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Señor

JEFE DE DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente No. 06 001.282 – solicitud de patente de invención a favor de NEUROSEARCH A/S.

Respuesta al oficio No. 13814 del 22 de octubre de 2010

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad NEUROSEARCH A/S, según lo acredita el documento de poder presentado ante esa División, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 01070 notificado por fijación en lista de fecha 22 de octubre de 2010.

Con el ánimo de subsanar las objeciones de claridad realizadas a la presente solicitud presentamos un nuevo conjunto de reivindicaciones, de 1-8, sin ampliar la materia inicialmente divulgada y mejorando el entendimiento técnico de la invención.

Con respecto al nivel inventivo de la presente solicitud, es importante anotar que el documento D1 lista no menos de 27 sales farmacéuticamente aceptables, las cuales son conocidas en el área de diseño de compuestos farmacéuticos. Sin embargo, D1 solo enseña el uso de sal de citrato y no la sal de tartrato, siendo esta última la de interés en la presente solicitud, pues antes del desarrollo de la presente invención, esta sal no había sido aislada y las propiedades farmacológicas no estaban reportadas. Por lo tanto, al tener en cuenta que lo general no puede afectar a lo específico, la actual invención

representa un avance sobre D1 y es inventiva porque su obtención está determinada por la capacidad inventiva del investigador, gracias a que como consecuencia de su trabajo en el laboratorio, pudo establecer las condiciones para su obtención sin ser estas predecibles, conocidas, o con una forma preestablecida.

Adicionalmente, al comparar la sal de tartrato de la presente invención con la sal de citrato de D1, se evidencian mejores propiedades relacionadas con la estabilidad, solubilidad, higroscopicidad (ver anexo 1), biocompatibilidad, reproducibilidad de la forma cristalina, propiedades importantes en el desarrollo de medicamentos ya que ofrece ventajas fármaco-terapéuticas respecto de las otras formas cristalinas conocidas del mismo compuesto.

El Señor Examinador parece alegar que todas las sales funcionan igual y omite el hecho que ciertas sales pueden poseer diferentes características. Las sales de un compuesto pueden tener propiedades muy diferentes que hacen que el desarrollo de un medicamento sea más o menos difícil y en especial con respecto al efecto de la estabilidad de las sustancias iniciales a varias condiciones ambientales, la estabilidad durante la producción de la formulación farmacéutica y la estabilidad en las composiciones finales del medicamento. Como prueba de esto en el Anexo 1, se observa que con la sal de tartrato consigue un perfil de una sal no higroscópica favoreciendo la producción de fármacos, contrario a lo que se observa en la sal citrato de documento D1. La selección de una sal adecuada es algo que no es predecible y en el presente caso no podría ser obvio que la sal de tartrato del compuesto tuviera unas propiedades ventajosas en el desarrollo de un medicamento.

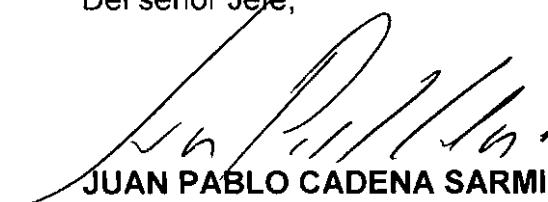
El examen realizado por el Señor Examinador queda sin sustento ya que queda demostrado el efecto de la sal de tartrato. Este efecto en ningún momento es obvio o esperado, las propiedades de una sal no son previsibles y menos cual sal es mejor que otra en términos de estas propiedades. Para dar un mayor soporte a esto, adjuntamos el artículo *"Physical characterization of polymorphic drugs: an integrated characterization strategy"* donde se establece

que los polimorfos presentan un reto para científicos que desean producir medicamentos de una calidad consistente (ver página 118, párrafo 1).

