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Nano-amorphous spray dried powder to improve oral bioavailability of itraconazole

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ABSTRACT

The objective of this study was to formulate nano-amorphous spray-dried powders of itraconazole to enhance its oral bioavailability. A combination approach of solvent-antisolvent precipitation followed by spray drying was used. DoE studies were utilized to understand the critical processing parameters: antisolvent-to-solvent ratio, drug concentration and stabilizer concentration. Particle size was the critical quality attribute. Spray drying of the nano-precipitated formulation was performed with several auxiliary excipients to obtain nano-sized amorphous powder formulations. PLM, DSC and PXRD were utilized to characterize the spray-dried powders. *In vitro* dissolution and *in vivo* bioavailability studies of the nano-amorphous powders were performed. The particle size of the nano-formulations was dependent on the drug concentration. The smallest size precipitates were obtained with low drug concentration. All high molecular weight auxiliary excipients and mannitol containing formulations were unstable and crystallized during spray drying. Formulations containing disaccharides were amorphous and non-aggregating. *In vitro* dissolution testing and *in vivo* studies showed the superior performance of nano-amorphous formulations compared to melt-quench amorphous and crystalline itraconazole formulations. This study shows superior oral bioavailability of nano-amorphous powders compared to macro-amorphous powders. The nano-amorphous formulation showed similar bioavailability to the nano-crystalline formulation but with a faster absorption profile.

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1. Introduction

The application of high throughput screening techniques, genomics, combinatorial chemistry and *in-silico* computational approaches has resulted in an increase in the number of leads identified as potential drug candidates [1–6]. These approaches tend to identify drug candidates with high molecular mass and lipophilicity, and therefore poor aqueous solubility. It has been reported that about 40% of identified potential drug candidates do not have "drug-like" properties, such as good aqueous solubility and/or dissolution rate [6–9]. There are number of approaches utilized to increase the dissolution rate and/or solubility and thus oral bioavailability of poorly soluble drugs. Traditional approaches to improve drug dissolution rate and/or solubility are: salt formation, use of solubilizing excipients, complexation agents *etc*. However, the success of these traditional approaches has been limited due to troublesome selection process of highly soluble salts, the requirement of large quantities of solubilizing excipients and complexation agents *etc.* For example, the marketed product of itraconazole (*i.e.* Sporanox IV), a poorly water-soluble drug contains only 10 mg of active ingredient per 400 mg of cyclodextrin (complexation agent) [10].

The use of nano-particles (either crystalline or amorphous) is an attractive alternative approach to enhance the rate of dissolution and/or solubility of poorly soluble drugs. Pharmaceutical nano-particles are defined as discrete drug particles in the range of 100–1000 nm. An increase in the exposed surface area (or surface area-to-volume ratio) by particle size reduction causes an increase in dissolution rate and thus oral bioavailability [11–13]. In addition, according to the Kelvin equation, saturation solubility (in terms of vapor pressure) of the drug is dependent on the drug particle size (which translates to curvature effect). Theoretically, reduction in particle size will cause an increase in drug solubility [14]. However, the actual increase in saturation solubility for "nano-crystalline suspensions" (colloidal size range 100–1000 nm) is marginal, approximately 2 - 10% compared to un-milled particles [15]. Thus, nano-sized crystalline powders may not be a useful approach for solubility-limited drugs (*i.e.* solubility is rate limiting for oral bioavailability) [16]. In the case of amorphous formulations, the solubility of the drug is increased over the crystalline form due to its high-energy state (higher Gibbs' free energy) [17–19]. However, amorphous formulations are unstable and they may convert to the stable crystalline form over

Abbreviations: AUC, Area under the curve; API, Active pharmaceutical ingredient; Cmax, Maximum concentration; DE, Dextrose equivalent; DoE, Design of experiment; PXRD, Powder x-ray diffraction; PLM, Polarized light microscopy; Tg, Glass transition temperature; Tmax, Time to reach maximum concentration; Tm, Melting temperature.

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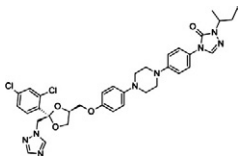
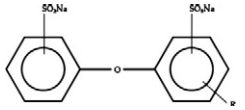
pharmaceutical relevant timescales [20]. Generally, amorphous drugs have been formulated as micro-sized solid dispersions prepared by spray drying, hot melt extrusion etc. where the drug is stabilized in a polymer matrix with higher glass transition temperature. Recently, nano-sized amorphous formulations, namely "nano-amorphous" have grabbed the attention of researchers to enhance the dissolution rates and solubilities of poorly soluble drugs. Theoretically, combining nano-technology and amorphization approaches may offer absolute or synergistic effects in terms of solubility and dissolution rates. Not much work [21–25] has been done in this area mainly because the stability of the amorphous and/or nano-amorphous formulations is a great challenge and depends on: API properties such as melting temperature (Tm), Tm/Tg ratio, and the properties of the polymer or stabilizer utilized.

