Innovare
Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 7, Issue 2, 2015

Original Article

EFFECT OF A PARTICLE ENGINEERING PROCESS ON POLYMORPHIC TRANSITION OF PYRAZINAMIDE

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Received: 18 Nov 2014 Revised and Accepted: 12 Dec 2014

ABSTRACT

Objective: The objective of this work was to investigate the effect of processing on physicochemical properties of spray dried Pyrazinamide.

Methods: Pyrazinamide was spray dried using several spray drying conditions, FTIR, XRD and thermal analysis were undertaken for all samples. A comparison of crystalline/amorphous nature of the starting material as well as processed materials was carried out.

Results: The unprocessed material was a typical crystalline material composed of a mixture of alpha and gamma polymorphic forms of pyrazinamide.

In contrast spray dried materials showed other mixtures of different polymorphs of pyrazinamide based on spray drying conditions. In other words, the solid state of spray dried material was dependent on processing parameters (solvent systems, inlet temperature), which may indicate the effect of processing conditions on the solid state of Pyrazinamide.

Conclusion: Processing of Pyrazinamide without excipients gave different polymorphs, according to the solvent mixture used in the spray drying process

Keyword: Pyrazinamide, Spray drying, Thermal properties, Crystalline materials, Polymorphism.

INTRODUCTION

Pyrazinamide (PZA) is considered as an important front-line anti-tubercular drug. Its importance came from the fact that it may shorten the therapy from the 9-12 months to 6 months because it kills a population of semi-dormant bacilli that are not killed by other tubercular drugs [1].

The inhalation route offers an enormous absorptive surface area in the range 35–140 m^2, thin (0.2 μm) and highly vascularise epithelium, which leads to high bioavailability. Furthermore, in most societies oral inhalation is well accepted by the general population [2]. In the literature, several methods are reported, including pressurized metered dose inhalation [3], nanoporousmicro particles[4]for preparation of particles suitable for inhalation.

Furthermore, Pandey et al., [5] prepared inhaled antitubercular formulation; their studies showed that pulmonary delivery of antitubercular drugs is feasible. Moreover, Pyrazinamide activity could be enhanced by concentrating the drug at the site of infection, where the bacteria are concentrated. Hence, in the case of pulmonary infection, administration of Pyrazinamide as inhalable particles could be promising.

Healy et al., [6] reported that particle engineering may be used for production of excipient free particles suitable for inhalation. However, Corrigan [7] showed that particle engineering may alter energy of the spray dried particles. These changes may include the disordering of the crystal lattice, the formation of polymorphic forms.

Moreover, Gad et al., [8]showed that the solid state of an anti-tubercular drug (para-aminosalicylic acid) was changed by spray drying from ethanol, resulting in a complex solvated form with a stoichiometry of the spray-dried product of 2: 1: 0.5 para-aminosalicylic acid: ammonia: water. In another study Ghaly et al. [9] showed that spray drying has potential to maintain the amorphous form of zafirlukastand avoids phase transformation using optimum spray drying parameters and the optimum formulation composition.

The importance of current work came from our need to understand the factors affecting the solid state of spray dried Pyrazinamide. Moreover, it is essential to investigate polymorphic transition of Pyrazinamide during processing. To our knowledge, there are no previous reports of the production and characterization of excipient-free particles of Pyrazinamide, from simple mixed solvent systems. Therefore the aim of the study was to investigate possible changes in the solid-state properties upon processing of Pyrazinamide.

MATERIALS AND METHODS

Materials

Pyrazinamide was purchased from Aldrich (Germany), Methanol was purchased from Lab Scan Analytical Sciences, Ireland, ethanol was purchased from Cooley distillery, Ireland, Butyl acetate was purchased from Merck, Germany, and Deionized water was produced by a Purite Prestige Analyst HP water purification system.

Methods

Spray drying

Solutions of Pyrazinamide were prepared in ethanol/water, methanol/ butyl acetate or methanol /water. The total solid concentration in solution was 1% (w/v). In the case of the ethanol/water solution spray dried (using air) with the dryer in the open mode; inlet temperature was set at 78 °C, with a resulting outlet temperature of 63 °C. While for the methanol/water solution inlet temperature was 110 °C and the outlet temperature was 68 °C. Pyrazinamide was also spray dried as 1% solutions from 80% (v/v) methanol and 20% (v/v) butyl acetate (spray dried in the closed mode), inlet temperature was set at 110 °C, with a resulting outlet temperature of 71 °C.

