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A high throughput platform for understanding the influence of excipients on physical and chemical stability

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ABSTRACT

The present study puts forward a miniaturized high-throughput platform to understand influence of excipient selection and processing on the stability of a given drug compound. Four model drugs (sodium naproxen, theophylline, amlodipine besylate and nitrofurantoin) and ten different excipients were selected. Binary physical mixtures of drug and excipient were transferred to a 96-well plate followed by addition of water to simulate aqueous granulation environment. The plate was subjected for XRPD measurements followed by drying and subsequent XRPD and HPLC measurements of the dried samples. Excipients with different water sorbing potential were found to influence distinctly on the phase transformation behaviour of each drug. Moreover, the amount of water addition was also a critical factor affecting phase transformation behaviour. HPLC analysis revealed one of the drug:excipient pairs with a tendency for chemical degradation. The proposed high-throughput platform can be used during early drug development to simulate typical processing induced stress in a small scale and to understand possible phase transformation behaviour and influence of excipients on this.

1. Introduction

The current drug design approach in the pharmaceutical field is moving towards more complex and high-molecular weight compounds, often with poor solubility and permeability. In such a scenario, it becomes very critical to control the particular solid form in the final dosage form to make sure that expected dissolution rate and solubility is obtained in order to achieve target bioavailability (Chemburkar et al., 2000). Moreover, an increased number of poorly soluble compounds also demands for utilization of salt forms to gain advantage of solubility (Tsutsumi et al., 2011). Therefore, it becomes crucial to understand factors affecting disproportionation of the salt form to its free form, which in turn, may lead to dramatic decrease in the solubility of the final product (Zannou et al., 2007). Development of lipid-based formulations is also one of the emerging trends to overcome poor solubility. However, there might be risk of precipitation from such formulations (Mullertz et al., 2010; Porter et al., 2007). Another strategy to deal with poorly soluble compounds is use of a high energy metastable polymorph or amorphous form of a drug (Kawabata et al., 2011). On the other hand, there is always a risk of transformation to the stable polymorph, again leading to the poor bioavailability from the final formulation (Bauer et al., 2001). Thus, it becomes essential to understand phase transformation behaviour among solid forms including polymorphism, salt formation and disproportionation and solvation and desolvation due to their significant impact on the successful development of drug candidates (Brittain, 2012; Debnath and Suryanarayanan, 2004; Morris et al., 2001).

On the other side, the key challenge during preformulation stage is to build the greatest possible knowledge about the candidate drug compound with minimal availability of resources. Need for the high-throughput platform in such scenario can be explained based on 3 logics: (1) If you study more compounds, you improve chances of finding the optimal one; (2) If you can eliminate the problematic compounds early, you will find the optimal one quickly and cost-effectively; (3) If you know the risk associated with the development of particular compound as early as possible, you can find the ways to mitigate the risk of failures during later stages of drug development (Balbach and Korn, 2004).

Many novel approaches for careful polymorph screening have been developed (Sistla et al., 2011; Aaltonen et al., 2009) following the sudden appearance of new polymorph of ritonavir (Chemburkar et al., 2000). Most of these approaches are based on finding all the possible polymorphs of the candidate drug compound from solution crystallization experiments. Moreover, excipients and water in the formulation has also found to have significant influence on the phase transformation behaviour (Airaksinen et al., 2005a; Jørgensen et al., 2004; Salameh and Taylor,

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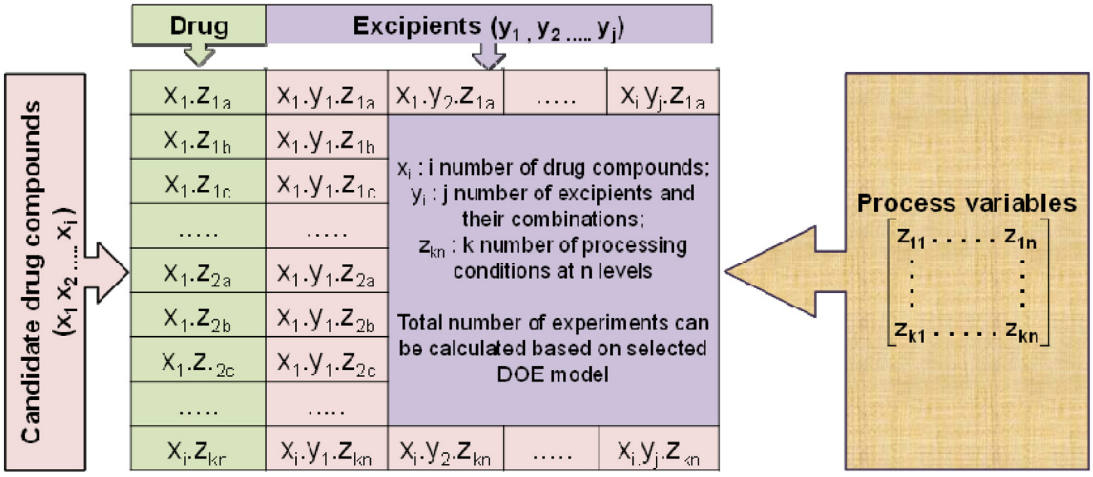

Fig. 1. Schematic presentation of high-throughput platform for the study of influence of excipients and process variables on the phase transformation behaviour of investigational compounds.

