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Physical Evaluation of Late Appearing Polymorph of Ritonavir Form III

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PURPOSE

Ritonavir (Figure 1), a marketed product for the treatment of HIV/AIDS, is a notorious example of disappearing polymorphs and has been shown to exist in different forms (1). In our laboratory, Form III was prepared via faster nucleation and growth conditions from melt/cool crystallization than had been previously reported (2). The current research describes results obtained from evaluation of Ritonavir Form III physical properties with respect to both equilibrium solubility and stability compared to previously known forms.

OBJECTIVE(S)

1. Physically characterize Ritonavir Form III
2. Evaluate the physical stability upon compression and upon long term storage
3. Evaluate solubility in aqueous media

METHOD(S)

Physical characterization of Ritonavir Form III:

- X-ray powder diffraction (XRPD) followed by indexing
- Differential scanning calorimetry (DSC)
- Thermogravimetry (TG)
- Hot-stage optical microscopy (HSOM)
- Dynamic vapor sorption (DVS)
- Raman spectroscopy

Physical stability of Ritonavir Form III:

- 40 °C/75% RH, monitored by XRPD, Raman
- High compression @ 700 lbs for 15 min
- Ambient, long-term stability, monitored by XRPD, Raman

Equilibrium solubility of Ritonavir Form III:

- Aqueous media, measured by UV/VIS spectroscopy
- Recovered solids by XPRD for form change

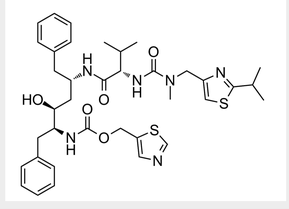

Figure 1. Structure of Ritonavir

Ritonavir Form III displayed a unique crystalline structure compared to known Forms I and II. The material was shown to be composed of a single phase by indexing (Figure 2). Thermal properties indicated a sharp melt with onset at ~114 °C and an endothermic maximum at ~118 °C (Figure 3). HSOM confirmed the thermal events (Figure 4). Negligible weight loss was observed by TG up to 180 °C (Figure 3), and Form III was shown to be slightly hygroscopic with weight gain of ~0.3% and no hysteresis (Figure 5).

Form III was also stable for one month following exposure to 40 °C/75% RH according to XRPD and Raman spectroscopy. Upon exposure to high compression (700 lbs. for 15 min) the form remained unchanged. After one year storage at ambient conditions, Form III is still stable (Figures 6–7). The equilibrium solubility of Form III in 0.1 N HCl was significantly higher than Form II (12-fold), moderately higher than Form I (4-fold) and on the same order of magnitude as amorphous material (Figure 8). The XRPD of the materials recovered after solubility measurements indicated no form change after 48 hrs.

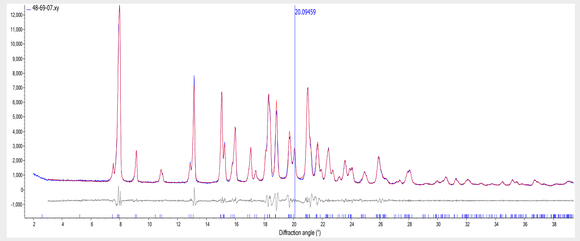

Figure 2. Indexing solution for Ritonavir Form III
Blue: experimental data; Red: fit; Grey: fit residual; Blue notches: allowed peak positions.

Space group	C2		
a (Å)	23.656	α (°)	90
b (Å)	5.031	β (°)	90.572
c (Å)	33.878	γ (°)	90
d_{samp} (mm)	−0.154	Cell Volume (Å^3)	4031.5
R_{wp}	6.2%	Density (g/cc)	1.1878

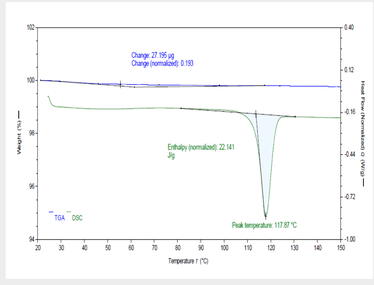

Figure 3. DSC and TG thermograms of Ritonavir Form III

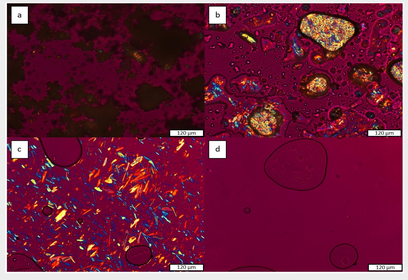

Figure 4. HSOM images of Ritonavir Form III:
a) Melt onset at 113.7 °C; b) continued melting at 115.8 °C;
c) continued melting at 117.0 °C; d) melt complete at 117.9 °C

