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MERCK Research Laboratories

MEMO

Pharmaceutical R&D - Rahway

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SUBJECT: L-000224715 Preformulation Report **DATE:** 30 Sep 2002

L-000224715 is a DP-IV inhibitor for the treatment of Type II Diabetes Mellitus. It was approved for development as a PCC by SARC in January of 2002 and began Phase I clinical trials in July 2002. This memo describes the chemical and physical properties of the compound known to date.

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cc: Dept. 854, A. Andrews, J. Armstrong, R. Franklin, J. Givand, K. Hansen, W. Hunke, P. Hurter, D. Ip, D. Kim, K. Kube, G. Kwei, G. Lankas, E. Luna, K. Lynn, N. Margaretten, D. Mendenhall, M. Moonis, D. Ostovic, S. Palkar, J. Pearson, S. Reynolds, I. Santos, S. Shelukar, C. Starbuck, M. Thien, N. Thornberry, R. Tillyer, E. Tsai, S. Vincent, A. Weber, J. Wyvratt, D. Zhang, J. Zimmerman

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1.0 SUMMARY

This memo summarizes the preformulation data available for the single known polymorphic form of the crystalline monobasic phosphate salt of L-000224715. The phosphate salt is a stable, high-melting, non-hygroscopic material with known isomorphic solvates. It is highly soluble in aqueous media across the physiological pH range and has adequate stability in solution below pH 6. The flow properties of the phosphate salt are good, suited to a direct compression formulation.

2.0 DESCRIPTION

L-000224715, a DP-IV inhibitor, is being developed for oral administration as a treatment for type II (adult-onset) Diabetes Mellitus. This compound is the second DP-IV inhibitor in development at Merck.

2.1 Name, Structure, Formula

L-000224715 has a molecular weight of 407.32 g/mol and a molecular formula of $C_{16}H_{15}F_6N_5O$. It is being developed as the monobasic phosphate salt, with molecular weight 505.32 g/mol (salt factor 1.24) and molecular formula $C_{16}H_{18}F_6N_5O_5P$. The structure of L-000224715 is shown in Figure 1, below.

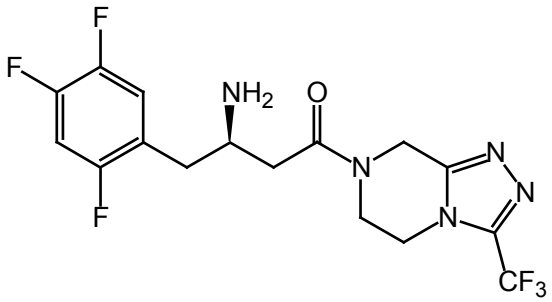

Figure 1. Structure of L-000224715

2.2 Color, Form, Appearance

The phosphate salt of L-000224715 is a white, crystalline powder with flake-like individual crystals. The powder shows some agglomeration and good flow properties.

3.0 TEST SUBSTANCES

All experiments were performed on lots of phosphate salt provided by Process Research. Stability, solubility, microscopy, particle sizing, XRPD, hygroscopicity, and thermal experiments were performed on lot L-000224715-006F006 (A-sheet). SEM data were obtained on lot L-000224715-006F007 (D-sheet). Particle size data are also shown for lots 006F003 (A-sheet) and 006F009 (A-sheet), which were used for assessing the feasibility of the Xcelodose* . Lots 006 and 007 came from the same chemical batch, which was split and released separately. Data obtained from other lots of phosphate salt are noted in the text. Both aqueous solubility as a function of pH and the pKa were determined with the crystalline free base, L-000224715-000T001.

4.0 PHYSICAL CHARACTERIZATION

4.1 Microscopy

Optical microscopy performed on lot L-000224715-006F006 at 200X magnification (Figure 2) reveals a birefringent, crystalline material. The primary crystals have a well-defined flake-like morphology; many of the flakes have a hexagonal shape. Some agglomeration of the crystals is observed.

