



MERCK

**Parallel Development of Multiple Crystal Forms
for a New Drug Candidate: Selection of the Final
Form via Integrated Chemical and Pharmaceutical
Process Evaluation**

Speakers

Cindy Starbuck, Patricia Hurter, Robert Wenslow

Co-authors

**Joseph Armstrong, Alex Chen, Stephen Cypes,
Russell Ferlita, Karl Hansen, Mahmoud Kaba, Ivan Lee, Dina Zhang**

Contributors

**Danielle Euler, Tom Gandek, Jeff Givand, Brad Holstine, Feng Li, Yun Liu, Ernest
Luna, Kari Lynn, Robert Meyers, James Ney, Saurabh Palkar, Leigh Shultz, Iris**

Outline

Salt Selection

Desired particle properties for early formulation work

- ◆ Crystallization studies
- ◆ Polymorph characterization
- ◆ Development targets

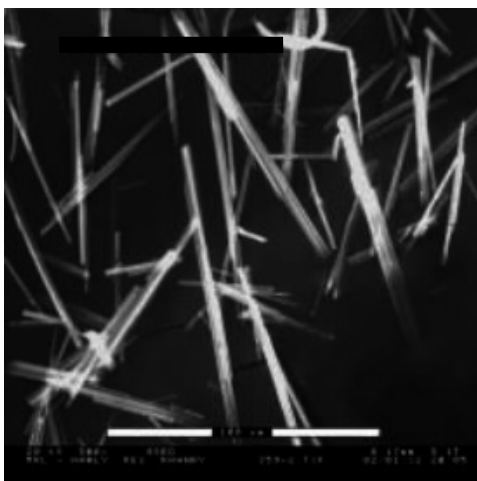
Emergence of a new crystal form during late stage development

- ◆ Chemical/Physical characterization
- ◆ Formulation characterization
- ◆ Biocomparability

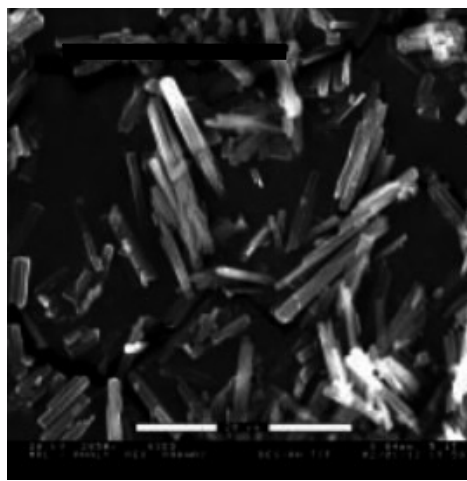
Early Salt Selection Activities

- ◆ For rapid entry into Phase I, wanted dry filled capsule
- ◆ Salt selection focused on morphology as well as stability (v. soluble drug bioavailability good)
- ◆ Targeted DC process for market formulation

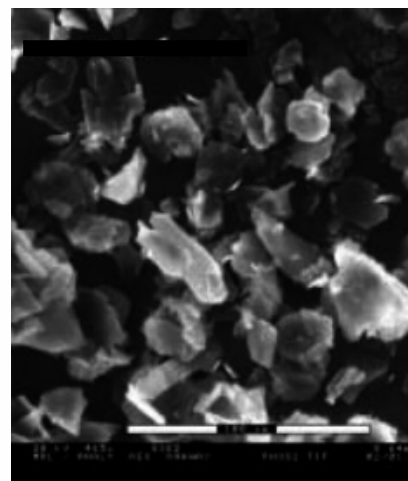
Salt A



Salt B



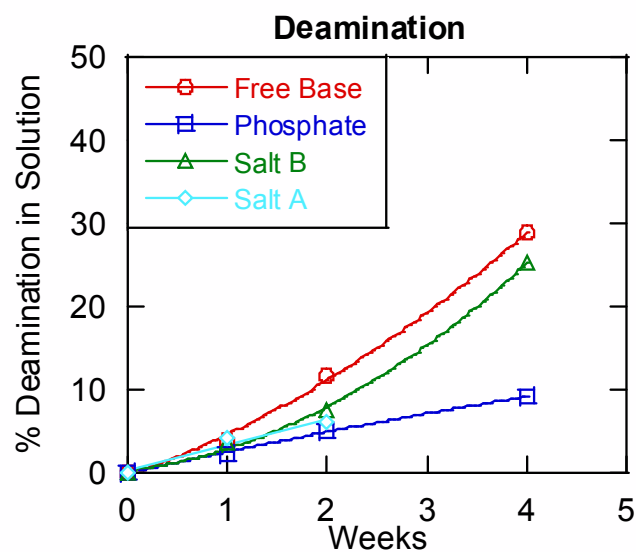
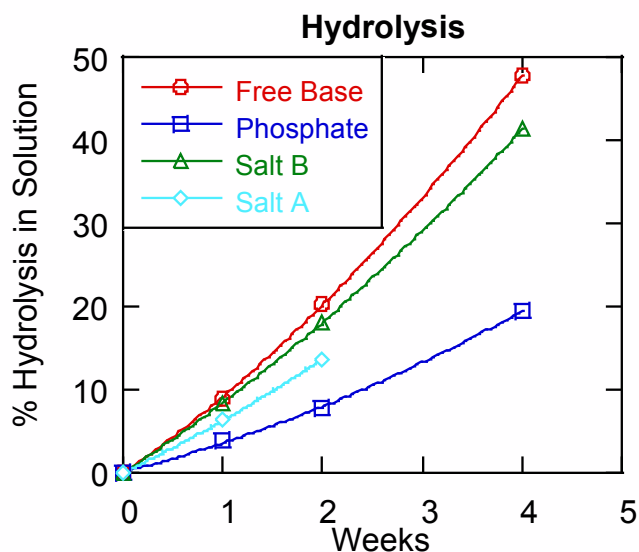
Phosphate



Early Salt Selection - Stability

All salts stable in bulk at 80°C/amb and 40°C/75%RH

- ◆ Hydrolysis and deamination occur in solution



- ◆ Phosphate salt chosen for Phase I, on the basis of morphology and stability

Market Formulation Development

Initial studies

- ◆ Probe formulations for excipient compatibility
- ◆ Investigation of physical stability, with wet granulation and compression
- ◆ Compaction simulator studies

Investigation of feasible drug loading range (1% to max.)

Process selection

- ◆ Wet granulation, roller compaction, direct compression options
- ◆ DC most desirable if particle characteristics amenable
- ◆ If DC promising, two processes in parallel until delivery of API from pilot plant lot

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