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Redispersible fast dissolving nanocomposite microparticles of poorly water-soluble drugs

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ABSTRACT

Enhanced recovery/dissolution of two wet media-milled, poorly water-soluble drugs, Griseofulvin (GF) and Azodicarbonamide (AZD), incorporated into nanocomposite microparticles (NCMPs) via fluidized bed drying (FBD) and spray-drying (SD) was investigated. The effects of drying method, drug loading, drug aqueous solubility/wettability as well as synergistic stabilization of the milled suspensions on nanoparticle recovery/dissolution were examined. Drug nanoparticle recovery from FBD and SD produced NCMPs having high drug loadings was evaluated upon gentle redispersion via optical microscopy and laser diffraction. During wet-milling, hydroxypropyl cellulose (HPC) alone stabilized more wettable drug (AZD) nanoparticles with slight aggregation, but could not prevent aggregation of the GF nanoparticles. In contrast, well-dispersed, stable nanosuspensions of both drugs were produced when sodium dodecyl sulfate (SDS) and HPC were combined. The FBD and SD NCMPs without SDS exhibited incomplete nanoparticle recovery, causing slower dissolution for GF, but not for AZD, likely due to higher aqueous solubility/wettability of AZD. For high active loaded NCMPs (FBD ~50 wt%, SD ~80 wt%) of either drug, HPC–SDS together owing to their synergistic stabilization led to fast redispersibility/dissolution, corroborated via optical microscopy and particle sizing. These positive attributes can help development of smaller, high drug-loaded dosage forms having enhanced bioavailability and better patient compliance.

1. Introduction

Poor aqueous solubility has been a major issue in achieving adequate oral bioavailability for a large percentage of newly discovered drug compounds (Kesisoglou et al., 2007). Size reduction of drug crystals increases the specific surface area, which can increase the dissolution rate of drugs according to the Noyes–Whitney equation (Noyes and Whitney, 1897). Wet stirred media milling is a robust process and has been commonly used to produce drug nanoparticles with desired drug loadings (Bruno et al., 1996; Muller and Peters, 1998; Bilgili and Afolabi, 2012). Nanoparticles show a strong tendency to aggregate due to enhanced Brownian motion, relatively high surface energy, and large specific surface area (Gupta and Kompella, 2006). Therefore, steric, electrostatic or a combination of both stabilizing mechanisms can be used during wet media milling to prevent aggregation and to stabilize the nanoparticles during storage (Kim, 2004). Combined use of polymers and anionic surfactants is known to have synergistic stabilization effects on the nanosuspensions (Ryde and Ruddy, 2002; Gupta and Kompella, 2006). In spite of the use of stabilizers, nanoparticle aggregation and particle size growth by Ostwald ripening may still take place gradually upon prolonged storage. To mitigate these issues and to meet high patient/clinical demand for solid dosage forms, nanosuspensions are usually converted into dry nanocomposite microparticles (NCMPs), which can be subsequently compressed into tablets or filled into capsules.

Spray drying (SD), freeze drying, and granulation/coating in fluidized bed (Ryde and Ruddy, 2002; Lee, 2003; Abdelwahed et al., 2006; Van Eerdenbrugh et al., 2008; Niwa et al., 2011; Bhakay et al., 2013; Cerdeira et al., 2013) have been widely used to convert nanosuspensions into nanocomposite microparticles and finally into various solid dosage forms. However, any form of drying of the nanosuspensions generally causes the nanoparticles to aggregate due to liquid removal leading to loss of the large surface area of nanoparticles (Lee, 2003). Lee (2003) and Bhakay et al. (2013) observed that due to aggregation during the drying processes, the drug nanoparticles formulated with a polymer, hydroxypropyl cellulose (HPC) as a dispersant, were not recovered fully and quickly from the NCMPs after redispersion of the powders in water. To overcome this issue, a significant amount of water-soluble dispersants/cryoprotectants such as sugars (lactose, trehalose, sucrose), sugar alcohols (Mannitol, xylitol), or cyclodextrins are added to the suspensions before drying for effective recovery of nanoparticles from the NCMPs (Schwarz and Mehnert, 1997; Konan et al., 2002; Ryde and Ruddy, 2002; Van Eerdenbrugh et al., 2008; Kim and Lee, 2010). Unfortunately, the increase in dispersant loading has a

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negative effect on the drug loading; hence, dispersant type/loading must be selected in such a way to ensure fast redispersibility/drug dissolution while still maintaining high drug loading in the NCMPs.

Recent studies have shown that drug nanoparticles were completely recovered from nanocomposite microparticles (NCMPs) prepared via fluidized bed-drying (Basa et al., 2008; Bhakay et al., 2013) or spray-drying (Niwa et al., 2011; Cerdeira et al., 2013) when a combination of polymer such as HPC, polyvinylpyrrolidone (PVP), and hydroxypropylmethyl cellulose (HPMC) with an anionic surfactant, sodium dodecyl sulfate (SDS), was used. Niwa et al. (2011) studied the effects of using a combination of PVP with SDS on the redispersion/dissolution of phenytoin nanoparticles from spray-dried NCMPs with/without Mannitol; however, they did not consider formulations with PVP alone or emphasize the effects of drug loading in NCMPs which changed with/without the addition of Mannitol. Basa et al. (2008) reported fast redispersion/dissolution of ketoconazole nanoparticles from fluidized bed granules that were formulated with a combination of polymer with SDS, but did not present a comparative analysis of the synergistic effects of the polymer with SDS. Bhakay et al. (2013) investigated the recovery of the GF nanoparticles from NCMPs, formulated with/without surfactants, and examined the synergy between HPC and SDS by considering the importance of redispersion in water as well as redispersion conditions. Their work compared various degrees of agitation/shear during redispersion tests in order to identify most suitable method that can easily discriminate between different formulations in terms of ability to recover nanoparticles from dry NCMPs. However, they did not assess the effects of drug loading, aqueous solubility/wettability of drugs, and the drying method either on the redispersion or on the dissolution. The effects of drug loading were addressed by Bose et al. (2012) by increasing the drug loading from 10% to 20% in fluidized bed granules, which slowed the dissolution rate of the drug from NCMPs formulated with HPMC and TPGS (non-ionic surfactant). It is noted that all of the above studies used a single drying method.

