

Small is big: Is Nanoamorphous Better than Amorphous Solid Dispersion and Nanocrystalline in Pharma?

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Commentary

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INTRODUCTION

The advancement of discovery sciences resulted in emergence of many promising new chemical entities (NCE) with exceptional therapeutic potentials. However, the complex chemistry of these NCEs is often associated with bioavailability challenges due to their poor water soluble properties. Thus, enabling technologies, to enhance solubility, dissolution and bioavailability: amorphous solid dispersion (ASD) and Nano-crystal (NC) are employed. Examples of ASD approved products are Kaletra[®], Sporanox[®], Prograf[®] and Incivek[®]. Some of the NC approved products are Rapamune[®], Emend[®], Tricor[®] and Megace[®]. The successful commercialization of ASD and NC catalyzed the inception of Nano amorphous (NA) formulation. NA formulation leverages on the added benefits of enhanced solubility through its amorphous state in addition to the reduced particle size. This advantage was clearly demonstrated through the application of NanoMorph[™] [1].

In this commentary, we will first compare the biopharmaceutical performance of NA versus NC or ASD, and highlight formulation selection rationale for poorly soluble drugs. Thereafter, we will discuss the solid state purity concerns surrounding NA formulations, whereby the understanding on the characterization and biopharmaceutical performance of NA formulations remains elusive. Key considerations for formulating a successful NA product amid the concern on the solid state purity of will be articulated.

Literature data to date has been able to distinguish and highlight superior bioavailability and/or onset of action of NA over NC and ASD formulations. NA formulation of itraconazole delivered to rats through inhalation demonstrated 3.8x bioavailability enhancement compared to the NC formulation [2]. This correlated with *in vitro* dissolution observation of superior super saturation of NA over NC. Kumar et al. [3] reported a 2.5x bioavailability enhancement in rats for itraconazole NA versus ASD formulation [3]. A BCS II compound, BMS-488043, demonstrated higher bioavailability in dogs when dosed orally as ASD compared to NC formulation. The relative AUC and C_{max} against reference API were at least 7.0 and 18.2, respectively for two ASD formulations, and 4.6 and 4.7, respectively for NC [4]. In a preclinical development effort on BCS Class II drug, Compound by Merck, the ASD formulation provided enhancement of AUC and C_{max} by 3.5x and 2.7x, respectively and decrease of T_{max} by 2x over the NC suspension [5]. In an effort to improve oral absorption of ziprasidone during fasted state, an attempt for amorphous cyclodextrin inclusion complex formulation demonstrated lowered bioavailability (AUC_{inf} ~0.67x) compared to NC formulation in dogs [6]. This futility was attributed to precipitation of the highly supersaturated NA formulation in the intestinal fluid, as observed during *in vitro* dissolution study. It should be noted that NA can also be susceptible to such phenomenon, hence applying the right formulation strategies based on the physicochemical properties of drug molecules cannot be overemphasized.

The fast onset characteristic of NA formulation was apparent in some studies and this is a result of high inherent solubility of the amorphous state. For example, Morgen et al. [7] reported 2.7x decrease in T_{max} for celecoxib NA over ASD formulation dosed orally in human [7], and Kumar et al. [3] reported 2x decrease in T_{max} for itraconazole NA over NC formulation dosed orally in rats [3].

An increase in C_{max} (1.3-1.5x) was also observed for NA formulation despite the similar bioavailabilities in NA, ASD, and NC formulations investigated in these studies. Sigfridsson et al. [8] compared the pharmacokinetics of an investigational BCS II compound, AZ68 in rats [8]. The absolute oral bioavailability of the AZ68 solution and NA suspensions were ~69% and NC suspension was ~48% but the data was not statistically different from each other. However, the NA formulation showed faster onset than NC (T_{max} 1.3 h vs. 3.5 h). The abovementioned studies have specifically highlighted the benefit of NA, NC and ASD formulations.

