Fast Dissolution of Poorly Water Soluble Drugs from Fluidized Bed Coated Nanocomposites: Impact of Carrier Size

5 **Mohammad Azad¹, Jacqueline Moreno, Ecevit Bilgili, Rajesh Davé***

Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering,
New Jersey Institute of Technology, Newark, NJ 07102, USA

*Address correspondence to Rajesh Davé. Phone: +1-973-596-5860; Email: dave@njit.edu

¹Current address: Department of Chemical Engineering, Massachusetts Institute of
10 Technology

ABSTRACT

Formation of core-shell nanocomposites of Fenofibrate and Itraconazole, model poorly water soluble drugs, via fluidized bed (FB) coating of their well-stabilized high drug loaded nanosuspensions is investigated. Specifically, the extent of dissolution enhancement, when fine carrier particles (sub-50 μ m) as opposed to the traditional large carrier particles (>300 μ m) are used, is examined. This allows testing the hypothesis that greatly increased carrier surface area and more importantly, thinner shell for finer carriers at the same drug loading can significantly increase the dissolution rate when spray-coated nanosuspensions are well-stabilized. Fine sub-50 μ m lactose (GranuLac[®] 200) carrier particles were made fluidizable via dry coating with nano-silica, enabling decreased cohesion, fluidization and subsequent nanosuspension coating. For both drugs, 30% drug loaded suspensions were prepared via wet-stirred media milling using hydroxypropyl methyl cellulose and sodium dodecyl sulfate as stabilizers. The stabilizer concentrations were varied to affect the milled particle size and prepare a stable nanosuspension. The suspensions were FB coated onto hydrophilic nano-silica (M-5P) dry coated sub-50 micron lactose (GranuLac[®] 200) carrier particles or larger carrier particles of median size >300 μ m (PrismaLac[®] 40). The resulting finer composite powders (sub-100 μ m) based on GranuLac[®] 200 were freely flowing, had high bulk density, and had much faster, immediate dissolution of the poorly water-soluble drugs, in particular for Itraconazole. This is attributed to a much higher specific surface area of the carrier and corresponding thinner coating layer for fine carriers as opposed to those for large carrier particles.

Keywords: Poorly Water Soluble Drug, Wet-Stirred Media Milling, Fluidized Bed Coating, Fine vs Large Carrier Particles, Thick vs Thin Polymer Coating, Fast Dissolving Nanocomposite Powders

1. Introduction

The bioavailability of a large percentage (between 40% and 70%) of newly discovered drug compounds is limited by their poor water solubility and slow dissolution rate (Kesisoglou et al., 2007; Lindenberg et al., 2004). Size reduction of drug crystals to nano-scale increases the specific surface area tremendously, which can increase the dissolution rate of drugs according to the Noyes–Whitney equation (Noyes and Whitney, 1897). Therefore, preparing a drug nanosuspension via wet media milling and subsequently converting it into various composite particles and/or nanoparticle agglomerates via spray drying (Azad et al., 2015a; Malamatari et al., 2015; Malamatari et al., 2016) and core-shell nanocomposite microparticles (NCMPs) via fluidized bed coating onto inert excipient particles (Basa et al., 2008; Bhakay et al., 2014a; Bhakay et al., 2014b; Malamatari et al., 2016) have become popular for preparation of oral solid oral dosages and inhalable dry powders.

Wet stirred media milling (WSMM) is an organic solvent-free process and has several distinct advantages such as tunable and relatively high drug concentration, low excipient side effects, ability to run continuously, scalable, etc., and can be universally formulated for most drug candidates with poor water solubility (Li et al., 2016; Malamatari et al., 2015; Merisko-Liversidge et al., 2003; Monteiro et al., 2013). During the WSMM process, drug suspension along with hard grinding beads is stirred at high speed and subjected to turbulent motion—high shear inside a chamber, which in turn leads to breakage of drug particles captured between the colliding beads (Afolabi et al., 2014). While WSMM can form a drug nanosuspension with a median size below 1000 nm, nanoparticles can increase in size due to agglomeration and ripening during the milling

60 and storage (Knieke et al., 2013). Important benefits such as the high surface area can be lost if the nanoparticles grow and/or form large clusters. Hence, it is of great importance to ensure suspension stability not only during the media milling, but also during the subsequent storage. In general, stabilization can be achieved either by electrostatic, steric or electrosteric interactions (Kim, 2004; Napper, 1970) with the use of various stabilizers
65 (refer to the review by Li et al., 2016) including polymers such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, etc.; surfactants such as sodium dodecyl sulfate, poloxamer 188/407, d-alpha tocopheryl polyethylene glycol 1000 succinate, Polysorbate 20 and 80, etc.; and novel class of stabilizers like colloidal particles of superdisintegrants such as sodium starch glycolate and croscarmellose
70 sodium (Azad et al., 2015b). Optimal concentration of the stabilizers is usually determined by assessing the particle size after wet media milling and during storage at various concentrations of the stabilizers (Knieke et al., 2013).

For the core-shell type NCMPs prepared via fluidized bed coating/drying of precursor drug nanosuspensions onto carrier particles, besides the drug particle size, the
75 type-solubility-concentration of the polymer in the shell as well as the thickness of the coating layer and carrier size can impact the drug release rate. The typical fluidized bed coating processes utilize carrier particles as large as 850 μm resulting in much larger final nanocomposites (Möschwitzer and Müller, 2006). In contrast, smaller carrier particles (<50 μm) can provide a higher specific surface area for coating, thus potential for
80 achieving fine NCMPs (sub-100 μm) (Knieke et al., 2015). Advantages of the fine nanocomposites include higher drug loadings in the final dosage, excellent content uniformity, minimum segregation tendency, controlled cohesion and good bulk density

for speedy downstream processing (e.g. capsule filling or tableting). Moreover, they are preferred for orally disintegrating dosage forms to minimize the sensation of a gritty mouth feel, and can also be used for controlled release of the drug through manipulation of the coating polymer(s). The challenge associated with fine carrier particles is that these carrier particles cannot be fluidized inherently due to their small particle size. Based on empirical observations of fluidization behavior, Geldart (1973) classified powders into four groups (A, B, C, and D) according to their size and the density difference between the particles and the fluidizing medium. Powders with fine particle sizes usually belong to group C, which are inherently un-fluidizable, and exhibit extremely erratic, poor fluidization even if they can be fluidized at all. Dry-coating with nanosized silica prior to the fluidized bed coating greatly reduces the particle cohesion, and hence shifts the powder fluidizability of the carrier from Geldart group C (cohesive) to Geldart group A (aeratable) (Chen et al., 2008; Yang et al., 2005). The purpose of silica coating is strictly to enhance fluidization and the silica gets covered after spray-coating with drug suspensions, hence has no subsequent role in dissolution performance.

Recent investigations show that if the milled suspensions are properly stabilized, core-shell NCMPs having water-soluble core prepared via fluidized bed coating of such stable suspensions can allow for fast dissolution rate for poorly water soluble drugs (Bhakay et al., 2014a; Bhakay et al., 2014b; Möschwitzer and Müller, 2006). Apart from direct assessment of dissolution behavior, the recovery of drug nanoparticles after redispersion from NCMPs has also been shown to be an important criteria to assess the overall performance of the NCMPs (Azad et al., 2015 a; Bhakay et al., 2014b; Bhakay et al., 2013). Doing so allows for evaluating if the nanoparticles form agglomerates or if

they exist in easily dispersible form. These investigations have then shown that both the stability of the milled suspensions and the redispersibility of the dried NCMPs are very important factors. However, the impact of the size of the carrier particle has not been investigated. In this paper, that is the main topic of investigation. It is hypothesized that 110 finer carriers could further enhance dissolution rate for highly water insoluble drugs because of larger composite particle specific surface area and more importantly, corresponding thinner shells for the same drug loadings as long as the drug particles are nano-sized and suspensions are well-stabilized. In this paper, besides studying the impact of milled drug particle size as modulated by stabilizers, this 115 hypothesis is examined by considering Fenofibrate and Itraconazole as model poorly soluble drugs; noting that the latter is more poorly water soluble and more hydrophobic.