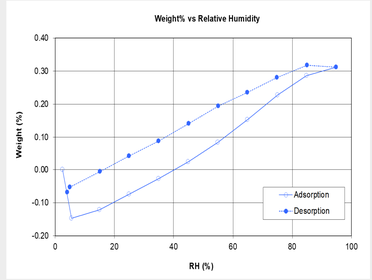

Figure 5. DVS of Ritonavir Form III

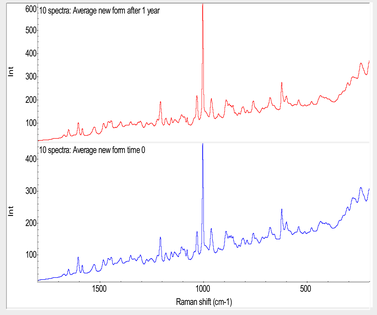

Figure 6. Ritonavir Form III long- term stability by Raman
Blue: T= 0; Red : T=1 year

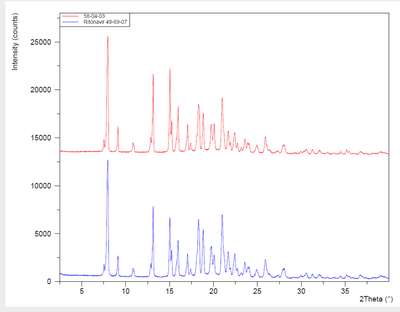

Figure 7. Ritonavir Form III long-term stability by XRPD
Blue: T=0; Red: T=1 year

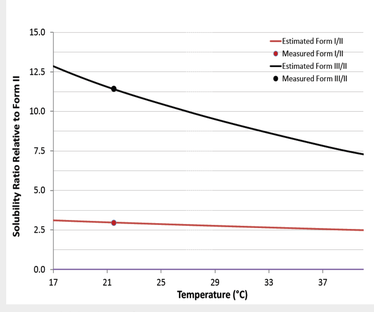

Figure 8. Solubility Curve of Ritonavir Form III

Technique	Result
XRPD	Crystalline, Form III (1 month, 40 °C/75% RH & 1 year, RT)
Indexing	Single phase
DSC	Endo @ 118 °C (onset 114 °C)
TG	~0.2% up to 180 °C
DVS	~0.3 %, no hysteresis
Raman	Form III (1 month, 40 °C/75% RH & 1 year, RT)
HSOM	Melt of needles confirmed
Compression	Form III (700 lbs, 15 min)
Solubility UV/Vis (247 nm)	~4.3 mg/mL @ pH 1.2 (12-fold higher than Form II) Form III (48 hrs)

CONCLUSION(S)

Ritonavir Form III was physically characterized using XRPD with indexing, DSC, TG, HSOM, DVS and Raman spectroscopy. The results indicated a crystalline material comprised of a single phase that melts at approximately 114 °C, with negligible weight loss and is slightly hygroscopic. Form III was also shown to be physically stable upon exposure to elevated temperature and humidity conditions for one month according to both XRPD and Raman spectroscopy, unlike amorphous material which crystallized to Form I after one month. Form III remained unchanged after being subjected to high compression, and has also remained unchanged after storage at ambient conditions for over a year. In addition, Form III displayed improved solubility in acidic media compared to both Forms I and Forms II and was similar to that of amorphous material after equilibrium conditions were obtained. Results of this research indicate that Ritonavir Form III has acceptable physical properties and it is advantageous compared to Form II and amorphous material when considering both solubility and stability, respectively.

REFERENCES

1. Bauer, J.; Spanton, S.; Henry, R.; Quick, J.; Dziki, W.; Porter, W.; Morris, J. Ritonavir: An Extraordinary Example of Conformational Polymorphism. *Pharmaceutical Research* **2001,** *18*(6), 859-866. DOI: 10.1023/a:1011052932607.
2. Parent S, Smith P, Purcell D, Smith D, Bogdanowich-Knipp S, Bhavsar A, Chan, L, Croom, J, Bauser, H, McCalip, A, Byrn, S and Radocea, A. Ritonavir Form III: A Coincidental Concurrent Discovery. *Crystal Growth & Design* **2023** *23*(1), 320-325. DOI: 10.1021/acs.cgd.2c01017.