

Evaluation of the Polymer Soluplus® for Spray-Dried Dispersions of Poorly Soluble Compounds

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Introduction and Objectives

Increasingly, a large number of NCEs fail in development due to poor solubility and bioavailability.¹ Recently, BASF introduced a new polymeric solubilizer, Soluplus®, a graft copolymer composed of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate². Its unique chemistry provides lipophilicity that enables complexation with poorly soluble molecules and has been shown to be highly desirable for hot melt extrusion processing². However, to our knowledge, no work has been published on the use of this novel polymer for spray-dried dispersions. The objective of this work was to determine the applicability of Soluplus® for use within spray dried dispersions.

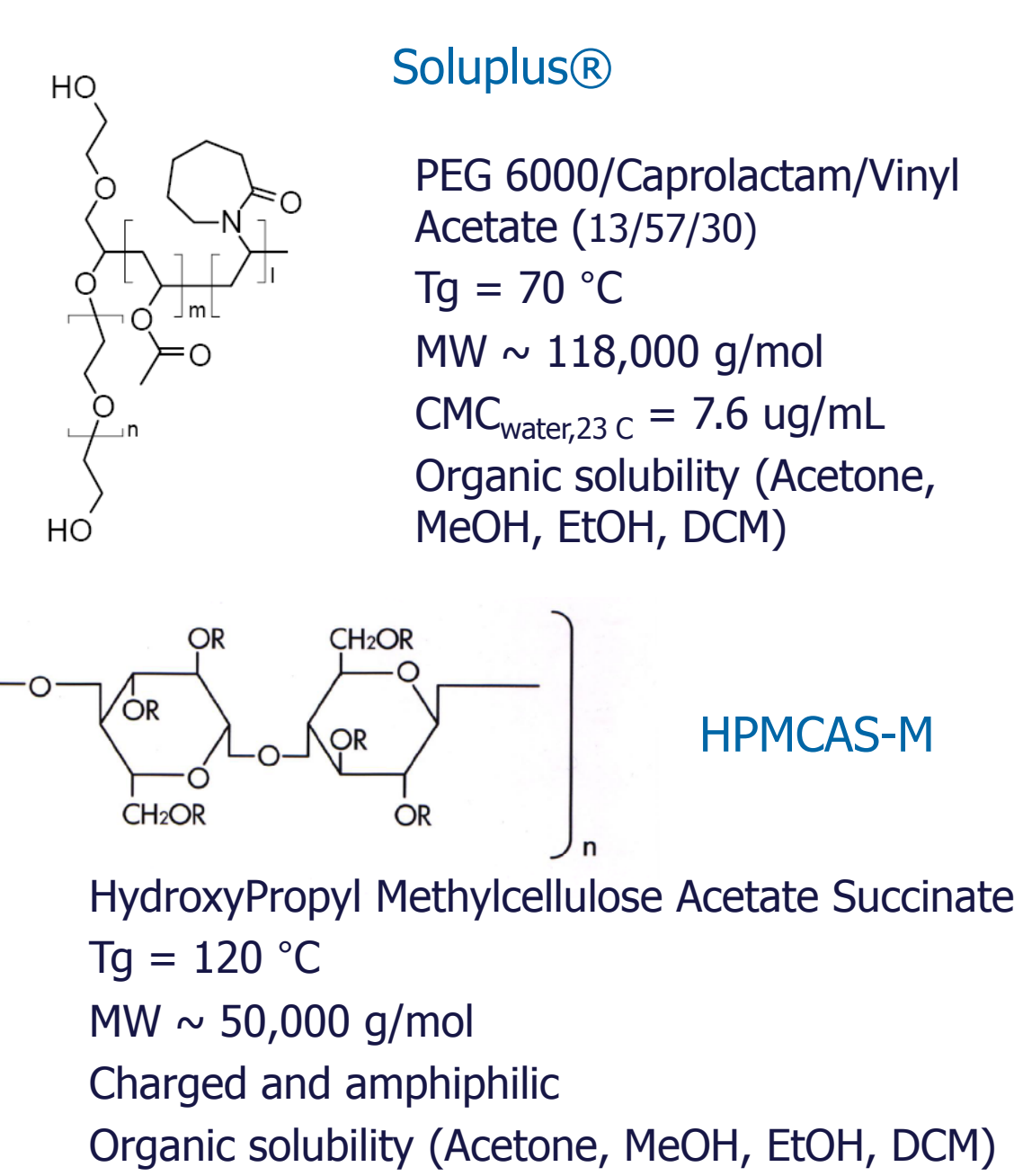
Methodology

Five poorly soluble compounds were spray dried with Soluplus® and HPMCAS-M to form solid dispersions. For comparison, two compounds, itraconazole and fenofibrate, were formed into solid dispersions using hot melt extrusions (HME). Spray drying was performed using a Buchi B290 spray dryer. HME samples were made using PolyLab PTW 16 extruder (ThermoFisher) at a feed rate of 1 kg/h, and a barrel temperature of 150°C for itraconazole and 100°C for fenofibrate, respectively. Analysis was performed using in vitro dissolution, modulated Differential Scanning Calorimetry (mDSC, Q100), Powder X-ray Diffraction (PXRD, Bruker D2 Phaser), and Fourier Transform Infrared spectroscopy (FTIR, Thermo Scientific iS10).