This study deals specifically with the preparation of NCMPs of two poorly water soluble BCS Class II drugs, Itraconazole and Fenofibrate. Highly concentrated (30% w/v) drug suspensions were prepared via WSMM. The combined use of a polymer and an 120 anionic surfactant at various concentrations enabled us to elucidate the impact of drug particle size and stability of the suspensions. Using a fluidized bed coater, these precursor suspensions having three different polymer loadings (1.25, 2.5, and 5%) were coated onto fine sub-50 micron lactose (GranuLac[®] 200) to produce fine NCMPs. Fluidization of fine carriers was made possible through dry coating based particle surface modification with 125 hydrophilic nano-silica (M-5P) via reduction of cohesion. To compare with fine carriers, large carrier particles of median size >300 micron (PrismaLac[®] 40) were also coated. PrismaLac[®] 40 particles are easily fluidized. Therefore, they were used as received without dry coating, which was not necessary. The milled drug particle size and

morphology were characterized via laser diffraction and scanning electron microscopy (SEM). In addition to the stability of the milled suspensions, examination of the recovery of drug nanoparticles after redispersion from NCMPs (Azad et al., 2015 a; Bhakay et al., 2014b; Bhakay et al., 2013) helped elucidate the impact of polymer loading and presence of surfactant. The extent of dissolution enhancement for fine carrier particles (sub-50 μm) as opposed to the traditional large carrier particles (>300 μm) was examined for both drugs to test the main hypothesis.

2. Materials and Methods

2.1. Materials

Itraconazole (ITZ, antifungal agent) and Fenofibrate (FNB, lipid lowering agent) were purchased from Jai Radhe Sales (Ahmedabad, India). ITZ and FNB were specifically chosen here as model drugs owing to their low water solubility (0.1 and 0.8 mg/L, respectively) and relatively hydrophobic nature (Log P: 7.13 and 4.75, respectively). Hydroxypropyl methylcellulose (HPMC, Methocel-E3, The Dow Chemical Company, Midland, MI) was used as neutral polymeric stabilizer. The anionic surfactant sodium dodecyl sulfate (SDS, GFS Chemicals, Inc., Columbus, OH) was used as wetting agent and secondary stabilizer. Its critical micelle concentration (CMC) in water is 0.23% at ambient temperature. The solvent acetone (ACS reagent, $\geq 99.5\%$) and dichloromethane (Anhydrous, $\geq 99.8\%$) were purchased from GJ Chemical (Somerset, NJ, USA). A fine grade (GranuLac[®] 200; d_{50} : 27.7 μm) and a coarse grade (PrismaLac[®] 40; d_{50} : 321.1 μm) of lactose particles were donated by Meggle Pharma (Wasserburg, Germany) and used as water-soluble carriers for fluidized bed coating. PrismaLac[®] 40 is a

crystalline, free flowing powder. Fumed silica CAB-O-SIL[®] M-5P was purchased from Cabot Corporation (GA, USA) and used to dry-coat the fine carriers.

155 **2.2. Preparation of Drug Suspensions**

A schematic of the process used in the preparation of the drug suspensions and nanocomposite powder (NCMPs) is given in Fig. 1. Drug pre-suspensions (30%, w/v) were prepared by dissolving the desired amount of stabilizer(s) in 200 ml de-ionized water followed by addition of the drug powder as mixing continued. In this paper, unless
160 otherwise specified, the drug and stabilizer concentrations are weight concentrations with respect to water. Drug nanosuspensions were produced via wet stirred media milling (MicroCer, Netzsch, Exton, PA). The details of mill and milling conditions used in this study can be found in (Knieke et al., 2013; Knieke et al., 2015). Samples were taken from the outlet of the milling chamber for particle sizing. The suspensions were stored under
165 refrigerated conditions (at 8 °C) for 7 days to check the storage stability.

2.3. Preparation of Drug Nanocomposite Powders via Fluidized Bed Coating

The milled drug suspensions (120 g) prepared with 0.2 % SDS (H formulations) were sprayed within the same day or the day after milling onto 150 g dry-coated fine
170 carrier particles (GranuLac[®] 200) (see F1–F6 in Table 2) and large as-received carrier particles (PrismaLac[®] 40) (see L1, L2 in Table 2) in a fluidized bed apparatus (Mini-Glatt 9950, Glatt Air, Ramsey, NJ, USA) with a top spray configuration. The dry coating of the GranuLac[®] 200 particles with silica was carried out in an acoustic mixer (LabRAM, Resodyn Acoustic Mixers, Inc., Butte, MT, USA). The operating conditions for the dry

175 coating were the same as those used in (Knieke et al., 2015). The air pressure to atomize the nanosuspension was kept constant at 1 bar. The inlet fluidization air was pre-heated to 68°C. GranuLac[®] 200 and PrismaLac[®] 40 were fluidized at an inlet air pressure of 0.2–0.3 and 0.4–0.6 bar, respectively. The nanosuspensions were continuously sprayed onto the fine carrier particles at 0.25–0.35 mL/min and the large carrier particles at 0.70–0.75
180 mL/min. To avoid agglomeration of the carrier particles during the coating process, the relative bed humidity was kept below 25% for GranuLac[®] 200 particles by operating at low spray rate. The suspensions were mixed with a magnetic stirrer throughout the coating run to prevent sedimentation of the milled drug particles. The relative bed humidity was calculated based on the bed temperature, exhaust air temperature, and
185 exhaust air relative humidity that were measured during fluidized bed coating. The coated powder continued to fluidize and dry for additional 10 min after all the suspension was sprayed. The coated powders were tested for drug assay, particle size, and morphology and were subsequently used in the redispersion and dissolution tests.

190 **2.4. Characterization of the Suspensions and Nanocomposite Powders**

Particle size distributions (PSDs) of the drug suspensions after 150 min milling and after 7 days storage were measured with the laser diffraction device LS 13 320 (Coulter Beckman, Miami, FL). A sample of ~1 mL suspension taken from the exit of the milling chamber was dispersed in 5 mL of the stabilizer solution corresponding to the
195 formulation being milled using a vortex mixer (Fisher Scientific Digital vortex mixer, Model No: 945415, USA), which rotated at 1500 rpm for 1 min. The PSD was determined using the Mie theory at polarization intensity differential scattering (PIDS) of 40% with a

dispersant refractive index of 1.33 and the drug particle refractive index of 1.64 and 1.546 for ITZ and FNB, respectively.

200 Dry powders (as-received, dry coated, and drug nanocomposites) were analyzed by a Rodos/Helos laser diffraction system (Sympatec, NJ, USA). Approximately 1 g of a powder sample was placed on the sample chute of the Rodos dispersing system and the particle size was measured at a dispersion pressure of 0.5 bar for the as-received and dry coated powders and 0.1 bar for the NCMPs. In order to quantify the degree of
205 agglomeration of the carrier particles that occurred during the fluidized bed coating, the so-called **agglomeration ratio** was calculated from the size distributions of coated and uncoated particles (see (Chen et al., 2009a; Knieke et al., 2015) for details). The flow function coefficient (**FFC**), bulk density, and **angle of repose** of the as-received and the dry coated powders as well as the NCMPs were measured with the FT4 Powder
210 Rheometer (Freeman Technology, Tewkesbury, UK) and Powder tester (Hosokawa Micron Ltd., UK) (see (Knieke et al., 2015) for details).

The morphology of the drug nanoparticles and the NCMPs, cross-section of the NCMPs, and NCMPs after the redispersion testing was observed via scanning electron microscopy LEO 1530 SVMP (Carl Zeiss, Inc., Peabody, MA, USA). A carbon tape was
215 placed on SEM stub, the NCMPs were then placed on the carbon tape and SEM images were taken. For the suspension or sample from the redispersion test, a silicon chip was placed on top of the carbon tape and a drop of the sample was placed on the silicon chip. For M4H and M5H suspensions, a drop of the suspension was first diluted in 10 mL of DI water. The dilution reduced the particle concentration to minimize charging. The stub
220 with the liquid sample was put in a desiccator and allowed to dry overnight under

vacuum. All samples were then coated with carbon using BAL-TEC MED 020 (BAL-TEC AG, Balzers, Switzerland) to reduce possible charging effects during the imaging followed by SEM imaging.

