

MEMO

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SUBJECT:Pharmaceutical Evaluation of L-224715

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L-224715 is a DP-IV inhibitor for the treatment of type II Diabetes Mellitus. The phosphate salt form has been chosen for development. The following report, written for inclusion in the SARC Technical Review Package, describes the chemical and physical properties of L-224715 phosphate known to date.

1. Summary

L-224715 is a DP-IV inhibitor for the treatment of Type II Diabetes Mellitus. It is being developed as the crystalline phosphate salt, which exists as a single anhydrous polymorph to date. The phosphate salt is chemically stable in the bulk for 4 weeks under all conditions studied and is most stable in solution between pH 2-4. It consists of flake-like particles, with the mean particle size of the A-sheet delivery lot around 100 μm . The material is cohesive and has good overall flow properties.

L-224715 was dosed to both rats and dogs in solution and exhibited linear pharmacokinetics with no adverse effects noted. The Phase I formulation will be neat drug dry-filled into HPMC capsules using the Xcelodose 600™, which was able to fill 0.1 mg (free base equivalents) of drug into a capsule in trials run by PR&D. HPMC capsules containing L-224715 phosphate show acceptable dissolution profiles both initially and after 4 weeks of storage at 40 °C/75% RH; 20-mg potency HPMC capsules dosed orally to dogs show similar exposures to the 2 mg/kg solution dose.

2. Description

L-224715 is a DP-IV inhibitor for the treatment of Type II Diabetes Mellitus. It has an improved in vitro profile over the Probiodrug compound P32/98 (L-000826), previously in development, and its backup, L-221869.

L-224715 is a β -amino acid derivative with a molecular weight of 407.321 g/mol and a molecular formula of $\text{C}_{16}\text{H}_{16}\text{F}_6\text{N}_5\text{O}$. It is being developed as the monobasic phosphate salt (L-224715-006F), molecular weight 505.317 g/mol (salt factor 0.806). The structure of the phosphate salt is shown in the figure below.

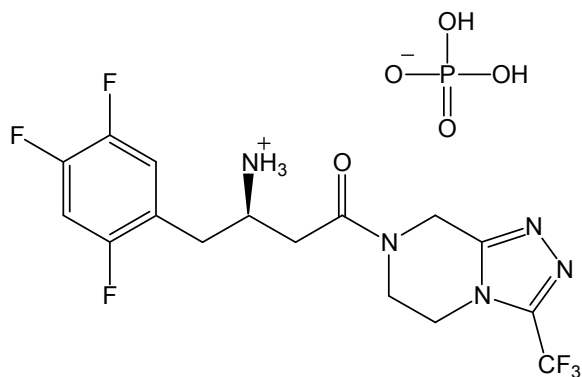


Figure 1. Structure of L-224715-006F (monobasic phosphate salt)

The phosphate salt is a white crystalline powder consisting of flake-like particles; this morphology affords good flow properties.

3. Test Substances

Chemical stability data were obtained using lot 70316-25 (bulk, gelatin mixtures, HPMC mixtures). Physical characterization data is primarily from the A-sheet delivery lot L-224715-006F006 (72471-11).

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Solubility data (exceptions noted in text) were generated with lot 70316-25. Physical stability data and Biopharmaceutical data were generated from lot 70316-35. Mechanical properties were determined using lot 70316-31.

4. Physical Characterization

Microscopy

Samples of L-224715 phosphate salt were examined by optical microscopy and SEM and were found to consist of flake-like particles with some agglomeration. A representative SEM image (L-224715-006F006, A-sheet delivery lot) is shown in Figure 4.1 below.

