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SUBJECT: Compilation of L-224715 Phosphate Salt
Anhydrous Polymorph Data

DATE: 26 Feb 2003

Summary

There are three known anhydrous polymorphs in the L-224715 phosphate salt system (Form I, II, and III).

Form II has only been witnessed from de-solvation of the ethanol solvate and is a metastable Form, which converts to predominately Form I with some Form III upon storage. Heating or exposure to water vapor accelerates the conversion.

The anhydrous polymorphs Form I and Form III are enantiotropically related. The thermodynamic conversion temperature, as measured by solubility in water using the shake-flask method, was determined to be 34°C. Form III is the thermodynamically stable form below 34°C, and Form I is the thermodynamically stable form above 34°C:

XRPD and SSNMR methods have recently been developed to perform Form quantitation of Forms I and III in bulk API. Both methods have ~10% limit of detection for either Form I or Form III. IR and Raman are also capable of distinguishing and possibly quantifying Form I and Form III in bulk API. SSNMR is currently the only method developed for Form quantitation in drug product samples.

Delivered lots of API to date have either been mixtures of Form I/Form III or Form II. Lots that were Form II on delivery converted to Form I in all stations except refrigeration. Lots that were mixtures of Form I/Form III do not change their polymorph content on stability.

Form I and II change to a mixture of Form I and III upon compression. Increasing compaction pressure increased Form III content, however, pure Form III has not been observed in any compact analyzed. Form III appears less affected by compression pressure with minimal Form content change upon compaction.

The difference in the flowability, intrinsic dissolution and compactability of the three forms are small. Overall, the impact of the form is relatively small compared to the particle characteristics.

All tablets end up with a mixture of Form I and III regardless of the starting point (Form I, II or III). In addition no apparent difference in the dissolution profiles of the tablets made by using three different forms was observed. The tablets were completely dissolved by 7 minutes, with full release by 10 minutes.

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I. Forms in all API lots and physical stability of lots

Below is a table with Physical Characteristic data for all delivered lots:

Lot	F006	F007	F016	F017	F019	F020	F023	F024
Crystal Form	I/III	I/III	I/III	I/III	II	I/III	II	II
Particle Size								
Average (µm)	92	63	48	62	42	15	47	65
95% < (µm)	212	143	118	139	83	30	104	167
% < 25 µm	13	17	28	20	22	87	21	19
Surface Area (m2/g)	NT	7.77	2.33	2.78	3.10	15.8	2.38	4.59
Morphology	NT	plates	plates	plates	plates	plates	plates	plates
Source	Lab	Lab	Lab	Lab	Lab	PP	PP	PP
Amount	450 g	590 g	5.1 kg	4.4 kg	2.5 kg	42.8 kg	19.2 kg	34.8 kg

Currently in our lab we have an XRPD and fluorine SSNMR method to quantitate polymorph Form I and Form III in bulk API. At actual time of delivery for all lots, neither of these methods was fully developed. Therefore, we do not have quantitative numbers for lots at actual time of delivery. However, Form content of various lots on chemical stability are displayed below:

<u>Stability</u> <u>Time = 0</u>	<u>Lot #</u>	<u>Time</u> <u>Point</u>	<u>Station</u>	<u>XRPD</u>	<u>Form I (%)</u>	<u>Form III (%)</u>
Apr-02	006F007	9 month	Freezer	-	58.9	41.1
	006F007	9 month	Refrig.	-	63.6	36.4
	006F007	9 month	25/60	-	65.3	34.7
	006F007	6 month	40/75	-	62.5	37.5
Jun-02	006F016	7 month	Freezer	-	74.6	25.4
	006F016	7 month	25/60	-	75.5	24.5
	006F016	7 month	40/75	-	73.1	26.9
Oct-02	006F019	3 month	Freezer	-	91.3	8.7
	006F019	3 month	25/60	-	87.1	12.9
	006F019	3 month	40/75	-	90.4	9.6
Oct-02	006F020	3 month	Freezer	-	81.2	18.8
	006F020	3 month	25/60	-	85.3	14.7
	006F020	3 month	40/75	-	86.1	13.9
Dec-02	006F024	1 month	Freezer	-	Form II + Form I	-
	006F024	1 month	25/60	-	89.5	10.5
	006F024	1 month	40/75	-	89.1	10.9

It is clear that all lots have converted to mixtures of Form I and Form III at elevated temperature and humidity conditions. If we assume the freezer sample is similar to what the Form content was at time of delivery, no significant Form conversion is occurring on stability. The only exception is lot 24 which originally contained Form II, this lot converts to Form I/Form III mixtures at elevated temperature and/or humidity. This suggests that Form I/Form III mixtures retain their form content on stability.

Action Items;

1. Continue monitoring physical form of delivered lots (will be performed as delivered and as pulled from stability station)

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