Model Compounds

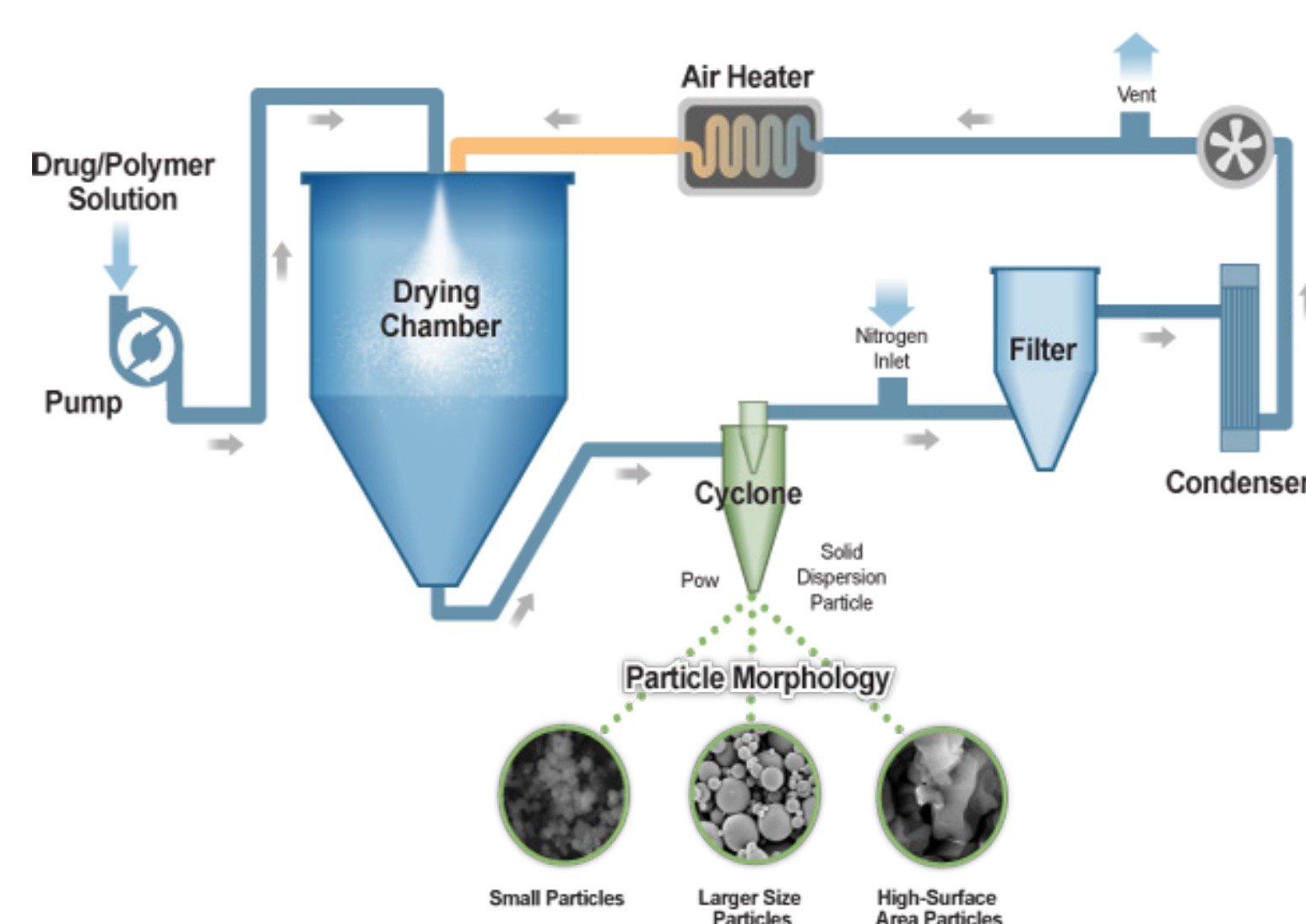
Structure	Solubility (µg/mL in PBS at pH = 6.5)	Log P	MW	Tm (°C)	Tg (°C)
Albendazole	2	2.7	265.33	209	79.5
Megestrol Acetate	0.27	3.2	384.51	214-216	71.3
Fenofibrate	0.5	4.75	360.83	80-81	-19.7
Itraconazole	0.05	7.13	705.63	167.0	58.7
Indomethacin	206	3.6	357.08	159.9	45.9

