

A Polymorphism Screen of Risperidone: A comparison of XRPD and Raman Spectroscopy

M. Leigh^{1*} T. Reimann² J. Grunkemeyer¹ B. Schneider² H. Schwebel¹ P. van Hoogevest^{1,3}

¹ Phares Drug Delivery AG, Muttens, Switzerland ² RPD TOOL AG, Muttens, Switzerland ³ Adjunct Professor, University of Basel, Institute of Pharmaceutical Technology, Basel, Switzerland
* Corresponding author, Tel: +41 (61) 317-9040, E-mail: info@phares.biz

Purpose

A modular approach has been designed for polymorphism, salt and co-crystal screening, including internally developed automated hardware to perform various types of screening experiments at a scale of either 1–2 or 10–20 mg per experiment.

Introduction

Risperidone, a poorly soluble, lipophilic pharmaceutically active compound (RISPERIDAL®), was chosen as a model substance because three polymorphs and their XRPD spectra were recently reported in a patent from Teva Pharmaceuticals [1].

Understanding polymorphism of poorly soluble pharmaceutical actives can assist in identifying options for solid oral dosage forms of such compounds. The physical stability of the active in a solid dosage form and the particular polymorph potentially present can dramatically influence the oral bioavailability and corresponding safety profile of the drug. In this study, the utility of Raman spectroscopy as a method of characterizing crystal polymorphism in pharmaceutical solids is compared with XRPD.

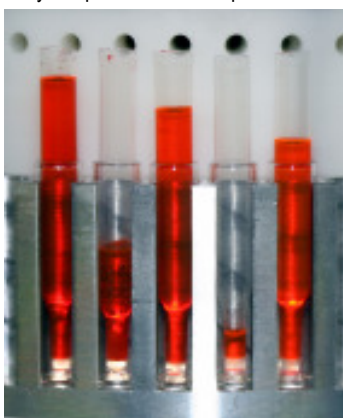


Figure 1: Evaporation Vials

Methods

- Polymorph Form A of Risperidone was the starting material for this study
- A number of different crystallization experiments were employed: evaporation (70), antisolvent precipitation (2) and slurry transformation experiments (8)
- The starting solutions were highly dilute and filtered before crystallization in order to eliminate seed crystals, which could influence the resulting polymorph
- The resulting crystals were measured using XRPD and Raman spectroscopy; the spectra were then analyzed for presence of specific preferred polymorphs using cluster analysis

Results

- Cluster analysis of Raman spectra of the resulting crystals identified four different forms ([2], see Fig. 2).

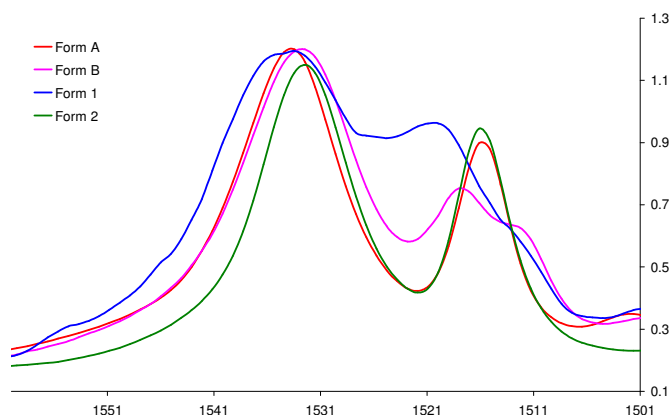


Figure 2: Selected range of Raman spectra (X-axis: cm^{-1} , Y-axis: normalized Raman scatter)

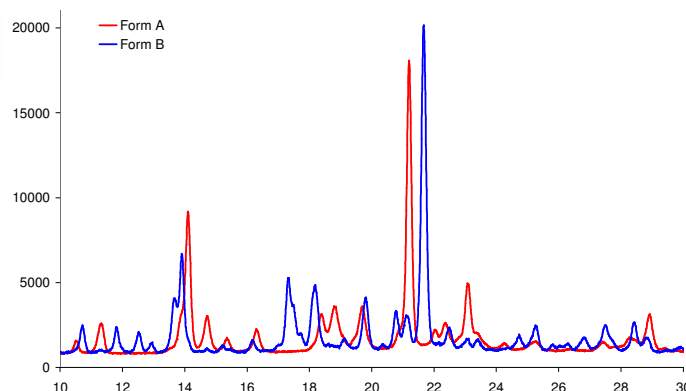


Figure 3: Selected Range of XRPD spectra (X-axis: 2 Theta; Y-axis: absolute intensity)

- XRPD spectra of Forms A and B were consistent with the patent (Fig. 3)
- Forms A and B melted at 170.2 and 170.6 °C, respectively, and Form B had a small exotherm at 164 °C, all consistent with the patent
- The existence of Form E of the patent could not be confirmed with these experiments
- Two additional forms not mentioned in the patent were identified by Raman: Forms 1 and 2
- Form 1 was deliquescent; therefore DSC or XRPD could not be measured
- The pseudopolymorph Form 2 was identified by Raman as an acetonitrile solvate of Risperidone, which was not mentioned in the patent
- With Forms A and 1, the evaporation temperature strongly influenced the solid state formed: Form A was preferentially formed at 40 °C and Form 1 at 10 °C
- Form B could be formed with a variety of solvents and evaporation temperatures 10 and 40 °C
- With a given solvent, irrespective of its polarity, if Form A or 1 was formed at one temperature (10 or 40 °C), then Form B could usually be formed at the other temperature
- Form 2 was only formed in slurry experiments with acetonitrile; evaporation experiments with acetonitrile never resulted in Form 2

Conclusions

- XRPD and Raman spectroscopy both delivered unique spectra for different polymorphs
- An important key to identifying all the polymorphs is the use of different crystallization and evaporation temperatures
- It was also demonstrated that Raman is also capable of *in situ* measurements of the polymorphic form of solid actives in slurries
- The screening method is equally suitable for co-crystal and salt studies, in which measurement of the solid state plays a key role in the identification of new forms

References/Endnotes

- [1] Krochmal et. al.: TEVA, US 6,750,341 B2, Jun. 15, 2004
- [2] Nomenclature: letters represent polymorphs confirmed in the patent, numbers for unconfirmed forms