Miniaturized Approach for Excipient Selection During the Development of Oral Solid Dosage Form

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ABSTRACT: The present study introduces a miniaturized high-throughput platform to understand the influence of excipients on the performance of oral solid dosage forms during early drug development. Wet massing of binary mixtures of the model drug (sodium naproxen) and representative excipients was followed by sieving, drying, and compaction of the agglomerated material. The mini-compacts were subjected to stability studies at 25°C/5% relative humidity (RH), 25°C/60% RH and 40°C/75% RH for 3 months. The physical stability of the drug was affected by the storage condition and by the characteristics of the excipients, whereas all the samples were chemically stable. Force–distance curves obtained during the compression of agglomerated material were used for the comparison of compressibility of different drug–excipient mixtures. The agglomerated drug–excipient mixtures were also subjected to studies of the dissolution trend under sequential pH conditions to simulate pH environment of gastrointestinal tract. Major factors affecting the dissolution behavior were the diffusion layer pH of the binary mixtures and the ability of the excipients to alter the diffusion layer thickness. The proposed approach can be used for excipient selection and for early-stage performance testing of active pharmaceutical ingredient intended for oral solid dosage form. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:900–908, 2014

Keywords: preformulation; excipients; dissolution; stability; salts; hydrate; phase transition; pH; compression; co-crystal

INTRODUCTION

Many novel dosage forms have been developed in recent years. However, the oral solid dosage forms still continue to be the most preferred pharmaceutical dosage forms.[1] The manufacturing of tablets is a complex multistage process involving various steps, such as powder blending, granulation, drying, and compaction. For the successful manufacturing of tablets, various excipients such as binders, diluents, disintegrants, and lubricants are needed. Although excipients are considered as inactive ingredients and are added to improve the functionality of the dosage forms, they may have deleterious effect on the performance of the dosage forms at various stages during manufacturing,[2–4] storage,[5–7] and/or dissolution.[5,8,9] This may be attributed to various properties of excipients such as water-sorbing potential,[4,6,10,11] phase transformation behavior,[7] hydrophobicity,[12] solubility,[13,14] microenvironment pH,[14–17] crystallinity,[10] and chemical incompatibility with active pharmaceutical ingredient (API).[18–20] Furthermore, properties of the byproducts produced because of drug–excipient interaction can also affect the performance of API. John et al.[21] observed a unique disproportionation behavior of an HCl salt in the presence of magnesium stearate because of *in situ* formation of magnesium chloride, and where its deliquescent nature was responsible for the enhanced disproportionation of the HCl salt. Thus, it is important to investigate the influence of excipients on the performance of oral solid dosage forms as early as possible during development to identify and avoid performance-related issues attributed to the excipients. A well-designed excipient screening study during early development can help selecting suitable excipients that improve the functionality of the API.[7,10,11,22,23] Also, it can help in the elimination of excipients having deleterious effect on the performance of API[5,15,16,19,21] and/or find the solutions to mitigate the issues attributed to the excipient.[7,24]

On the contrary, one of the major challenges during early drug development is minimal availability of candidate drug compounds limiting the possible batch sizes and the number of studies that can be performed. Therefore, it is important to develop approaches that enable achieving the maximum information about the candidate drug compounds with minimal use of resources.[25] An approach for solid form screening in the presence of processing-induced stress has been reported by Allesø et al.[26] The current study presents a miniaturized approach for the combined investigation of the influence of the excipients and processing-induced stress (wet granulation and compression) on the performance of oral solid dosage forms (tablets). The model drug, sodium naproxen (NS), and 10 model excipients with representative physicochemical properties[27] have been selected. Model excipients with a variety of water-sorbing potential, microenvironment pH, crystallinity, and with different functionalities were selected.[27] Thus, a systematically chosen representative set of excipients and small-scale simulated processing conditions during typical secondary manufacturing can support risk-based assessment during formulation development.

EXPERIMENTAL

Materials

Sodium naproxen anhydrate form (NS AH) (CSD refcode: ASUBUL, USP grade) was received from Divi's Laboratories Limited (Hyderabad, India). NS is known to exist as anhydrate

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form (AH) and four different hydrate forms[28–31] [monohydrate (MH), dihydrate-I (DH-I), dihydrate-II (DH-II), and tetrahydrate (TH)]. The drug is known to be sensitive to hydration and dehydration behavior under the range of temperature and humidity conditions.[29–31]