2006; Wikström et al., 2008). However, implication of the high-throughput approach to understand influence of excipients and process variables on the possible phase transformation behaviour and also to use the same as a way to explore new solid forms has not been widely explored (Allesø et al., 2010). Therefore, the present study has been carried out as a step towards developing a high-throughput platform for understanding the phase transformation behaviour of drugs during processing and to explore the possibility of appearance of new solid forms in that environment.

Fig. 1 depicts a high-throughput platform to understand influence of excipients and process variables on the phase transformation behaviour of the candidate drug compounds under investigation. The experimental design can be built on the high-throughput platform to explore behaviour of different drug compounds in the presence of various excipients and processing conditions at multiple levels. The complexity of the experimental design can vary according to the stage of the drug product development. Furthermore, various predictive DOE (design of experiment) models can be used to estimate various factors affecting critical quality attributes (Andersson et al., 2007).

In the current study, four model compounds (Table 1) (Caira et al., 1996; Dogan-Topal et al., 2009; Koradia et al., 2010; Malaj et al., 2009; Phadnis and Suryanarayanan, 1997), two different processing conditions (water levels of 0.5 g/g and 1 g/g) and ten different excipients (Table 2) (Rowe et al., 2009) were used, thus generating 88 experiments.

2. Materials and methods

2.1. Materials

Sodium naproxen anhydrate (NS-AH, CSD refcode: ASUBUL) and amlodipine besylate anhydrate (AB-AH, CSD refcode: XOZRUZ) forms were received from Divi's Laboratories Ltd. (Hyderabad, India) and from Matrix Laboratories Ltd. (Secunderabad, India), respectively. Theophylline (TP) anhydrate form II (TP-AH, CSD refcode: BAPLOT01) and nitrofurantoin (NF) anhydrate β form (NF-AH, CSD refcode: LABJON02) were purchased from Shandong Xinhua Pharmaceutical Co. Ltd. (Shandong, China) and Fagron A/S (Copenhagen, Denmark), respectively. All the model compounds were of USP grade.

Anhydrous lactose (Supertab® 22AN) and lactose monohydrate (Pharmatose® 350M) were purchased from DMV-Fonterra Excipients (Goch, Germany). Mannitol (Pearlitol® 160C) was obtained from Roquette Pharma (Germany, Klotze). Pregelatinized corn starch 1500 (Lycatab® C) and tartaric acid were purchased from Fagron A/S (Copenhagen, Denmark). Low substituted hydroxyl propyl cellulose (L-HPC®, LH-21), microcrystalline cellulose (Avicel® PH101) and silicified microcrystalline cellulose (Prosolv® SMCC 90) were received from Shin-Etsu Chemical Ind. Co. Ltd. (Tokyo, Japan); FMC International (Cork, Ireland), and JRS Pharma (Rosenberg, Germany), respectively. Anhydrous sodium carbonate was purchased from Merck KGaA, Darmstadt, Germany. Micronized synthetic amorphous silica gel (Syloid® 244FP) was provided by Grace Davison Discovery sciences (Columbia, MD, USA). Tartaric acid and anhydrous sodium carbonate were of analytical grade, while all the other excipients were of Ph. Eur. grade.

Potassium sulphate (analytical grade, VWR International, Leuven, Belgium) was used for generation of 95% RH in desiccator. Potassium dihydrogen phosphate (Sigma Aldrich) and phosphoric acid were of analytical grade and were used for phosphate buffer preparation for HPLC analysis. Acetonitrile (HiPerSolv CHROMANORM, VWR International, Leuven, Belgium) used for mobile phase preparation was of HPLC grade. MiliQ water (Millipore, Billerica, MA, USA) was used for the preparation of wet samples and for mobile phase preparation and sample preparation for HPLC analysis.

2.2. 96-well plate sample preparation

Binary mixtures of drug and excipients were prepared in 1:1 ratio to generate 15 mg of the physical mixture. The mixtures were transferred to a 96-well plate followed by addition of 1 g/g (15 μl) or 0.5 g/g of water (7.5 μl), respectively, for each drug–excipient mixture. Table 3 summarizes the setup of samples in the 96-well plate (samples are annotated accordingly throughout the article). The plate with the wet drug–excipient mixtures was kept at 95% RH for 6 h for equilibration of water in the physical mixtures. The well plate was then covered with X-ray transparent film to prevent drying of the samples during measurement by XRPD. The wet samples in 96-well plate were then subjected to 3 consecutive XRPD measurements (referred as W1, W2 and W3, corresponding to 0 h, 12 h and 24 h of measurement after equilibration period of 6 h at 95% RH). Subsequently, the plate was dried at 60 °C for 2 h before XRPD measurement of the dried samples (referred as D1). HPLC analysis was performed for all the samples to verify chemical stability.