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Research Paper

Incorporation of surface-modified dry micronized poorly water-soluble drug powders into polymer strip films

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ABSTRACT

Recent work has established polymer strip films as a robust platform for delivery of poorly water-soluble drugs via slurry casting, in particular using stable drug nanosuspensions. Here, a simpler, robust method to directly incorporate dry micronized poorly water-soluble drug, fenofibrate (FNB), is introduced. As a major novelty, simultaneous surface modification using hydrophilic silica along with micronization was done using fluid energy mill (FEM) in order to reduce FNB hydrophobicity and powder agglomeration. It is hypothesized that silica coating promotes easy, uniform dispersion of micronized and coated FNB (MC-FNB) during direct mixing with aqueous hydroxypropyl methylcellulose (HPMC-E15LV) and glycerin solutions. Uniform dispersion leads to improved film critical quality attributes (CQAs) such as appearance, drug content uniformity and drug dissolution. The impact of polymer solution viscosity (low and high), mixer type (low versus high shear), and FNB surface modification on film CQAs were also assessed. Films with as-received FNB (AR-FNB) and micronized uncoated FNB (MU-FNB) were prepared as control. When MC-FNB powders were used, films exhibited improved appearance (thickness uniformity, visible lumps/agglomerates), better drug content uniformity (expressed as relative standard deviation), fast and immediate drug release, and enhanced mechanical properties (tensile strength, elongation percentage), regardless of the polymer solution viscosity or mixer type. These results compare favorably with those reported using nanosuspensions of FNB, establishing the feasibility of directly incorporating surface modified-micronized poorly water-soluble drug powders in film manufacturing.

1. Introduction

Orodispersible drug dosage forms are gaining popularity, particularly for pediatric and geriatric patients as well as patients suffering from dysphagia, due to the ease of handling and convenient application leading to high patient compliance (Averineni et al., 2009; Brniak et al., 2015; Dixit and Puthli, 2009; Hoffmann et al., 2011). Amongst those, orodispersible films (European Pharmacopoeia, 2013) present a relatively new dosage form having advantages such as larger available surface area and capability for precision dosing as compared to drops or syrups (Borges et al., 2015; Brniak et al., 2015). Additionally, film formulation can be readily adjusted to allow for customized disintegration and dissolution rate allowing for creating immediate or extended drug release dosages that may also be used for applications such as patches and implants (Dixit and Puthli, 2009). In that context, terms "thin strip films" or "polymeric films" are used in this paper instead of orodispersible films to maintain generality.

The traditional approaches for preparing films with poorly water-soluble drugs are solvent casting and hot melt extrusion (HME) (Dixit and Puthli, 2009; Hoffmann et al., 2011). The major weakness of solvent casting is that drug recrystallization may occur during drying, leading to drug loading limitations, poor drug particle size control and the instability of APIs in the products, along with the presence of residual solvents. HME, on the other hand, has been proposed as a solvent-free manufacturing process for films, in particular for poorly water-soluble drugs (Aitken-Nichol et al., 1996). HME method has several advantages, including ability to create amorphous forms. However, the method may pose a few limitations such as the need to carefully consider compatibility of the drug and polymer, their miscibility, melting temperatures, potential for degradation due to high temperatures, etc. Further, most extruders cannot produce films thin enough (less than 100 μm) required for fast disintegration; their minimum thickness being 254–305 μm (Repka et al., 2005; Repka and McGinity, 2000).

More recent work reveals that films formed via aqueous slurry casting that include drug nano-particles may have advantages over solvent and HME cast films for poorly water-soluble drugs (Sievens-Figueroa et al., 2012a). In this process, stable aqueous drug

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nanosuspensions are mixed with aqueous solution of polymer and plasticizer, preferably having high viscosity to prepare film precursors that are then cast and dried (Krull et al., 2015b; Susarla et al., 2013). Based on such slurry casting, it has been demonstrated that film is a promising, robust platform for the delivery of crystalline nanoparticles of poorly water-soluble drugs (Krull et al., 2015b). It has been shown that this approach can be used to prepare thin films with enhanced film critical quality attributes (CQAs) such as drug content uniformity (expressed through relative standard deviation, RSD), high drug load, smooth film appearance, dissolution control, desired mechanical properties, stability of drug form and overall film performance, etc. (Krull et al., 2017a, b; Krull et al., 2016a, b; Krull et al., 2015a, b; Sievens-Figueroa et al., 2012a; Susarla et al., 2013). However, all of these studies concerned use of stable drug nanosuspensions to prepare films via mixing, casting and drying.

In the film literature using drug nanosuspensions cited above, media milling is used, which requires high energy and long processing times and may pose manufacturing limitations, including high cost at production scales. In addition, surfactants and other additives are required during milling to achieve smaller size and to ensure drug nanosuspension stability (Azad et al., 2015). Other than the potential for toxicity arising from the use of surfactants, there is also the risk of product contamination due to milling media wear (Juhnke et al., 2012). Considering these factors, one could question if nanomilling down to 200 nm is necessary to achieve good film CQAs. In fact, particles larger than 500 nm or low-micron sizes have been used before (Beck et al., 2013; Bhakay et al., 2016). Using liquid-antisolvent precipitation (Beck et al., 2013), films prepared with low-micron sizes of griseofulvin, a poorly water soluble drug, were shown to achieve immediate release profiles and low RSD, although at low drug loading (5 wt%). In another paper, an interesting particle formation approach based on melt-emulsion of fenofibrate was used to prepare stable ~600 nm particle suspensions that led to the immediate release of fenofibrate at acceptable drug RSD, again at about 6 wt% drug loading (Bhakay et al., 2016). Interestingly, a less stable formulation in the same paper achieved similar CQAs even when the drug particles were agglomerated to several microns in size. Such results, both requiring use of surfactants, suggest that some but not all of the desired film CQAs may be achieved without using drug nanosuspensions.