Nano-particles can be prepared either *via* "top-down" or "bottom-up" approaches. The top-down approaches are based on milling or grinding of the drug particles in the aqueous or mixture of aqueous and non-aqueous solvents to achieve the required particle size [26]. In contrast, bottom-up approaches are based on precipitation of the drug from its solution (drug dissolved in organic solvent) using a poor solvent such as water [26]. Precipitation is driven by deviation from the phase equilibrium condition, and thus depends on supersaturation. Typical supersaturation-driving forces are dependent on the concentration gradient or temperature. For example, in non-thermal precipitation techniques, poorly soluble drug is dissolved in a good solvent and precipitation is achieved by adding antisolvent (bad solvent). Supersaturation of the drug drives nucleation of the drug particles and then particle growth occurs *via* condensation. The bottom-up approach is better compared to the top-down approach in terms of generation of amorphous systems (as precipitation can be achieved rapidly and therefore generates the amorphous state), which can be "locked" through the use of appropriate polymers/stabilizers [27].

To date there are only a few publications in the area of nano-sized amorphous formulations or amorphous nano-particles as liquid formulations [21–25]. These publications refer to liquid suspension preparation mainly either *via* solvent antisolvent precipitation or solvent evaporation and *in vitro* dissolution testing [21–25]. However, one of the major challenges is to formulate solid dosage forms due to instability (*i.e.* drug crystallization and aggregation) issues related to these liquid suspension formulations. There is only one study [28] published in the area of solid nano-amorphous formulation, however re-dispersion of the powder required sonication due to aggregation following drying and this was a major concerns in this study. In the current study, we have formulated stable, nano-amorphous spray dried powders of a poorly soluble drug, which is easily re-dispersible and non-aggregating and have shown oral bioavailability advantage compared with other amorphous (such as melt quench powder) and crystalline formulations (nano versus macro-crystalline powder). In the current research, a combination approach of antisolvent-solvent precipitation followed by spray drying to achieve nano-amorphous powders is utilized. Itraconazole (Biopharmaceutics Classification System, class II compound) was selected as a model compound and Dowfax 2A1 (ionic surfactant) was utilized as a small molecule surfactant in antisolvent (water) to prevent agglomeration of nano-precipitates. A design of experiment (DoE) approach was utilized to understand the effect of critical process and formulation parameters involved during the precipitation method. The optimized formulation was spray dried to achieve nano-amorphous powders. Different spray drying auxiliary excipients (such as sucrose, lactose *etc.*) were evaluated to achieve non-crystallizing, non-aggregating spray-dried nano-amorphous powders of a poorly soluble drug. The optimized nano-amorphous formulations were tested for *in-vitro* dissolution and *in-vivo* oral absorption using a rat model. To best of our knowledge, this is the first study to show the formulation of stable non-aggregating, nano-amorphous powders *via* a combination of solvent-antisolvent precipitation and spray drying techniques. In addition, a significant bioavailability advantage was shown for the nano-amorphous powders compared to macro-amorphous, nano-crystalline and macro-crystalline powder formulations.

Table 1
Chemical structure of the drug and excipients.

Name	Structure
Itraconazole (BCS class II drug)	
Dowfax 2A1 (alkyldiphenyloxide disulfonate)	

2. Materials and methods

2.1. Materials

Crystalline itraconazole was purchased from Jai Radhe Sales, Ahmedabad, Gujarat, India. Dowfax-2A1 (alkyldiphenyloxide disulfonate) was generously gifted by Dow Chemical Company (Midland, MI). The chemical structure of itraconazole and Dowfax 2A1 is shown in Table 1. HPLC grade acetonitrile (ACROS chemicals) was purchased form Fisher Scientific (Pittsburgh, PA). Dichloromethane (high purity) was purchased from Sigma Aldrich (St. Louis, MO). Waters symmetry C18 (4.6 × 150 mm) and Luna C18 [2] columns (4.6 × 150 mm) were purchased from Waters Corp. (Milford, MA) and Phenomenex (Torrance, CA), respectively.

2.2. Methods

2.2.1. Antisolvent-solvent precipitation

Crystalline itraconazole was dissolved in dichloromethane (DCM) at different concentrations as described under the DoE design and utilized as the "solvent". A Dowfax-2A1 solution in distilled water was utilized as the "antisolvent". The drug containing solvent (1 mL) was slowly added to the 10 ml anti-solvent and later sonicated using a probe sonicator (550 sonic dismembrator, Fisher Scientific) for two minutes

Table 2
Cubic centered (Face centered) design space for solvent antisolvent precipitation process and particle size after solvent-antisolvent precipitation.

Sample number	Drug conc. (mg/ml)	Solvent-to-Antisolvent ratio (v/v)	Conc. of surfactant (%w/v)	Particle size (nm)
1	105	1–7.5	0.4	173.4
2	10	1–5	0.6	103.0
3	105	1–7.5	0.2	179.9
4	10	1–7.5	0.4	103.0
5	200	1–5	0.6	192.8
6	10	1–10	0.2	120.1
7	10	1–10	0.6	116.0
8	200	1–10	0.6	234.1
9	105	1–7.5	0.6	177.7
10	105	1–5	0.4	169.5
11	105	1–7.5	0.4	186.6
12	105	1–7.5	0.4	152.6
13	200	1–10	0.2	180.6
14	200	1–5	0.2	216.0
15	10	1–5	0.2	129.0
16	105	1–7.5	0.4	195.9
17	105	1–7.5	0.4	193.7
18	200	1–7.5	0.4	208.3
19	105	1–10	0.4	211.0
20	105	1–7.5	0.4	178.0

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