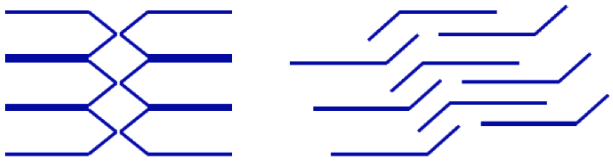
Polymorphism

- Different crystal arrangements of molecules
- All solid, but different physical properties



Form I Form II

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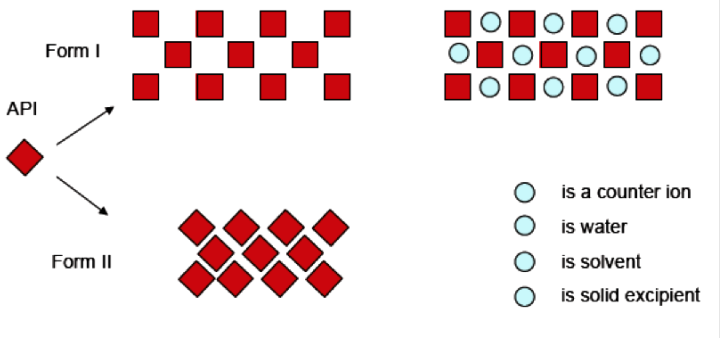
Polymorphism



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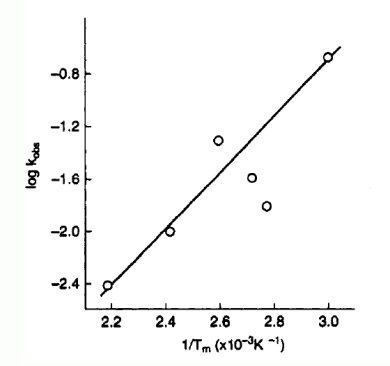
Polymorphism Considerations

- a) Selection of the lowest energy polymorph as it is the most thermodynamically stable form;

Relationship between the degradation rates of various vitamin A derivatives at 50 C and their melting points (Tm)



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Polymorphism Considerations

- Avoidance of the metastable forms
  - though they are more physically stable, but chemically less stable. Attempts should be made to play with the excipients to achieve the set pharmaceutical goals, instead of selecting the metastable form
  - Example: Cortisone Acetate

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Polymorphism Considerations

- Maintenance of such conditions which will avoid transitions from metastable form to the stable form throughout the shelf-life of the product, (if the former form is selected due to a particular reason like bioavailability enhancement)
  - Example: Chloramphenicole palmitate

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Polymorphism Considerations

- Assurance of avoidance of any polymorphic transition in the dosage form throughout its shelf-life, if so, the same should not significantly affect the product quality and bioavailability

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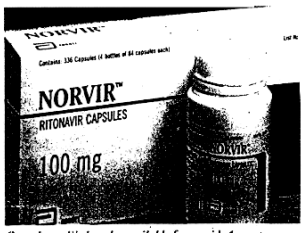
Case example: The Story Of Ritanovir

Manufacturing problems hit Abbott's HIV drug ritonavir



Capsules unlikely to be available from mid-August

Capsules of Abbott Laboratories' protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.

The problem relates to "undesirable" crystal formation. Abbott says that a series of recent production batches of Norvir capsules failed the approved test for dissolution, and were not released for marketing. Investigation of the reason for the failure showed the presence of a new crystalline form of ritonavir which affects the way it dissolves, and possibly its absorption. Retained samples from a number of marketed batches of capsules were examined and there was no evidence of the unwanted crystalline form.

Mr Mark Haywood (managing director, Abbott Laboratories) said that teams were working round the clock to try to resolve the issue, but at present the company had no idea why the problem was occurring.

THE PHARMACEUTICAL JOURNAL (VOL 261) August 1, 1998

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Ritanovir

- "After two-and-a-half years of closely monitored and tested formulation manufacturing, we encountered a new form of ritonavir, a crystal form...Previous to [May-June 1998] we had manufactured about 240 batches of ritonavir and none of those batches had ever failed a dissolution test."

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Ritanovir

- "What has happened is that a new crystal form of ritonavir has appeared. Although it has the same purity, this form has different properties that make it more difficult to formulate. Specifically, the crystalline structure makes ritonavir dissolve more slowly…, which affects its bioavailability."

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Ritanovir

- "While we have speculated on the cause of this chemical transformation, we don't have conclusive proof what happened…Abbott could not solve the problem for reasons which now are more apparent than they were when the problem was first discovered…Thermodynamics govern everything we do in the pharmaceutical industry."

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Ritanovir

- "We tried everything. We conducted countless experiments. We reconditioned our facilities. We rebuilt facilities and new lines. We looked at alternative sites. We visited a number of [other] organizations around the world…to see if we could start clean in a new environment free of Form II."

- "In a matter of weeks – maybe five or six weeks, every place the product was became contaminated with Form II crystals."

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Ritanovir

- "…our initial activities were directed toward eliminating Form II from our environment. Then we finally accepted that we could not get rid of Form II. Then our subsequent activities were directed to figuring out how to live in a Form II world."

- Product removed from market while a new formulation was developed
- Took 1 year and cost $100s millions
- 1 year of sales lost ($250 million)

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