Polymers



Results

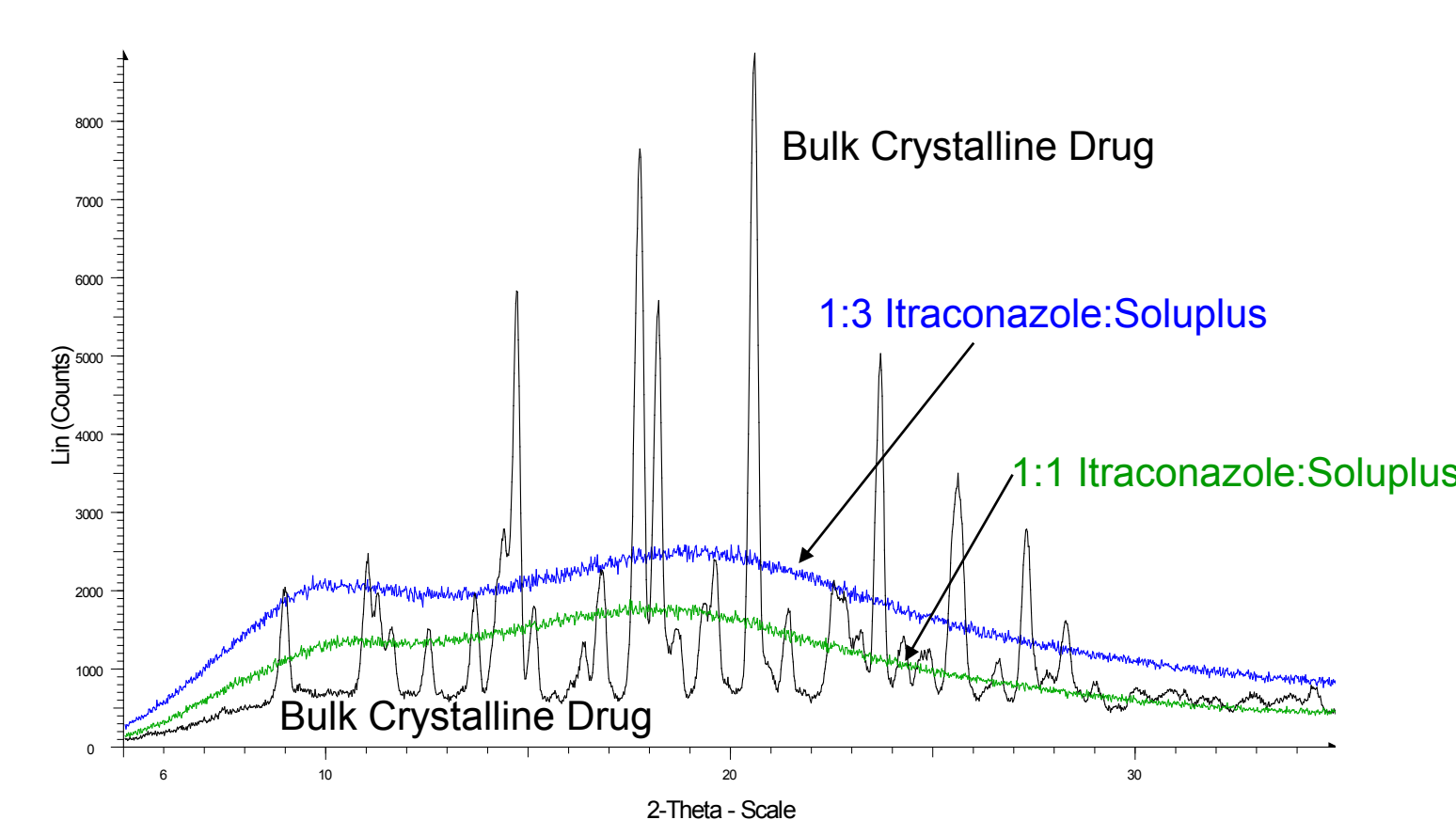
Spray Drying Process



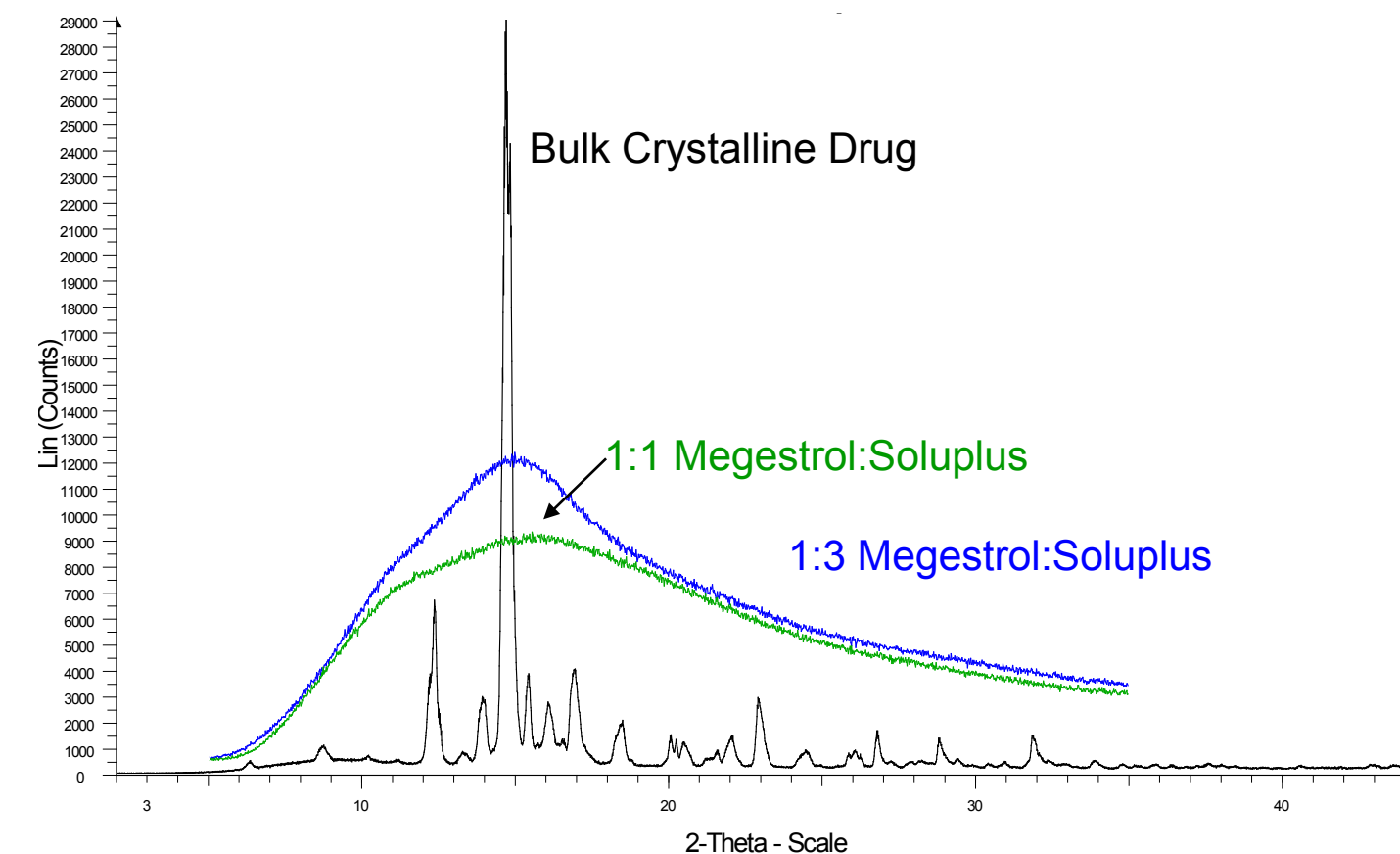
Compound	Drug Loading (Drug: Polymer)	Spray Drying Solvent	Spray Solution Concentration (wt% (g solids/g solvent))	Tin (°C)	Solution Flow rate (mL/minute)	Yield (%)
Albendazole	1:3	THF:MeOH	1	130	27	80
	1:1	THF:MeOH	0.5	130	27	56
Megestrol Acetate	1:3	Acetone	5	80	11	74
	1:1	Acetone	5	80	11	34
Fenofibrate	1:3	Acetone	5	80	11	20
Itraconazole	1:3	THF	3.75	80	11	68
	1:1	THF	3.1	80	11	54
Indomethacin	1:3	Acetone	5	80	11	80
	1:1	Acetone	5	80	11	80

