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Fast dissolution of poorly water soluble drugs from fluidized bed coated nanocomposites: Impact of carrier size

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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 μm) as opposed to the traditional large carrier particles (>300 μm) 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 μm 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 μm lactose (GranuLac® 200) carrier particles or larger carrier particles of median size >300 μm (PrismaLac®40). The resulting finer composite powders (sub-100 μm) 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.

1. Introduction

The bioavailability of a large percentage (between 40% and 70%) of newly discovered drug compound 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, 2016) and core-shell nanocomposite microparticles (NCMPs) via fluidized bed coating onto inert excipient particles (Basa et al., 2008; Bhakay et al., 2014a,b; 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 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

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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 (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 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 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 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–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,b; 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., 2015a; Bhakay et al., 2014b, 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 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 loading 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 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 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 μm lactose (GranuLac® 200) to produce fine NCMPs. Fluidization of fine carriers was made possible through dry coating based particle surface modification with hydrophilic nano-silica (M-5P) via reduction of cohesion. To compare with fine carriers, large carrier particles of median size >300 μm (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., 2015a; Bhakay et al., 2014b, 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 methyl cellulose (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, ≥99.5%) and dichloromethane (Anhydrous, ≥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.

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 otherwise specified, the drug and stabilizer concentrations are weight concentrations with respect to water.