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Impact of formulation and process variables on solid-state stability of theophylline in controlled release formulations☆

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ABSTRACT

Understanding the impact of pharmaceutical processing, formulation excipients and their interactions on the solid-state transitions of pharmaceutical solids during use and in storage is critical in ensuring consistent product performance. This study reports the effect of polymer viscosity, diluent type, granulation and granulating fluid (water and isopropanol) on the pseudopolymorphic transition of theophylline anhydrous (THA) in controlled release formulations as well as the implications of this transition on critical quality attributes of the tablets. Accordingly, 12 formulations were prepared using a full factorial screening design and monitored over a 3 month period at 40 °C and 75%. Physicochemical characterization revealed a drastic drop in tablet hardness accompanied by a very significant increase in moisture content and swelling of all formulations. Spectroscopic analysis (ssNMR, Raman, NIR and PXRD) indicated conversion of THA to theophylline monohydrate (TMO) in all formulations prepared by aqueous wet granulation in as early as two weeks. Although all freshly prepared formulations contained THA, the hydration–dehydration process induced during aqueous wet granulation hastened the pseudopolymorphic conversion of theophylline during storage through a cascade of events. On the other hand, no solid state transformation was observed in directly compressed formulations and formulations in which isopropanol was employed as a granulating fluid even after the twelve weeks study period. The transition of THA to TMO resulted in a decrease in dissolution while an increase in dissolution was observed in directly compressed and IPA granulated formulation. Consequently, the impact of pseudopolymorphic transition of theophylline on dissolution in controlled release formulations may be the net result of two opposing factors: swelling and softening of the tablets which tend to favor an increase in drug dissolution and hydration of theophylline which decreases the drug dissolution.

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1. Introduction

Most pharmaceutical solids exist in more than one crystalline form or in a disordered amorphous state. Some crystalline drugs have the propensity of incorporating in their crystal lattice solvents; either in a stoichiometric or non-stoichiometric way (Hilfiker et al., 2006). The different solid forms exhibit dissimilar physical, mechanical and chemical properties which may affect their processability during product manufacturing, and alter product performance, such as stability, dissolution, bioavailability and clinical efficacy (Huang and Tong, 2004; Kobayashi et al., 2000; Raw et al., 2004; Yu et al., 2003). Also, pharmaceutical processes such as wet granulation, drying, milling; compression and lyophilization can induce polymorphic transition during manufacturing. Conversely, judicious selection of formulation excipients can be employed to retard or inhibit solid-state transition during processing and storage (Airaksinen et al., 2004; Zhang et al., 2004).

Theophylline is a bronchodilator used in the management of reversible airway obstruction associated with asthma and chronic obstructive pulmonary disease. Currently, the therapeutic use of theophylline in developed countries is restricted to patients whose disease conditions are poorly controlled due to the drug's higher incidence of side effects; nonetheless theophylline is the most widely used bronchodilator due to its lower cost (Barnes, 2003; ZuWallack et al., 2001). Theophylline exists either as a monoclinic channel hydrate or an anhydrate. Additionally, anhydrous

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theophylline has been identified to exist in three different forms; Form I is the most stable state at high temperature, Form II, which is used in pharmaceutical formulations is stable at room temperature and Form III the metastable anhydrous intermediate (Seton et al., 2010). However, the commonly encountered solid state transition of theophylline during the pharmaceutical manufacturing process and product storage is the transposition between anhydrous Form II (THA) and theophylline monohydrate (TMO) with or without Form III as an intermediate.

Ando et al. (1986) first reported the conversion of THA to TMO upon storage at 90% relative humidity (Ando et al., 1986). This transition was also reported to occur upon storage at a relative humidity of 75% (Alvarez-Lorenzo et al., 2000; Phadnis and Suryanarayanan, 1997; Zhu et al., 1996). Additionally, THA has been shown to convert to the monohydrate form irrespective of the choice of formulation excipient used, during wet granulation (Airaksinen et al., 2004; Jørgensen et al., 2004; Wikström et al., 2008). The formation of anhydrous Form III has also been identified upon drying of the wet theophylline granules (monohydrate) under low pressure (Nunes et al., 2006; Phadnis and Suryanarayanan, 1997; Tantry et al., 2007). These transitions are associated with decrease in the dissolution and drug bioavailability owing to the lower solubility of the monohydrate crystals as well as an increase in binding interaction between theophylline and formulation excipients (Alvarez-Lorenzo et al., 2000; Herman et al., 1988, 1989; Rodriguez-Hornedo et al., 1992). Theophylline has a narrow therapeutic window and is associated with a high incidence of adverse events and sudden deaths (eHealthMe, 2015). Consequently, minor alterations in theophylline product quality may have significant impact on the clinical efficacy and toxicity observed in patients. For this reason, a thorough understanding of the impact of the manufacturing process, excipient choice as well as their interactions on the solid-state stability of theophylline during storage is vital.