Adicionalmente, la presente invención soluciona un problema recurrente en la industria farmacéutica al proporcionar procesos que pueden llegar a ser realmente escalables a nivel industrial y satisfacer adecuadamente las necesidades de los usuarios de los medicamentos. Además, se establece en el documento citado anteriormente que estos compuestos reflejan una necesidad práctica de caracterizar todas las formas sólidas de una sustancia para que pueda ser exitosamente producida mediante procesos farmacéuticos estándar (ver página 118, párrafo 2). En este sentido, consideramos que se demuestra la necesidad de desarrollar procesos, como el reivindicado, que involucren este tipo de compuestos para lograr un proceso realizable y eficiente que permita producir el agente activo, que en este caso es la sal de tartrato. Por esta razón, la solución desarrollada por los inventores constituye un aporte sustancial inventivo al arte previo conocido, el cual no debe en ningún momento ser subestimado por el Señor Examinador.

Por las razones anteriores, el solicitante sostiene que las reivindicaciones actuales deben ser consideradas inventivas en vista del arte previo citado y conceder el privilegio de patente.

Del señor Jefe,



JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

T.P. No. 57492 del C.S.J.

Calle 70A No. 4-41

Bogotá, 19 de enero de 2011

MXB/AOB

Anexos

REIVINDICACIONES

1. Una sal seleccionada de las formas anhidra e hidratada de tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo [3.2.1] octano.
2. La sal de la reivindicación 1 seleccionada de las formas anhidra e hidratada de L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano.
3. La sal de la reivindicación 1, que es monohidrato de L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano.
4. La sal de la reivindicación 1, que es una forma anhidrida de L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano.
5. La sal de la reivindicación 4, que es una forma polimórfica (forma II) de anhídrido de L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano caracterizada por los siguientes picos principales en el patrón de difracción de rayos X del polvo:

Pico N°	1	2	3	4	5	6	7	8	9	10
2Theta°(Cu Kα)	10,35	11,68	12,53	14,81	15	15,77	16,82	17,41	17,77	18,87
espacio d (Å)	8,5	7,6	7,1	6,0	5,9	5,6	5,3	5,1	5,0	4,7
Pico	11	12	13	14	15	16	17	18	19	
2Theta°(Cu Kα)	20,29	21,26	21,66	23,44	23,73	25,44	25,99	27,58	28,14	
espacio d (Å)	4,4	4,2	4,1	3,8	3,7	3,5	3,4	3,2	3,2	

6. La sal de la reivindicación 4, que es una forma polimórfica (forma III) del anhídrido del L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano caracterizada por los siguientes picos en el patrón de difracción de rayos X del polvo:



Pico N°	1	2	3	4	5	6	7	8	9	10
2Theta°(Cu Kα)	5,37	10,6	10,82	11,58	11,88	12,79	14,78	16,57	16,5	17,03
espacio d (A)	16,4	8,3	8,2	7,6	7,4	6,9	6,0	5,4	5,4	5,2
Pico	11	12	13	14	15	16	17	18	19	
2Theta°(Cu Kα)	17,84	19,29	20,01	21,2	22,99	23,46	24,54	25,15	26,59	
espacio d (A)	5,0	4,6	4,4	4,2	3,9	3,8	3,6	3,5	3,3	

7. La sal de la reivindicación 4, que es una forma polimórfica (forma IV) del L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano caracterizada por los siguientes picos en el patrón de difracción de rayos X del polvo:

Pico N°	1	2	3	4	5	6	7	8	9	10
2Theta°(Cu Kα)	5,31	10,19	11,23	12,13	12,35	12,69	14,31	14,55	14,77	16,43
espacio d (A)	16,6	8,7	7,9	7,3	7,2	7,0	6,2	6,1	6,0	5,4
Pico	11	12	13	14	15	16	17	18	19	20
2Theta°(Cu Kα)	17,48	18,21	18,43	18,81	19,36	19,61	20,26	20,5	21,29	21,46
espacio d (A)	5,1	4,9	4,8	4,7	4,6	4,5	4,4	4,3	4,2	4,1
Pico	21	22	23	24	25	26	27	28	29	30
2Theta°(Cu Kα)	21,59	22,53	22,77	23,38	23,59	23,9	24,45	25,02	25,56	26,19
espacio d (A)	4,0	3,9	3,9	3,8	3,8	3,7	3,6	3,6	3,5	3,4
Pico	31	32								
2Theta°(Cu Kα)	26,83	27,21								
espacio d (A)	3,3	3,3								

8. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de una sal de cualquiera de las reivindicaciones 1 – 7, junto con al menos un portador, excipiente o diluyente farmacéuticamente aceptable.