Differential scanning calorimetric analysis (DSC)

DSC was performed using closed 40 μl aluminium pans with three-vent holes on accurately weighed samples (2 – 6 mg). Samples were run at a specific heating rate of 10°C/minute under nitrogen purge from 25 – 300°C using a TA Q200 DSC. TA universal® software was used for analysis of thermodynamic events. The DSC base line was calibrated using sapphire loaded pans and entropy and temperature was calibrated using indium loaded pan.

Fourier transform infrared spectroscopy (FTIR)

FTIR was carried out using a Magna – IR 560 Spectrometer E. S. P. (Thermo Electron Corporation, U. S. A.) Fourier Transform Infrared Spectrometer. Potassium bromide discs were prepared based on 1 % w/w sample loading. Discs were prepared by grinding the sample with Potassium bromide in an agate mortar and pestle, placing the sample in an evacuable Potassium bromide die and applying 8 tons of pressure in an IR press. The OMNIC E. S. P. Software was used for processing the data.

Powder X- ray diffraction (XRD)

XRD scans were made on samples in low background silicon mounts. A MiniFlex II desktop X-Ray diffractometer was used. Measurements were taken from 5° to 40° on the 2 theta scale with a step size of 0.05° per second.

RESULTS AND DISCUSSION

Characterization of unprocessed pyrazinamide

In the solid phase, Pyrazinamide has bands in the FTIR spectrum due to a primary amide N-H at 3413 cm^{-1}, and an absorption band at 3162 cm^{-1}due to N-H stretching (Symmetrical) [10]. FTIR spectra of unprocessed Pyrazinamide (fig. 1) show a band at 3411 cm^{-1} due to the primary amide and a band at 3160 cm^{-1} due to N-H stretching.

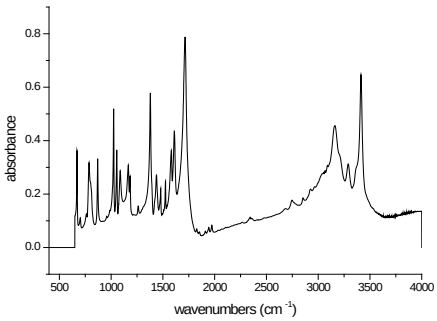

Fig. 1: FTIR scans of Pyrazinamide

DSC scans shown in fig. 2 revealed that Pyrazinamide is crystalline in nature. A melting endotherm was visible on investigation of Pyrazinamide unprocessed material, which had an onset temperature at ~188°C and peaking at ~189 °C, which is in good agreement with the melting point reported in the literature at 188 °C to 191 °C [11].

The crystallinity of Pyrazinamide was confirmed by XRD pattern as shown in fig. 3. The crystalline form of the sample was evident from the presence of peaks. It should be noted that powder X-ray difractograms of Pyrazinamide raw material was compared to the published crystal structures of different polymorphs of Pyrazinamide. The results obtained from the comparative study revealed that the unprocessed material was typical of a crystalline material. Moreover, the X-ray scans of Pyrazinamide were consistent with the XRD data presented by Takaki et al., [12] for alpha Pyrazinamide. Therefore, the starting material represents

