Salt Screens and Polymorph Screens

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Salts

- A salt is typically defined as a chemical compound formed by reaction of an acid with a base
  - For example, the base enalapril reacts with the acid maleic acid to form a salt (Fig 1)
- Salts can provide large increases in solubility and bioavailability and improve properties like stability (Fig 2)

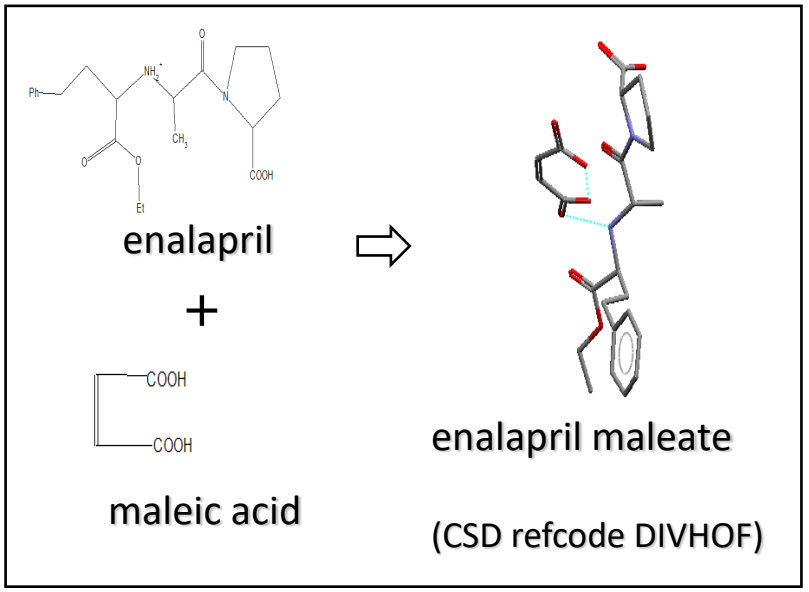

Figure 1. Acid + Base reacting to form a salt

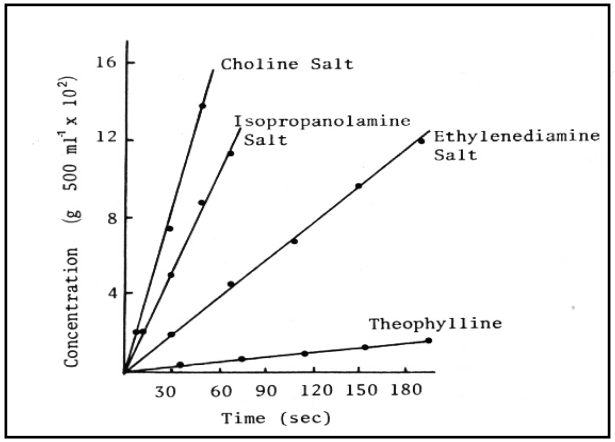

Figure 2. Solution rate of theophylline salts

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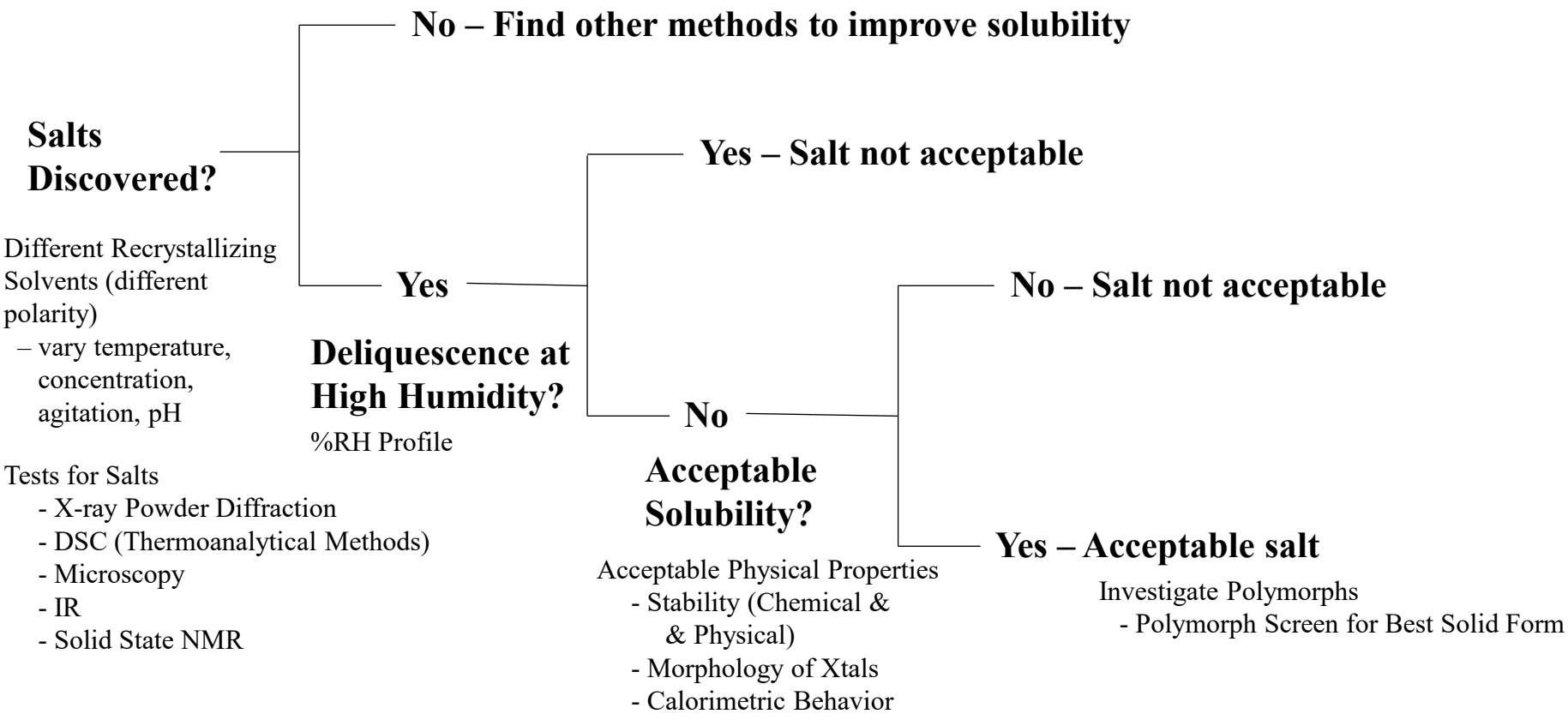
SALTS

Drug Substance



Polymorphs -1995 Paper

- Each salt could exist in multiple polymorphs
  - Famous examples include ranitidine, clopidogrel
- To the FDA hydrates are considered as polymorphs and each hydrate can have different properties
  - Famous examples include paroxetine HCl

Pharmaceutical Research, Vol. 12, No. 7, 1995

Review

Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations

Stephen Byrn,[1,4] Ralph Pfeiffer,[1] Michael Ganey,[2,3] Charles Hoiberg,[2] and Guirag Poochikian[2]

Purpose. This review describes a conceptual approach to the characterization of pharmaceutical solids. ***Methods.*** Four flow charts are presented: (1) polymorphs, (2) hydrates, (3) desolvated solvates, and (4) amorphous forms. ***Results.*** These flow charts (decision trees) are suggested as tools to develop information on pharmaceutical solids for both scientific and regulatory purposes. ***Conclusions.*** It is hoped that this review will lead to a more direct approach to the characterization of pharmaceutical solids and ultimately to faster approval of regulatory documents containing information on pharmaceutical solids.

KEY WORDS: polymorph; hydrate; amorphous form; desolvated solvate.

Interest in the subject of pharmaceutical solids stems in part from the Food and Drug Administration's (FDA's) drug substance guideline that states "appropriate" analytical procedures should be used to detect polymorphic, hydrated, or amorphous forms of the drug substance. These guidelines suggest the importance of controlling the crystal form of the drug substance. The guideline also states that it is the applicant's responsibility to control the crystal form of the drug substance and, if bioavailability is affected, to demonstrate the suitability of the control methods.