Physical characterization of polymorphic drugs: an integrated characterization strategy

Lian Yu, Susan M. Reutzel and Gregory A. Stephenson

The potential impact of changing crystal forms during late-stage drug development, in terms of cost and product delay, justifies systematic and early characterization of polymorphism. A thorough understanding of polymorph characteristics also allows selection of the best form to market. The authors review the key elements of polymorph characterization (identification and quantitation, structures, properties and structure–property relationships). The emphasis is on recent developments and an integrated characterization strategy for different types of polymorphs using crystallographic, spectroscopic, microscopic and thermal techniques.

Lian Yu*, Susan M. Reutzel and Gregory A. Stephenson
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, IN 46285, USA
*tel: +1 317 276 1448
fax: +1 317 277 2154
e-mail: yu_lian@lilly.com

▼ Pharmaceuticals may exist in numerous solid forms which may feature different physical and chemical properties. These solid forms include 'true' polymorphs, solvates (pseudo-polymorphs), desolvates and amorphous solids (Figure 1). This phenomenon, broadly referred to as 'polymorphism' in this review, presents both a challenge to pharmaceutical scientists who wish to produce drugs of consistent quality and an opportunity for materials scientists who are interested in understanding the structure–property relationships in organic solids. Thus the importance of polymorphism has prompted much interest in the characterization of pharmaceutical solids^{1–4}.

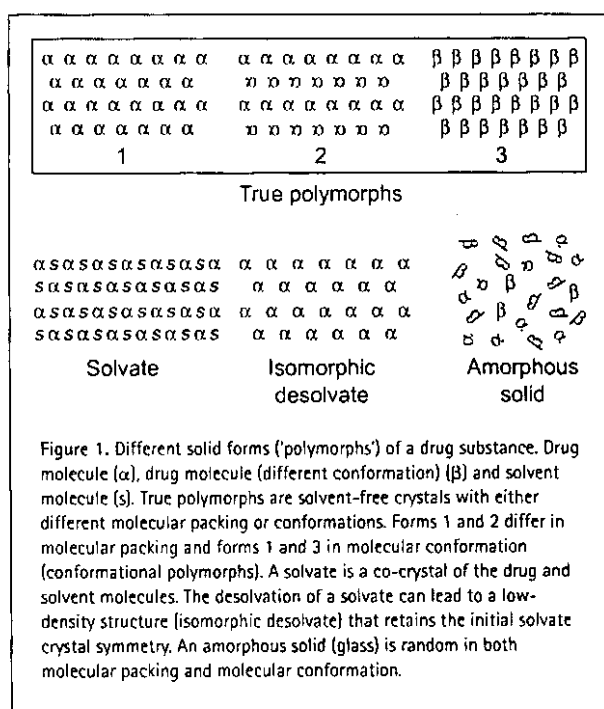
The authors use an extended definition of polymorphism¹ that includes all solid forms of the same molecule that have the same vapor, liquid or solution phase. Thus, true polymorphs, desolvates, liquid crystals, amorphous materials and mixtures thereof are all considered to be polymorphs, and solvates were also included in this definition. This extended definition reflects a practical need to characterize all solid forms of a

drug substance that can be produced by standard pharmaceutical processes: crystallization, milling, freeze drying, spray drying, wet granulation, solid dispersion, and 'accelerated' storage (Figure 2).

