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Effects of stabilizers on particle redispersion and dissolution from polymer strip films containing liquid antisolvent precipitated griseofulvin particles

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ABSTRACT

In this work, we provide experimental evidence supporting the dual role of stabilizers on controlling growth and agglomeration of formed particles via liquid antisolvent (LAS) process and use this knowledge to demonstrate the feasibility of integrating these engineered particles into fast dissolving edible pharmaceutical strip films (PSF). A T-mixer was used to produce griseofulvin (GF) particles for incorporation into PSF in continuous mode, while the experiments crucial to elucidate the role of stabilizers were conducted in batch system. Stabilization was examined via addition of the non-ionic surfactant Pluronic F127 (PF 127), the polymer hydroxypropyl methyl cellulose (HPMC LV 15) and their combinations. Centrifugation was evaluated as a means to concentrate suspensions and minimize levels of residual solvent, while keeping the produced particles non-agglomerated. Laser diffraction, SEM imaging, Differential scanning calorimetry (DSC), X-ray diffractometry (XRD) and Near-infrared Spectroscopy (NIR) were employed to characterize the particles and strip films. It was observed that the simultaneous evolution of particle growth and agglomeration is controlled if HPMC LV 15 and PF 127 are present before precipitation while only agglomeration is suppressed if added after precipitation. The addition of PF 127 along with HPMC LV 15 to GF suspensions results in controlling initial growth and suppression of agglomeration during downstream processing via synergistic effects. The optimal formulation results in faster and higher extent of dissolution than a poorly stabilized suspension, a film made from the unprocessed drug, a physical mixture or a compact of similar composition. Along with particle size data, cluster size analysis from NIR imaging emphasizes the role of wettability and re-dispersion in the particle dispersion in the film and recoverability of engineered particles to improve bioavailability.

1. Introduction

Many currently used as well as recently discovered drugs tend to exhibit significantly lower water solubility thus lower dissolution rate and bioavailability. It has been shown [1] that by increasing/controlling specific surface area, the dissolution rate may be significantly improved. A commonly used approach to poor water solubility is drug particle size reduction, thus increasing its surface area, through either top-down or bottom-up techniques. In this work, we consider liquid antisolvent precipitation (LAS), a bottom-up method, in order to make high surface area particles under kinetically controlled conditions with improved dissolution. LAS is a low energy intensive, cost-effective engineering and scalable [2] approach used in a variety of applications such as in cosmetic [3], paint [4,5], semi-conductor [6,7] and pharmaceutical [8–11] industries. If carried out properly, precipitation route affords a viable approach to producing particles with controllable properties [12–15]. In this work, our objective is to use a T-mixer as a simple embodiment for producing stable suspensions of drug particles via liquid antisolvent (LAS) process. The emphasis of the work is on controlling growth and agglomeration of formed particles and subsequently demonstrate the feasibility of integrating these engineered particles into fast dissolving edible pharmaceutical strip films.

The particle formation using LAS is affected by many factors, beginning with mixing, for which, in this work, the main purpose is to satisfy the necessary condition of the Damkohler number (Da) to be less than 1 as demonstrated by Johnson and Prud'homme [16]. Beck et al. calculated Da for a modified T-mixer and showed that in the presence of ultrasound, the Damkohler number is significantly smaller than 1 and particle size is not affected by the mixing conditions [17]. Subsequently, in the present work, the use of ultrasound ensures operating at Da well below 1. It is believed that sound propagation dynamics damp out nonlinear effects from the Navier–Stokes equations [18] and improve energy dissipation to the smallest achievable eddy sizes given by the Kolmogorov length scale [19], thereby facilitating precipitation of fine particles. However, as discussed in Dalvi and Dave [20], there are

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several steps involved in the precipitation process; namely, nucleation due to high supersaturation and simultaneous growth of nuclei by coagulation and condensation. Higher nucleation rates result in low or negligible growth and hence can potentially produce submicron particles. The stability of these particles in colloidal suspensions further depends on agglomeration or flocculation, driven by hydrophobic effects, electrostatic interactions as well as weak Van der Waals attractive forces. The Derjaguin–Landau–Verwey–Overbeek (DLVO) theory effectively describes such interactions and suggests steric and electrostatic stabilization as a way to improve the colloidal stability. Thus, in order to control the particle size, particle size distribution (PSD), and improve the stability, it is necessary to increase nucleation rate, inhibit the particle growth and control agglomeration of particles by steric or electrostatic stabilization.

During precipitation, stabilizers can affect a multitude of mechanisms including nucleation, growth and agglomeration. Stabilizers are classified according to their mechanism of action: electrostatic [21–24] and steric interactions [25–32]. As has been previously shown, for an LAS process, various surfactants and polymeric stabilizers may be used to effectively control nucleation [17,20]. A survey of the literature reveals the existing ambiguity regarding their exact role on precipitation, including prevention of growth and/or agglomeration. Based on [33], adsorption during particle formation occurs by favorably interacting with the particles at the solid–liquid and by shielding them from the surrounding environment through reduction of the solid–liquid interfacial tension [34,35]. While, one hypothesis indicates that the addition of stabilizers increases nucleation rates, thereby decreasing particle size [36–38], Lindfors et al. [39] counted the number of nuclei in the presence and absence of stabilizers and concluded that a polymer does not affect nucleation or growth. Using shock-Freeze Cryo-Transmission Electron Microscopy, Rieger et al. [40] demonstrated that crystallization of calcium carbonate particles at low supersaturation followed classical nucleation, while at high supersaturation, “emulsion” like structures aggregated into nanoparticles. While, the authors believed that the addition of polycarboxylate inhibited the transition to the solid nanoparticle, their series of successive images portrayed the dissolution of particles as a function of time. Additionally, they recounted significant evidence pointing to the importance of agglomeration during particle growth of inorganic nanostructures, thus supporting Lindfors' observations. In this paper, we studied the impact of stabilizers on growth and agglomeration in pharmaceutical precipitation. Accordingly, we performed batch crystallization, measured particle size and compared the data to a T-mixing experiment.