To determine the drug content, ITZ composites (100 mg) (F1–F3, L1) and FNB
225 composites (300 mg) (F4–F6, L2) were dispersed in dichloromethane (10 ml) and
acetone (8 ml), respectively followed by sonication for 20 min. After sonication, they were
allowed to settle, and an aliquot was taken from the clear supernatant. For ITZ
composites, 0.1 ml aliquot was diluted by 5 ml dichloromethane. For FNB composites, 1
ml aliquot was diluted by 8 ml acetone. The diluted aliquots were further sonicated for 2
230 min to ensure homogeneous mixing and used for Ultraviolet (UV) measurement. The
absorbance of ITZ and FNB composites was measured at a wave-length of 260 and 350 nm,
respectively, by UV Spectrophotometer (Evolution 60S, Thermo Fisher Scientific, USA).
The absorbance was then converted into the drug concentration via established
calibration curves of absorbance versus concentration having linear range for ITZ: 0.002-
235 0.10 mg/ml and FNB: 0.06-1.5 mg/ml. Four replicates from each run were used to find
the mean drug content in the composites. This information along with the relative
standard deviation (RSD) is presented in Table 2.

2.5. Dissolution, UV imaging, and Redispersion of the NCMPs

240 A dissolution study was carried out using USP II apparatus (paddle method, Distek®
2100, North Brunswick, NJ, USA). NCMPs containing the equivalent of 48 mg of drug
(ITZ, FNB) were placed into 900 mL of 25 mM (7.2 mg/ml) SDS at $37 \pm 0.5^\circ\text{C}$ and
stirred at 50 rpm. To obtain a better differentiation for FNB composites (F4–F6),

additional dissolution testing was done using 10 mM (2.88 mg/ml) SDS solution. At 1, 2,
245 5, 10, 20, 30 and 60 min time points, 4 mL of sample was drawn manually and filtered
using a PVDF membrane type syringe filter with a nominal pore opening size of 0.1 μm
(see for example,(Cerdeira et al., 2010; Juenemann et al., 2011)). The amount of ITZ
and FNB dissolved were measured by UV at wavelengths of 260 and 290 nm,
respectively. The respective SDS solution was used as the baseline background for UV
250 measurements. The mean value and standard deviation of three replicates at each
dissolution time point were reported.

UV imaging was performed for ITZ composites (F3 and L1) using an Actipix
SDI300 dissolution imaging system (Paraytec Ltd, York, UK). Compacts were made by
weighing 6–8 mg of NCMPs (F3, L1) into a stainless steel cylinder (inner diameter: 2
255 mm) held in a manual press (Actipress, Paraytec Ltd.). A Quickset MINOR torque
screwdriver (Torqueleader, M. H. H. Engineering Co. Ltd., UK) was used to compress
the composite samples at a constant torque of 20 cN·m for 30 s. The compacts were used
for the UV imaging during the drug dissolution. The syringe pump (model: Fusion 200,
Chemyx Inc., USA) was used for infusion of dissolution medium (7.2 mg/mL SDS)
260 through the quartz channel-flow cell and standard solutions for construction of calibration
curves. The flow rate of dissolution medium was at 0.2 mL/min. The selected imaging
area was $9 \times 7 \text{ mm}^2$ and the pixels ($7 \times 7 \mu\text{m}^2$) were binned horizontally in sets of 10
(10 $\times$ 1 pixel binning). UV imaging was performed at 253.7 nm (light path 4.0 mm).
Images were recorded with 2.8 frames per s and analyzed using Actipix D100 software
265 version 1.8 (Paraytec). Pixel intensity was converted into absorbance using the Actipix
software, which allows the concentration of the drug substances to be determined as a

function of position and time by the use of calibration curves. All experiments were carried out at a temperature of $37 \pm 0.5^\circ\text{C}$ and in triplicate. The intrinsic dissolution rate (IDR) at one minute intervals was calculated using the software. The software calculates
270 IDR from the absorbance values at each pixel row within the quantification region located downstream from the dissolving sample surface combined with the corresponding flow rate profile (defined by the software), the surface area of the drug compact, the molar mass and the molar absorptivity of ITZ (determined from calibration curves). The calculated dissolution rates were subsequently used by the software to compute the
275 cumulative amount of drug dissolved(Boetker et al., 2011; Gordon et al., 2013).

In order to evaluate the redispersibility of the NCMPs, particle size measurements were carried out after a distinct redispersion procedure mentioned below and the PSD was compared with that of the initial nanosuspensions similar to (Bhakay et al., 2014a). About 1 g of the NCMPs was weighed and dispersed in 30 mL 7.2 (F1–F3, L1) or 2.88 mg/mL
280 SDS (F4–F6, L2) in a 40 mL beaker and stirred with a laboratory stirrer (CAT R18, Scientific Instrument Center Limited, Winchester, UK) at a speed of 110 rpm for 2 min. Samples were agitated for 2 min to determine if the drug particles are released from the NCMPs fast. Approximately 0.5 mL aliquot of this suspension was taken while stirring and was added to the sample cell of Beckmann Coulter LS13320 for size measurement.
285 The redispersion media and SDS concentration was kept the same as dissolution media to mimic redispersibility of NCMPs during dissolution. However, to minimize drug dissolution effect and for the sake of stringent discrimination of the potential for full nanoparticle size recovery, small volume of redispersion media (30 mL) and sampling at 2 min was chosen (Bhakay et al., 2014a).

290 3. Results and Discussion

3.1. Physical Stability of the Drug Suspensions

Highly concentrated (30%) suspensions of BCS Class II drugs Itraconazole and Fenofibrate (FNB) were prepared via WSMM using HPMC–SDS combination as the stabilizer system. The desired amount of HPMC (1.25, 2.5, and 5%) and SDS (0.05 and 295 0.2%) were added initially (see Table 1). A low amount of SDS (0.05%) was used before milling to minimize foaming–clogging and ensure proper wetting during milling in all milling experiments. The maximum SDS concentration used was 0.2% (H formulations in Table 1), which is below the critical micelle concentration (CMC) of 0.23%, because higher SDS concentration could have significant deleterious effects. Richetti and 300 Kekicheff (Richetti and Kekicheff, 1992) found that the presence of charged micelles could facilitate agglomeration of particles in a suspension. Moreover, with increasing SDS concentration above the CMC, the water-solubility of drug increases significantly (Ghosh et al., 2011; Jamzad and Fassihi, 2006), which could facilitate Ostwald ripening (Ghosh et al., 2011).

305 Table 1 presents the milling results for various suspension formulations (M1–M6) and the impact of the HPMC concentration at 0.05% and 0.2% SDS. In general, Table 1 shows that for ITZ and FNB an increase in HPMC concentration reduced the extent of aggregation and enhanced the suspension stability (M1–M6). As the primary particles become finer and finer during milling, the surface area and the number concentration of 310 the particles increase leading to an increase in the collision frequency and a decrease in inter-particle distances. These changes upon further milling can cause an increase in the agglomeration rate if the particles are not protected properly against agglomeration

(Bilgili et al., 2004; Sommer et al., 2006). This was indeed the case with 1.25 or 2.5% HPMC concentrations as the newly created surfaces were not adequately covered by the relatively small amount of HPMC along with smaller amount of SDS. The SEM images (Figs. 2a, b, c, g) showed primary particles with sizes in the range of 50–200 nm. However, particle size distribution after milling (Table 1), as measured via laser diffraction, indicated larger particles, which confirms insufficient suspension stability and associated agglomeration of the ITZ or FNB particles due to turbulent shear and Brownian motion during the milling. Higher HPMC concentrations, in particular at level of 5%, help to reduce the particle size drastically by allowing the de-agglomeration of the agglomerates and stabilization of the newly formed particles to a certain extent. HPMC reduces agglomeration through steric stabilization. The HPMC adsorption on FNB nanoparticles follows Langmuir isotherm, which describes the enhanced steric stabilization at higher HPMC concentration (Knieke et al., 2013). 1.25 and 2.5% HPMC did not lead to complete surface coverage of the drug nanoparticles, and could not effectively prevent agglomeration through steric mechanism, whereas 5% HPMC provides almost full surface coverage according to the Langmuir isotherm. This is also confirmed from primary particle size in SEM images (Figs. 2e, f). Additionally, the particles might have been protected against agglomeration more effectively due to a synergistic stabilization action of the HPMC–SDS combination although as discussed next, higher SDS amounts help further.