Solid-State Analysis

PXRD Of Itraconazole Dispersions

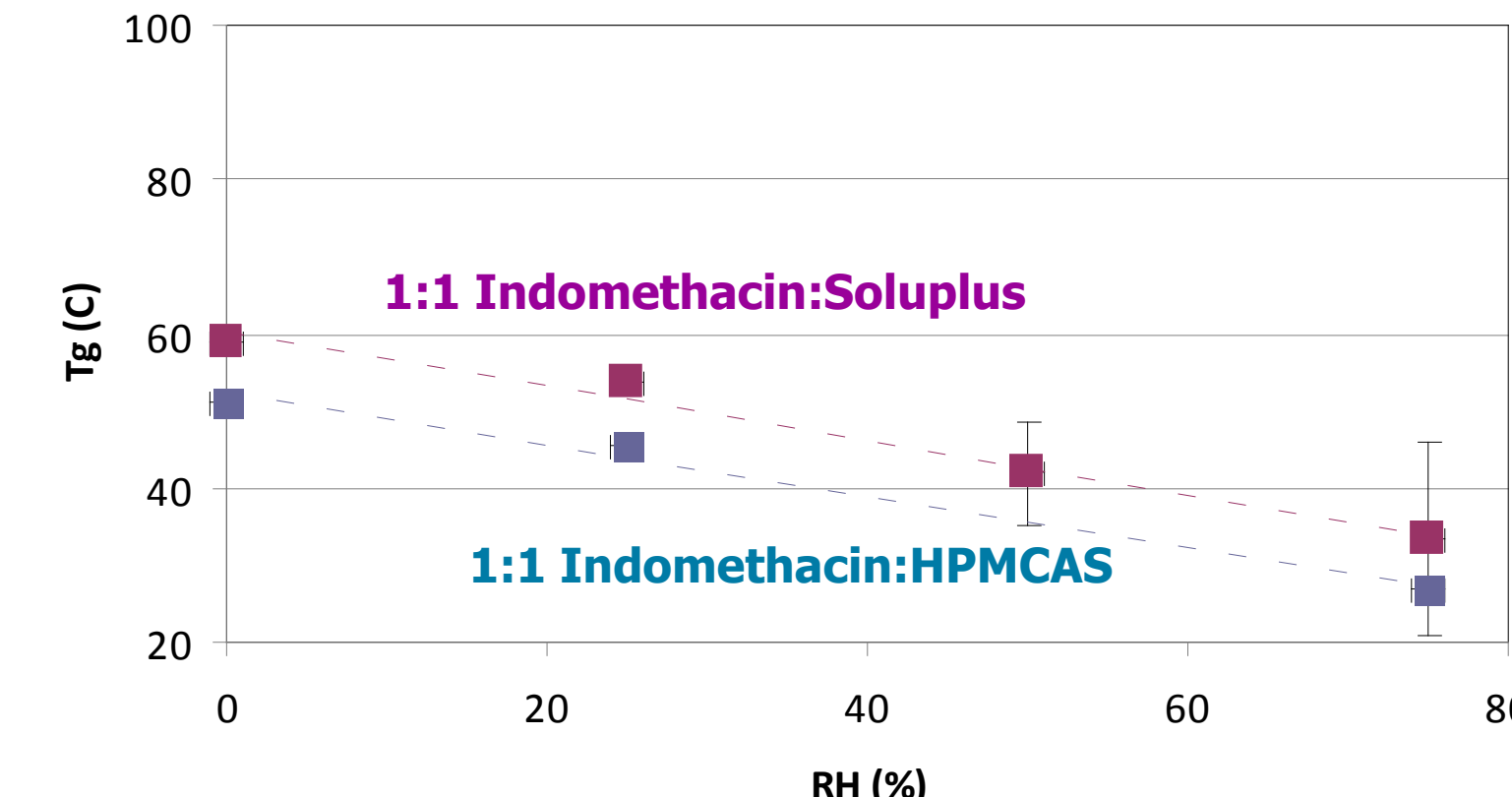
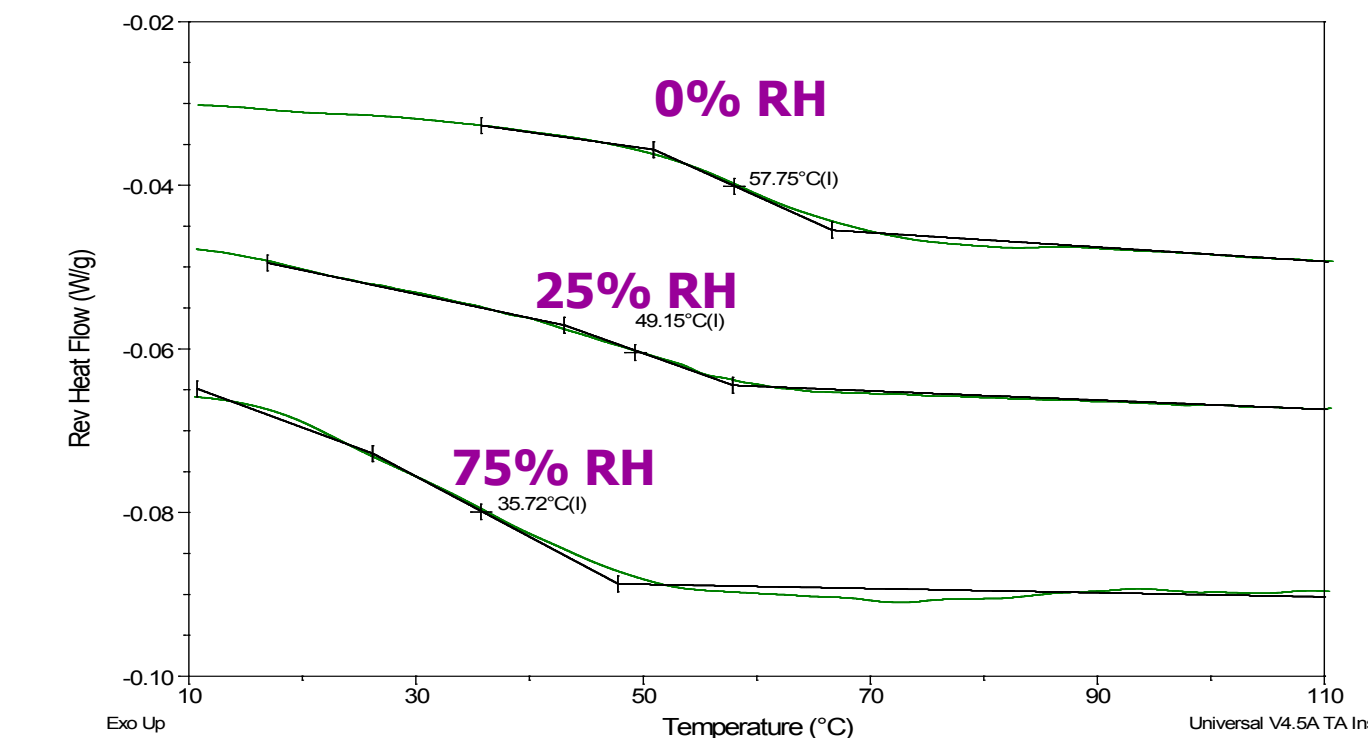