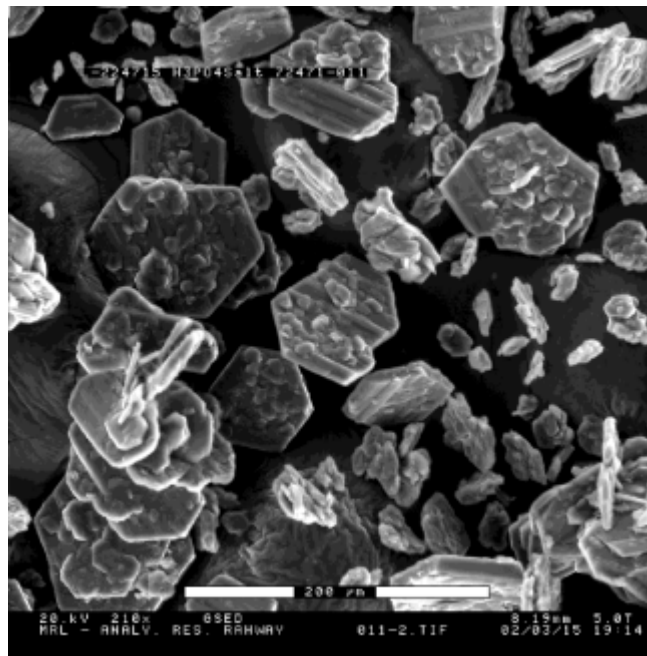


Figure 4.1. SEM image of L-224715-006F006 (210X magnification)

Particle Size Distribution

The PSD of several lots of L-224715 phosphate salt were determined in Physical Measurements on the Microtrac SRA150 (Table 4.1). Samples were sonicated for 30 seconds in Isopar G prior to measurement.

Table 4.1. Particle size of L-224715-006F

Lot	Mean (μm)	95%< (μm)	%<5 μm
70316-077 (006F003)	38.4	90.0	1.5
70316-079 (006F004)	35.1	75.8	0.1
72471-011 (006F006)	92.3	212.4	5.6

The mean particle size of the flakes increased in the A-sheet delivery lot (006F006) with respect to earlier lots. The particle size distributions are illustrated graphically in Figure 4.2 below.

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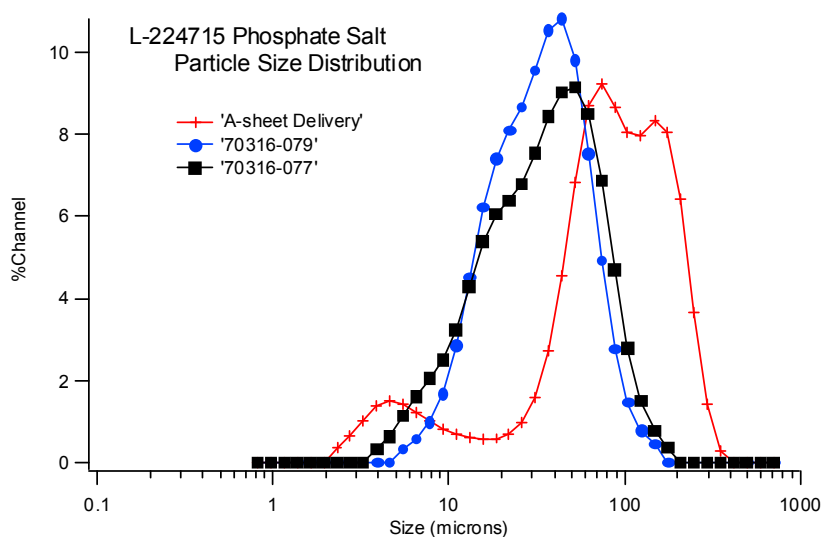
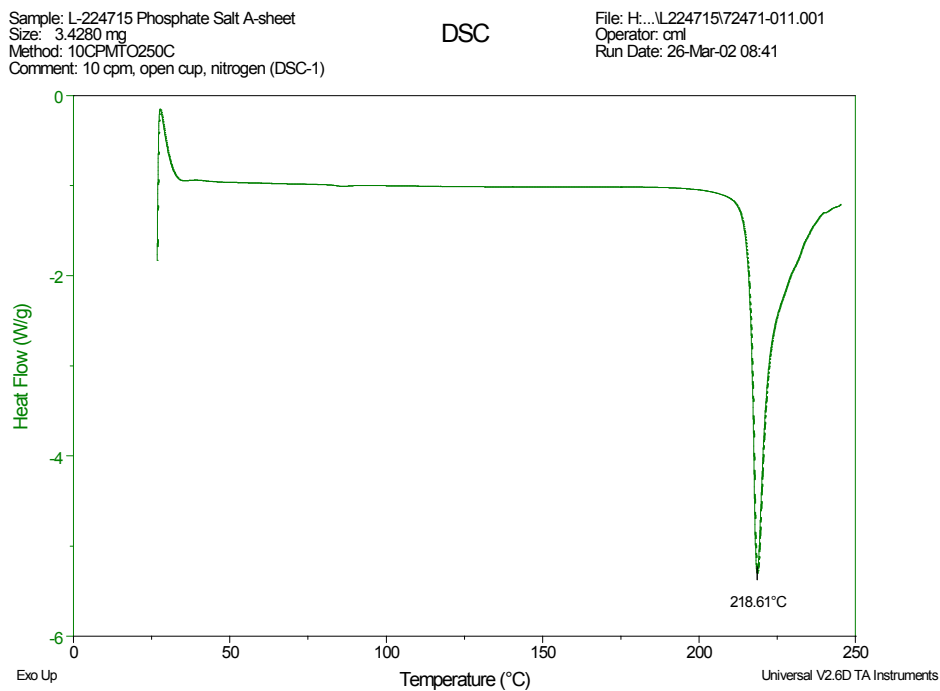