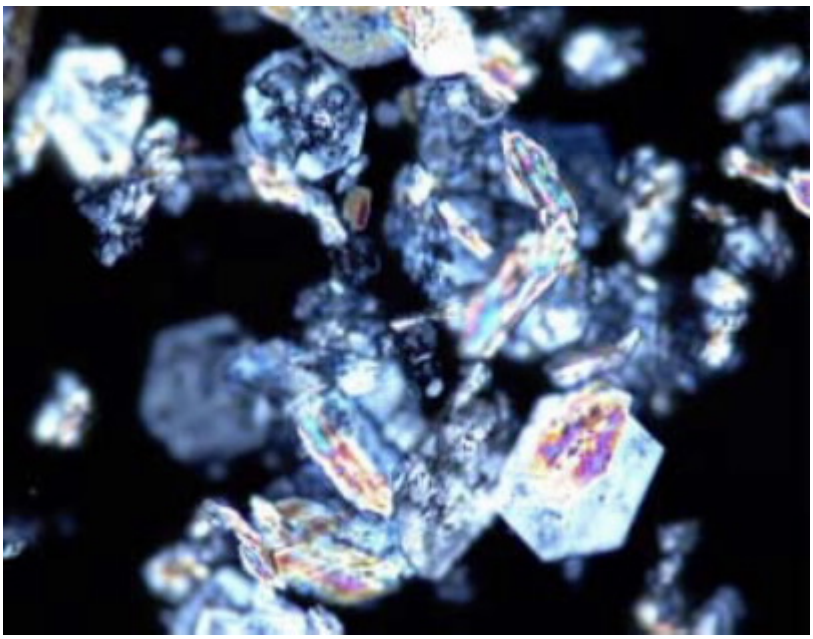

Figure 2. Optical microscopic image of L-000224715-006F006 (200X)

SEM images of L-000224715-006F007 are shown in Figure 3. Agglomeration of the individual crystals is evident in these images.