PXRD Of Megestrol Acetate Dispersions



Soluplus spray dried dispersions show no evidence of crystallinity

Tg Vs. RH (%) for 1:1 Indomethacin:Soluplus Dispersions



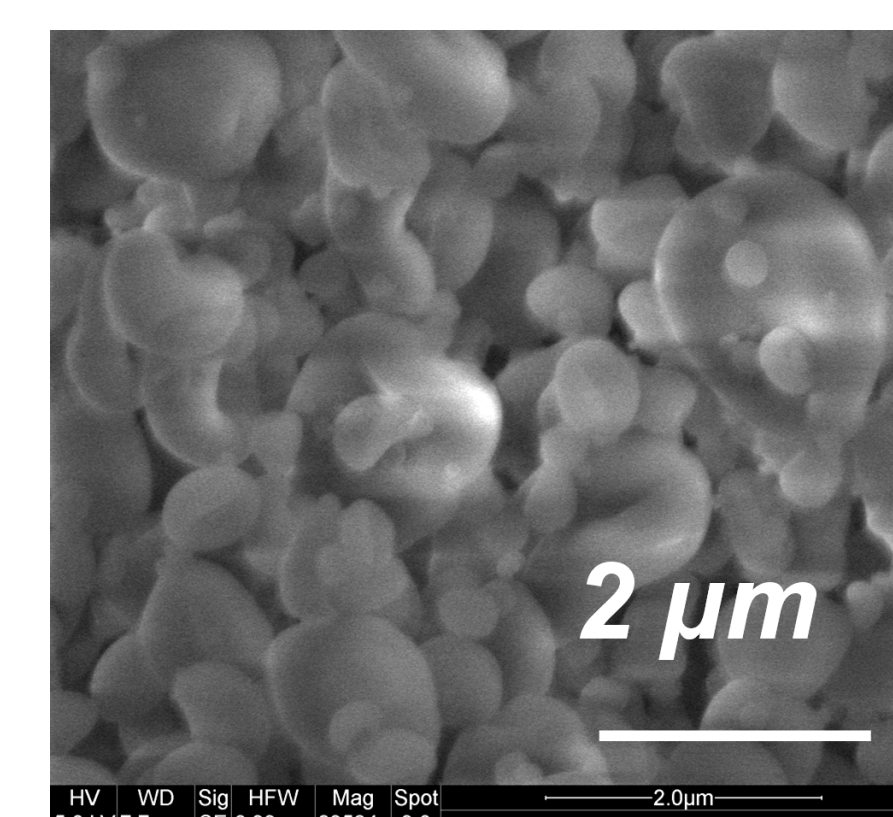
Samples were equilibrated in a controlled humidity chamber for > 24 hrs and then sealed using hermetic DSC pans.

1:1 Soluplus dispersions show higher Tgs at all RH values; may have superior stability compared to HPMCAS

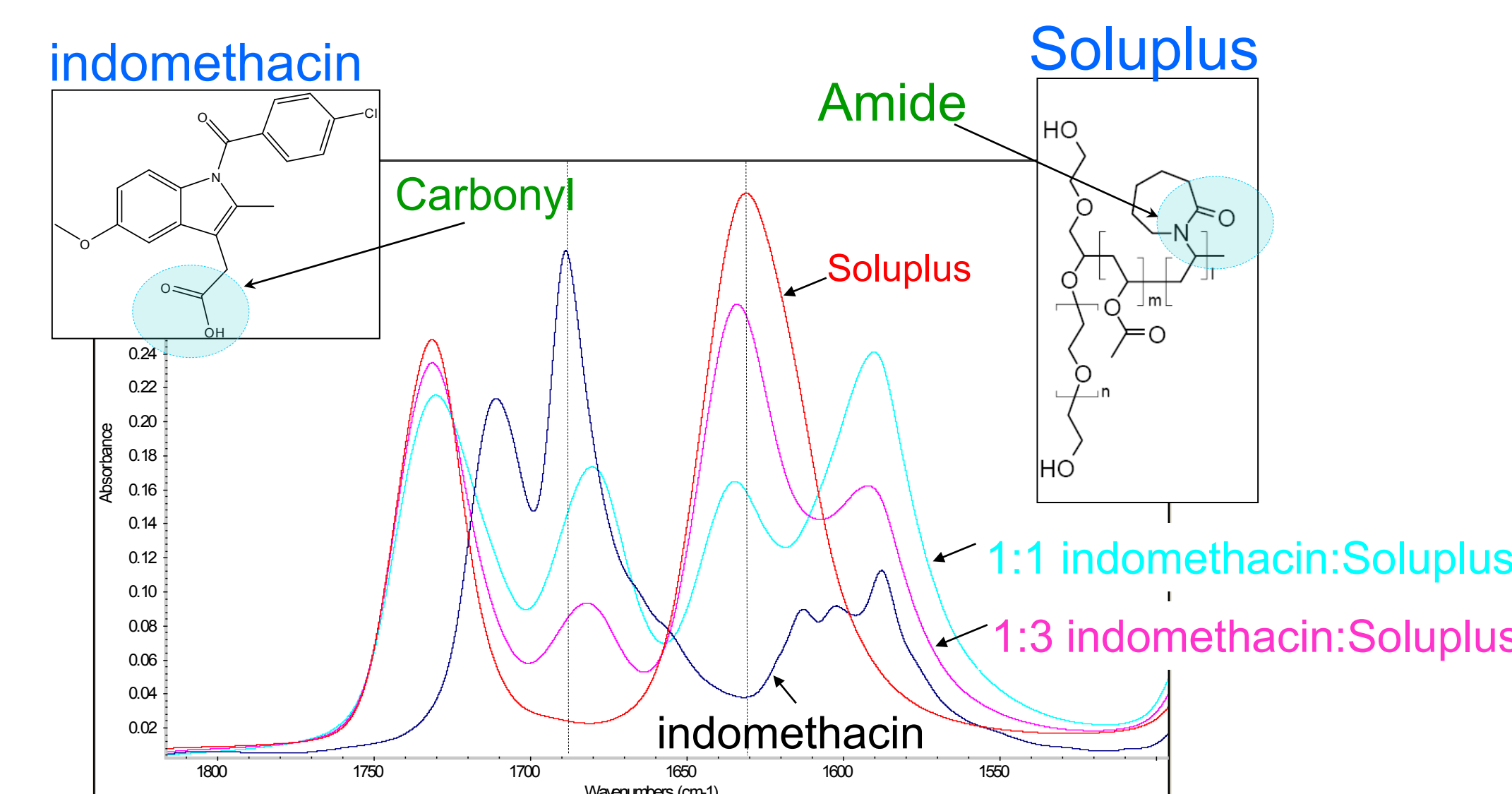
Summary Of mDSC Analysis Of Spray-Dried Dispersions

