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Design of Potent Amorphous Drug Nanoparticles for Rapid Generation of Highly Supersaturated Media

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Abstract: Controlled precipitation produced aqueous nanoparticle suspensions of a poorly water soluble drug, itraconazole (ITZ), in an amorphous state, despite unusually high potencies (drug weight/total weight) of up to 94%. Adsorption of the amphiphilic stabilizer hydroxypropylmethylcellulose (HPMC) at the particle–aqueous solution interface arrested particle growth, producing surface areas from 13 to 51 m^2/g. Dissolution of the particles in acidic media yielded high plateau levels in supersaturation up to 90 times the equilibrium solubility. The degree of supersaturation increased with particle curvature, as characterized by the surface area and described qualitatively by the Kelvin equation. A thermodynamic analysis indicated HPMC maintained amorphous ITZ in the solid phase with a fugacity 90 times the crystalline value, while it did not influence the fugacity of ITZ in the aqueous phase. High surface areas led to more rapid and levels of supersaturation higher than those seen for low-surface area solid dispersions, which undergo crystallization during slow dissolution. The rapid generation of high levels of supersaturation with potent amorphous nanoparticles, containing small amounts of stabilizers oriented at the particle surface, offers new opportunities for improving bioavailability of poorly water soluble drugs.

Keywords: Supersaturation; amorphous pharmaceutical; nanoparticle dissolution; poorly water soluble drug; metastable solubility; itraconazole

1. Introduction

For biopharmaceutical classification system (BCS) type II drugs with high permeability through biomembranes, bioavailability in oral delivery is limited by the dissolution rate.[1–4] Particle size reduction of crystalline materials increases the surface area, A, while high-energy polymorphs, including the amorphous state, increase the solubility, C_{sat}, both leading to faster dissolution rates[4–10] as predicted by the Noyes–Whitney equation

$$\frac{dm}{dt} = \frac{DA}{h}(C_{sat} - C) \quad (1)$$

where D is the diffusion coefficient, h is the diffusional path length, and C is the concentration in solution. Precipitation of an organic drug solution with either water or a supercritical fluid antisolvent is commonly used to form high-surface area particles, both crystalline and amorphous. During precipitation, mixing energy[11–13] and stabilization with polymers are

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used to control particle size and morphology.[14–19] Therapeutic proteins are often formulated in the amorphous state with stabilizing excipients to ensure physical and chemical stability.[20,21] Theoretical solubilities of amorphous pharmaceuticals in aqueous media have been predicted with thermodynamic models to be 100-fold and up to 1600-fold greater than that of the crystalline form.[3,19,22] Experimentally measured solubilities, however, often reach only a fraction of the theoretical value, for example, 4.5 experimental versus ~100 theoretical for indomethacin.[3,19] A high degree of supersaturation for amorphous formulations will increase C_{sat} and thus the flux across biomembranes.[2,23–27] In this case, drug molecules are in a metastable state and may precipitate by nucleation and growth to lower the free energy. Particle growth of embryo crystals may be inhibited by coating drug particles with polymeric stabilizers,[25,28–31] particularly HPMC.[5,23,25,29]

Storage stability of an amorphous solid is a great concern, as the high-energy solid state may relax to the lower-free energy crystalline form. Properties such as the glass transition (T_g), reduced crystallization temperature ($T_c - T_g$ or $T_m - T_g$), and fragility of the amorphous drug can be used to describe the molecular mobility and characterize the stability at typical storage temperatures.[3,19,32–34] Solid dispersions and solid solutions with high-T_g polymers are often utilized to

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reduce the mobility of drug molecules, thereby preventing crystallization during both the particle formation step and storage.[5,35,36]

Amorphous drug formulations, either solid dispersions or co-ground mixtures with polymers such as HPMC,[5,36–41] poly(vinylpyrolidone),[42] polyethylene glycol,[43] aminoalkyl methacrylate copolymer (Eudragit E 100),[44] methacrylic acid-methacrylic acid methyl ester copolymer (Eudragit L),[45] carboxymethylethylcellulose,[45] and microcrystalline cellulose,[7] have been used to create supersaturated solutions. Suzuki et al. produced solid dispersions of nifedipine stabilized with HPMC and PVP at drug loadings (drug weight/total weight) from 11 to 33%, where supersaturation levels were up to 6 times the crystalline nifedipine solubility.[38,40] A supersaturation of 45 in 2 h was achieved in 0.1 N HCl for a solid dispersion of ITZ with HPMC formed by hot melt extrusion at a drug loading of 40%.[36,41] Amorphous solid dispersions of tacrolimus produced by solvent evaporation with PEG 6000, PVP, and HPMC at 50% drug loading were shown to supersaturate 0.1 N HCl up to 25 in 2 h.[5] In all of these studies, supersaturation levels were obtained only for drug loadings of ≤50%.

Previous studies of supersaturation from amorphous drug particles have focused primarily on solid dispersions with stabilizers dispersed throughout the entire particle.[5,36–45] These formulations had relatively low surface areas (<1 m^2/g) and required a large amount of stabilizer, typically 50% (weight) or more, to inhibit crystallization of drug domains and to achieve sufficient hydrophilicities on the particle surfaces for wetting. For high-dose drugs, it would be beneficial to produce amorphous particle formulations with larger drug loadings to achieve desired dosage sizes and to avoid side effects from excipients. The amount of amphiphilic stabilizer may be reduced by forming the particles in the presence of water to orient the stabilizer preferentially at the interface between the drug particle and aqueous solution. This approach has been utilized to form crystalline particles in antisolvent processes[16,46,47] and evaporative precipitation of organic[48–50] and supercritical fluid[51,52] solutions. Aqueous suspensions of sub-300 nm ITZ particles have been produced by CP with poloxamer 407 at drug loadings

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up to 86%;[53] however, the morphology and dissolution behavior were not investigated. To date, supersaturation of dissolution media from amorphous nanoparticles of poorly water soluble drugs has not been reported for particles with high drug loadings.