Besides formulation/drug parameters mentioned above, different drying processes can affect the morphology of the NCMPs and their redispersibility. Most studies on the recovery of drug nanoparticles from spray-dried (Lee, 2003; Niwa et al., 2011), fluidized bed-dried (Basa et al., 2008; Bhakay et al., 2013), freeze-dried (Abdelwahed et al., 2006) and spray-granulated (Bose et al., 2012) dry powders used a single drying method. On the other hand, Kim and Lee (2010) compared the effects of three drying methods namely vacuum, convective and freeze drying, on the recovery of five poorly water-soluble drug nanoparticles formulated with HPC and polymeric dispersants such as carrageenan, gelatin, alginic acid after drying. However, they did not examine the subsequent effects on the dissolution profiles of these powders. Bourezg et al. (2012) compared the effects of fluidized bed drying, spray drying, and freeze drying on the redispersibility of lipid nanoparticles containing the drug, spirinolactone, and their dissolution. However, the drug loading in the dried NCMPs was low (~2.3%, w/w) which was limited by the drug solubility in the lipid, and also drug was not in the form of nanocrystals. Overall, these studies provide many useful insights by examining one or more important aspects, but also point to a need for comprehensive assessment of the combined effects of drug loading, drying method, aqueous drug solubility/wettability, and synergistic effects of polymer with anionic surfactant on the redispersion/dissolution of drug nanoparticles, which is the subject of the current paper. To be specific, based on the results presented in the literature discussed above, it would not be possible to answer questions such as (a) would the synergistic stabilization work on any given drug; (b) what would be the concentration of the polymer/surfactant that will be required for enhanced redispersion/dissolution as various other conditions are changed such as the drug aqueous solubility, drying method, etc.; (c) how would the drying methods and use of additional dispersants affect the synergistic stabilization; and, (d) would the change in drug loading require a different polymer/surfactant concentration for improved drug nanoparticle recovery. The present paper makes an attempt to answer some of these questions.

This study deals with the preparation of redispersible, fast-dissolving nanocomposite microparticles with high drug loading via drying of wet-milled suspensions of poorly water-soluble drugs. Two drying methods: fluidized bed drying (FBD) and spray drying (SD) are compared and their effects are examined on the structure/morphology/size of the NCMPs with various loadings of two model drugs, Azodicarbonamide (AZD) and Griseofulvin (GF). The two drying methods differ significantly with regards to drying time scales of a drop of suspension: spray drying occurring within few seconds while fluidized bed coating taking few minutes (Masters, 1985; Bilgili et al., 2011). Additionally, each drying method produces different morphologies and hence different microstructure upon drying that could affect the recovery and dissolution from dried drug nanosuspensions, in particular considering that FBD employs water-soluble carrier particles. The two drugs were selected because they differ in aqueous solubility and wettability (see Table 1), which is unlike most previously reported studies. HPC or a combination of HPC with SDS was used for imparting physical stability to the wet media-milled AZD and GF suspensions. HPC also acts as a dispersant or matrix former during drying. In addition to HPC and SDS, Mannitol was used as an additional dispersant in one of the spray-dried formulations, which helps lower the drug loading if required and for the purpose of comparing with the nanocomposites formed using the fluid-bed drying method. The prepared suspensions were dried via spray drying or fluid bed drying, in the latter, wet-milled suspensions were sprayed onto Pharmatose® carrier particles. The NCMPs were dispersed in water employing paddle stirring (Bhakay et al., 2013) to evaluate the extent of drug nanoparticle recovery which closely resembles the hydrodynamics for drug dissolution in a USP II (paddle) apparatus. As will be shown, this study demonstrates that synergistic use of HPC–SDS combination as dispersants leads to enhanced redispersibility and drug dissolution for two drugs, irrespective of the method of drying and resultant particle size of the NCMPs, even at high drug loadings in the NCMPs. Hence, such NCMPs may help formulators to develop smaller tablets/capsules with higher loading of poorly water-soluble drugs for better patient compliance and enhanced efficacy of the drug.

2. Material and methods

2.1. Materials

GF and AZD were used as model poorly water-soluble drugs in this study (see Table 1 for details). GF and AZD were purchased from Letco Medicals (Decatur, Alabama, USA) and Pfaltz and Bauer Inc. (Waterbury, CT, USA), respectively. HPC (SL grade) and SDS

Table 1
Physicochemical properties of the poorly water-soluble drugs.

Drugs	Molecular weight (g/mol)	log *P*	Solubility in water (μg/ml)	Contact angle with water (°)	Initial particle size (μm) D10, D50, D90
Griseofulvin (GF)	352.7	3.5	8.9	57 ± 1.0	5.1, 19.9, 54.1
Azodicarbonamide (AZD)	116.1	−1.7	60	44 ± 1.7	2.2, 5.1, 11.2