API	Polymer	Tg (°C) 1:3 Dispersion	Tg (°C) 1:1 Dispersion
Albendazole	Soluplus	63	62
	HPMCAS	82	69
Indomethacin	Soluplus	59	59
	HPMCAS	66	51
Fenofibrate	Soluplus	36	NA
	HPMCAS	47	NA
Itraconazole	Soluplus	61	57
	HPMCAS	NA	NA
Megestrol Acetate	Soluplus	63	60
	HPMCAS	88	77

SEM of 1:3 Itraconazole:Soluplus Spray-Dried Dispersions

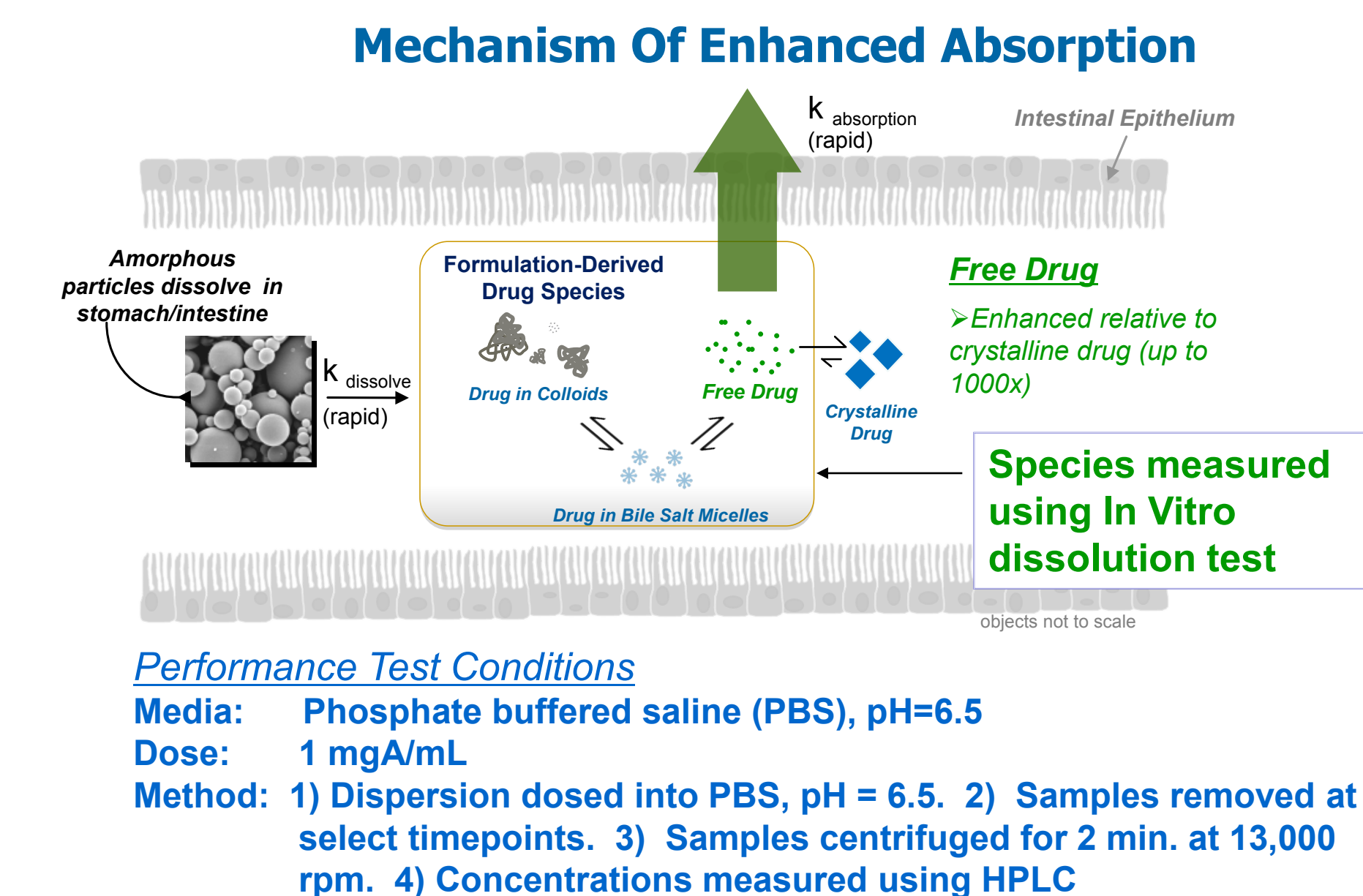


Indomethacin-Soluplus FTIR Spectra



Spectral shifts are consistent with H-bonding interactions between indomethacin acid (donor) interacting with Soluplus amid (acceptor)

