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Determination of tacrolimus crystalline fraction in the commercial immediate release amorphous solid dispersion products by a standardized X-ray powder diffraction method with chemometrics☆

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ABSTRACT

Clinical performance of an amorphous solid dispersion (ASD) drug product is related to the amorphous drug content because of the greater bioavailability of this form of the drug than its crystalline form. Therefore, it is paramount to monitor the amorphous and the crystalline fractions in the ASD products. The objective of the present investigation was to study the feasibility of using a standardized X-ray powder diffraction (XRPD) in conjunction with chemometric methods to quantitate the amorphous and crystalline fraction of the drug in several tacrolimus ASD products. Three ASD products were prepared in which drug to excipients ratios ranged from 1:19 to 1:49. The amorphous and crystalline drug products were mixed in various proportions so that amorphous/crystalline tacrolimus in the samples vary from 0 to 100%. XRPD of the samples of the drug products were collected, and PLSR and PCR chemometric methods were applied to the data. The R^2 was greater than '0.987' for all the models and bias in the models were statistically insignificant ($p > 0.05$). RMSEP and SEP values were smaller for PLSR models than PCR models. The models prediction capabilities were good and can predict as low as 10% when drug to excipient ratio is as high as 1:49. In summary, XRPD and chemometric provide powerful analytical tools to monitor the crystalline fractions of the drug in the ASD products.

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1. Introduction

Solid forms of drugs are commonly delivered as crystalline forms, but amorphous forms are of increasing interest due to their better physicochemical and absorption properties (Yoo et al., 2009; Chokshi et al., 2007). However, the amorphous form of the drug is thermodynamically unstable, may revert to its stable crystalline form under various environmental conditions such as high humidity, temperature or both (Rumondor et al., 2011; Rahman et al., 2013; Sinclair et al., 2011). Due to stability reasons, most of the drugs present in the commercial products are crystalline and only a very few products contain the amorphous form of the drug (Janssens and Van den Mooter, 2009). Unlike a crystalline drug which has finite melting point, the amorphous drug is characterized by glass transition temperature, T_g. T_g is a temperature range over which the amorphous drug properties change from solid-like (glass) to liquid-like (supercooled liquid). T_g is often used as a benchmark to assess amorphous system stability and storage condition because chemical and physical stability of the amorphous system is affected if stored above its T_g (Wu et al., 2013; Yoshioka and Aso, 2007). In general, an amorphous solid dispersion (ASD) formulation (which contains only an amorphous drug and amorphous/crystalline excipient(s) or only amorphous/crystalline excipient(s) and crystalline drug or both drug and excipient(s) are in amorphous forms) is considered stable if stored at 50 K or greater below the T_g of the formulation (Hancock et al., 1995; Newman et al., 2012). However, T_g often fails to predict stability of the ASD especially in the multicomponent system formulation (Baird and Taylor, 2012).

Commercially available formulations of tacrolimus are the ASD intended to improve its dissolution rate and bioavailability (Janssens and Van den Mooter, 2009). As with any amorphous drug form, it is intrinsically unstable and reverts to its stable forms (Newman et al., 2012). The conversions are even faster if not formulated (high drug loading and improper selection of excipients e.g., low T_g and/or immiscible polymer etc.) or processed properly (improper process and uncontrolled/unmonitored process parameters etc.) or exposed to high humidity/temperature conditions (Rumondor et al., 2011; Rahman et al., 2013; Sinclair et al., 2011).There were recalls of the tacrolimus ASD products due to their failure to meet critical quality attributes (CQAs) (FDA, 2014). The clinical performance of ASD can only be ensured if the

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amorphous/crystalline ratio meet its release specification and maintain that ratio/fraction throughout product shelf life. The amorphous/crystalline ratio change in the ASD products can be measured by direct and indirect method. The indirect method involves performing discriminating dissolution methods. The product will show sign of crystalline reversion by not meeting dissolution specification if tested in discriminating dissolution conditions (Newman et al., 2012; Zidan et al., 2012). Direct methods, however, involve quantitating the crystalline drug fraction in the product by various analytical techniques such as DSC, NIR, FTIR, Raman, terahertz-pulsed, ssNMR and X-ray powder diffraction (XRPD) (Shah et al., 2006; Siddiqui et al., 2014). Vibration spectroscopies such as NIR, FTIR and Raman are not always sensitive to differentiate between amorphous and crystalline forms of the drug. Moreover, newer vibration technique, terahertz-pulsed spectroscopy probe lattice and low energy hydrogen bonding vibrations, and it showed more pronounced spectral changes for amorphous and crystalline forms compared to FTIR and NIR, however, this technique is still evolving (Shah et al., 2006). On the other hand, XRPD is the most definitive detection and quantification method for the crystalline/amorphous fraction due to distinctive diffractogram pattern of the two forms. XRPD have an advantage over DSC in terms of displaying multiple peaks and some of which are overlapping with the excipients of the formulation. In such cases non-overlapping peaks can be utilized in quantification of the crystalline fraction in the products (Siddiqui et al., 2014). Another technique that produced results similar to XRPD is ssNMR, however, it takes a very long time to collect good signal to noise spectra, especially for low dose drug products (Shah et al., 2006).