Thus, while it is clear that the New Drug Application (NDA) should contain information on solid state properties, particularly when bioavailability is an issue, the applicant may be unsure about how to scientifically approach the gathering of information and perhaps what kind of information is needed. This review is intended to provide a strategic approach to remove much of this uncertainty by presenting concepts and ideas in the form of flow charts rather than a set of guidelines or regulations. This is especially important because each individual compound has its own peculiarities which require flexibility in approach. The studies proposed herein are part of the Investigational New Drug (IND) process.

Solid drug substances display a wide and largely unpredictable variety of solid state properties. Nevertheless, application of basic physicochemical principles combined with appropriate analytical methodology can provide a strategy for scientific and regulatory decisions related to solid state behavior in the majority of cases. By addressing *fundamental* questions about solid state behavior at an early stage of drug development, both the applicant and the FDA are in a better position to assess the possible effects of any variations in the solid state properties of the drug substance. The resulting early interaction of the parties with regard to this area would not only tend to ensure uniformity of the materials used throughout the clinical trials but also fully resolve solid state issues before the critical stages of drug development. A further benefit of these scientific studies is the development of a meaningful set of solid state specifications which critically describe the solid form of the drug substance. These specifications would thus also facilitate the approval of a change in supplier or chemical process.

Our approach in this review is to suggest a sequence for collecting data on a drug substance that will efficiently answer specific questions about solid state behavior in a logical order. In "difficult" cases, perhaps where mixtures of forms must be dealt with, or other unusual properties are encountered, the suggested sequences would still have to be followed as a first stage in this investigation.

We have chosen to present this approach in the form of a series of decision trees, or flow charts (algorithms), one for each of the most common solid state forms. The charts are accompanied by examples from the literature representing the kind of data that would be useful in supporting the various decisions.

Decision trees provide conceptual frameworks for understanding how the justification for different crystal forms might be presented in the drug application. Industry may wish to use these decision trees as a strategic tool to organize the gathering of information early in the drug development process. Put another way, these decision trees provide a thought process that will lead to development of the most

