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Research paper

Investigation of polymorphic transitions of piracetam induced during wet granulation

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ABSTRACT

Piracetam was investigated as a model API which is known to exhibit a number of different polymorphic forms. It is freely soluble in water so the possibility exists for polymorphic transformations to occur during wet granulation. Analysis of the polymorphic form present during lab-scale wet granulation, using water as a granulation liquid, was studied with powder X-ray diffraction and Raman spectroscopy as off-line and inline analysis tools respectively. Different excipients with a range of hydrophilicities, aqueous solubilities and molecular weights were investigated to examine their influence on these solution-mediated polymorphic transitions and experimental results were rationalised using molecular modelling. Our results indicated that as an increasing amount of water was added to the as-received piracetam FIII, a greater amount of the API dissolved which recrystallised upon drying to the metastable FII(6.403) via a monohydrate intermediary. Molecular level analysis revealed that the observed preferential transformation of monohydrate to FII is linked with a greater structural similarity between the monohydrate and FII polymorph in comparison to FIII. The application of Raman spectroscopy as a process analytical technology (PAT) tool to monitor the granulation process for the production of the monohydrate intermediate as a precursor to the undesirable metastable form was demonstrated.

1. Introduction

Due to regulatory restrictions it is of the utmost importance that the polymorphic form of the active pharmaceutical ingredient (API) in a final solid dosage form is the desired one and that the particular polymorph is stable over the lifetime of the product. In this work polymorphism is defined as in the International Conference on Harmonization (ICH) Guideline Q6A (2) to also include solvation products [1]. An understanding of the form of polymorph present during all stages of processing is important due to the differences in physical properties which can be attributed to various polymorphs of a given API, for example compaction, flow properties or aqueous solubility, and therefore bioavailability or bioequivalence. Furthermore, differences in the melting point or heat capacity of various polymorphs could have an impact on the outcome from non-ambient processing such as hot melt extrusion. Industrially a thorough knowledge of the polymorphic form of the API present at each stage of processing, and most importantly in the final product, is an important regulatory issue. Paragraph IV Drug Product Applications: Generic Drug Patent Challenge Notifications, published by the FDA has recently been used to challenge original drug product patents based on the drug product containing a different API polymorph from that of the original product [2]. For example the crystalline form I of the antiretroviral, Ritonavir, has significantly higher solubility than the polymorphic crystalline form II due to the differing hydrogen bonds in the respective crystals [3]. Furthermore a study by Yoshinari et al. [4] detailed how a downstream-processing, moisture-induced polymorphic transition in mannitol resulted in an improvement of its physical compaction properties.

Piracetam is a nootropic agent prescribed for myoclonus, a twitching or jerking symptomatic of neural disorder. It is a highly aqueous-soluble drug with five reported polymorphs; FI(6.747), FII (6.403), FIII(6.525), FIV(8.954) and FV(6.390); however the latter two of these are generated only at high pressures (>0.5 GPa) [5,6]. It can also exist as a mono- and di-hydrate, and is therefore prone to process-induced transitions during wet granulation. In this work the system used for naming polymorphs is the form number followed by the *a* lattice parameter reported for the particular polymorph in the Cambridge Crystallographic Database (CCD) file in parentheses.

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While many other industries have embraced the economic efficiencies in moving from batch to continuous processing, this adaptation has been much slower in the pharmaceutical industry, mainly due to difficulties in accurately measuring the required quality attributes of the product during continuous operation as the vast majority of this analytical work is currently carried out using off-line analysis methods [7]. The development of wet granulation as a continuous process using twin screw granulation is currently of great interest [8,9] however, in order for it to be embraced on an industrial scale co-current research into methods of rapid non-contact, real time monitoring is also required [7].

Various spectroscopic techniques have been recently utilised to monitor the polymorphic form of APIs during processing including Raman spectroscopy [10], near-infrared spectroscopy [11] and ATR-FTIR [12]. Near-infrared spectroscopy (NIR) has long been used as a process analytical technology (PAT) tool in the development of pharmaceutical formulations but is not particularly suitable for use in monitoring a wet granulation process due to the strong absorbance of water in the mid-infrared spectral region near 1645 cm^{-1}. Important infrared (IR) bands for the identification of piracetam occur at 1695 cm^{-1} for the amide carbonyl group and 1659 cm^{-1} for the cyclic ketone group [13] so in this work Raman spectroscopy was investigated as an alternative PAT tool. Raman spectroscopy has recently been shown as a promising technology for both qualitative and quantitative in-line monitoring of formulations in the late phase of drug development [14,15]. Furthermore, Raman does not exhibit the same sensitivity to water as IR, and is therefore more suitable for use as an in-line tool during wet granulation.