The stability condition is further improved with the increase of SDS concentration. A comparison between the milling results with 0.05 and 0.2% surfactant at the same polymer concentration shows decrease of particle size as presented in Table 1. In

fact, for FNB, 2.5% HPMC may be sufficient but as will be seen later from redispersion results, higher HPMC even with 0.2 % SDS is necessary. Overall, in the low submicron range, where the milling response is mainly governed by the quality of stabilization, an increase of SDS concentration (yet smaller than the CMC) facilitates a considerable reduction in particle size. This can be partly explained by enhanced wetting of the particles in the presence of SDS: more effective and faster deagglomeration took place because the stabilizer solution with SDS can penetrate into the small pores of the agglomerates and wet both the primary particles and the agglomerates faster(Kissa, 1999). The SEM images (Figs.2d, f, h) confirm the particle size obtained in Table 1. The particle sizes of the suspension after storage for 7 days exhibited size increase during the storage for ITZ with 1.25 and 2.5 % HPMC even having 0.2% SDS (see Table 1). It is noted that the 7 day stability was found to be rather poor and hence was not quantified for suspensions with 0.05% SDS. This increase in size during 7-day storage could be attributed to Brownian agglomeration of the particles caused by insufficient stabilization. It appears that 5%HPMC–0.2%SDS (M3H) and 2.5% HPMC–0.2% SDS (M5H) combination in the formulation was sufficient to fully stabilize the ITZ and FNB suspensions, respectively during the milling and storage.

3.2. Core-Shell Type NCMPs Production via Fluidized Bed Coating

Drug carrying NCMPs were prepared in a fluidized bed coater via spraying of drug suspensions onto carriers, GranuLac[®] 200 and PrismaLac[®] 40. GranuLac[®] 200 was dry-coated with nanosized hydrophilic silica (M-5P) to reduce powder cohesion, enhance flow properties and fluidization characteristics. NCMPs F1–F6 were prepared using

GranuLac[®] 200, whereas L1 and L2 were prepared using PrismaLac[®] 40. Table 2 presents
360 the **agglomeration ratio**, nanocomposite powder size, the mean drug assay, and flow
properties (bulk density, angle of repose, and **FFC**). The drug content of the composites
ranged from 12% to 16%, with most composites having a relative standard deviation
(RSD) <6%, which is satisfactory as per the United States Pharmacopoeia standards. The
FFC of the majority of the composite powder was >10, which indicates that the
365 composite powder is free flowing. For ITZ composites, higher polymer loading led to
improved powder flowability (higher **FFC**), and all ITZ composites were characterized as
easy flowing (Schulze, 2008). The **angle of repose** of composites is in the range 37–42°,
which also suggests good flow properties. Along with these favorable flow properties, the
bulk density of composites was in the range 0.49–0.65 g/cm³, which allows for direct
370 compression of the composite powder for a tablet dosage form (Jallo et al., 2012). Thus
the composites have excellent packing and compression properties.

The variations of polymer loading of the sprayed suspension (M1H–M6H) play
an important role in the agglomeration behavior of the composite powders. As can be
seen in Table 2, an increase in the polymer loading in the composite due to increase of
375 polymer concentration in the suspension, caused an increase in **agglomeration ratio**. A
higher polymer concentration in the drug suspension led to a higher viscosity which
results in higher viscous dissipation of the kinetic energy of the colliding carrier particles
and larger droplet sizes at the same atomization conditions (Bilgili et al., 2011; Chen et
al., 2009b; Hemati et al., 2003), and thus, to more pronounced agglomeration during the
380 coating process. Although an increase of **agglomeration ratio** was observed for high
polymer loading, the d_{50} was still well under 100 µm for GranuLac[®] 200 coated

composites powders. It is also pointed out that the agglomeration ratio followed here (Chen et al., 2009b) is a rather strict measure of agglomeration, which accounts for the shift in the entire PSD in contrast to conventional size ratio enlargement measured in terms of particle d_{50} . The median particle size of PrismaLac[®] 40 increased from 321 μm to 380–385 μm due to coating and some low extent of agglomeration.

SEM images of dry-coated GranuLac[®] 200, as-received PrismaLac[®] 40, and the composite powders were taken in order to observe the morphology of carrier particles, coating uniformity and particle structure of the composite powders. Fig. 3a shows the SEM images of the GranuLac[®] 200 particles after dry-coating with silica. GranuLac[®] 200 particles have irregular shapes (Fig. 3a) due to milling in a dry grinding step by the manufacturer and have rather wide size distribution. Clearly, the as-received GranuLac[®] 200 particles cannot be fluidized without being dry coated with M-5P silica. The presence of silica nanoparticles on a single dry coated GranuLac[®] 200 particle was confirmed via a higher magnification SEM (see Fig. 3b). PrismaLac[®] 40 particles are granulated lactose particles that were of narrow sieve-cut (see Fig. 3c) and have excellent flowability. The SEM images of the coated GranuLac[®] 200 particles for ITZ (F3), FNB (F6), and coated PrismaLac[®] 40 particles for ITZ (L1) are given in Figs. 3d–i. The discreteness of the GranuLac[®] 200 and PrismaLac[®] 40 particles were preserved after coating (see Figs. 3d, f, h), which suggests that the extent of agglomeration was indeed low. Some finer spherical spray-dried particles were observed in the SEM (Figs. 3d, h). A closer view of the corresponding coated particle surfaces indicates the presence of drug nanoparticles (Figs. 3e, g, i). The lack of smoothness in core particles led to a non-homogenous coating of the suspensions with a variable thickness. The coating layer consisting of drug

405 nanoparticles appears to surround the core GranuLac[®] 200 and PrismaLac[®] 40 particles (core-shell morphology).

3.3. Drug Dissolution from NCMPs

The main motivation for producing nanoparticles of poorly water-soluble drugs is to
410 improve their dissolution rate. Temporal evolution of drugs (ITZ, FNB) dissolved from the NCMPs (coated on GranuLac[®] 200) during the USP II dissolution test are shown in Fig. 4. In general, Fig. 4 illustrates that wet-milled drugs embedded in the composites (NCMPs) prepared via fluidized bed coating dissolved faster than as-received drugs. For all drug composites, immediate drug release (80% dissolved within 20 min) was realized
415 for most of the formulations. Spraying the nanosuspension onto the carrier particles led to the formation of core-shell type nanocomposite microparticles, whose structure is clearly quite different from the structure of the as-received drug. The fine carrier particles offer a high surface area which allows thin coating layers (discussed further in the next section) where drug particles were embedded. During dispersion of the core-shell composite
420 powder into the dissolution medium, a large amount of drug particles is wetted at the same time which can immediately start dissolving from the shell.

A comparison of the ITZ and FNB dissolution profiles obtained from discriminating test methods presented in Figs. 4a and respectively shows that an increase in polymer loading led to faster dissolution, which can be explained by the smaller drug
425 particle size in the precursor milled suspensions (refer to Table 1) as well as faster and more complete recovery of the drug nanoparticles during the dissolution. Moreover, when HPMC concentration was too low, hard aggregates might form during the drying

process, causing slow and incomplete nanoparticle recovery during the dissolution. For FNB, there is no difference observed in dissolution profiles (see Fig.4b) of composites (F4–F6) that have different polymer concentration in their shells, which originated from the polymer concentration difference in the milled suspensions sprayed (M4H–M6H). This might be due to the dissolution media used (7.2 mg/ml SDS solution), which is well above the critical micellar concentration (CMC, 2.3 mg/ml) (Jamzad and Fassihi, 2006). Such high SDS level led to very fast dissolving of FNB due to the micellar solubilization. Since FNB has very low aqueous solubility, such high concentration of SDS is suggested in order to dissolve 48 mg of FNB. However, such high level of SDS does not allow for discriminating the impact of different HPMC levels in FNB composites (F4–F6) as compared with the redispersion testing. The dissolution profiles in Fig. 5c were obtained at a lower SDS concentration (2.88 mg/ml), albeit still slightly above the CMC value, which allowed for the discrimination of the faster dissolution at higher polymer loading and revealed a trend similar to that observed for ITZ. It is noted that as the solubility was not significantly increased, the maximum dissolution achieved was 81%, but the dissolution profiles were discriminated sufficiently. A similar observation was made in other studies, e.g., as in Shah et al. (2016), where dissolution of spray-dried griseofulvin powders was modulated by varying the non-sink conditions to quantitatively discriminate the impact of various formulations, although maximum dissolution was below 60%.

