_{inlet}=110°C	10.39
Spray drying—Optimized 2	Poloxamer 188, sodium deoxycholate	2.5% (*w/v*) Mannitol	T_{inlet}=90°C	10.98
Spray drying—Optimized 3	Poloxamer 188, sodium deoxycholate	5% (*w/v*) Mannitol	T_{inlet}=90°C	11.25

A coarse microsuspension and the starting nanosuspension were used as controls in the study.

While Lee saw this transition occurring over 24 h, our formulations showed the transition occurring on the order of minutes. While the dissolution curve shows the transition over 3–4 min, it is expected that the real transition time starts as soon as the powder is added to water for reconstitution (which is an additional 10 min). Nevertheless, the disintegration phase for Formulation Category III was seen to be over a span of less than an hour. This time frame is much more suitable for oral drug delivery applications.

The dissolution of the spray-dried nanosuspensions was modeled using the Weibull model. The Weibull model uses an empirical function to describe dissolution rates and is shown in the following equation:

$$\frac{M_t}{M_\infty} = 1 - e^{-at^b} \tag{2}$$

M_t is the mass dissolved at time t and M_∞ is the total mass dissolved at infinite time. Symbols 'a' and 'b' represent scale and shape parameters, respectively. The Weibull function was chosen due to its prior success in modeling S-shaped dissolution curves, like the ones seen for other solid dosage forms (21). One of the drawbacks previously reported for the Weibull model was its empirical nature. However, a recent study utilizes the Noyes–Whitney equation to derive the Weibull function whereby the various physiological parameters, such as the dissolution rate, mean dissolution rate and lag time can be obtained from the function (22). Curve fitting with the Weibull function was performed via non-linear regressional analysis. As can be seen in Fig. 4, a very good fit could be obtained between the curves obtained using the Weibull function, and the experimentally derived dissolution profile of Itraconazole suspensions. For the nanosuspension control, dissolution appeared to start immediately upon addition of the suspension to the SLS medium, as seen from the continuous increase in %transmittance following the precipitous drop upon addition of the suspension. However, for the spray-dried powders, modeling of the dissolution profiles suggested the presence of two regions—an initial lag time, followed by a dissolution curve that was similar to that observed for the nanosuspension. It is hypothesized that the initial lag time is associated with the disintegration of the loose aggregates. Based on the two regions for the dissolution curves, the quality of the spray-dried powders could be quantified using the lag time during the disintegration phase, and the slope of the linear region in the dissolution phase as two parameters. Table IV lists the dissolution rates for a number of spray-dried batches as compared to a microsuspension and the original nanosuspension. As expected, the coarse microsuspension of Itraconazole does not show any appreciable solubility profile with less than 10% dissolved in 15 min. On the other hand, the nanosuspension dissolved within 10 min in the dissolution medium. The spray-dried powders had a particle size that was similar to the micronized API used to make the microsuspension. Hence, although the dry particle size of the microsuspension and spray dried nanosuspension were similar, the dissolution rate of the latter was 20-fold higher for Category III formulations. The difference was only twofold for Category I and II formulations indicating the importance of an optimized formulation. Spray dried powders from Category III formulations showed a dissolution rate similar to the nanosuspension beyond the lag phase. Both the lag time and dissolution rate appeared to be related to the processing conditions used for spray drying. Spray drying at high inlet temperatures led to powders with higher lag time as well as lower dissolution rates. By optimizing these parameters, a dissolution rate of within 10% of the original nanosuspension dissolution rate could be obtained.

CONCLUSIONS

This article provides a case study for developing a dry powder form for a nanosuspension of a poorly soluble drug. The stabilizers used for the suspension appeared to have by far the most significant impact on the quality of the final dry powder as compared to the impact provided by process manipulations. Presence of charged surfactants was seen to be important for making a redispersible dry powder. Spray dried powders in absence of a charged surfactant showed higher particle size as well as low dissolution rates. Sugars were important for enhanced flowability. Past studies for freeze drying of nanoparticles had indicated the utility of sucrose as a protectant to avoid aggregation of the dried particles (23). However, this excipient was not optimal for spray drying due to its low glass transition temperature. Of the various high Tg sugars tested, Mannitol provided the most desirable particle morphology and flowability. The optimized formulation was then tested to examine the effect of altering the spray drying parameters. The inlet suspension concentration and feed temperature were seen to be important parameters for effective drying. Suspension made from spray-dried nanoparticles dissolved much more rapidly as compared to suspensions of micronized drug. Dissolution of the spray-dried powders appeared to follow a sigmoidal pattern that could be modeled using the Weibull function. The dissolution profiles of the spray dried powders showed distinct disintegration (lag time) and dissolution regions. The optimized process resulted in powders that demonstrated minimal lag time and provided dissolution rates that were comparable to the original nanosuspension. It is expected that the optimized powders would provide the oral bioavailability enhancement that is characteristic of nanoparticulate dosage forms.

ACKNOWLEDGMENTS

The authors would like to thank Sabine Graham, Baxter Healthcare for zeta potential measurements and Drs. Jane Werling and Sarah Lee for review of the manuscript.

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