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Critical Material Attributes of Strip Films Loaded With Poorly Water-Soluble Drug Nanoparticles: II. Impact of Polymer Molecular Weight

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ABSTRACT

Recent work established polymer strip films as a robust platform for delivery of poorly water-soluble drug particles. However, a simple means of manipulating rate of drug release from films with minimal impact on film mechanical properties has yet to be demonstrated. This study explores the impact of film-forming polymer molecular weight (MW) and concentration on properties of polymer films loaded with poorly water-soluble drug nanoparticles. Nanoparticles of griseofulvin, a model Biopharmaceutics Classification System class II drug, were prepared in aqueous suspension via wet stirred media milling. Aqueous solutions of 3 viscosity grades of hydroxypropyl methylcellulose (14, 21, and 88 kDa) at 3 viscosity levels (~9500, ~12,000, and ~22,000 cP) were mixed with drug suspension, cast, and dried to produce films containing griseofulvin nanoparticles. Few differences in film tensile strength or elongation at break were observed between films within each viscosity level regardless of polymer MW despite requiring up to double the time to achieve 100% drug release. This suggests film-forming polymer MW can be used to manipulate drug release with little impact on film mechanical properties by matching polymer solution viscosity. In addition, changing polymer MW and concentration had no negative impact on drug content uniformity or nanoparticle redispersibility.

Introduction

Polymer strip films are gaining recognition as a robust and versatile platform for drug delivery, thanks in part to notable advantages over traditional solid dosage forms. These advantages include faster disintegration and dissolution in the oral cavity, improved patient compliance,[1] and an inherently continuous manufacturing process.[2,3] Although initial studies and commercial applications for pharmaceutical films focused on incorporation of water-soluble drugs,[1,4-6] recent studies have begun to explore the potential for incorporation of poorly water-soluble drugs into polymer strip films. Although this is commonly performed via hot melt extrusion[7,8] or organic solvent casting,[9] both may lead to drug instability and drug-loading limitations in the resulting films.[10] In light of these issues, various particle engineering techniques have emerged as alternative ways to produce stable poorly water-soluble drug particles for faster dissolution from strip films, including wet stirred media milling (WSMM), liquid antisolvent precipitation, high pressure homogenization, and melt emulsification.[11-20] With the groundwork in place for strip films as a stable and robust platform for poorly water-soluble drug delivery, attention has shifted from process development to intelligent formulation design and gaining a better understanding of how various critical material attributes influence film properties.

One of the greatest strengths of the strip film format is its inherent versatility as a drug delivery platform. With excipients including the film-forming polymer, plasticizing agent, and various other additives, there is a wide array of formulation options available in strip film development, even for poorly water-soluble drugs. Exploration of this flexibility is made even more enticing by the relative simplicity of the film manufacture process compared with the manufacture of more traditional solid dosage forms,[2] which has been the subject of recent literature. For instance, some have manipulated the mechanical properties of films containing poorly water-soluble drug in both the amorphous[21] and crystalline states[14] by adjusting plasticizer and plasticizer concentration while attempting to preserve the enhanced dissolution rate of the drug. Others have investigated the use of viscosity-enhancing agents,

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such as natural gums or superdisintegrants, for modulation of drug nanoparticle release from films,[13,19] although both observed differences in film mechanical properties as well. However, to the best of the authors' knowledge, a simple means of manipulating poorly water-soluble drug release from strip films without significantly affecting film mechanical properties has yet to be demonstrated.

One particularly useful property of polymers as film-forming agents is the variety of molecular weights (MWs) available for a given polymer. Varying polymer MW has been used in several dosage forms as a means of controlling drug release. Ramkissoon-Ganorkar et al.[22] observed slower insulin release from higher MW N-isopropylacrylamide/butyl methacrylate/acrylic acid polymeric beads, noting a shift in controlling release mechanism from polymer erosion to drug diffusion. Mittal et al.[23] observed a similar shift in controlling release mechanism from estradiol-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles with increasing PLGA MW. Rowe[24] observed slower release of a propanolamine derivative from coated granules of ethylcellulose−hydroxypropyl methylcellulose (EC−HPMC) with higher MW EC, presumably due to cracks and flaws in the lower MW film coatings. Omelczuk and McGinity[25] observed slower theophylline release from tablets made using higher MW grades of PLA up to ~138 kDa, above which no differences in drug release rate were observed. Marucci et al.[26] observed slower release of metoprolol from pellets coated with hydroxypropyl cellulose−ethylcellulose (HPC−EC) using higher MW EC due to slower HPC leaching and, consequently, slower drug diffusion. Prodduturi et al.[9] observed slower release of amorphous clotrimazole from higher MW poly(ethylene oxide) films produced via hot melt extrusion. Huang et al.[27] observed slower water absorption and drug release from higher MW PLGA films loaded with amorphous paclitaxel. However, none of these studies investigated films containing poorly water-soluble drug particles. In addition, existing literature suggests that film-forming polymer MW has a significant effect on film mechanical properties when the concentration of film-forming polymer is held constant.[27-29] To the best of the authors' knowledge, a simple means of manipulating drug release rate without significantly affecting film mechanical properties has yet to be demonstrated for drug particle-laden films.