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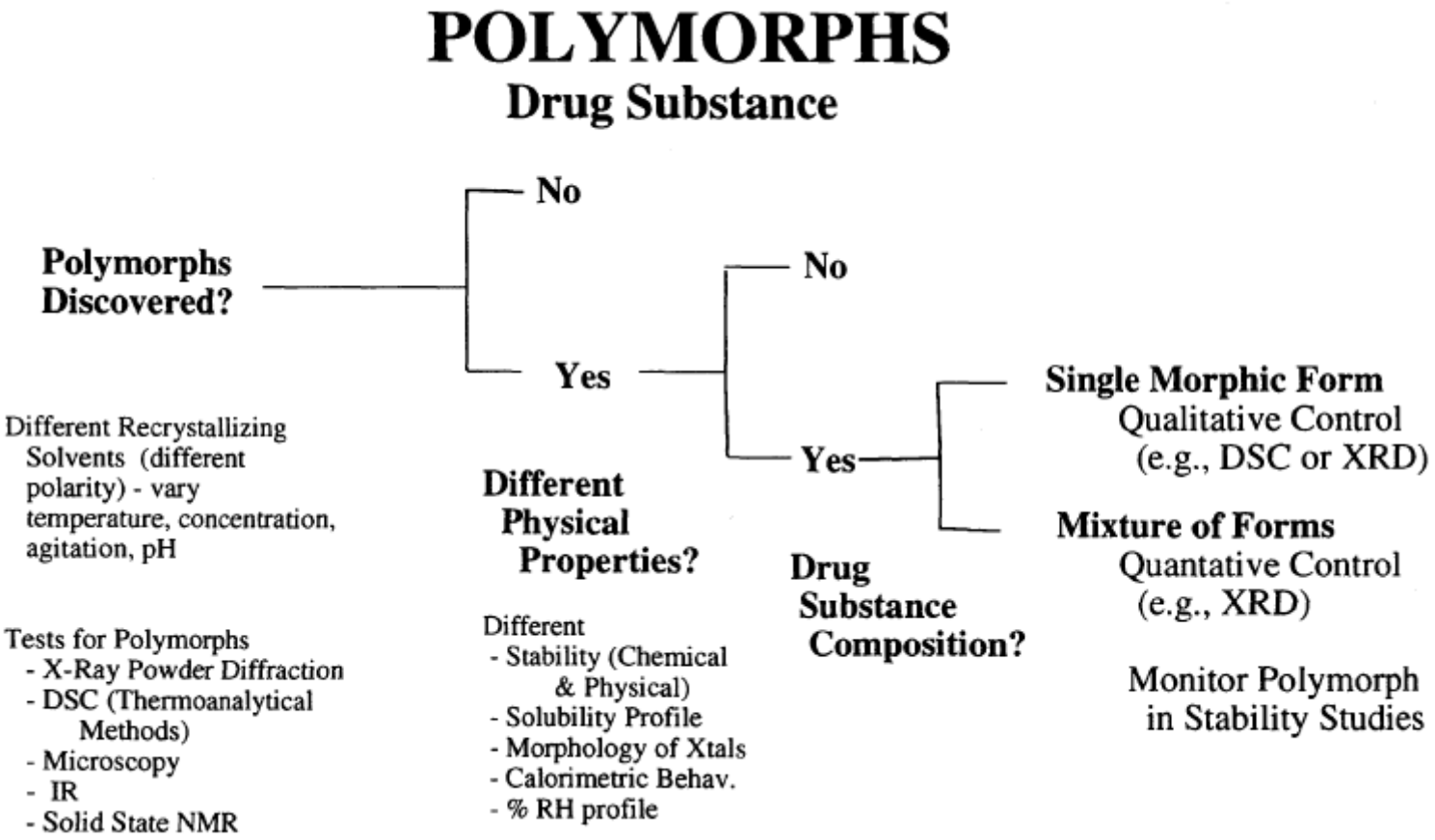


Figure 1. Flow chart from 1995 paper on Pharmaceutical Solids (See Byrn et al., Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations, Pharm. Res., 12, 945-954 (1995))

Are Polymorphs Obvious?

- United States Court of Appeals for the Federal Circuit says "No"
  - Simply following the flow charts in the Byrn paper will not provide a person of skill with a reasonable expectation of success that they will find the new polymorph
  - A person of skill would have to manipulate the variables "to determine what the crystal landscape looks like" because "you don't know what the result is going to be" – Professor Joel Bernstein, Cross-Appellants' expert
- "Byrn does not disclose when it would be appropriate to use particular solvents or a particular mixture of solvents for recrystallization"
- "Byrn does not outline a particular method to definitely test for polymorphism. Instead, it provides a decision tree outlining, among other things, different ways to gain additional information about whether polymorphs exist for a particular chemical compound and lists various analytical tests to identify polymorphs"
- "Byrn also instructs a person of skill to "vary temperature, concentration, agitation, pH", but does not provide guidelines regarding which temperature, concentration, agitation, or pH levels are likely to result in polymorphs of particular compounds."
- Highest chance of success comes when the screen is tailored to the properties of the drug and the client's goals, and is done by experienced solid-state chemists