In Vitro Performance



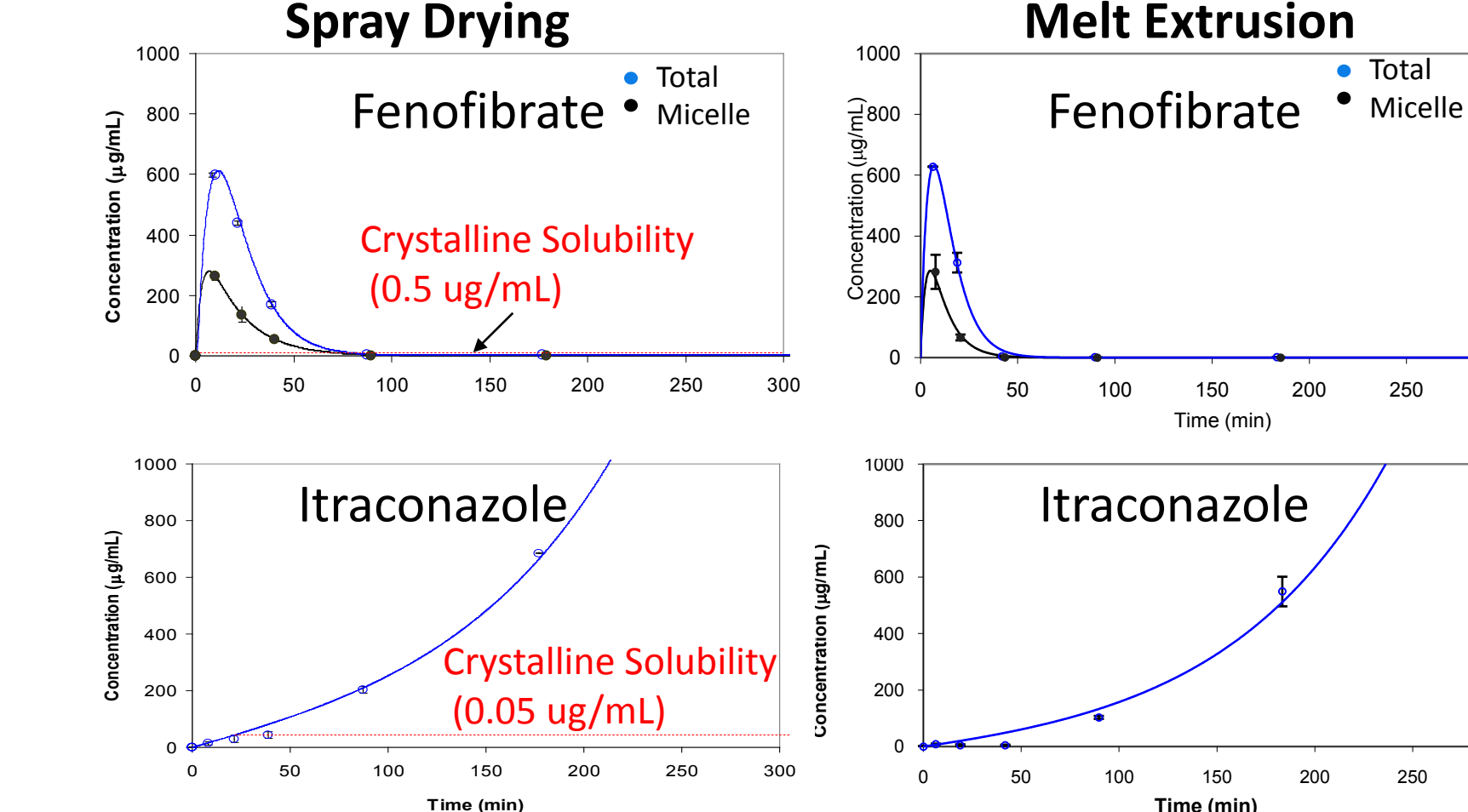
Performance Test Conditions

Media: Phosphate buffered saline (PBS), pH=6.5

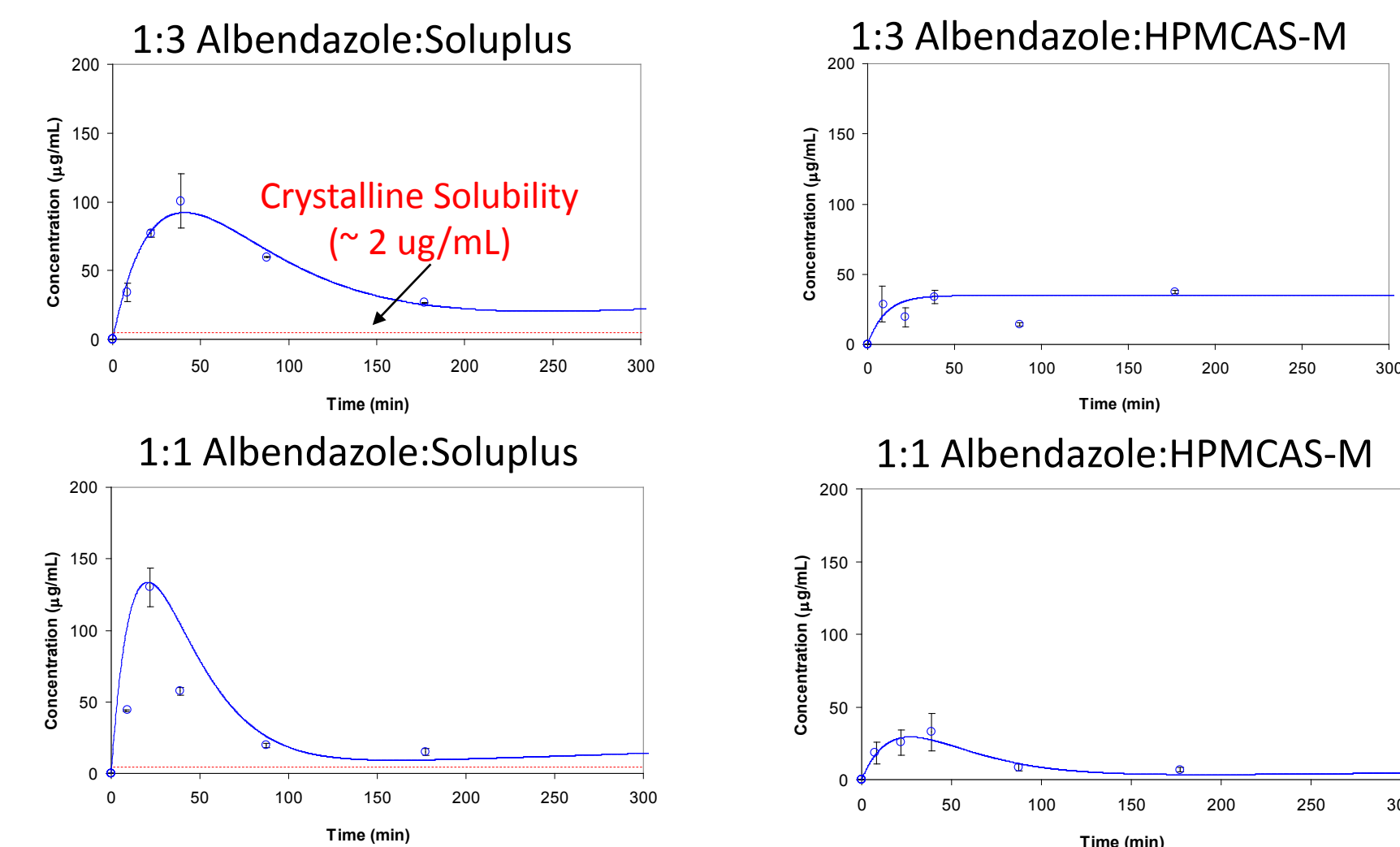
Dose: 1 mgA/mL

Method: 1) Dispersion dosed into PBS, pH = 6.5. 2) Samples removed at select timepoints. 3) Samples centrifuged for 2 min. at 13,000 rpm. 4) Concentrations measured using HPLC