To gain further insight into the impact of the polymer loading, separate redispersion tests were performed in which NCMPs were redispersed in the discriminating SDS media under stirring for 2 min and resulting particle size distributions

were measured. However, it is critical to note that redispersion tests with 30 mL SDS medium were designed to minimize drug dissolution within 2 min with the objective of measuring particle sizes, unlike the dissolution tests with 900 mL SDS medium. A comparison of the redispersed particle sizes (after 2 min) in Table 3 for the formulations F1–F6 suggests that most drug nanoparticles were not recovered from the composite particles, except for formulations with 5% HPMC ($d_{50} < 0.5 \mu\text{m}$). The smaller d_{50} and d_{90} values after redispersion tend to correlate with faster dissolution (Figs.4a and 4c). As compared with previous investigations of the redispersion from drug nanocomposites prepared via fluidized bed coating (Bhakay et al., 2014a; Bhakay et al., 2013), the redispersion from the nanocomposites in this study appears to be relatively poor, which can be mainly explained by the extremely high drug loading (theoretical values of 85–95%) and low polymer:drug mass ratios in the shell of the nanocomposites. For example, the dried shell from 2.5% HPMC–0.2% SDS suspension had over 91% drug and hence high hydrophobicity of the drug appears to retard redispersion and consequently, dissolution. Moreover, when HPMC:drug mass ratio is low as in all these formulations, hard aggregates might have formed during the drying process, causing slow and incomplete nanoparticle recovery during the redispersion/dissolution. Nonetheless, both the redispersion and dissolution tests show that higher HPMC level along with 0.2 % SDS provide faster drug release for both drugs. In summary, fast dissolving 60 μm or smaller freely flowing composites powders can be produced by fluid bed coating of wet-milled poorly water soluble drugs on nano-silica coated GranuLac[®] 200.

3.4. Fluidized Bed Coating on Fine Carrier vs. Large Carrier Particles

475 Next, the advantages, especially fast drug dissolution, of fluidized bed coating on fine carrier (GranuLac[®] 200) as compared with large carrier (PrismaLac[®] 40) are assessed. For this purpose, the same amount of drug suspensions (M3H and M5H) was sprayed on GranuLac[®] 200 and PrismaLac[®] 40, yielding the composites F3 and F5 and L1 and L2, respectively. Suspension M5H was chosen instead of M6H as there is no particle size
480 difference observed between them (Table 1). This also helps to minimize agglomeration of NCMPs. The dissolution profiles obtained from USP-II dissolution apparatus for large composites L1 and L2 were compared with dissolution profiles for fine composites F3 and F5 (Fig. 5a for ITZ and Fig. 5b for FNB). Based on the results from previous section shown in Figs. 4b and 4c, lower level of SDS (discriminating medium) was used for FNB
485 composites (Fig. 5b). As may be seen, the fine core-shell nanocomposite powder with GranuLac[®] 200 exhibited significantly faster drug dissolution than the composite powder with PrismaLac[®] 40. Comparing the behavior of two drugs, it is apparent that the impact of the carrier size is more dominant in case of ITZ, which is significantly less soluble than FNB, for which a more discriminatory dissolution buffer was required for
490 identifying the carrier size impact. A comparison of the redispersed particle sizes (after 2 min) in Table 3 for the formulations F3–L1 and F5–L2 also corroborate the dissolution results since L1 and L2 have much larger particles as compared to F3 and F5 respectively. While d_{50} of the redispersed L2 composites was slightly lower than that of the redispersed F5 composites, the volume-mean diameter for L2 (17.8 μm) was much higher than that
495 for F5 (6.99 μm), which also explains the observed dissolution behavior. These results support the main hypothesis that smaller carrier owing to their higher surface area per

unit mass and corresponding thinner drug-polymer shells, provide much faster drug release than the larger carrier with smaller surface area per unit mass and corresponding thicker drug-polymer shells.

500 Traditional USP II dissolution testing method is based solely on bulk solution concentration measurements as a function of time. The lack of real-time information may preclude the possibility for understanding the behavior of a specific formulation. The UV imaging instrument is a novel emerging technique that can be used to visualize spatial variation of the drug solution concentration around a given solid sample in real time (Boetker et al., 2011; Østergaard et al., 2010; Qiao et al., 2013). In this work, UV imaging was utilized to gain further insights and find corroborating evidence for the impact of the carrier size. It is used for the *qualitative assessment* of differences in dissolution rates for large carrier and fine carrier coated composites. Fig. 6a shows selected UV absorbance maps for the dissolution of ITZ coated on GranuLac[®] 200 particles (F3) and PrismaLac[®] 40 particles (L1). Figs. 6b and 6c show cumulated amount of dissolved drug and intrinsic dissolution rate (IDR), respectively. Intense color in absorbance map represents high dissolution of drug. The absorbance maps in Fig. 6a show that ITZ dissolved faster from F3 composite than from L1 composite. The composite prepared with the fine carrier had higher cumulated amount of dissolved drug and IDR 510 than both that prepared with the large carrier and the as-received drug (Figs. 6b,c). The wide variation observed in Figs. 6b,c seems to be a characteristic of the channel-flow cell set-up and the method, and has been observed by other researchers, albeit to different extent (Boetker et al., 2011; Gordon et al., 2013). Østergaard et al. (2010) cautioned that 515 this instrument is very sensitive to movements, vibrations, and residual flow and

520 turbulence within the channel-flow cell. In addition, the drug content variability and porosity variation of the compacted samples ($n = 3$) used in this study could have contributed to the wide variability observed here. Noting that we have only used the UV imaging for a qualitative assessment, results overall support the hypothesis that finer carriers can enhance drug release of very hydrophobic and poorly water soluble drugs.

525 Since the difference in the dissolution behavior may be largely attributed to the shell film thickness, here it is estimated for both large and fine carriers. Given a mass of solid in the coating layer and a size of core particle, film thickness can be predicted based on mass balance and spherical particles assumption, as in Dewettinck and Huyghebaert (Dewettinck and Huyghebaert, 1998).

$$530 \quad d_c = \left(\left(\left(\frac{\rho_{carrier}}{\rho_{cm}} \right) \cdot \left(\frac{m_{cm}}{m_{carrier}} \right) + 1 \right)^{\frac{1}{3}} - 1 \right) \cdot \left(\frac{D_{carrier}}{2} \right) \quad (1)$$

where d_c is coating thickness (μm), $\rho_{carrier}$ is density of carrier material (kg/m^3), ρ_{cm} is density of coating material (kg/m^3), $m_{carrier}$ is mass of carrier material (g), m_{cm} is mass of deposited coating material (g), and $D_{carrier}$ is diameter of the carrier material (μm).

Equation (1) indicates that the coating thickness (d_c) is dependent on the carrier material diameter as expected. In this study, $\rho_{carrier}$, ρ_{cm} , $m_{carrier}$, and m_{cm} remained constant. 535 The theoretical coating thickness for GranuLac[®] 200 particles (F3) and PrismaLac[®] 40 particles (L1) was calculated using Eq. (1) considering $\rho_{carrier} = 1.52$ and $1.544 \text{ g}/\text{cm}^3$ for GranuLac[®] 200 and PrismaLac[®] 40 respectively, $\rho_{cm} = 0.98 \text{ g}/\text{cm}^3$, $m_{carrier} = 150 \text{ g}$, and $m_{cm} = 31.24 \text{ g}$ (considering 120 g suspension sprayed). The calculated coating thicknesses 540 are $1.35 \mu\text{m}$ for GranuLac[®] 200 particles (F3) and $15.93 \mu\text{m}$ for PrismaLac[®] 40 particles (L1). The calculated thickness suggests that the composite L1 coating layer is about

twelve times as thick as the composite F3 coating layer. The coated particles of F3 and L1 were investigated under SEM to observe coating thickness and surface. Figs.7a and c present typical cross-sectional images of the composites and Figs.7b and d present surface images that show the presence of ITZ nanoparticles. The coating thickness difference observed in SEM for F3 and L1 composites was in good agreement with the theoretically predicted thickness (Figs.7a and c).