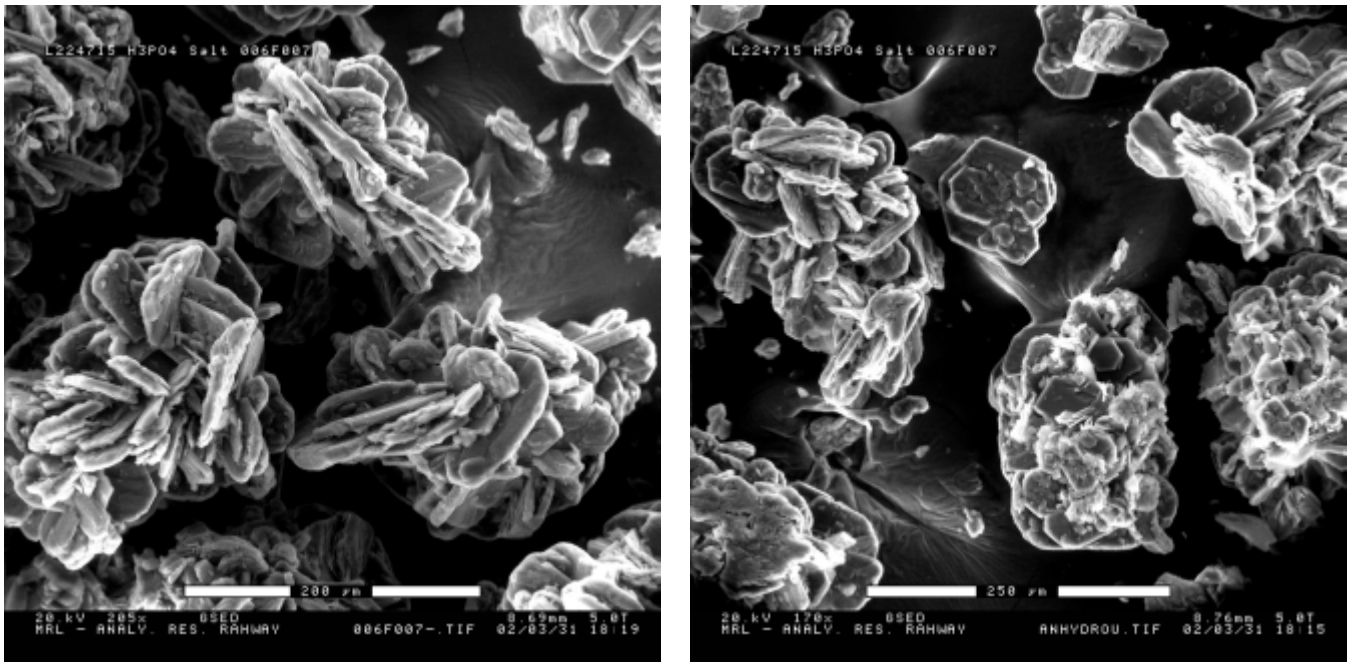

Figure 3. SEM images of L-000224715-006F007, showing agglomeration (205X, left; 170X, right)

Figure 4 shows particle size data for three lots of L-000224715, obtained using a MicroTrac light-scattering instrument with isopropanol as the medium. Lot 006 shows a broad, monomodal particle size distribution with a mean of 79 µm after 30 s of sonication (D_{10} = 23 µm, D_{95} = 190 µm). Prior to sonication, the mean particle size was 113 µm, with a D_{10} of 27 µm and a D_{95} of 285 µm. The decrease in both D_{95} and the mean on sonication indicates the loose nature of the agglomerates shown in Figure 3. Lots 003 and 009, used for testing the feasibility of the Xcelodose* , have similar average particle sizes, but show less agglomeration, decreasing from mean particle sizes of 46 and 65 µm, respectively, to 42 and 56 µm on sonication.

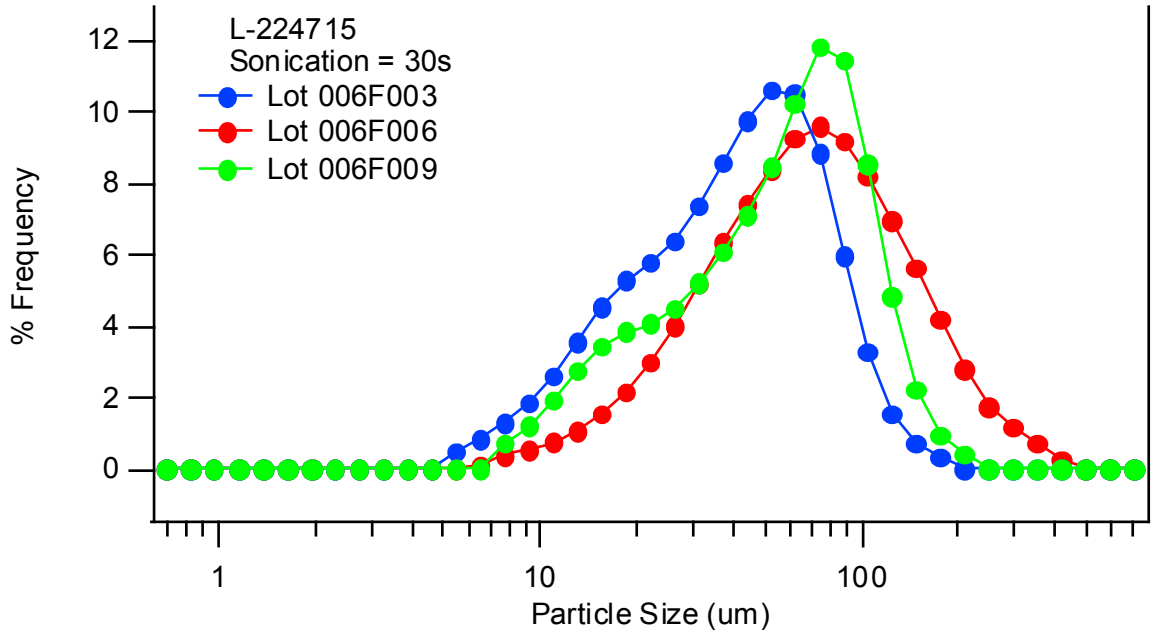

Figure 4. Comparison of particle size distribution for L-000224715-006F003, -006F006, and 006F009

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