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Root cause evaluation of particulates in the lyophilized indomethacin sodium trihydrate plug for parenteral administration☆

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ABSTRACT

Particulate growth in parenteral product frequently results in product recalls causing drug shortages. While this is mostly attributed to quality issues in a firm, particulates growth could also be due to inadequate product, process, or environmental understanding. Therefore, the objective of this study was to use indomethacin sodium trihydrate (drug) as a model drug for lyophilization and evaluates short-term stability with respect to particulate growth at different storage temperatures. Under aseptic condition, each vial filled with filtered drug solution was lyophilized, and stoppered in LyoStar3. Crimped vials were kept at 5 °C, 15 °C, 25 °C, 25 °C/60%RH, and 40 °C/75%RH. At predefined time interval, samples were characterized using X-ray powder diffraction (XRPD), thermal, and spectroscopic method. Lyophilized formulation showed four thermal events: 60–90 °C demonstrating glass transition, 110–160 °C showing recrystallization exotherm,170–220 °C exhibiting endotherm of potential polymorph, and 250 °C showing melting endotherm. XRPD of the lyophilized powder demonstrated peak at 2θ 11.10. Spectroscopic studies of lyophilized powder indicated alteration in symmetric and asymmetric carboxylate peaks over time indicating initiation of crystallization and crystal growth. Reconstitution studies indicated higher reconstitution time after six weeks for sample stored at 40 °C/75%RH. Furthermore, reconstituted solution showed presence of particulates after 8 weeks storage. These studies suggest that particulate growth can stem from poorly developed formulation and not necessarily due to frequently ascribed filtration issues.

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1. Introduction

Product instability or defect has been the reason for nearly 91 drug-products, which contain small-molecules, recall by FDA during 2011–2013 and alarmingly 80% of injectables recalled were due to the presence of particulates or crystals (Guo et al., 2013). Based on the severity of health consequences, recalls can be either Class I, in which product exposure to the patient may result in serious adverse health consequences or death, or Class II in which product usage may cause temporary or medically reversible adverse health consequences (FDA, 2009). Class III recalls are initiated when the use of the product does not cause adverse health consequences (FDA, 2009). For example, nimodipine capsules was recently recalled due to the presence of crystals (FDA, 2012) and were classified as class II recall (FDA, 2011a). Similarly, lyophilized indomethacin sodium trihydrate for injection has recently been recalled due to presence of crystals when the product was reconstituted (FDA, 2013) and the recall was classified as Class I (FDA, 2011b).

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) indicated for the treatment of the joint inflammatory conditions in adults and patent ductus arteriosus (PDA) in prematurely born infants (Jain, 2008; Qi et al., 2011). Commercially, it is available as capsules (25, 50 and 75 mg), lyophilized powder for reconstitution (1 mg/vial), suppositories (50 mg), and suspension (25 mg/5 ml) (DailyMed 2010; Lundbeck Inc., 2010). Despite an established therapeutic value, the potential benefit of the drug is marred by its aqueous solubility. Being a biopharmaceutics classification system (BCS) Class II drug, it exhibits poor aqueous solubility (0.02 mg/ml) (Jain, 2008) and high permeability (ElShaer et al., 2011). Therefore, enhancing solubility of the drug under this class to increase dissolution and bioavailability necessitates the application of strategies including salt formation, selection of metastable polymorphs, and amorphization with each techniques having merits and shortcomings (Karmwar et al., 2012). Because it is a hydrophobic molecule containing a carboxylic acid group, its

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conversion into crystalline indomethacin sodium salt has mproved solubility (Tong and Zografi, 1999). Furthermore, the salt form of the drug has been demonstrated to possess greater physical and chemical stability than the acid (Indomethacin) because of higher T_g, absence of molecular dimerization, enhanced molecular interaction, low free volume and high density (Tong and Zografi, 1999). Transformation of the crystalline salt to amorphous form of drug added further improvement in solubility of the drug. In amorphization, long range order as found in the crystalline drug is either absent or order is minimally present. Regardless of different methods of preparation to enhance solubility-limited oral bioavailability (Hancock and Parks, 2000; Kao et al., 2012), amorphous system is not a stable system especially when it is kept for long-term storage or exposed to unfavorable temperature and humidity during excursion and usage (Marsac et al., 2006).

Amorphous system, a thermodynamically unstable system, is produced by quench-cooling the molten drug or by freeze or spray drying and storing below glass transition temperature (T_g) (Badii et al., 2005; Kao et al., 2012). At this temperature, molecular translational and rotational motion is reduced and vibration is the principal molecular motion (Bhugra et al., 2008; Craig et al., 1999). Therefore, the process of crystallization from amorphous system is only slowed down by storing the drug below T_g. The presence of water in the amorphous system acts as plasticizer and therefore lower the glass transition temperature, and this greatly influences the tendency of the amorphous drug to crystallize (Andronis and Zografi, 1998). In case of intravenous (IV) drug administration, re-crystallization of drug before, during, and after IV administration can result in adverse health consequences as crystals in the blood vessels may cause their irritation and embolism (Xiong et al., 2008).

