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Sugars as bulking agents to prevent nano-crystal aggregation during spray or freeze-drying

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ABSTRACT

In this study, the effect of low and high molecular weight sugars on indomethacin nano-crystalline suspension powders prepared by spray or freeze-drying was evaluated. Dowfax 2A1 (negatively charged surfactant) was utilized as indomethacin nanosuspensions stabilizer. Dried crystalline powders with or without sugars were characterized for crystallinity, particle size and powder yield. Interactions between the nanosuspension stabilizer (*i.e.* Dowfax 2A1) and sugars were investigated by utilizing IR spectroscopy and contact angle measurements. The nanosuspension formulations containing small molecular weight sugars were non-aggregating compared to those containing polysaccharides. Additionally, higher powder yields were observed with formulations containing sugars with higher glass transition temperature during spray drying. The formulations containing low glass transition temperature sugars were sticking to the spray drier glass walls and thus resulted in lower yields. The small molecular weight sugars showed favorable interactions with Dowfax 2A1, as evident by the IR and contact angle data, possibly resulting in minimal nano-crystal aggregation during spray or freeze-drying. A combination of sugars (*i.e.* small molecular weight and polysaccharides) may be utilized to achieve higher spray-drying yields and non-aggregating nano-crystalline powders.

1. Introduction

Active pharmaceutical ingredients can be classified into four different categories (as per the Biopharmaceutics Classification System (BCS), Class I–IV) according to their solubility and permeability (Amidon et al., 1995). In the last two decades, 30–40% of the newly discovered or synthesized chemical compounds have poor aqueous solubility and thus poor oral bioavailability (classified under BCS Class II/IV) (Lipinski, 2000, 2002; Gribbon et al., 2005; Gribbon and Sewing, 2005). There are many formulation technologies utilized to increase solubility and/or dissolution rate to enhance oral bioavailability. One of the approaches utilized to increase dissolution rate is formulation of nano-crystalline suspensions (Liversidge and Cundy, 1995; Merisko-Liversidge et al., 2003).

In recent years, the popularity of nano-technology has increased tremendously and many nano-based formulations are already on the market (Kumar and Burgess, 2012). Nano-crystalline suspensions can be described as colloidal dispersions of discrete drug crystals in the stabilizer/s solutions of aqueous or non-aqueous media. The typical size range for pharmaceutical nanosuspensions is 100–1000 nm but most of the pharmaceutical nano-crystalline suspensions have sizes below 500 nm. Size reduction significantly increases the specific surface area (or surface area-to-volume ratio) and hence dissolution rate as described by the Noyes–Whitney equation (Noyes and Whitney, 1897). Accordingly, in case of "dissolution-rate limited" poorly water-soluble drugs, nano-crystalline suspensions can significantly enhance the drug dissolution and thus oral absorption.

Nano-crystalline suspensions can be formulated as solid-dosage forms (*i.e.* nano-crystalline powders) to improve the physical and chemical instabilities associated with liquid nano-crystalline suspension formulations such as, Ostwald ripening, aggregation *etc.* There are different methods utilized to formulate nano-crystalline powders such as, freeze or spray drying of nano-crystalline suspensions (Beirowski et al., 2010; Chaubal and Popescu, 2008; Cheow et al., 2010; Schiffter et al., 2010; Van Eerdenbrugh et al., 2008a,b; Zhao et al., 2007) and spraying of nano-crystalline suspensions on the carrier beads (such as sugar beads) followed by drying (Kayaert et al., 2011). In case of spray and freeze-drying, the material experiences thermal or freezing stress, respectively and the stress may affect product performance such

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as, dissolution performance *etc*. In addition, the drying process brings about concentration of the originally dispersed and dissolved materials and this may adversely affect both the physical and chemical stability of the formulation (Wang, 2000). For example, reduction in the solvent volume can lead to a decrease in the solubility of the surfactant or stabilizer, resulting in stabilizer precipitation and nano-crystal aggregation. One of the major problems associated with spray or freeze-drying of nano-crystalline suspensions is "nano-crystal aggregation" which leads to poor or inappropriate dissolution performance (Beirowski et al., Dec, 2010; Van Eerdenbrugh et al., 2008a,b). It has been shown that the aggregation of nano-crystals during drying is dependent on the drug properties. For example, drugs with higher hydrophobicity such as, itraconazole and cinnarizine, resulted in higher agglomerates and were harder to disintegrate compared to the drugs with lower hydrophobicity (Van Eerdenbrugh et al., 2008a).

Several auxiliary or bulking agents have been utilized during spray and/or freeze-drying to prevent nano-crystal aggregation (Van Eerdenbrugh et al., 2008b,c). In one study, the authors have used un-conventional matrix formers such as, Avicel PH101, Fujicalin, Aerosol 200 and Intutec SP1 to prevent nano-crystal aggregation during spray drying (Van Eerdenbrugh et al., 2008b). Typical matrix formers or bulking agents utilized in spray and/or freeze-drying of nano-crystalline suspensions are: low molecular weight sugars (such as, sucrose and trehalose); sugar alcohol (such as, mannitol); and high molecular weight sugar polysaccharides (such as, maltodextrins). In this paper, the general term sugar will be used to include all the above three categories. There are few reports available involving the use of these sugars against nano-crystal aggregation, but many cases exist where their ability to prevent nano-crystal aggregation was questioned (Van Eerdenbrugh et al., 2008a,b; Abdelwahed et al., 2006a,b; Saez et al., 2000). In addition, none of the available study/literature compared the spray and freeze-drying processing of nano-crystalline formulations.