This work was the extension of our previous work in which we have shown the use of XRPD in the quantification of the crystalline tacrolimus from the ASD formulations (Siddiqui et al., 2014). Our findings indicated that crystalline tacrolimus as low as 4% (when total drug content is 24.4%) can be quantitated with good precision in the ASD. However, detection and quantification limits depend upon the drug loading in the ASD formulation (Siddiqui et al., 2014). There is no literature report for quantification of crystalline fraction of tacrolimus in the commercial products by XRPD and chemometrics to the best of our knowledge. However, many investigator reported the use of XRPD in quantification of amorphous/crystalline or polymorphs fraction in the bulk drug substance (Chadha et al., 2012). Few investigators attempted to use XRPD univariate method to quantitate crystalline/amorphous fraction in the product for high dose drug or low drug to excipients ratio (higher drug percentage with respect to excipient) (Kommavarapu et al., 2013). Therefore, focus of present investigation was to study the feasibility of XRPD and chemometrics in quantification of the crystalline and amorphous fractions of tacrolimus in commercial ASD products that contained 2–5% drug. Furthermore, this manuscript provides novel methods to the sponsors of tacrolimus products that are otherwise unavailable in United States Pharmacopeia or literature.

2. Materials and methods

2.1. Materials

Tacrolimus monohydrate (Ria International LLC, East Hanover, NJ, USA), hydroxypropyl methyl cellulose USP (HPMC) (Shin-Etsu Chemical Co., Ltd., Chiyoda-Ku, Tokyo, Japan), lactose monohydrate NF (LM) (Foremost Farms, Baraboo, WI, USA), magnesium stearate (MGS) (Sigma–Aldrich, St. Louis, MO, USA), colloidal silicon dioxide (CSD) (Aerosil 200, Evonik Industries AG, Hanau-Wolfgang, Germany), croscarmellose sodium (CC) (FMC Biopolymer, Philadelphia, PA), ethanol 200 proof (Decon Labs, Inc., King of Prussia, PA, USA) were purchased and used as received.

2.2. Methods

2.2.1. Preparation of sustained release ASD

Three ASD products were selected that contained LM, HPMC, CC, MGS and CSD as excipients. Drug to excipients ratio of the products are given in Table 1. The ASDs were prepared by solvent evaporation method as described by Zidan et al. (2012) and resultant formulations were called the amorphous tacrolimus products. Similarly, placebo ASDs were prepared in the same way and have identical composition as that of the products but without the drug. Crystalline drug was added to placebo ASDs to make their composition equal to the amorphous tacrolimus products. The resultant formulations were called crystalline tacrolimus products. The drug physical forms in the products were confirmed by XRPD. The amorphous and crystalline tacrolimus products were mixed in various ratios to make sample matrices for product A (drug: excipients 1:19 and total drug content 5%), product B (drug: excipients 1:27 and total drug content 3.6%) and product C (drug:excipients 1:49 and total drug content 2%). Furthermore, the amorphous/crystalline tacrolimus in the sample matrices of the products vary from 0 to 100%. These sample matrices of each product were used to collect XRPD data and chemometric models development for the crystalline/amorphous fraction determination in the samples.

2.2.2. X-ray powder diffraction

Tacrolimus forms in the amorphous product A, product B, product C, and their corresponding crystalline products were confirmed by XRPD. Diffractograms were collected using a Bruker D8 Advance with DaVinci design (Bruker AXS, Madison, Wisconsin) equipped with the LYNXEYE scintillation detector and Cu K_α radiation (λ = 1.5405 Å) at a voltage of 40 KV and current of 40 mA. Before measurement, the instrument functionality was checked using corundum as an external standard. About 650 mg of sample was placed in the sample holder and six replicate diffractograms of each sample were collected over 2θ range of 4–30° with an increment of 0.00915 at 1 s per step (3000 total steps). Sample holder was rotated during run to get the average diffractogram of the sample. The XRPD operation, data collection, and data analysis were achieved through Diffract. Suite (V2.2).

2.2.3. Data analysis

XRPD data were analyzed by Unscrambler X software (version 10.1, Camo Process, Oslo, Norway) for the development of chemometric models.

3. Results and discussion

3.1. X-ray powder diffraction

XRPD is shown in Fig. 1A. HPMC and CSD showed diffuse and halo diffraction patterns which are the characteristics of an

Table 1
Composition of Tacrolimus Products.

Components	Product A	Product B	Product C
Drug:excipients ratio	1:19	1:27	1:49
Excipients	LM, HPMC, CC, MGS and CSD	LM, HPMC, CC, MGS and CSD	LM, HPMC, CC, MGS and CSD

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