The coating layer thickness analysis and corresponding SEM imaging explain the slower dissolution rates for larger carriers due to thicker shell. The thicker shell also contributed to the poorer redispersion as evident from Table 3. Overall, thinner shell breaks down faster so that even highly hydrophobic ITZ nanoparticles get dispersed fairly rapidly. In contrast, thicker shell of larger carriers does not break down readily and redispersion PSD suggests presence of rather large chunks. The differences in their morphology were further assessed qualitatively via SEM imaging of the redispersed suspensions. Fig.8 shows SEM images of ITZ and FNB coated fine and large carrier composites after redispersion. Clusters of nanoparticles as well as fragments of the coating shell and shrunken undissolved composites were found for L1 and L2 composites (see Figs.8c, g). As GranuLac[®] 200 and PrismaLac[®] 40 are freely water soluble and dissolved within a minute or less, with a shell containing about 85% hydrophobic drug particles the core dissolution will be delayed. Depending on the coating quality on different particles, some core-shell NCMPs (same formulation) will mostly dissolve releasing nanoparticles; others will shrink to smaller sizes. The broken shell and shrunken undissolved composites are around few μm (see Figs.8c, g) and consist of ITZ or FNB nanoparticles with sizes of around 200 nm or less (see Figs.8d, h). Only a very little

565 amount of individual nanoparticles is dispersed in the surrounding medium. Most of them
stick together in the dense coating shell without being wetted by SDS solution. On the
other hand, excellent wettability of the fine nanocomposite particles due to high specific
surface area along with minimal hard aggregation of the drug nanoparticles explains the
fast redispersibility imparted by fine nanocomposites.

570

4. Summary and Conclusions

The impact of the size of the water-soluble carrier, i.e., core particle, on dissolution
behavior of poorly water-soluble drugs from their core-shell nanocomposite micro-
particles was investigated. High drug loaded (30%) stable nanosuspensions of two BCS
575 class II drugs, Itraconazole and Fenofibrate, were produced via wet media milling using
HPMC and SDS as stabilizers. It was found that while sufficient yet below CMC, 0.2 %
SDS is critical for stability, higher HPMC loading led to finer milled drug particle
sizes. Physical stability of drug suspension was also improved with the increase of HPMC
loading. The nanosuspensions were then incorporated into a thin soluble shell of the
580 core-shell nanocomposite powders via fluidized bed coating on fine dry-coated
GranuLac[®] 200 carrier particles (median particle sizes <50 μm). The suspensions were
also FB coated onto larger carrier particles of median size >300 μm (PrismaLac[®] 40). The
final composite micro-powders based on GranuLac[®] 200 were significantly smaller, i.e.,
significantly less than 100 μm, as compared to those prepared by conventional fluidized-
585 bed coating with PrismaLac[®] 40. The finer powders had very good bulk density and flow
properties that are suitable for sachet filling, capsule filling, and compression into tablets
in pharmaceutical industry. Better nanoparticle redispersibility and dissolution were

observed with the increase of HPMC loading for fine nanocomposites due to improved stabilization of the nanosuspensions and enhanced wettability of the shell. Moreover, the fine carrier particles offer a large surface area, which resulted in a thinner coating layer on carriers and subsequently faster dissolution and redispersion compared to thicker coating obtained due to large carriers. In-situ real-time dissolution imaging provided additional qualitative confirmation of improved dissolution. Overall, the hypothesis that greatly increased carrier surface area and corresponding thinner shell at the same drug loading formed using well-stabilized drug suspensions for finer carriers can significantly increase the dissolution rate was proven. The results suggest that use of finer carriers may be useful for achieving immediate release from highly hydrophobic drugs such as Itraconazole.

Acknowledgement

The authors gratefully acknowledge financial support for this work from National Science Foundation through award IIP-1312125.

References

- Afolabi, A., Akinlabi, O., Bilgili, E., 2014. Impact of process parameters on the breakage kinetics of poorly water-soluble drugs during wet stirred media milling: a microhydrodynamic view. *European Journal of Pharmaceutical Sciences* 51, 75-86.
- Azad, M., Arteaga, C., Abdelmalek, B., Davé, R., Bilgili, E., 2015 a. Spray drying of drug-swellable dispersant suspensions for preparation of fast-dissolving, high drug-loaded, surfactant-free nanocomposites. *Drug Development and Industrial Pharmacy* 41, 1617-1631.

- Azad, M., Afolabi, A., Bhakay, A., Leonardi, J., Davé, R., Bilgili, E., 2015 **b**. Enhanced physical stabilization of fenofibrate nanosuspensions via wet co-milling with a superdisintegrant and an adsorbing polymer. *European Journal of Pharmaceutics and Biopharmaceutics* 94, 372-385.
- 615 Basa, S., Muniyappan, T., Karatgi, P., Prabhu, R., Pillai, R., 2008. Production and in vitro characterization of solid dosage form incorporating drug nanoparticles. *Drug Development and Industrial Pharmacy* 34, 1209-1218.
- Bhakay, A., Azad, M., Bilgili, E., Dave, R., 2014a. Redispersible fast dissolving nanocomposite microparticles of poorly water-soluble drugs. *International Journal of Pharmaceutics* 461, 367-379.
- 620 Bhakay, A., Azad, M., Vizzotti, E., Dave, R.N., Bilgili, E., 2014b. Enhanced recovery and dissolution of griseofulvin nanoparticles from surfactant-free nanocomposite microparticles incorporating wet-milled swellable dispersants. *Drug Development and Industrial Pharmacy* 40, 1509-1522.
- 625 Bhakay, A., Davé, R., Bilgili, E., 2013. Recovery of BCS Class II drugs during aqueous redispersion of core-shell type nanocomposite particles produced via fluidized bed coating. *Powder Technology* 236, 221-234.
- Bilgili, E., Hamey, R., Scarlett, B., 2004. Production of pigment nanoparticles using a wet stirred mill with polymeric media. *China Particuology* 2, 93-100.
- 630 Bilgili, E., Rosen, L.A., Ko, J.S., Chen, A., Smith, E.J., Fliszar, K., Wong, G., 2011. Experimental study of fluidized bed co-granulation of two active pharmaceutical ingredients: an industrial scale-up perspective. *Particulate Science and Technology* 29, 285-309.
- 635 Boetker, J.P., Savolainen, M., Koradia, V., Tian, F., Rades, T., Müllertz, A., Cornett, C., Rantanen, J., Østergaard, J., 2011. Insights into the early dissolution events of amlodipine using UV imaging and Raman spectroscopy. *Molecular Pharmaceutics* 8, 1372-1380.
- Cerdeira, A.M., Mazzotti, M., Gander, B., 2010. Miconazole nanosuspensions: influence of formulation variables on particle size reduction and physical stability. *International Journal of Pharmaceutics* 396, 210-218.
- 640 Chen, Y., Yang, J., Dave, R.N., Pfeffer, R., 2008. Fluidization of coated group C powders. *AIChE Journal* 54, 104-121.

- Chen, Y., Yang, J., Mujumdar, A., Dave, R., 2009a. Fluidized bed film coating of cohesive Geldart group C powders. *Powder Technology* 189, 466-480.
- 645 Chen, Y., Yang, J., Dave, R.N., Pfeffer, R., 2009b. Granulation of cohesive Geldart group C powders in a Mini-Glatt fluidized bed by pre-coating with nanoparticles. *Powder Technology* 191, 206-217.
- Dewettinck, K., Huyghebaert, A., 1998. Top-spray fluidized bed coating: effect of process variables on coating efficiency. *LWT-Food Science and Technology* 31, 568-575.
- 650 Ghosh, I., Bose, S., Vippagunta, R., Harmon, F., 2011. Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth. *International Journal of Pharmaceutics* 409, 260-268.
- Gordon, S., Naelapaa, K., Rantanen, J., Selen, A., Mullertz, A., Ostergaard, J., 2013. Real-time dissolution behavior of furosemide in biorelevant media as determined by UV
- 655 imaging. *Pharmaceutical Development and Technology* 18, 1407-1416.
- Hemati, M., Cherif, R., Saleh, K., Pont, V., 2003. Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics. *Powder Technology* 130, 18-34.
- Jallo, L.J., Ghoroi, C., Gurumurthy, L., Patel, U., Davé, R.N., 2012. Improvement of flow
- 660 and bulk density of pharmaceutical powders using surface modification. *International Journal of Pharmaceutics* 423, 213-225.
- Jamzad, S., Fassihi, R., 2006. Role of surfactant and pH on dissolution properties of fenofibrate and glipizide—a technical note. *AAPS Pharmaceutical Science & Technology* 7, E17-E22.
- 665 Juenemann, D., Jantratid, E., Wagner, C., Reppas, C., Vertzoni, M., Dressman, J.B., 2011. Biorelevant in vitro dissolution testing of products containing micronized or nanosized fenofibrate with a view to predicting plasma profiles. *European Journal of Pharmaceutics and Biopharmaceutics* 77, 257-264.
- Kesisoglou, F., Panmai, S., Wu, Y., 2007. Nanosizing—oral formulation development
- 670 and biopharmaceutical evaluation. *Advanced Drug Delivery Reviews* 59, 631-644.
- Kim, C., 2004. Surface chemistry and colloids, *Advanced pharmaceutics, physicochemical principles*. CRC Press: Boca Raton, pp. 193–256.
- Kissa, E., 1999. *Dispersions: characterization, testing, and measurement*. CRC Press.