In pharmaceutical industry, solid dosage forms are used to confer physical stability to drug formulations and are considered more attractive due to their convenience and consumer preference aspects. However, in order to prepare them, suspensions of drug particles have to be dried, which would likely lead to agglomeration of particles, poor redispersion and poor recovery [41–49]. So far, several groups have worked on integrating the LAS process with a drying unit operation. While Hu et al. [49] demonstrated the feasibility of producing re-dispersible LAS particles in continuous mode, Kumar and Prud'homme's flash evaporation system [50] validated the necessity for solvent removal. However, there have not been any attempts to incorporate particles engineered through LAS into pharmaceutical strip film (PSF). It has been shown recently that films can be an ideal final dosage form for BCS class II drugs since they provide an alternate platform with significant advantages over tablets such as fast dissolution, low manufacturing cost, ease of administration, greater portability and improved control over drug loading [51]. In particular, they are attractive for use in conjunction with drug particle suspensions produced via LAS, because as will be seen in this paper, processing and handling of fine, dry drug particles are largely avoided.

The Strip film platform has emerged as a dosage form, as successfully demonstrated in several marketed products such as Zofran [52]. The principles of this process were first implemented in 1952 by Glenn N. Howatt [53]. The strips are produced by casting films from a non-aqueous substrate unto a polymeric film [54]. Subsequently, the solvent is evaporated to increase the active's concentration and improve its texture. Recently, the integration of nanosuspensions produced via wet stirred media milling (WSMM) into hydroxypropyl methyl cellulose (HPMC) films was demonstrated [55]. For this purpose, cellulose derivatives serve as suitable matrix formers due to good gelation properties, which enhance their film forming capability [56,57]. It was found that polymer films are effective carriers of particles, allowing for good re-dispersion and recovery of particles, and also enhancement in drug dissolution [55]. Thus, there is a strong motivation for incorporating LAS precipitated drug particles into strip films as opposed to spray drying, oven drying or freeze drying.

In this study, GF was used as the model BCS Class II drug, hence poorly water soluble drug with high permeability. It is an orally administered drug used to treat fungal infections of the skin, hair, and nails that do not respond to creams or lotions [58]. GF suspensions were prepared by the combination of LAS precipitation and sonication via T-mixing. An appropriate amount of the drug was dissolved in acetone with some surfactant, while an amount of HPMC was dissolved in DI water. Following precipitation, centrifugation of the suspensions was performed to remove a significant amount of the solution and hence increase their concentrations, and remove most of the organic solvent. Following centrifugation, small amount of water was added to redisperse the particles and the resultant suspensions were then mixed with a high viscosity polymer solution followed by film casting and drying. Throughout the processing steps, redispersion of the particles and recovery of the particle size were considered critical to ensure improved dissolution as in [55]. Particle and film characterizations were done using laser diffraction, SEM and NIR imaging, DSC and XRD. The addition of surfactant and polymer resulted in reduction of particle size and minimization of agglomeration. The presence of surfactant was critical not only for wetting and dispersing particles, but also for fast dissolution in discriminating media. Thus it is demonstrated for the first time that strip films carrying LAS formed particles as a novel class of solid dosage forms can be a feasible approach to improving dissolution of poorly water-soluble APIs.

2. Materials and methods

2.1. Materials

Griseofulvin was purchased from Letco Medical (Livonia, MI, USA). The initial volume-based particle size distribution of the as-received drug has d_{10}, d_{50} and d_{90} of 3.45 μm, 11.5 μm and 21.2 μm, respectively (Rodos/Helos system, Sympatec, NJ, USA dispersing method: 0.2 bar 50%). Low molecular weight hydroxyl propyl methyl cellulose (HPMC LV 15 Methocel, 80–120 cp) was kindly provided by DOW Chemical (Newark, DE, USA). The wetting agent, poly (ethylene oxide)–poly (propylene oxide)–poly (ethylene oxide) (PF 127) was obtained from Sigma-Aldrich (Saint Louis, MO, USA). The molecular formula of PF-127 is given as $EO_{100}PO_{65}EO_{100}$ with a molecular weight of 12,500 g/mol. The organic solvent used for dissolving GF was acetone (Sigma-Aldrich, Saint Louis, MO). High molecular weight hydroxypropyl methyl cellulose (HPMC E4M, 3500–5000 cp) was kindly donated by Dow Chemical (Newark, DE, USA) and glycerin (Gly) was purchased from Sigma-Aldrich (Saint Louis, MO, USA). All these materials were used as received. Table 1 highlights the physico-chemical properties of materials employed in the current set of experiments.

2.2. Methods

2.2.1. Preparation of organic and aqueous phases

The experimental conditions pertaining to preparation of organic and aqueous phases are summarized in Table 2. The antisolvent solution was prepared by dissolving 100 mg, 200 mg, 400 mg and 800 mg (Runs 1–4) of HPMC LV 15 in 180 mL of DI water. The antisolvent