MiliQ water (Millipore, Billerica, Massachusetts) was used for wet massing and for high-performance liquid chromatography (HPLC) analysis. Potassium dihydrogen phosphate and phosphoric acid were of analytical reagent grade. Acetonitrile (HiPerSolv CHROMANORM; VWR International, Leuven, Belgium) was used for mobile phase preparation for HPLC analysis. Anhydrous lactose (LAH) (Supertab® 22AN) and lactose monohydrate (LMH) (Pharmatose® 350 M) were received from DMV-Fonterra Excipients (Goch, Germany). Mannitol (Mnt) (Pearlitol® 160C) was purchased from Roquette Pharma (Germany, Klotze). Partially pregelatinized corn starch 1500 (starch) (Lycatab® C) and tartaric acid (TA) were obtained from Fagron A/S (Copenhagen, Denmark). Low-substituted hydroxyl propyl cellulose (L-HPC®, LH-21), microcrystalline cellulose (Avicel® PH101) and silicified microcrystalline cellulose (SMCC) (Prosolv® SMCC 90) were received from Shin-Etsu Chemical Ind. Company Ltd. (Tokyo, Japan), FMC International (Cork, Ireland), and JRS Pharma (Rosenberg, Germany), respectively. Anhydrous sodium carbonate (SC) was received from Merck KGaA (Darmstadt, Germany). Micronized porous silicone dioxide (SL; Syloid® 244FP) was provided by Grace Davison Discovery sciences (Columbia, Maryland). TA and SC were of analytical reagent grade, whereas all the other excipients were of Ph. Eur. grade. Sodium bromide and sodium chloride (both from Merck KGaA) were used in desiccators for stability studies under 25°C/60% relative humidity (RH) and 40°C/75% RH conditions, respectively. Potassium dihydrogen phosphate (Sigma–Aldrich) was used for the preparation of buffer media for dissolution studies and for HPLC studies. Phosphoric acid was used for adjustment of pH of the buffer media for HPLC analysis, whereas HCl or NaOH were used for pH adjustment of the dissolution media.

Preparation of Mini-Compacts

Binary powder mixtures of the drug (NS AH) and excipients were prepared by mixing 1 g of the drug and 1 g of excipient. The wet massing of the powdered binary mixture was performed by grinding the binary mixtures in the presence of 0.5 g/g (1 mL) of water using mortar and pestle. The wet masses were then sieved through a 1000-μm sieve and dried at 60°C for 2 h. The dried agglomerated material was then sieved through a 500-μm sieve to obtain approximately uniform agglomerated particles for all the drug–excipient mixtures. Twenty milligram of agglomerated material was weighed and compressed under low pressure using texture analyser. Mini-compacts were prepared using a 6-mm die and a flat-faced punch fitted on a TA-XT2 texture analyser (Stable Micro Systems Ltd., Godalming, UK), equipped with a 30-kg load cell. The pretest speed, test speed, and posttest speed were 5, 0.2, and 10 mm/s, respectively. Maximum applied force was 280 N. Six mini-compacts were prepared for each set of agglomerated material for 1 month and 3 months stability studies under each storage condition. Compression in the empty die was also performed to correct for the elasticity of the system. The preliminary data were examined using TX32 software (Stable Microsystems, Godalming, UK). Later on, the force–distance curves were transformed to specific volume versus pressure curves. The Walker model was applied by fitting the specific volume versus pressure data using logarithmic regression ($V = w_w \log P + V_w$). The relative Walker coefficient values were calculated using the following equation[32]:

$$w_{w,rel} = -\frac{w_w}{V_w - w_w} \times 100$$

where, w_w is the Walker coefficient, V is the specific volume (cm^3/g), and V_w is the specific volume (cm^3/g) at 1 MPa. The pressure range used for the regression was 5–100 N (0.18–3.54 MPa).

Stability Studies

Stability studies were performed by exposing the mini-compacts under 25°C/5% RH, 25°C/60% RH, and 40°C/75% RH for 1 and 3 months. The samples at each time point were subjected to X-ray powder diffraction (XRPD) and HPLC analysis for evaluation of the physical and chemical stability, respectively.

X-Ray Powder Diffraction

Diffraction patterns were recorded on a programmable XYZ stage that can hold 96-well plate[17] under ambient conditions in transmission mode using a PANalytical X'Pert Pro powder diffractometer (Almelo, The Netherlands), consisting of a θ/θ goniometer and a solid-state PIXcel detector. CuKα ($\lambda = 1.5418$ Å) radiation, generated at a tube voltage of 45 kV and a current of 40 mA was used. Sample oscillation was applied in X-mode in the range of 1 mm. A continuous 2θ scan was performed in the range of 2°–40° 2θ with a step size of 0.026° 2θ and at a speed of 96.39 s/point. Data were collected using X'Pert data collector version 2.2 and were analyzed with X'Pert high score plus version 2.2.4 (both from PANalaytical B.V., Almelo, The Netherlands).

High-Performance Liquid Chromatography

High-performance liquid chromatography analyses were performed on a 1100 series LC system from Agilent Technologies (Waldbronn, Germany) equipped with an online degasser (G1379A), a high-pressure binary pump (G1312A), an autoinjector (G1329A), a thermostated column compartment (G1316A), and a photodiode array detector (G1315B). For data processing and acquisition, Chemstation 01.03 software (Agilent Technologies) was used. The mini-compacts were dispersed in 10 mL acetonitrile (ACN)–water (80:20), followed by sonication for 10 min and subsequent filtration using 0.22 μm nylon filters. Ten microliter of the filtrate was injected into an HPLC system for all samples. Chromatographic separations were achieved on a C-8 column (150 mm, 4.6 mm i.d., particle size 5 μm; Agilent Zorbax, Agilent Technologies, Glostrup, Denmark). Mobile phase system was 95% of 10 mM KH_2PO_4 buffer (10 mM, pH 2.5, adjusted with phosphoric acid) and 5% of ACN as mobile phase A and ACN as mobile phase B; the gradient employed was: T_{min}/A:B (v/v): $T_{0.01–2}$/80:20 (v/v), T_{12}/60:40 (v/v), $T_{15–17}$/10:90 (v/v), and T_{20}/80:20 (v/v). A flow rate of 1 mL/min was employed for all the measurements. Column equilibration period of 10 min was used between two subsequent runs. Detection wavelength was 260 nm.