Aside from its impact on drug quality, it is important to characterize polymorphism for other reasons:

- Crystal forms may be patentable
- The types of solid forms that a molecule produces may be variable. Thus, some molecules yield true polymorphs and others solvates; some crystallize easily, others form glasses; and some polymorphs crystallize predictably, whereas others are elusive ('disappearing polymorphs')⁵
- Regulatory expectations for the characterization of new drug products have expanded to include the polymorph types and their purity levels⁶
- Polymorphism provides a unique opportunity to study structure–property relationships in organic solids⁷ and the thermodynamic and kinetic control of crystallization⁸
- Solid forms may be 'engineered' to optimize certain physical properties (e.g. dissolution rate and bioavailability)

In today's pharmaceutical industry, a discussion of the strategy for characterization of polymorphic drugs is necessarily complicated. Whereas a 'universal' approach is desirable, different polymorphs require different strategies and techniques (crystalline vs. amorphous, true polymorphs vs. solvates, small vs. large molecules, pure forms vs. mixtures, etc.). Researchers now have access to many analytical techniques that allow them to study many



aspects of polymorphism, but a balance between adequacy and depth is essential.

The approach that we have adopted is to recognize the basic elements of polymorph characterization, and these are best described by addressing the questions in Box 1:

- Identification and quantitation
- Structures
- Properties
- Structure–property relationships

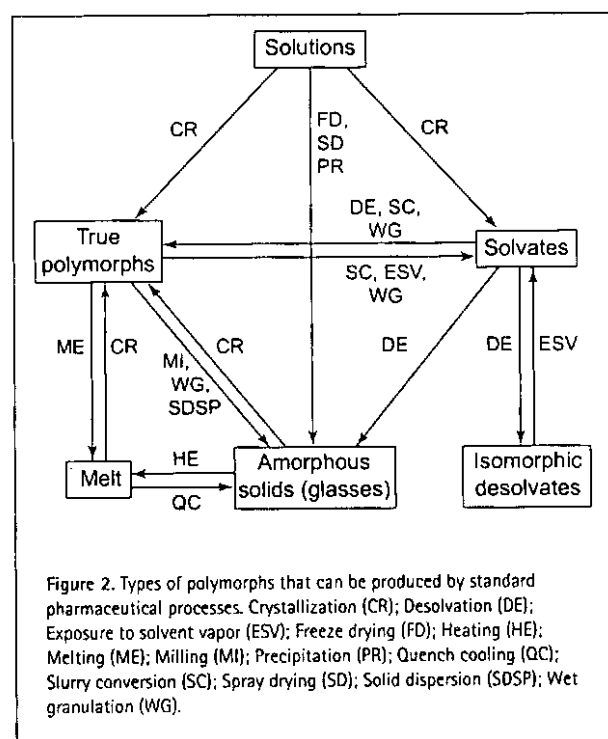
Different questions must be asked for the various types of polymorphs at different phases of drug development. Once a question is clearly framed, the choice of techniques or strategy is then usually straightforward. The scope of these questions, which range from structural to thermodynamic, necessitates an integrated characterization strategy. This review will discuss the applications of various physical techniques for answering these questions for different polymorphs.

Techniques for characterizing polymorphs

The techniques considered in this section – crystallography, spectroscopy, microscopy and thermal techniques – examine different aspects of structure, dynamics and energetics in the solid state. Single-crystal x-ray crystallography provides the best structural evidence for (true) polymorphism. However, the stringent sample requirement limits its applications to

Box 1. Questions to be addressed in describing the basic elements of polymorph characterization

- What type of polymorphism does a drug substance exhibit?
- How can polymorphs be distinguished and, if necessary, quantitated?
- What is the structural difference between polymorphs (e.g. crystal packing, hydrogen bonding, molecular conformation)?
- How do polymorphs differ in properties that affect the quality and performance of drugs (stability, solubility, hygroscopicity, etc.)?
- Can physical properties be predicted from structures and vice versa?



high-quality, single crystals. Fortunately, alternative techniques are available to characterize materials that are not perfectly crystalline or pure, including powder x-ray diffraction and solid-state spectroscopy (NMR, IR and Raman). Microscopy (light and electron) distinguishes polymorphs through crystal–optical and morphological properties and thermal techniques distinguish polymorphs through thermodynamic properties and provide the stability relationship between polymorphs.