https://foiadocuments.uspto.gov/federal/17-1153_1.pdf

Synchrotron-Based Salt/Polymorph Screens

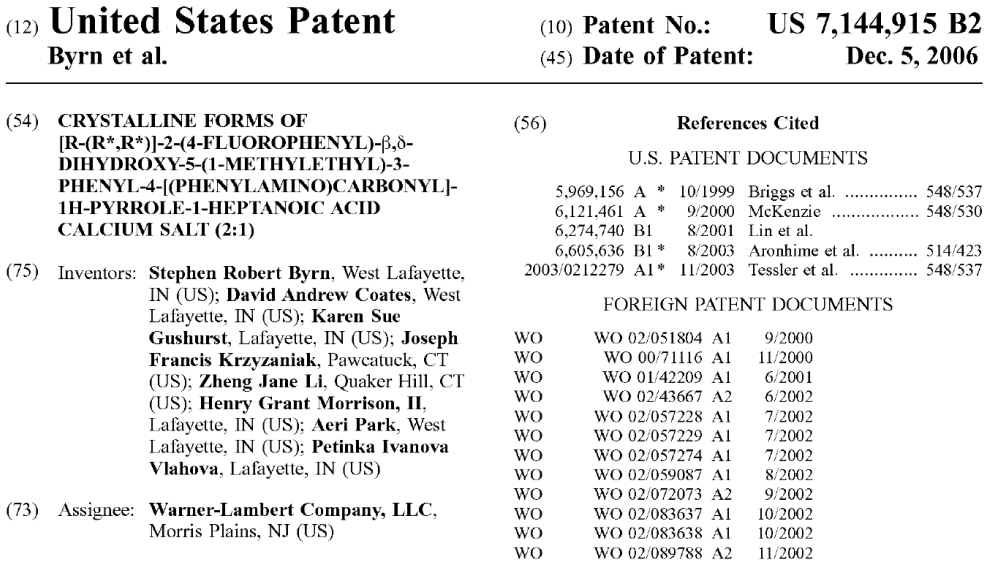
- Standard salt and polymorph screens are often plagued with questions like “Do these X-ray patterns represent pure forms?” and “How many pure forms have I found?”
- Synchrotron-based screens can address these questions and greatly increase the significance of screens. Synchrotron-based screens can:
  - Verify crystal form identity
  - Index patterns to verify phase purity of the form
  - Rietveld analysis – quantitative phase analysis
  - Aid structure elucidation from powder
  - Suggest methods of analysis and guide future experiments
  - Facilitate patent development

Microscopy Techniques– a Powerful Adjunct in Screening Studies

- Can conduct salt/polymorph screening experiments with very little material using hot stage optical microscopy in conjunction with FTIR and/or Raman microscopy
- Can use polarized light microscopy to quickly identify birefringence, and only collect additional data from crystalline samples
- Can analyze/verify optimal form
- Can verify purity of discovered form(s)
- Can determine thermal properties of optimal form(s)
- Can utilize FTIR/Raman microscopy to analyze forms and detect form transitions and stability issues

Patents and Intellectual Property

- Suggest Intellectual Property strategy from a solid-state chemistry standpoint
- Suggest most unique solid-state properties
- Byrn Lipitor patent – Forms V through XIX
- Explore dissolution properties
- Suggest patent attorneys



(12) **United States Patent**
Byrn et al.

(10) **Patent No.: US 7,144,915 B2**
(45) **Date of Patent: Dec. 5, 2006**

(54) **CRYSTALLINE FORMS OF [R-(R*,R*)]-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID CALCIUM SALT (2:1)**

(75) Inventors: **Stephen Robert Byrn**, West Lafayette, IN (US); **David Andrew Coates**, West Lafayette, IN (US); **Karen Sue Gushurst**, Lafayette, IN (US); **Joseph Francis Krzyzaniak**, Pawcatuck, CT (US); **Zheng Jane Li**, Quaker Hill, CT (US); **Henry Grant Morrison, II**, Lafayette, IN (US); **Aeri Park**, West Lafayette, IN (US); **Petinka Ivanova Vlahova**, Lafayette, IN (US)

(73) Assignee: **Warner-Lambert Company, LLC**, Morris Plains, NJ (US)

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Regulatory Consulting

- Extensive regulatory experience
- Coauthors on the 1995 paper were FDA scientists
- Advice on IND submission
- Advice on NDA submissions
- Advice on analytical strategies and analytical methods
- Advice on late appearing polymorphs or solid forms

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  - Abbreviated
  - Comprehensive
  - Microscopy-based screens
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