Formulation strategy for a drug candidate is dependent on multiple factors such as biopharmaceutical performance, processing, stability and shelf life requirements. For a more amenable manufacturing process and scale-up, NC products afford obvious advantages due to the use of established technologies and avoidance of organic solvent consumption. In addition, a wealth of knowledge on manufacturing NC products is evident from the number of marketed products. With the absence of recrystallization risk, NC formulations offer more robust stability against long term storage and common downstream processing involving heat, moisture and/or pressure such as spray drying, coating and tableting. However, to enable such stability, absence or low amorphous impurity needs to be achieved through formulation and process control. This remains one of the toughest challenges in NC processing.

From the biopharmaceutical performance perspective, the dissolution advantages of the amorphous states make ASD or NA the formulations of choice. Simple, reliable and solvent-free processing exists with ASD formulations as corroborated by hot melt extruded products such as Kaletra®, Norvir® and Onmel®. Processing with certain extent of solvent consumption such as spray drying, solvent evaporation, solvent/antisolvent precipitation and fluid bed bead layering are also industrially viable as proven by a host of products in the market [9].

To achieve an edge in biopharmaceutical performance, NA formulation seems to be a good choice. The Nano sizes and high energy amorphous state impart significant solubility advantages by enhancing super saturation and driving absorption through a high concentration gradient, hence fulfilling the key prerequisite for bioavailability enhancement of poorly soluble drugs. However, complex processing and formulation efforts are expected for NA products due to the stability challenges such recrystallization and particle aggregation during processing and storage. The common incorporation of hygroscopic stabilizing excipients such as polymers and surfactants in NA and ASD formulations necessitates special attention and dedication to packaging configurations, operations and storage conditions.

A major and universal concern on NA formulations shared by regulators and scientific community is the solid state purity and its implications on biopharmaceutical performance. To mitigate this concern, we will evaluate current advanced analytical tools applied to accurately distinguish NA from NC and assess the significance of solid state purity and its lack of, on biopharmaceutical performance.

X-ray powder diffraction, thermal analysis (differential scanning calorimetry and thermogravimetric analysis), spectroscopy (Fourier transformed infrared spectroscopy and raman spectroscopy), water vapor sorption, solid state nuclear magnetic resonance, microscopy (polarize light microscopy, scanning electron microscopy and transmission electron microscopy) and dissolution apparatus are common tools for characterization of ASD products [10]. However, these methods may not be sensitive to accurately characterize NA formulations.

The application of small-angle X-ray scattering (SAXS) measurement was feasible to detect crystalline surroundings with radius of 3.5 nm [11,12]. Gonser et al. Irradiated Germanium single crystal with deuterons and observed NA regions (circa 7 nm diameter) using small angle scattering measurements [12,13]. Chiang et al. also demonstrated the application of SAXS in amorphous silica thin films [13]. SAXS was applied to ensure that the amorphous nanoparticle formulation (~20 nm) has no crystalline profile [14]. SAXS was also used to monitor the changes from amorphous to crystalline structure [15]. During evaluation of Zuotai (Tibetan medicine), which has particle size range of 100-600 nm, synchrotron radiation X-ray absorption fine structure (SR-XAFS) managed to differentiate 59% crystallinity and 41% amorphous substance [16].

TEM can complement the X-ray technique and detect in nanoparticle range In TEM, morphology differences between amorphous and crystalline nanoparticles has been clearly shown [7,17-20]. Electron microscopy in combination with deuterons irradiation also observed highly disordered regions at 3 to 5 nm diameter [12]. In addition, TEM provides particle size information to supplement dynamic light scattering (DLS) data.

A single method with the capability to discriminate amorphous nanoparticles from crystalline nanoparticles and macro amorphous is non-existent. Current analytical methods have limited capabilities to detect trace NC elements in a NA matrix. From analytical method perspective, SAXS and TEM appear as promising tools to complement other multilateral and traditional approaches such as XRD.