Crystallography

Single-crystal x-ray crystallography provides the most precise structural information for crystals, including:

- Unit cell parameters
- Density
- Crystal disorder
- Molecular conformation
- Molecular packing
- Hydrogen-bonding pattern

This classic technique has seen recent advances in high-intensity synchrotron sources⁹, neutron powder diffraction¹⁰, high sensitivity CCD detectors¹¹, low-temperature data collection¹², structure solution by direct methods^{13,14}, faster computers, and databases¹⁵. It is now routine to solve structures in 1–2 days (even hours) and by using crystals as small as 0.05–0.10 mm. Structures that were previously deemed to be insoluble can now be determined. Absolute configurations of molecules containing single chiral centers are determined readily for compounds that contain elements of atomic mass of sulfur or greater¹⁶, which makes such determinations feasible for the most common pharmaceutical salt, the hydrochloride. Determining absolute configuration by relation to a known stereocenter is, in the main, straightforward.

The x-ray powder-diffraction technique captures the three-dimensional scattering in a two-dimensional plot. This technique has been improved through recent advances in rotating anodes, scintillation detectors, solid-state detectors and position-sensitive area detectors¹⁷. These advances allow for rapid data collection (less than 1 min) and time-resolved study (e.g. of phase changes). Controlled environment stages allow studies of polymorphic conversions as a function of temperature and humidity¹⁸, as well as low-temperature phases in frozen solutions¹⁹. Standards that cover the typical d-spacing ranges for organic crystals (e.g. SRM675) have become available²⁰. The average accuracy of data from conventional diffractometers has been determined to be approximately $0.05^\circ \pm 2\sigma$ (Ref. 21) although the USP-accepted tolerance is far greater.

Analysis of powder diffraction data has become more sophisticated. Crystal indexation packages now offer a high success rate for low-symmetry space groups that are favored by organic crystals, provided that data are collected properly²². Powder data are used widely for quantitating polymorphic mixtures^{23–26}. Rietveld refinement has been applied to powder data, although the 'whole-pattern' approach that utilizes both line positions and intensities can be complicated by preferred orientation^{27–29}. The Powder Diffraction File³⁰ has facilitated polymorph identification. Calculated powder-diffraction patterns from single-crystal data have been used to assess preferred

orientation and phase purity³¹. Structure determinations from powder patterns have been accomplished by direct methods³² and 'genetic algorithms'³³.

Spectroscopy

In contrast to diffraction techniques, which are sensitive to long-range order, solid-state spectroscopy (IR, Raman and NMR) is sensitive to short-range structure in molecular solids. Therefore, these two techniques complement each other in the characterization of polymorphs. An advantage of solid-state spectroscopy over diffraction techniques is that spectroscopic analysis can be performed across the crystalline-amorphous spectrum of materials. Thus, conformational changes upon crystallization³⁴ and hydrogen-bond-directed aggregation prior to crystallization³⁵ can be studied. Solid-state spectroscopy is also important for characterizing 'isostructural solvates' and 'isomorphic desolvates', for which diffraction techniques indicate only subtle changes in long-range order. Finally, solid-state spectroscopy complements diffraction techniques in the characterization of polymorphic mixtures, because individual crystalline and amorphous components can be detected and identified based on chemical structure. Spectroscopic techniques have played an important role for characterizing pharmaceutical solids^{36–38}.

IR and Raman spectroscopy are used in the study of fundamental molecular vibrations, providing a 'fingerprint' of a molecular solid³⁹. These techniques complement one another in that IR requires a change in dipole moment, whereas Raman requires a change in polarizability for observation. Thus, IR-inactive vibrations can be strong in Raman spectra and vice versa. In addition, Raman spectra are collected readily in the $40\text{--}400\text{ cm}^{-1}$ spectral region (typically unavailable on an IR spectrometer), where lattice vibrations occur. Glass optics can be used in Raman spectroscopy and hence minimal sample preparation is required⁴⁰. Because compression of KBr pellets for IR transmission can cause polymorphic transformations, diffuse reflectance IR and micro-IR are routinely employed to differentiate polymorphs. With the introduction of IR and Raman microscopy, polymorphism can be characterized for small particles⁴¹.

