Wet granulation induced polymorphic transitions in Piracetam

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Abstract
Piracetam is a highly aqueous-soluble drug which can exist in many polymorphic forms including hydrates. It is therefore potentially prone to process-induced transformations during wet granulation. Knowledge of the polymorphic form of the API present in a final formulation is an important regulatory issue. The polymorphic transitions of Piracetam during wet granulation were studied using Raman and XRD. Different excipients with a range of hydrophilicities, aqueous solubilities and molecular weights were examined.

1. Introduction
Wet granulation is one of the most popular techniques used during the post processing of active pharmaceutical ingredients (APIs) due to its ability to improve powder flow and compaction properties. However, the addition of water can affect the crystal structure of certain APIs exhibiting polymorphism. Process-induced polymorphic transitions in APIs are a major challenge in the pharmaceutical industry as these unpredictable phase transitions can cause altered bioavailability and result in regulatory non-compliance.

Piracetam (PIR) is a highly aqueous-soluble nootropic drug with five reported polymorphs which forms a monohydrate on contact with water. It therefore is challenging to use in a wet granulation process. It is known that polymers can have a stabilizing and inhibitory effect on the polymorphic transitions in APIs so this work aims to investigate the effect of different excipients on wet granulation induced polymorphic transitions in Piracetam [2-5].

2. Piracetam
Piracetam undergoes polymorphic transitions under the influence of both solvent and temperature. FIII of Piracetam is the most stable form at room temperature. FIII transforms to FI when heated to 140°C which transforms to metastable FII upon cooling to room temperature following the Ostwald’s step rule of successive transformation [1]. At ambient conditions FII will eventually transform to the more stable FIII.

3. Methodology
Piracetam was wet granulated with excipients with drug to excipient ratio of 3:2, as Piracetam being a high dosage drug. Excipients used for wet granulation were Lactose monohydrate (LMH), microcrystalline cellulose (MCC), Hydroxy propyl methyl cellulose (HPMC), Hydroxy propyl cellulose (HPC) and Polyethylene glycol (PEG). LMH was chosen as the excipient representing low molecular weight; MCC, HPMC and HPC represent the excipients with varying degree of hydrophilicity while PEG is a water soluble polymer.

The granules produced were dried overnight at room temperature and the dried granules were then analysed at pre-determined times points using XRD. Raman was also employed to investigate the use of this technique as an in-situ analysis method. Principle component analysis (PCA) and direct cluster analysis (DCA) were used to process the Raman spectra. Prior to processing all spectra were normalised and the first derivative was taken.

4. Results & Discussion
4.1 Granulation of Piracetam
XRD showed that PIR granulated without any excipients transformed from FIII to Piracetam monohydrate (PIR-MH) in the presence of water and then recrystallized to FII upon drying. FII so obtained gradually recrystallised to the stable FIII at room temperature within two weeks.

The Raman spectra gained from the granulation and drying of PIR were analysed using PCA and DCA and showed clustering into three distinct spectra which were confirmed to be those of FII, FIII and PIR-MH using XRD. Raman was therefore used in conjunction with
XRD to inspect the progress of the transformation both from FII to PIR-MH and from FII to FIII (Figure 1).

Figure 1: Raman map illustrating the transformation of Piracetam FII to FIII during thirty days at ambient temperature.

4.1 Granulation with excipients
Granules of PIR containing LMH, MCC, HPMC and HPC exhibited similar transformations as pure PIR during granulation, namely that FIII transformed to monohydrate in the presence of water which recrystallised to FII upon drying (Figures 2 & 3).

Figure 2: XRD diffractograms of wet granules of PIR with various excipients indicating the transformation of Piracetam to its monohydrate form.

Figure 3: Raman spectra showing transformation of Piracetam from monohydrate to FII upon drying.

The kinetics of solid state transformation of FII to FIII at room temperature was retarded in the presence of excipients in comparison to that of pure PIR and by different degrees depending on the polymer. This was attributed to the interaction of excipients with the active functional groups in the drug and by the hydrophilicity and molecular weight of the excipients.

However PEG had a different effect on these polymorphic transitions. Piracetam remained in its stable FIII throughout the processes of wetting and drying. Unlike the other excipients used in the study PEG is freely soluble in water and therefore it is possible for PEG to competitively inhibit the interaction between PIR and water. It is suggested that PEG inhibited the solution-mediated polymorphic transition of FIII to FII through the intermediate monohydrate.

5. Conclusion
Through the use of the complimentary techniques of XRD and Raman spectroscopy the polymorphic transformations exhibited by Piracetam during wet-granulation have been investigated. The importance of detecting the monohydrate form of the API as a precursor to the production of the metastable FII, the effectiveness of Raman spectroscopy in this detection, and the importance of understanding the excipients typically used during wet granulation have been demonstrated.

6. References