The objective of this work was to demonstrate that the release rate of poorly water-soluble drug nanoparticles, also commonly referred to as nanocrystals, from polymer films can be manipulated with minimal impact on film mechanical properties or nanoparticle redispersibility. WSMM was used to prepare aqueous nanosuspensions of griseofulvin (GF), used as a model poorly water-soluble drug. GF nanosuspension was then mixed with one of several concentrations and MW grades of HPMC polymer solution, containing glycerin as plasticizer. The resulting film precursor suspensions were cast and dried to form films loaded with GF nanoparticles. The viscosity of each polymer solution and film precursor suspension was measured using a coaxial cylinder rheometer. The size distributions of GF particles redispersed from films into deionized water were compared with that of the milled GF nanosuspension, all measured via laser diffraction, to assess the ability of the film format to physically stabilize the GF nanoparticles. Mechanical properties, including tensile strength (TS), yield strength (YS), Young's modulus (YM), and percent elongation at break (EB), were also measured for all films. Drug content and uniformity within each film were assessed via assay. Drug dissolution rate from films was measured using a USP IV flow-through cell dissolution apparatus and qualitatively assessed using a surface dissolution imaging device. Thermogravimetric analysis was used to analyze residual moisture content of the films. Drug particle size and morphology were investigated qualitatively using scanning electron microscopy (SEM).

Materials and Methods

Materials

GF (Letco Medical, Decatur, AL) was selected as a model Biopharmaceutics Classification System (BCS) class II drug. Three different viscosity grades of HPMC (Methocel E15 Premium LV, MW ~14 kDa; E50 Premium LV, MW ~21 kDa; E4M Premium, MW ~88 kDa; The Dow Chemical Company, Midland, MI) served as film formers. E50 and E4M samples were generously donated by The Dow Chemical Company. HPMC-E15LV also served as a nanoparticle stabilizer during WSMM, along with the surfactant sodium dodecyl sulfate (SDS; Fisher Scientific, Pittsburgh, PA). Glycerin (Sigma−Aldrich, St. Louis, MO) was used as a film plasticizer. GF particle size reduction was performed by WSMM according to the preparation of GF nanosuspension section. All other materials were used without further processing.

Preparation Methods

Preparation of GF Nanosuspension

GF nanosuspension was prepared via WSMM using a Netzsch mill (Microcer; Fine Particle Technology LLC, Exton, PA). Methods and stabilizer concentrations were selected according to previous optimization studies.[30,31] The suspension consisted of 10% GF dispersed in a stabilizer solution of 2.5% HPMC-E15LV and 0.5% SDS (all wt/wt w.r.t. water) and was milled for 120 min. A single GF nanosuspension formulation was used across all film formulations, as opposed to using different polymer MWs for each film formulation, to ensure consistency in the size and morphology of the milled GF particles (for a thorough investigation of the effect of polymer MW in WSMM, readers are referred to Li et al.[32]). This meant that the HPMC-E15LV stabilizer, which adsorbed onto the surface of the GF nanoparticles during milling, was present in all film precursors, including those that used E50 and E4M as film formers. The resulting mass ratios of film-forming polymer to HPMC-E15LV stabilizer were ~9.9 for E50 film precursor formulations and ~3.5 for E4M film precursor formulations.

Preparation of Film Precursor Suspensions

As per Dow® protocol, polymer solutions were prepared by adding the appropriate amounts of HPMC and glycerin to water at 90°C, after which the solution was allowed to cool to room temperature under continuous magnetic stirring. Polymer concentrations were selected such that the polymer solutions were sufficiently viscous to ensure a uniform film while not too viscous to hinder mixing or casting. To account for this, and to minimize the effect of viscosity variation on film properties seen in previous work,[19,20] a "viscosity matching" technique was used in which 3 target viscosity ranges were identified for study across all 3 HPMC grades: 9000−10,000 cP (Low), 11,000−13,000 cP (Med), and 19,000−25,000 cP (High). This required careful selection of polymer concentrations in the polymer solution formulations by decreasing polymer concentration with increasing polymer MW, as seen in Table 1. The ratio of polymer-to-plasticizer was maintained within each trio of viscosity ranges, although this ratio had to be slightly increased with increasing viscosity to prevent overplasticization in E4M films (3.0, 3.4, and 3.8, respectively). Each of the resulting polymer solutions was mixed with GF nanosuspension in a 2:1 ratio by mass using a Thinky ARE-310 planetary centrifugal mixer (Thinky, Laguna Hills, CA). Polymer solution and nanosuspension were mixed at 2000 rpm for 30 s, followed by 7 min of deaeration at 2200 rpm, to form film precursor suspension. If bubbles were still present in the precursor suspension after mixing, the precursor was left overnight to settle before casting.