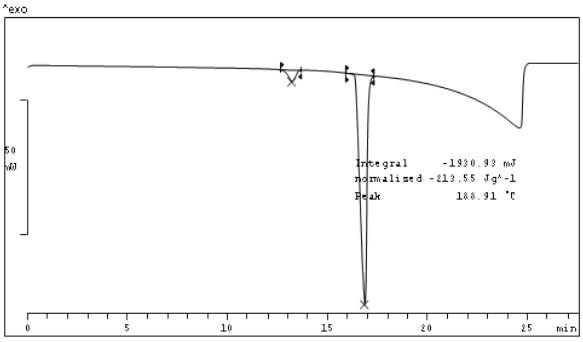

Fig. 2: DSC scans of Pyrazinamide

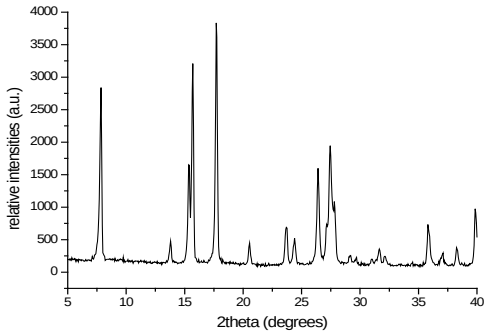

Fig. 3: XRD difractograms of Pyrazinamide

Effect of spray drying on solid state properties of pyrazinamide

The powder X-ray difractograms of Pyrazinamide raw material was typical of a crystalline material. The peak positions were consistent with the XRD spectrum presented by Takaki et al. [12] for alpha and gamma Pyrazinamide.

X-ray difractograms of spray dried Pyrazinamideare shown in fig. 4. Although the patterns for the spray dried samples are still crystalline and show some of the features of the pattern of the unprocessed Pyrazinamide, it is obvious that the XRD patterns of the spray dried samples differ considerably in comparison to that of unprocessed Pyrazinamide.

The peak positions in the scans of processed materials were not consistent with the XRD scan presented by Takaki et al., [12]in alpha form of Pyrazinamide. Moreover, both peak positions and relative intensities were different from the pattern shown by the unprocessed material. This may be an effect of processing of Pyrazinamide. Furthermore, there were differences in XRD diffraction patterns of spray dried materials, and these changes were based on the processing parameters. In other words, changing spray drying conditions resulted in different XRD difractograms of Pyrazinamide as showed in fig. 4.

It should be noted that samples spray dried from either ethanol/ water or methanol/ water showed similar patterns regarding peak positions and relative intensities, mean while these patterns were different from that obtained from spray dried sample spray dried from methanol/ butyl acetate.

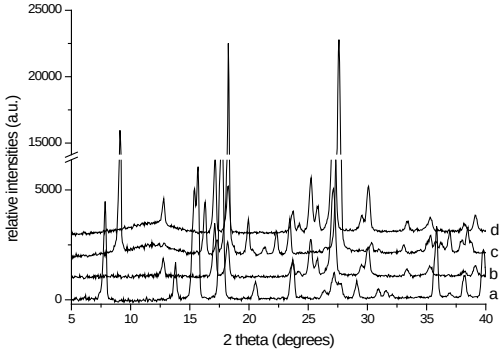

Fig. 4: XRD difractograms of Pyrazinamide (a) unprocessed and spray dried from (b) methanol/ water, (c) methanol/ butyl acetate (d) ethanol/ water

Pyrazinamide presents four polymorphic forms: alpha, beta, gamma and delta Pyrazinamide [12, 13, 14 and 15]. However, the pharmacopoeias do not specify any specific polymorph. Unfortunately, these articles do not display the powder pattern of the polymorphs; therefore, it is not possible to make a direct comparison with an experiment. As the structure of alpha, beta and delta are available; it was possible to generate theoretical XRD patterns of these forms and to compare with the experimental

patterns. This has been done using the software TOPAS. However, as the structure of gamma-Pyrazinamide has not been published (atomic position inside the lattice are missing) the software could not generate the theoretical pattern of the gamma form and therefore a quantitative analysis was not possible. Nevertheless, it was possible to determine qualitatively the polymorphs present in our samples.

Although the pharmacopoeias do not specify any specific polymorph to be used therapeutically, it is important to understand the effect of processing on the solid state of therapeutically active agent.

The powder X-ray difractograms of Pyrazinamide raw material, as well as different spray-dried samples were compared to the published crystal structures of different polymorphs of Pyrazinamide. The results obtained from the comparative study revealed that the unprocessed material was typical of a crystalline material. Moreover, scans of Pyrazinamidewere in a good agreement with the XRD data presented by Takaki et al. [12] for alpha and gamma Pyrazinamide(fig. 5).

Pyrazinamide spray dried from ethanol/water solution displayed a diffraction pattern similar to delta Pyrazinamide which is described by Ro and Sorum[15] and gamma form of Pyrazinamide(fig. 6).