The aim of this study was to better understand the role of sugars or matrix formers to prevent nano-crystalline aggregation during the drying processes. In this study, several disaccharides, sugar alcohol and polysaccharides were investigated to prevent nano-crystal aggregation during spray or freeze-drying of nano-crystalline suspensions. Spray drying technology was investigated due to its economy and wide application in the pharmaceutical industry and academic settings, whereas freeze-drying was utilized for spray drying comparison purposes. Indomethacin (BCS class II) was selected as a model compound and Dowfax 2A1 (ionic surfactant, negatively charged) was utilized as the stabilizer for the nano-crystalline suspensions. The sugars were dissolved in the nano-crystalline suspensions and spray or freeze-drying was performed to evaluate their role in prevention of nano-crystal aggregation during the drying process.

2. Materials

Indomethacin USP, γ polymorph, was purchased from PCCA (Houston, TX). Dowfax 2A1 (alkyldiphenyloxide disulfonate) was generously gifted by Dow Chemical Company (Midland, MI). HPLC grade acetonitrile (ACROS chemicals) was purchased form Fisher Scientific (Pittsburgh, PA). Hermetic pans and lids were purchased from TA instruments.

3. Methods

3.1. Preparation of indomethacin nanosuspensions

The indomethacin suspensions were prepared *via* the top–down approach using a Netzsch wet media mill. The required amount of indomethacin (1% w/v or 2%) was suspended in the stabilizer solution (Dowfax 2A1, 0.5% w/v or 0.1% w/v) and the suspension was stirred to achieve homogenous macro-suspensions. The macro-suspensions were milled at a milling speed of 2000 rpm in the recirculation mode. The temperature of the suspensions was maintained below 25 °C during the milling process to prevent any instability issues. The milling was performed for 90–120 min to achieve the required size of indomethacin nano-crystalline suspensions.

3.2. Spray drying of nano-crystalline suspensions

Indomethacin nano-crystalline suspension formulations were spray dried using a lab scale Buchi spray dryer B-190. Briefly, the spray dryer was pre-conditioned at the pre-set conditions of aspiration rate (−31 mbar), feed rate (9.3 mL/min) and inlet temperature (150 °C) using 100 mL of distilled water. The optimized conditions were selected based on our previous study. Once the spray dryer was equilibrated, 100 mL of the prepared nano-crystalline suspension formulations with or without sugars were spray dried. Spray gas (atomizing air) was maintained at 40 mm Hg (air flow was approximately 600 L/h) for all the formulations. The dried samples were removed from the collection chamber using a plastic scraper and evaluated for percent yield, particle size and polymorphic changes, if any.

3.3. Freeze-drying of nano-crystalline suspensions

Indomethacin–Dowfax 2A1 nano-crystalline suspensions (2% w/v indomethacin – 1% w/v Dowfax 2A1) were prepared as described above. Samples were prepared in 5 mL tubing glass vials (Wheaton Sciences Products) (2 mL fill volume) and freeze-dried in FTS system Lyostar™ II (SP scientific). Briefly, the indomethacin nano-crystalline suspensions (2% w/v, 1 mL) and different concentrations of bulking agent solutions (5% w/v, 10 w/v or 20% w/v, 1 mL) were added to these vials and vortexed to achieve homogenous mixing. The shelf temperature during primary drying was set at −40 °C (freezing protocol was 5 °C: 15 min; −5 °C: 15 min and −40 °C: 2 h or 14 h) and increased at 0.1–40 °C for secondary drying and held for 6 h. All the experiments were performed at a shelf temperature −40 °C unless specified (−60 °C in some cases). Chamber pressure throughout the primary drying was set at 60 mTorr, and in all cases the product temperature was maintained below the collapse temperature. Vials were sealed in the chamber under vacuum and stored at −20 °C until use.

3.4. Particle size analysis

Particle size measurements were performed using a Zetasizer Nano ZS90 (Malvern Instruments) to determine the *Z*-average (at 90° scattering angle) and PDI of the nanosuspensions before and after the drying processes. Briefly, the dried samples were re-suspended in a saturated and filtered (0.2 μm membrane filter) solution of indomethacin in 30% glycerin solution to avoid any discrepancy from dissolution of nano-particles during the measurements. The viscosity of this dispersant solution was measured using a Brookfield viscometer (Model DV-III) and this was used to calculate the particle size of the re-dispersed nano-suspension. Each sample was analyzed in triplicate and the results were reported as the mean values of these runs.

3.5. Determination of percent yield

For calculation of percent yield, the drug amounts in liquid and dried nano-crystalline suspensions were determined using an HPLC–UV method (as described below). Briefly, the nano-