Figure 4.2. Particle size distributions for lots of L-224715-006F

Thermal Properties

Samples of L-224715-006F were analyzed by DSC and TGA to determine the melting point and residual solvent level of the salt. Representative DSC and TGA traces are shown below (Figure 4.3).



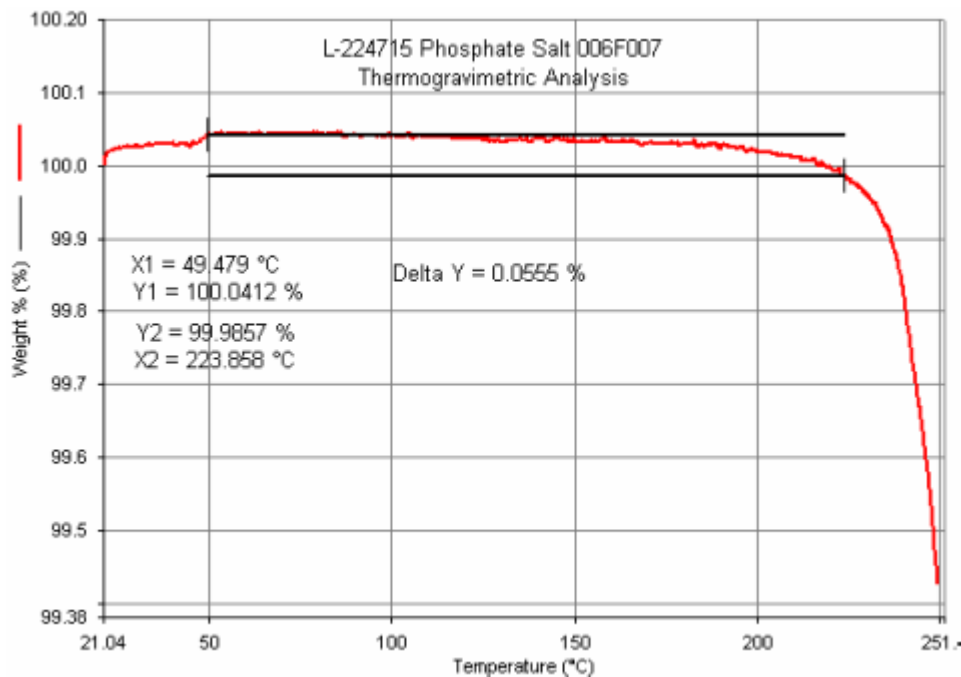


Figure 4.3. DSC (top) and TGA (bottom) traces for L-224715-006F006

DSC data were collected in an open pan with heating at 10 °C/min under nitrogen. The melting point of the salt is 218.6 °C. The melt endotherm cannot be quantitated due to immediate decomposition of the solid upon melting. TG analysis shows 0.056% weight loss between 50 °C and the onset of melting, indicating little solvent remaining on the solid.

X-ray Powder Diffraction

XRPD analysis of the phosphate salt of L-224715 shows several strong reflections between 2-40 °2θ, indicating this high crystallinity of the salt. No amorphous halo has been noted in any sample to date. The XRPD pattern for the A-sheet delivery lot is shown in Figure 4.4 below and is representative of the data obtained from samples of L-224715 phosphate salt from Process Research.

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