The key objective of this study was to form amorphous ITZ nanoparticles with high drug loadings up to 80% to achieve unusually high supersaturation levels in acidic media. During particle formation, the orientation of the hydrophilic stabilizer HPMC near the surface of the particles may be expected to facilitate high drug loadings while still inhibiting particle growth and crystallization. In contrast, nearly all amorphous conventional solid dispersions, for example, ITZ and HPMC, are limited to 50% loading and surface areas of <2 m^2/g. The rapid dissolution of high-surface area nanoparticles has the potential to minimize the time window for solvent-mediated crystallization of the remaining solid phase and thereby favor higher supersaturation levels than for low-surface area solid dispersions.

Itraconazole was chosen as a model poorly water soluble drug, given its extremely high lyophilicity, that is, octanol/water partition coefficient (log P) of 5.66, as reported by Janssen Pharmaceutica. The particles were characterized by modulated differential scanning calorimetry and X-ray diffraction to determine the crystallinity, scanning electron microscopy, Z-contrast transmission electron microscopy, X-ray photoelectron spectroscopy, BET surface area analysis, and contact angle measurements. The supersaturation behavior of aqueous suspensions and dry powders containing ITZ was investigated in 0.1 N HCl acidic media. Contact angles with 0.1 N HCl were compared for the CP powders relative to solid dispersions formed by solvent evaporation to demonstrate preferential orientation of HPMC on the particle surface for the CP powders.

The ITZ/HPMC suspensions were added to the dissolution media in increments to determine the maximum supersaturation level, which will be shown to approach the metastable solubility limit. High supersaturation values are facilitated by trapping ITZ in the amorphous state even for high drug loading. To place these results in perspective, the metastable solubility of a pure amorphous ITZ suspension was measured without any HPMC. A thermodynamic scheme was developed to examine the effect of HPMC on the fugacity of ITZ in the solid phase relative to the aqueous phase and to determine the ratio of amorphous and crystalline ITZ fugacity. The HPMC concentration influences the particle surface area during controlled precipitation and thus the supersaturation as predicted by the Kelvin equation. Mass transfer models were developed in an attempt to understand how the surface area and erosion of slowly dissolving HPMC influenced the dissolution rate. The exceptionally high surface area of the aggregated nanoparticles, with high wetted hydrophilic surface areas, will be shown to produce more rapid and higher levels of supersaturation than in the case of lower-surface area solid dispersions (SD) with less hydrophilic surfaces.

2. Materials and Methods

2.1. Materials. BP grade ITZ was purchased from Hawkins, Inc. (Minneapolis, MN). HPMC E5 (viscosity of 5 cP in a 2% aqueous 25 °C solution) grade was a gift from The Dow Chemical Co. Poly(vinylpyrolidone) K15 (PVPK15) and poloxamer 407 (P407) NF grade were both obtained from Spectrum Chemical (Gardena, CA). Stabilized pa grade 1,3-dioxolane was purchased from Acros Organics (Morris Plains, NJ). HPLC grade acetonitrile (ACN), ACS grade hydrochloric acid (HCl), and diethanolamine (DEA) were used as received from Fisher Chemicals (Fairlawn, NJ).

2.2. Controlled Precipitation into Aqueous Solution. The method of CP developed by Rogers et al.[16] was used to produce nanoparticle suspensions of itraconazole. Deionized water (120 g) containing an appropriate quantity of HPMC was used as the antisolvent phase into which 30 g of 1,3-dioxolane containing 3.3% (weight) ITZ was injected to form a fine precipitate. The organic phase was separated from the aqueous suspension via vacuum distillation. In some cases, the aqueous suspension was added dropwise to liquid nitrogen and lyophilized to form a powder using a Virtis Advantage Tray Lyophilizer (Virtis Co., Gardiner, NY) with primary drying at −35 °C for 24 h followed by secondary drying at 25 °C for 36 h. Dried powders were stored in a 13% relative humidity environment.

2.3. Solvent Evaporation To Form a Solid Dispersion (SD). Approximately 2 g of ITZ was added to 20 mL of dichloromethane and the mixture agitated until the ITZ was completely dissolved. The ITZ solution was placed in a mortar, and an appropriate amount of HPMC was slowly added while the mixture was gently stirred with a pestle without any precipitation. The solution was stirred gently until approximately 90% of the dichloromethane volume was evaporated, leaving a clear viscous gel. The remaining dichloromethane was removed by heating to 50 °C at a reduced pressure of ∼500 mtorr for 2 h. The resulting drug/polymer film was removed from the mortar and pestle with a straight razor blade and ground to a fine powder for 30 min using a ceramic ball mill (1 cm bead size). The final powder was collected after filtration through a size 16 mesh sieve (<1190 μm pore size).

2.4. Solubility Determination. To determine the solubility of crystalline ITZ at 37.2 °C, approximately 1.5 mg of bulk ITZ was placed in a glass vials containing 100 mL of 0.1 N HCl (pH 1.2). Two aliquots were removed from each vial after 18 h, immediately filtered with a 0.2 μm syringe filter, and diluted by one-half with ACN. Similarly, solubility was determined for solutions containing HPMC. Approximately 50 mg of ITZ was added to 100 mL of HPMC dissolved in 0.1 N HCl at concentrations of 0.5, 1, and 3.4 mg/mL. In all cases, drug concentrations were determined by high-performance liquid chromatography as described below with

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