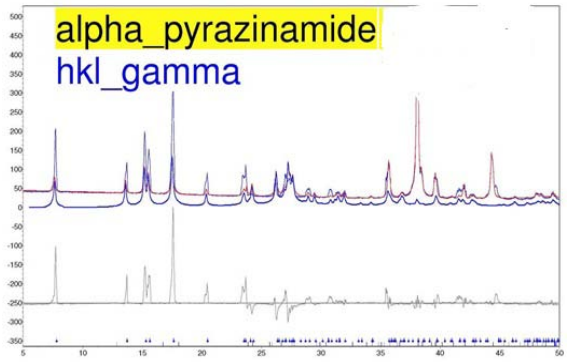

Fig. 5: XRD scans of unprocessed material compared to alpha and gamma Pyrazinamide

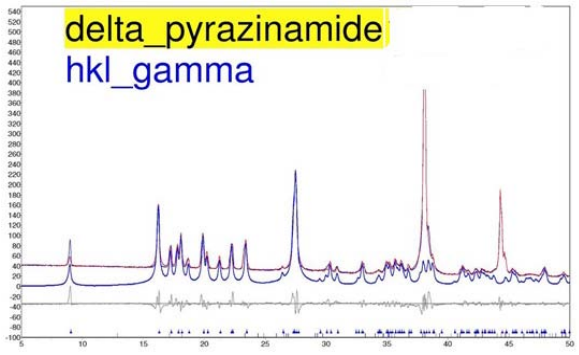

Fig. 6: XRD scans of spray dried material (ethanol/water) compared to delta and gamma Pyrazinamide

The results obtained from the qualitative comparative study of spray dried drug from methanol/ butyl acetate revealed that the obtained material is a mixture of beta, gamma and delta Pyrazinamide (fig. 7).

Fig. 8 showed a qualitative study of the spray dried samples obtained from ethanol/ water. It is clear from the study that the sample is a mixture of gamma and delta Pyrazinamide which are described by Tamura et al., [12] and Ro and Sorum, [15].

It is clear from previous data that the conditions of processing may have an impact on the product, furthermore, using all spray drying conditions no one single polymorph was produced and all conditions resulted in the production of a mixture of at least two polymorphs.

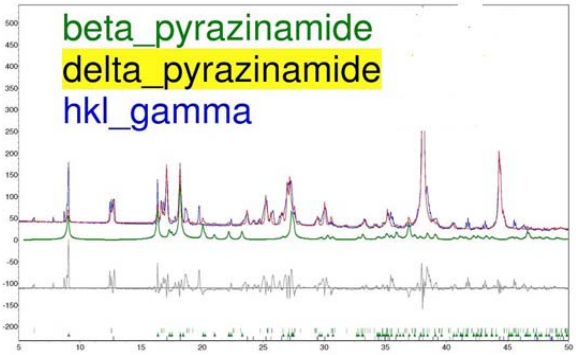

Fig. 7: XRD scans of spray dried material (methanol/water) compared to beta, delta and gamma Pyrazinamide

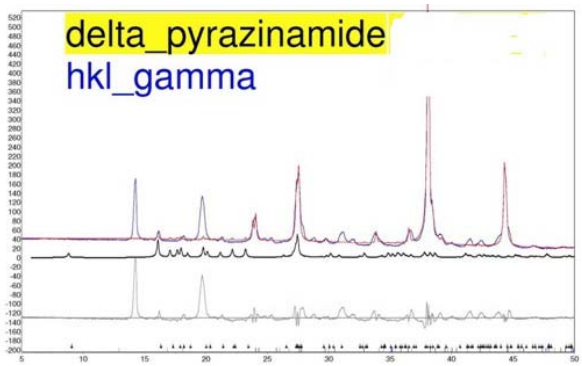

Fig. 8: XRD scans of spray dried material (methanol/butyl acetate) compared to delta and gamma Pyrazinamide

CONCLUSION

Processing of Pyrazinamide without excipients gave different polymorphs, according to the solvent mixture used in the spray drying process; a mixture of delta and gamma Pyrazinamide was produced when Pyrazinamide spray dried from ethanol/water solution, while a mixture of beta, gamma and delta Pyrazinamide was produced when Pyrazinamide spray dried from methanol/butyl acetate solution, while using methanol/ water resulted in production of a mixture of gamma and delta Pyrazinamide.

CONFLICT OF INTERESTS

Declared None

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