- 675 Knieke, C., Azad, M., Davé, R., Bilgili, E., 2013. A study of the physical stability of wet media-milled fenofibrate suspensions using dynamic equilibrium curves. *Chemical Engineering Research and Design* 91, 1245-1258.
- Knieke, C., Azad, M.A., To, D., Bilgili, E., Davé, R.N., 2015. Sub-100 micron fast dissolving nanocomposite drug powders. *Powder Technology* 271, 49-60.
- 680 Li, M., Azad, M., Davé, R., Bilgili, E., 2016. Nanomilling of Drugs for Bioavailability Enhancement: A Holistic Formulation-Process Perspective. *Pharmaceutics* 8, 17.
- Lindenberg, M., Kopp, S., Dressman, J.B., 2004. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *European Journal of Pharmaceutics and Biopharmaceutics* 58, 265-278.
- 685 Malamatari, M., Somavarapu, S., Bloxham, M., Buckton, G., 2015. Nanoparticle agglomerates of indomethacin: The role of poloxamers and matrix former on their dissolution and aerosolisation efficiency. *International Journal of Pharmaceutics* 495, 516-526.
- 690 Malamatari, M., Somavarapu, S., Taylor, K.M.G., Buckton, G., 2016. Solidification of nanosuspensions for the production of solid oral dosage forms and inhalable dry powders. *Expert Opinion on Drug Delivery* 13, 435-450.
- Merisko-Liversidge, E., Liversidge, G.G., Cooper, E.R., 2003. Nanosizing: a formulation approach for poorly-water-soluble compounds. *European Journal of Pharmaceutical Sciences* 18, 113-120.
- 695 Monteiro, A., Afolabi, A., Bilgili, E., 2013. Continuous production of drug nanoparticle suspensions via wet stirred media milling: a fresh look at the Reh binder effect. *Drug Development and Industrial Pharmacy* 39, 266-283.
- Möschwitzer, J., Müller, R.H., 2006. Spray coated pellets as carrier system for mucoadhesive drug nanocrystals. *European Journal of Pharmaceutics and Biopharmaceutics* 62, 282-287.
- 700 Napper, D.H., 1970. Colloid stability. *Industrial & Engineering Chemistry Product Research and Development* 9, 467-477.
- Noyes, A.A., Whitney, W.R., 1897. The rate of solution of solid substances in their own solutions. *Journal of the American Chemical Society* 19, 930-934.

- 705 Østergaard, J., Meng-Lund, E., Larsen, S.W., Larsen, C., Petersson, K., Lenke, J., Jensen, H., 2010. Real-time UV imaging of nicotine release from transdermal patch. *Pharmaceutical Research* 27, 2614-2623.
- Qiao, N., Wang, K., Schlindwein, W., Davies, A., Li, M., 2013. In situ monitoring of carbamazepine–nicotinamide cocrystal intrinsic dissolution behaviour. *European Journal of Pharmaceutics and Biopharmaceutics* 83, 415-426.
- 710 Richetti, P., Kekicheff, P., 1992. Direct measurement of depletion and structural forces in a micellar system. *Physical Review Letters* 68, 1951.
- Schulze, D., 2008. Powders and bulk solids: behavior, characterization, storage and flow. Springer Science & Business Media.
- 715 Shah, D.A., Patel, M., Murdande, S.B., Dave, R.H., 2016. Influence of spray drying and dispersing agent on surface and dissolution properties of griseofulvin micro and nanocrystals. *Drug Development and Industrial Pharmacy* 42, 1842-1850.
- Sommer, M., Stenger, F., Peukert, W., Wagner, N., 2006. Agglomeration and breakage of nanoparticles in stirred media mills—a comparison of different methods and models.
- 720 *Chemical Engineering Science* 61, 135-148.
- Yang, J., Sliva, A., Banerjee, A., Dave, R.N., Pfeffer, R., 2005. Dry particle coating for improving the flowability of cohesive powders. *Powder Technology* 158, 21-33.

List of Tables

Table 1	Particle size of various drug suspensions after milling and after 7 days storage.
Table 2	Properties of the nanocomposite (NCMPs) powders prepared with various milled suspensions via fluidized bed coating.
Table 3	Particle size statistics of the milled suspensions and redispersed NCMPs at 2 min.

Table 1

Particle size of various drug suspensions after milling and after 7 days storage

Drug	Milled suspension ID	Drug loading (%) ^a	HPMC (%) ^a	SDS (%) ^a	Particle size (after milling) (nm)			Particle size (after 7 days) (nm)		
					<i>d</i> ₁₀	<i>d</i> ₅₀	<i>d</i> ₉₀	<i>d</i> ₁₀	<i>d</i> ₅₀	<i>d</i> ₉₀
Itraconazole (ITZ)	M1L	30	1.25	0.05	262±7	2988±198	9652±176	—	—	—
	M1H			0.2	195±24	314±18	1407±69	209±5	349±9	1714±81
	M2L	30	2.5	0.05	164±8	502±24	1766±177	—	—	—
	M2H			0.2	118±1	179±3	287±7	121±0	187±1	307±3
	M3L	30	5	0.05	122±1	185±1	287±4	—	—	—
	M3H			0.2	121±2	172±1	241±1	123±3	173±2	243±3
Fenofibrate (FNB)	M4L	30	1.25	0.05	167±14	321±13	1569±675	—	—	—
	M4H			0.2	140±22	277±20	512±37	259±22	377±18	530±12
	M5L	30	2.5	0.05	153±16	273±15	464±10	—	—	—
	M5H			0.2	115±1	170±1	247±0	110±1	169±1	258±8
	M6L	30	5	0.05	107±4	220±11	411±12	—	—	—
	M6H			0.2	114±2	171±2	248±0	115±1	173±1	250±1

^a % w/v is with respect to DI water (200 mL).

Table 2

Properties of the nanocomposite (NCMPs) powders prepared with various milled suspensions via fluidized bed coating

NCMPs ID ^a	Milled suspension ID	Agglomeration ratio	Particle size of NCMPs d_{50}	Drug content and RSD in NCMPs	Bulk density	Angle of repose	FFC
		(%)	(μm)	(%) ^b	(g/cm^3)	($^{\circ}$)	
F1	M1H	13.4	35.5	15.7 (5.3)	0.60	40.2	4.7
F2	M2H	14.8	40.3	14.9 (4.0)	0.61	38.9	5.9
F3	M3H	16.7	55.3	14.8 (4.7)	0.53	37.3	9.2
F4	M4H	13.7	31.4	12.3 (5.3)	0.61	38.0	>10
F5	M5H	18.2	54.4	13.9 (3.3)	0.59	37.9	>10
F6	M6H	21.1	60.5	13.6 (7.0)	0.49	39.0	>10
L1	M3H	18.9	385.3	14.3 (6.9)	0.65	38.8	>10
L2	M5H	11.7	379.7	14.9 (2.0)	0.55	41.9	>10

^aFor F1–F6 drug suspension was coated on fine grade particles GranuLac[®] 200 whereas, for L1–L2 drug suspension was coated on large grade particles PrismaLac[®] 40.

^bw/w is the weight of drug with respect to the weight of NCMPs. %RSD is in parenthesis.