Although several authors have reported on the hydration and dehydration of theophylline, most of these studies were either conducted in binary mixtures of theophylline and excipients or in immediate release formulations. However, most marketed theophylline products are controlled release formulations. Secondly, the impact of these solid-state transitions during manufacturing on the storage stability of the product remains unexplained.

The present study was an attempt to investigate the impact of excipient selection, manufacturing process and their interactions on solid-state transitions of theophylline in controlled release formulation during storage and use. Physicochemical and spectroscopic characterizations were carried to monitor for any solid-state transitions as well changes in product quality attributes.

2. Materials and method

2.1. Materials

Hydroxypropyl methylcellulose K4M and K100M (Colorcon, Harleysville, PA, USA), theophylline anhydrous Form II (THA), magnesium stearate (MgS) (Sigma, St. Louis, MO, USA), lactose monohydrate (LM) and anhydrous lactose (LA) (Foremost farms, Baraboo, WI, USA), Colloidal silicon dioxide (Aerosil 200)(Evonik, Parsippany, NJ, USA), polyvinylpyrrolidone (PVP K15, K30 and K90) (Sigma Aldrich, St. Louis, MO, USA) were used.

2.2. Methods

2.2.1. Design of experiment

The effect of formulation and process variables on solid-state stability and product quality were assessed using a full factorial design. The most commonly used formulation excipients and process variables were chosen for this study. The formulations variables studied were; the polymer viscosity/molecular weight (HPMC K4M and HPMC K100M) and the diluent (LA and LM). The formulation composition was as follows: THA 53.33%, K4M/K100M 33.33%, LA/LM 10.7%, Aerosil 0.1% and MgS 2.5%. In addition, the impact of the manufacturing processes (wet granulation and direct compression) and the granulating fluid employed (water and isopropanol) during wet granulation were considered. The experimental design and data analysis was conducted with JMP software version 11.1.1 from SAS (Cary, NC, USA). In all twelve formulations were prepared according to the experimental design shown in Table 1.

2.2.2. Granulation and tableting

Mixing and granulation were performed with the KG-5 high shear granulator/mixer (Key International, Cranbury, New Jersey, USA). Solid-state transitions during granulation were monitored by in-line Luminar 5030 AOTF-NIR probe (Sparks Glencoe, Maryland, USA) and offline X-ray powder diffractometry. The wet granules were dried at 50 °C until the moisture content was below 2%. The moisture content of the dried granules was determined by loss on drying (MB 45 moisture analyzer, Ohaus Corporation, Parsippany, NJ, USA). The dried granules were sieved, blended with magnesium stearate and aerosil 200. The granules were compressed into tablets with a rotary tablet press using a 10 mm punch size (Globe Pharma, New Brunswick, New Jersey, USA). The initial tablet hardness was 6–8 kp for all the formulations.

2.2.3. Physicochemical characterization

Moisture content analysis was performed with Karl Fisher V30 compact titrator from Mettler Toledo- (Columbus OH, USA) using Aquastar® Comp-2 Karl fisher reagent (EMD Millipore, Billerica, MA, USA). About 100 mg of powdered sample was used for moisture analysis. tablet hardness was measured with the PTB 11EP hardness tester (Pharma Test, Hainburg, Germany). Scanning electron microscopy (JSM-6390 LV- JEOL, Tokyo, Japan) images of the tablets were taken before and after stability studies at a magnification of 100X. The dissolution profiles were obtained with USP dissolution apparatus I (basket) at 100 rpm. The dissolution media used was 900 ml of 0.05 M phosphate buffer pH 6.6 maintained at 37 °C. Sample collection was done over 24 hrs and analyzed for their theophylline content. HPLC analysis was conducted with an Agilent 1260HPLC system equipped with an auto sampler, a quaternary pump, diode array detector set at 271 nm wavelengths, and column temperature maintained at 25 °C. A Zorbax® eclipse plus C-18 column (4.6 × 100 mm, 3.5 μm packing) was used with a mobile phase composition of 7% acetonitrile and 93% acetate buffer (10 mM pH 3.5) run isocratically at 1 ml/min.

Table 1
DOE of formulations used (abbreviations used: IPA-isopropanol; DC-direct compression).

	Pattern	Polymer	Diluent	Granulating fluid
F1	−+−	HPMC K4M	LM	IPA
F2	+−−	HPMC K100M	LA	IPA
F3	−−+	HPMC K4M	LA	Water
F4	+++	HPMC K100M	LM	Water
F5	−++	HPMC K4M	LM	Water
F6	+−+	HPMC K100M	LA	Water
F7	++−	HPMC K100M	LM	IPA
F8	−−−	HPMC K4M	LA	IPA
F9	22	HPMC K100M	LM	DC
F10	21	HPMC K100M	LA	DC
F11	12	HPMC K4M	LM	DC
F12	11	HPMC K4M	LA	DC