Therefore, the hypothesis of the current work is that particles can grow in amorphous or freeze-dried system from within, which might explain the root cause of some recalls. In light of the information presented above, it is essential to evaluate the effect of temperature and humidity on the stability and thereby quality of formulation. In particular, an assessment of these factors on lyophilized indomethacin is necessary as these factors, depending upon the drying process efficiency or determining drying endpoint and product excursion, may affect the product quality.

2. Materials and methods

2.1. Materials

Indomethacin trihydrate sodium was obtained from Ria International LLC (East Hanover, NJ). Type I glass tubing vials (3 ml and 20 ml) was purchased from Wheaton (Millville, NJ). FlouroTec 20 mm and 13 mm "Ready Pak" lyophilization stoppers, and 20 mm and 13 mm flip top crimp seals were purchased from West Pharmaceutical Services (Lionville, PA).

2.2. Methods

2.2.1. Preparation of indomethacin solution

Indomethacin sodium trihydrate solution was prepared by dissolving 1.216 gm of drug equivalent to 1.0 gm of indomethacin base in 1 l of 0.22 μm filtered water under stirring. The clear solution thus formed was aseptically filtered under laminar flow hood using 0.22 μm filter and transferred 5 ml of solution into either each 20 ml vials or 1 ml into each 3 ml vials. The two types of lyophilization vials were chosen to simulate the commercial product and to prepare the product in large enough quantity to enable drug characterization, respectively. These vials were then partially stoppered before placing the sample in the lyophilization chamber.

2.2.2. Lyophilization

Type I glass tubing vials (20 ml or 3 ml) were first arranged on the stainless steel tray and filled with 5 ml or 1 ml of indomethacin sodium trihydrate solution (1.216 mg/ml) in each vial. Empty dummy vials were arranged on the outer ring of the trays to minimize the effect of radiant heat from the chamber door and walls of the freeze dryer (Awotwe-Otoo et al., 2013). The solution filled vials were partially stoppered using 20 mm lyophilization stoppers.

Lyostar3™ lyophilizer, which is fitted with SMART™ and ControLyo™ Nucleation on Demand Technology (SP Industries, Stone Ridge, NY), were employed to perform lyophilization cycles. Lyophilization were conducted in SMART™ mode, which applies user-defined input (number of vials, inner area of the vial, fill volume, fill weight, T_g, concentration) into its algorithm to decide, modify, and execute the primary drying step until completion. Based on SMART™ technology, primary drying was conducted at a chamber pressure of 60 mTorr and initial shelf temperature of −33 °C. Shelf temperature was adjusted by SMART™ to 5 °C during the primary drying cycle. After primary drying was over, shelf temperature was increased at the ramp rate of 0.1 °C/min to 35 °C, where secondary drying was conducted for 8 h. More details about the lyophilization cycle are summarized in Table 1. After secondary drying step was over, vials were automatically stoppered and stored at 5 °C. Stoppered vials are crimped, and stored at 5 °C, 15 °C, 25 °C, 25°/60%RH, and 40 °C/75%RH. These samples were investigated at time 0, 1, 2, and 2.5 months to evaluate changes in the product quality attributes.

2.2.3. Preparation of samples in glove box

Samples for differential scanning calorimetry (DSC) and powder X-ray diffractrometry (XRPD) were prepared in glove box (Type 2100-2A, one channel N_2 purge control unit, Cleatech LLC, Santa Ana, CA). Prior to equilibration of the glove box, pre-weighted empty DSC aluminum hermetic pan with lid was placed in the scintillation vial. Pre-weighed pans, and specially designed low background, air-tight XRPD sample holder with built-in beam stoppering knife in the dome like cap (Bruker, Part number A100B138-B141), crimping accessories, and de-crimped lyophilized indomethacin trihydrate sodium were placed in the glove box. When an inside relative humidity of less than 5% was achieved, samples were packed in the sample holder and hermetically sealed wherever necessary. The sealed DSC samples were weighed before thermal analysis.

2.2.4. Reconstitution time

Reconstitution time of the lyophilized indomethacin sodium trihydrate was recorded by adding 2 ml or 10 ml of either 0.22 μm filtered water or 0.9% (w/v) of 0.22 μm filtered saline in product

Table 1
Parameters used in lyophilization cycle of indomethacin sodium trihydrate.

	Freezing	
Temperature set point (°C)	−42	
Ramp time (min)	67	
Hold time (min)	120	
	Primary drying	
Temperature set point (°C)	−33	5
Ramp time (min)	14	76
Hold time (min)	90	1836
Vacuum set point (mTorr)	60	60
	Secondary drying	
Temperature set point (°C)	35	
Ramp time (min)	300	
Hold time (min)	480	
Vacuum set point (mTorr)	60	

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