Table 3

Particle size statistics of the milled suspensions and redispersed NCMPs at 2 min

NCMPs ID	Milled suspension ID	Particle size of suspensions after milling (μm)		Particle size after redispersion ^a (μm)	
		d_{50}	d_{90}	d_{50}	d_{90}
F1	M1H	2.99	9.65	27.63	51.02
F2	M2H	0.50	1.77	29.40	52.40
F3	M3H	0.17	0.24	0.49	12.83
F4	M4H	0.28	0.51	17.60	33.37
F5	M5H	0.17	0.25	3.85	16.75
F6	M6H	0.17	0.25	0.29	6.86
L1	M3H	0.17	0.24	56.16	141.80
L2	M5H	0.17	0.25	2.21	49.84

^aRedispersion was done using 7.2 mg/mL SDS solution for NCMPs (F1–F3, L1) and 2.88 mg/mL SDS solution for NCMPs (F4–F6, L2)

List of Figures

Fig. 1.	Process flow diagram (schematic) for the production of core-shell drug nanocomposite powders using fine/large carrier particles (Figure does not represent true shape). Figure is not drawn to scale.
Fig. 2.	SEM images of the milled ITZ suspensions with: (a, b) 1.25 % HPMC (M1L, H), (c, d) 2.5 % HPMC (M2L, H), (e, f) 5% HPMC (M3L, H) and the milled FNB suspensions with: g) 1.25 % HPMC (M4H), h) 2.5 % HPMC (M5H). For ITZ, first image belongs to the milled suspension with 0.05% SDS and second image belongs to the milled suspension with 0.2% SDS.
Fig. 3.	SEM images of the (a) dry coated GranuLac [®] 200, (b) the surface of a dry-coated GranuLac [®] 200, c) as-received PrismaLac [®] 40, and drug coated NCMPs in the presence of 2.5% HPMC, 0.2% SDS: (d, e) ITZ coated on GranuLac [®] 200 (F3); (f, g) FNB coated on GranuLac [®] 200 (F6); (h, i) IND coated on GranuLac [®] 200 (F9); (j, k) ITZ coated on PrismaLac [®] 40 (L1). For each case, the second image was obtained at a higher magnification to show the drug nanoparticles/nanosilica on the surface.
Fig. 4.	Evolution of drug dissolved from the NCMPs (coated on GranuLac [®] 200) during the USP II dissolution test: (a) ITZ coated NCMPs (F1–F3) and (b, c) FNB coated NCMPs (F4–F6). Dissolution was done using 7.2 mg/mL SDS solution for (a, b) and 2.88 mg/mL SDS solution for (c).
Fig. 5.	Comparison of drug dissolved from the NCMPs: (a) ITZ coated on PrismaLac [®] 40 (L1) vs GranuLac [®] 200 (F3), (b) FNB coated on PrismaLac [®] 40 (L2) vs GranuLac [®] 200 (F5), during the USP II dissolution test. Dissolution was done using 7.2 mg/mL SDS solution for (a) and 2.88 mg/mL SDS solution for (b).
Fig. 6.	(a) Selected UV absorbance maps for the dissolution of ITZ coated on GranuLac [®] 200 particles (F3) and PrismaLac [®] 40 particles (L1). Cumulated amount of dissolved drug (b) and intrinsic dissolution rate (c) of as-received ITZ, ITZ coated on GranuLac [®] 200 particles (F3), and ITZ coated on PrismaLac [®] 40 particles (L1) in 7.2 mg/mL SDS as studied by UV imaging at 0.2 mL/min ($n=3$, mean $\pm$ SD).
Fig. 7.	SEM images of the coated (a), (b) GranuLac [®] 200 particles (F3) and (c), (d) PrismaLac [®] 40 particles (L1) that carry ITZ nanoparticles. (a) and (c) are cross-sectional images; (b) and (d) are images of the drug nanoparticles embedded in HPMC film on the surface.
Fig. 8.	SEM images of the drug composites after redispersion in SDS solution: (a–b) ITZ coated on GranuLac [®] 200 particles (F3); (c–d) ITZ coated on PrismaLac [®] 40 particles (L1); (e–f) FNB coated on GranuLac [®] 200 particles (F5); and (g–h) FNB coated on PrismaLac [®] 40 particles (L2).

Fig. 1. Azad et al. (2016), intended for *Int. J. Pharm.*

Process flow diagram (schematic) for the production of core-shell drug nanocomposite powders using fine/large carrier particles (Figure does not represent true shape). Figure is not drawn to scale.

Fig. 2. Azad et al. (2016), intended for *Int. J. Pharm.*

SEM images of the milled ITZ suspensions with: (a, b) 1.25 % HPMC (M1L, H), (c, d) 2.5 % HPMC (M2L, H), (e, f) 5% HPMC (M3L, H) and the milled FNB suspensions with: g) 1.25 % HPMC (M4H), h) 2.5 % HPMC (M5H). For ITZ, first image belongs to the milled suspension with 0.05% SDS and second image belongs to the milled suspension with 0.2% SDS.

Fig. 3. Azad et al. (2016), intended for *Int. J. Pharm.*

SEM images of the (a) dry coated GranuLac[®] 200, (b) the surface of a dry-coated GranuLac[®] 200, c) as-received PrismaLac[®] 40, and drug coated NCMPs in the presence of 2.5% HPMC, 0.2% SDS: (d, e) ITZ coated on GranuLac[®] 200 (F3); (f, g) FNB coated on GranuLac[®] 200 (F6); (h, i) ITZ coated on PrismaLac[®] 40 (L1). For each case, the second image was obtained at a higher magnification to show the drug nanoparticles/nanosilica on the surface.

(a)

(b)

(c)

Fig. 4. Azad et al. (2016), intended for *Int. J. Pharm.*

Evolution of drug dissolved from the NCMPs (coated on GranuLac®200) during the USP II dissolution test: (a) ITZ coated NCMPs (F1–F3) and (b, c) FNB coated NCMPs (F4–F6). Dissolution was done using 7.2 mg/mL SDS solution for (a, b) and 2.88 mg/mL SDS solution for (c).

Fig.5. Azad et al. (2016), intended for intended for *Int. J. Pharm.*

Comparison of drug dissolved from the NCMPs: (a) ITZ coated on PrismaLac® 40 (L1) vs GranuLac® 200 (F3), (b) FNB coated on PrismaLac® 40 (L2) vs GranuLac® 200 (F5), during the USP II dissolution test. Dissolution was done using 7.2 mg/mL SDS solution for (a) and 2.88 mg/mL SDS solution for (b).

Fig. 6. Azad et al. (2016), intended for intended for *Int. J. Pharm.*

(a) Selected UV absorbance maps for the dissolution of ITZ coated on GranuLac[®] 200 particles (F3) and PrismaLac[®] 40 particles (L1). Cumulated amount of dissolved drug (b) and intrinsic dissolution rate (c) of as-received ITZ, ITZ coated on GranuLac[®] 200 particles (F3), and ITZ coated on PrismaLac[®] 40 particles (L1) in 7.2 mg/mL SDS as studied by UV imaging at 0.2 mL/min ($n=3$, mean $\pm$ SD).

Fig.7. Azad et al. (2016), intended for intended for *Int. J. Pharm.*

SEM images of the coated (a), (b) GranuLac[®] 200 particles (F3) and (c), (d) PrismaLac[®] 40 particles (L1) that carry ITZ nanoparticles. (a) and (c) are cross-sectional images; (b) and (d) are images of the drug nanoparticles embedded in HPMC film on the surface.

Fig.8. Azad et al. (2016), intended for intended for *Int. J. Pharm.*

SEM images of the drug composites after redispersion in SDS solution: (a–b) ITZ coated on GranuLac[®] 200 particles (F3); (c–d) ITZ coated on PrismaLac[®] 40 particles (L1); (e–f) FNB coated on GranuLac[®] 200 particles (F5); and (g–h) FNB coated on PrismaLac[®] 40 particles (L2).

Graphical Abstract

Fast Dissolution of Poorly Water Soluble Drugs from Fluidized Bed Coated Nanocomposites: Impact of Carrier Size

USP II Dissolution of Fine Nanocomposite Powders

UV Imaging

Fine carrier Large carrier

Dissolution Improvement: Fine vs Large Carrier