We have observed residual crystallinity from the XRD diffractograms of two NA formulations of celecoxib prepared by spray drying and freeze drying [21,22]. However, significantly enhanced biopharmaceutical performances were still demonstrated by the NA formulations. The spray dried NA formulation achieved 100% drug release in 5 min as compared to only 30% drug release in the physical mixture and crystalline drug drying [21]. The bioavailability and C_{max} of the spray dried formulation in beagle dogs

were 3x and 2x superior respectively, than marketed celecoxib capsules, Malkani et al. [22] reported a suspension of freeze dried celecoxib NA formulation with more favorable dissolution profile than the pure API and marketed capsule [22]. The Nano suspension of the same formulation exhibited significantly higher anti-inflammatory activities in the rats paw edema model as compared to the marketed celecoxib capsule. Burapapadh et al. [23] acknowledged presence of low crystallinity in pectin-based itraconazole nanoparticles but this did not compromise *in vitro* dissolution even after 6 months of ambient product storage. Bioavailability enhancement of 1.6x over itraconazole commercial product was demonstrated for this formulation [23]. The examples described above showed that residual crystallinity may not be completely preventable in some NA formulations but such occurrence may not necessarily impede biopharmaceutical performance of these formulations.

In addition, superior *in vitro* and *in vivo* efficacy of NA formulations in comparison with the marketed product [24,25], micronized formulation [26,27], macro-amorphous formulation and crystalline drug [26,28] had been demonstrated. It can be seen from the above studies that the biopharmaceutical advantages provided by NA formulations significantly outweigh the current analytical detection limit on trace residual crystals.

Despite characterization limitation, NA formulations have demonstrated obvious advantages in their biopharmaceutical performances versus their ASD and/or NC counterparts as highlighted in the examples described above. In our opinion, the key attributes for a successful NA formulation is not an absolute solid state purity but its stability against significant growth of the initially observed trace crystallinity, a controlled extent of particle growth within an acceptable range, and a consistent biopharmaceutical performance over time. Kumar et al., Liu et al., and Romero et al. reported such physical stability (i.e. particle growth and recrystallization) from 2 months to 12 months for their NA formulations [3,21,27]. However, the stability or consistency of biopharmaceutical performance over time is still lacking and this gap needs to be addressed to strengthen the foundation for commercialization of NA formulations.

In summary, the favorable attributes of NA formulations can be distinctly elucidated through their biopharmaceutical performance despite presence of trace crystallinity in some formulations. Amorphous and particle size stability are critical, but consistent biopharmaceutical performance remain as the key attributes for a highly efficacious NA product. However, in view of the additional challenges behind formulation and production to enable sufficient product stability, NA formulations will only be a rational choice when significant biopharmaceutical improvement is shown *in vivo*.

DISCLOSURES

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REFERENCES

1. Auweter H, et al. Precipitated waterinsoluble colorants in colloid disperse form. Google Patents. 2002.
2. Yang W, et al. Comparison of bioavailability of amorphous versus crystalline itraconazole nanoparticles via pulmonary administration in rats. *Eur J Pharmaceut Biopharma*. 2010;75:33-41.
3. Kumar S, et al. Sugars as bulking agents to prevent nano-crystal aggregation during spray or freeze-drying. *Int J Pharm*. 2014;471:303-311.
4. Fakes M G, et al. Enhancement of oral bioavailability of an HIV-attachment inhibitor by nanosizing and amorphous formulation approaches. *Int J Pharm*. 2009;370:167- 174.
5. Lohani S, et al. Physicochemical properties, form, and formulation selection strategy for a biopharmaceutical classification system class II preclinical drug candidate. *J Pharm Sci*. 2014;103:3007-3021.
6. Thombre AG, et al. *In vitro* and *in vivo* characterization of amorphous, nanocrystalline, and crystalline ziprasidone formulations. *Int J Pharm*. 2012;428:8-17.
7. Morgen M, et al. Polymeric nanoparticles for increased oral bioavailability and rapid absorption using celecoxib as a model of a low-solubility, high-permeability drug. *Pharm Res*. 2012;29:427-440.
8. Sigfridsson K, et al. A formulation comparison, using a solution and different Nano suspensions of a poorly soluble compound. *Eur J Pharm Biopharm*. 2007;540-547.
9. Brough C and Williams RO 3rd. Amorphous solid dispersions and nano-crystal technologies for poorly water-soluble drug delivery. *Int J Pharm*. 2013;453:157-166.