Wet granulation is a complex process involving several competing physical phenomena, namely wetting, nucleation, growth and attrition and breakage [16]. During wet granulation the drug may partially dissolve in the binder fluid, typically water, and the fraction of drug which will dissolve as well as the rate and extent of removal of the water will affect the recrystallisation of the drug [17]. It has been shown in the case of glycine, which can exist in a number of polymorphic forms, that the rate of drying of the wet granules can have an effect on the relative quantity of each polymorph present in the final product [18]. Furthermore, Baaklini et al. recently demonstrated the ability of excipients to induce the crystallisation of a specific polymorphic form of pyrazinamide and to suppress undesired solid-solid transformations in the formulation during storage [19]. In studying hydrate formation in the wet granulation of theophylline it was shown that while silicified microcrystalline cellulose (SMCC) was better at inhibiting hydrate formation during wet granulation than α-lactose monohydrate, SMCC could not inhibit hydrate formation at moisture levels required to form granules [20]. This work aims to investigate the challenges involved in the application of in-line Raman spectroscopy to wet granulation and to further understand the phenomena involved, especially in the case of freely soluble APIs with the tendency to exhibit polymorphism.

2. Materials and methods

2.1. Materials

Piracetam (FIII(6.525)), complying with European Pharmacopoeia 6.5 quality and purity standards, was supplied by UCB Pharma SA (CAS Number: 7491-74-9, Batch Number: 09G06-B93). Hydroxy propyl cellulose LH-21 (HPC) and Hydroxy propyl methyl cellulose, grade 50 mPa s viscosity, (HPMC) were kindly provided by Shin Etsu UK (Livingstone, UK). Microcrystalline cellulose (MCC), brand name Avicel® PH-101 was purchased from Pharmatrans Sanaq AG (Basel, Switzerland) and α-lactose monohydrate (LMH) was obtained from VWR (Dublin, Ireland). Polyethylene glycol 1500 (PEG) was purchased from Sigma Aldrich (Arklow, Wicklow, Ireland).

2.2. Production of FI(6.747), FII(6.403) and FIII(6.525)

Three pure polymorphic forms of piracetam were produced using the method suggested by Maher et al. [21]. Initially FIII (6.525) was prepared by cooling crystallisation from methanol and ground using a mortar and pestle. The mortar was then covered with a clock glass and placed in an oven at 413 K for three days. The ground powder was agitated every 12 h using a pre-heated pestle. After three days a sample was analysed using PXRD and compared to reference spectra in the Cambridge Crystallographic Database which confirmed that the transition to FI (6.747) was complete (Fig. 1a). The mortar was then transferred to a fume hood and left at room temperature (293 K) for one week and isolation of the pure polymorphic form FII(6.403) was again confirmed using PXRD.

2.3. Behaviour of piracetam in water

1 g of piracetam FIII was added to a mortar and ground to reduce particle size. Water was added gradually in aliquots of 20 μL and distributed evenly using a pestle. The resulting wet powder was analysed using PXRD. Separately water was added to 1 g of piracetam FIII until all crystals were dissolved, then the solution was left to dry in a fume hood. The solution and wet and dry powder were analysed at regular time intervals using PXRD.

2.4. Wet granulation

Piracetam was wet granulated with and without excipients using a drug to excipient ratio of 3:2 and deionised water as binder. LMH was chosen as an excipient with a low molecular weight while HPC, HPMC and MCC were chosen as cellulose-based excipients with varying degrees of hydrophilicity. PEG was selected as a water soluble polymer. A total 5 g of piracetam and excipient were mixed thoroughly using a mortar and pestle to ensure uniformity of the physical mixture. Water was then gradually added while triturating to produce a wet mass consistent enough to produce wet granules. The hand squeeze test was used to determine the end point of granulation. The wet mass was then passed through a C40 sieve to produce granules and the wet granules were dried overnight in a fume hood at room temperature.

2.5. Long term stability of polymorphic forms

All granules were stored in a fume cupboard at room temperature and humidity for thirty days to investigate the stability of the polymorphic form contained in each formulation.

2.6. Differential scanning calorimetry (DSC)

DSC studies were conducted on a PerkinElmer DSC 8500 equipped with a refrigerated cooling accessory (PerkinElmer, UK). Nitrogen, 30 mL/min, was used as purge gas. The instrument was calibrated using a heating rate of 10 °C/min using high purity indium and zinc to standardise the temperature and heat flow signal. Then 2.0–5.0 mg samples were weighed and placed in crimped DSC pans. Samples were ramped from 0 to 180 °C at 10 °C/min. Analysis was carried out using PE Pyris Thermal Analysis software, version 10.1 and any numerical values reported are the average ± SD of three independently prepared samples.