The main objective of this paper is to examine a simpler route based on dry milling to achieve very fine drug powders as an alternate to wet milling in the film formation process without negatively affecting film CQAs. However, typical micronization leads to downstream problems attributed to their high cohesion, causing poor flow, severe agglomeration and poor dispersion, hence, failing to achieve expected dissolution rate enhancements (de Villiers, 1996; Kendall and Stainton, 2001; Perrut et al., 2005). Poor flow and agglomeration are expected to lead not only to difficulties in handling, but also in mixing of dry agglomerated hydrophobic drug particles with aqueous solution of polymer and plasticizer. Preparing slurries using such powders may not provide films with desirable CQAs. Fortunately, severe agglomeration may be tackled using a novel simultaneous micronization and surface modification method, where additives such as hydrophilic silica may be dry coated onto micronized drug particles using the fluid energy mill (FEM) (Han et al., 2013, 2011; Young et al., 2012). It was shown that ibuprofen powders might be micronized down to 5 or 10 μm and simultaneously dry coated with hydrophilic silica to greatly enhance flow, packing, dispersion and most importantly, dissolution of micronized powders (Han et al., 2011). It was also shown that micronized and surface modified ibuprofen powders provide excellent flow properties for 60% drug loaded blends and very fast dissolution from their tablets (Han et al., 2013). However, to best of our knowledge, the effectiveness of hydrophilic silica on dry coated, micronized hydrophobic drug particles for their direct mixing with aqueous polymer solution and subsequently forming films has not been previously reported.

Consequently, the incorporation of micronized and surface modified drug powders into film formulations was considered. Fenofibrate, a BCS Class II drug, was used as the model drug and micronization was carried out in the FEM with or without surface modification with hydrophilic silica, M5P. Two additional factors, the mixer type (a high-shear planetary mixer and a low-shear impeller mixer) and the viscosity of polymer solution (9000 cP and 15000 cP) were also investigated due to their potential impact on film CQAs (Kulshreshtha et al., 2010; Susarla et al., 2013). Overall, a systematic investigation was performed to test the hypothesis that surface modified micronized powders may be directly incorporated to manufacture films with enhanced CQAs such as drug content uniformity, dissolution and mechanical properties. As will be discussed later, much smaller film sample size is selected in order to better discriminate various outcomes, and hence drug content uniformity is evaluated as the relative standard distribution (RSD) of a number of film samples in each case. In addition, the impact of the viscosity of polymer solution as well as the type of mixer were evaluated. The results are compared to those previously reported using stable drug nanosuspensions (Krull et al., 2015b).

2. Materials and methods

2.1. Materials

Fenofibrate (FNB; Jai Radhe Sales, Ahmedabad, India) was selected as a model BCS Class II poorly water-soluble drug. Pharmaceutical grade amorphous hydrophilic silica (M5P, Cabot Corporation, MA) with primary particle size of 16 nm was used as the coating material for dry FNB particles. Low molecular weight hydroxypropyl methylcellulose (HPMC; Methocel E15 Premium LV, M_w ~ 40,000, The Dow Chemical Company, Midland, MI) and glycerin (Sigma-Aldrich, Saint Louis, MO) were used as the film former and the film plasticizer respectively. Sodium dodecyl sulfate (SDS) (Sigma-Aldrich, Saint Louis, MO) was used as the surfactant in the dissolution media. The FNB particles, with or without M5P, processed via FEM (qualification model, Sturtevant Inc., Hanover, MA) were referred to as MC-FNB and MU-FNB particles respectively. All other materials were used as received.

2.2. Preparation of micronized uncoated and micronized coated FNB powders

The procedure for pre-mixing of powders via Laboratory Resonant Acoustic Mixer (LabRAM; Resodyn Acoustic Mixers, Inc., Butte, MT), a high-intensity vibrational mixer, and preparation of micronized uncoated and micronized coated dry powders using FEM were followed based on previously established protocols (Davé et al., 2011; Han et al., 2011).

As-received FNB powders did not require any secondary pre-milling. Pre-mixing of FNB powder (97 g) and silica (3 g) was performed in the LabRAM by placing powders in a plastic cylindrical jar. LabRAM during pre-mixing process was operated at a frequency of 61 Hz with an acceleration of 70 G for 5 min to ensure that the silica particles were well distributed and attached to FNB particles. The MU-FNB particles were prepared without the pre-mixing step, and the FNB powders were fed directly into FEM.

Simultaneous micronization and surface modification of pre-mixed FNB powders was achieved through FEM process as follows. Powder feeding rate was controlled by a volumetric feeder (Model 102M, Schenck Accurate, WI, USA) at a rate of 1 g/min. A constant feeding pressure (FP) of 45 psi and a constant grinding pressure (GP) of 40 psi were maintained. Processed powders were stored in a vacuum desiccator at room temperature for subsequent scanning electron microscopy (SEM) and particle size tests.

2.3. Preparation of FNB microparticle-laden films

The method for incorporation of nano drug particles into HPMC