Comparison of Spray Drying and Melt Extrusion 1:3 API:Soluplus

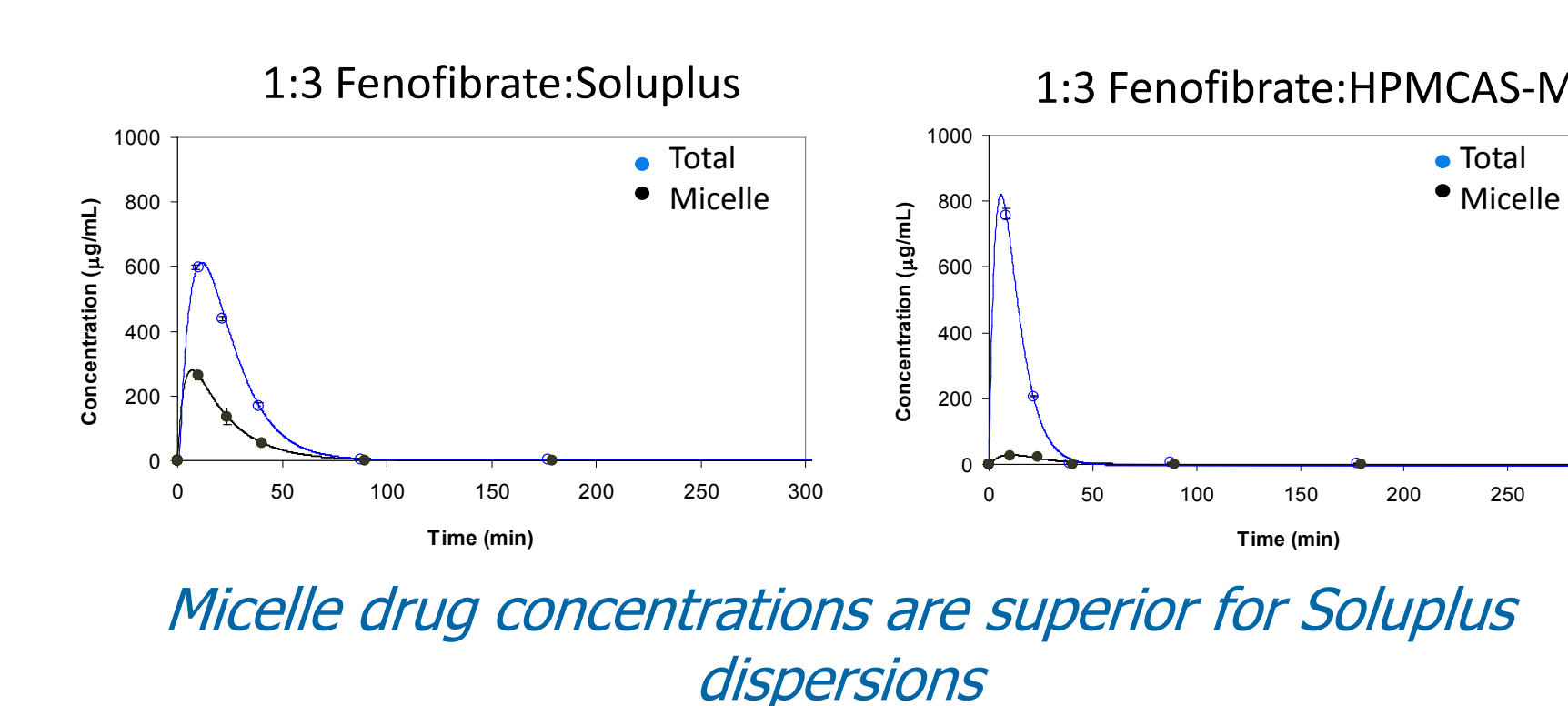


In Vitro Analysis Of Albendazole Solid Dispersions



$$Conc = A(1 - e^{-k_1 t}) \left(B + e^{-k_2 t} \right)$$

In Vitro Analysis Of Fenofibrate Solid Dispersions



Summary Of In Vitro Dissolution Of Spray-Dried Dispersions

API	Polymer	1:3 API:Polymer		1:1 API:Polymer	
		AUC (hr*ug/mL)	Cmax (ug/mL)	AUC (hr*ug/mL)	Cmax (ug/mL)
Albendazole	Soluplus	134.2	35	146.4	133.6
	HPMCAS	192.1	92.2	41.9	29.3
Indomethacin	Soluplus	1560	520	2190	730
	HPMCAS	NM	NM	NM	NM
Fenofibrate	Soluplus	125	279.9	NA	NA
	HPMCAS	13.9	28.6	NA	NA
Itraconazole	Soluplus	1244	1049	185.5	53
	HPMCAS	NM	NM	NM	NM
Megestrol Acetate	Soluplus	191.7	78	151.8	78.3
	HPMCAS	155.7	81.7	111.9	90.9

Conclusions

- Solid dispersions using Soluplus® are readily processable using spray drying.
- Solid-state analysis demonstrate that all dispersions are amorphous and have acceptable glass transition temperatures.
- Potential exists for strong hydrogen bonding between API and Soluplus®.
- Tg Vs. RH is acceptable, and in some cases superior to HPMCAS-M solid dispersions.
- In vitro performance is equivalent or superior to HPMCAS-M based solid dispersions.

References

1. Mehta M. AAPS/FDA Workshop on Biopharmaceutics Classification Systems, September 2002, 25-27.
2. Ali, et al, Drug Delivery Technologies, March 2010