10. Baghel S, et al. Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs. *J Pharm Sci*. 2016;105:2527-2544.
11. Fujita FE and Gonser U. Small angle scattering of X-rays by deuterium-irradiated germanium crystal. *J Phys Soc Japan*. 1958;13:1068-1069.
12. Gonser U and Fujita FE. Nanocrystalline versus Nanoamorphous Materials. *Phy Status Solidi (B)*. 1992;172:13-17.
13. Chiang CC, et al. Relationships between the solution and solid-state properties of solution-cast low-k silica thin films. *Phy Chem Chem Phy*. 2016;18:20371-20380.
14. Bach S, et al. Thermally highly stable amorphous zinc phosphate intermediates during the formation of zinc phosphate hydrate. *J Am Chem Soc*. 2015;137:2285-2294.
15. Wu H, et al. Stress-induced nanoparticle crystallization. *J Am Chem Soc*. 2014;136,7634-7636.
16. Li C, et al. Chemical Components, Mercury Coordination Structure and MicroMorphology of Tibetan Medicine Zuotai. *Guang Pu Xue Yu Guang Pu Fen Xi*. 2015;35:1072-1078.
17. Bartůněk V, et al. Preparation of amorphous antimicrobial selenium nanoparticles stabilized by odor suppressing surfactant polysorbate 20. *Mater Lett*. 2015;152:207-209.
18. Gali OA, et al. Amorphous iron nanoparticles formed on aluminum surfaces during thermomechanical treatment. *Mater Lett* 2016;176:159-164.
19. Karimi M, et al. A facile and sustainable method based on deep eutectic solvents toward synthesis of amorphous calcium phosphate nanoparticles: The effect of using various solvents and precursors on physical characteristics. *J Non Cryst Solid*. 2016;443:59-64.
20. Thakral NK, et al. Compression-induced crystallization of amorphous indomethacin in tablets: characterization of spatial heterogeneity by twodimensional X-ray diffractometry. *Mol Pharm*. 2015;12:253-263.
21. Liu Y, et al. Mechanism of dissolution enhancement and bioavailability of poorly water soluble celecoxib by preparing stable amorphous nanoparticles. *J Pharm Pharm Sci* 2010;13:589-606.
22. Malkani A, et al. Celecoxib nanosuspension: single-step fabrication using a modified nanoprecipitation method and *in vivo* evaluation. *Drug Del Transl Res*. 2014;4:365-376.
23. Burapapadh K, et al. Novel pectin-based nanoparticles prepared from nanoemulsion templates for improving *in vitro* dissolution and *in vivo* absorption of poorly watersoluble drug. *Eur J Pharm Biopharm*. 2012;82:250-261.
24. Liu D, et al. Fabrication of carvedilol nanosuspensions through the anti-solvent precipitation-ultrasonication method for the improvement of dissolution rate and oral bioavailability. *AAPS Pharm Sci Tech*. 2012;13:295-304.
25. Wang Y, et al. Preparation, characterization and *in vivo* evaluation of amorphous tacrolimus Nano suspensions produced using CO₂-assisted in situ nanoamorphization method. *Int J Pharm*. 2016;505:35-41.
26. Liu Y, et al. Modulating Drug Release and Enhancing the Oral Bioavailability of Torcetrapib with Solid Lipid Dispersion Formulations. *AAPS Pharm Sci Tech*. 2015;16:1091-1100.
27. Romero GB, et al. Amorphous cyclosporin A nanoparticles for enhanced dermal bioavailability. *Int J Pharm*. 2016;498:217-224.
28. Dhumal RS, et al. Preparation of amorphous cefuroxime axetil nanoparticles by sonoprecipitation for enhancement of bioavailability. *Eur J Pharm Biopharm*. 2008;109-115.