Solid-state NMR (SSNMR) spectroscopy, by virtue of its sensitivity to electronic environments of specific nuclei, is relatively useful for differentiating solid-state structures. The acquisition of high resolution spin- $\frac{1}{2}$ SSNMR spectra has become routine with the introduction and implementation of the cross polarization/magic angle spinning (CP/MAS) technique and hardware advances^{42–44}. The most widely used SSNMR technique for structural characterization of pharmaceutical solids is ^{13}C CP/MAS NMR

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spectroscopy⁴⁵ and ³¹P SSNMR has also been used to distinguish polymorphs⁴⁶. SSNMR spectra of crystalline materials often feature sharp resonances at chemical shifts characteristic of the molecular and crystal structure. The resolution of SSNMR spectra, although approximately two orders of magnitude less than its solution counterpart, is often sufficient to differentiate polymorphs.

SSNMR also provides information about molecular dynamics. Although molecular motions can be studied using anisotropic displacement parameters from x-ray diffraction, this technique is limited to motions that are comparatively fast ($\sim 10^{-18}$ s; Ref. 47). Therefore, slow dynamic processes cannot be distinguished from static disorder in molecular solids using diffraction techniques. SSNMR methods complement x-ray methods in that SSNMR allows for the study of a wide range of timescales ($\sim 10^2$ – 10^{-10} s) over which molecular motions occur^{48,49}. Relaxation time ($T_{1\rho}$) experiments have been conducted to study the molecular mobility of polymorphic solids⁵⁰. Information pertaining to molecular dynamics has also been obtained using variable temperature SSNMR⁵¹.

Microscopy

Light microscopy (LM) determines the optical properties (birefringence, indices of refraction, interference figure, dispersion color, etc.) and morphological properties of particles⁵². LM combined with fusion methods [hot-stage microscopy (HSM)] is a powerful tool for discovering polymorphs and determining their stability relationships^{53,54}. HSM coupled with differential scanning calorimetry (DSC) can help interpret complicated polymorphic conversions⁵⁵ and, in the hands of experts, the simple tool of LM yields a surprising amount of information in a short period of time.

LM is also interfaced easily with spectroscopy. Hot-stage IR microscopy, for example, has been used to characterize polymorphic purity and conversions⁵⁶. Operating in the visible- or near-IR region, Raman microscopy can benefit from higher spatial resolution, better polarizers and detectors⁵⁷. Polarized UV-visible absorption spectra of crystals have been used to determine conformation-spectrum relationship⁵⁸.

Electron microscopy (EM) provides higher resolution than LM⁵⁹, and the number of morphology studies conducted using EM has increased. The main disadvantage is the need to place samples in vacuum and bombard them with electron beams – conditions that may change the native structures of some materials. EM and LM are ideal complementary techniques. Atomic force microscopy (AFM) and scanning probe microscopy (SPM) are, in general, new micro-analytical tools for material characterization. In polymorphism research, AFM has been used to study the mechanisms of crystal growth, such as ledge-directed epitaxy⁶⁰.

Thermal techniques

Commonly used thermal techniques for the characterization of polymorphs include:

- DSC
- Thermal gravimetric analysis (TGA)
- Solution calorimetry
- Isothermal calorimetry [e.g. thermal activity monitor (TAM)]

Polymorphs can be distinguished by DSC and TGA according to the types of phase transitions they undergo during heating, such as melting, desolvation, solid–solid transition, crystallization and glass transition. DSC, TGA and HSM, separately or together, are often the first steps in a comprehensive search for polymorphs and the determination of their stability relationship; this is because results can be obtained quickly with small quantities of material. Several recent developments enhanced the power of thermal analysis in polymorph characterization:

- Modulated DSC allows the separation of reversible (e.g. glass transition) and non-reversible (e.g. melting of most organics) events
- TGA-IR permits the identification of the solvent(s) in a solvated crystal⁶¹
- TG/DTA allows simultaneous weight-change and heat-flow information

Aside from providing the stoichiometry of solvates, TGA is used to measure desolvation kinetics and sublimation rates, which yield information about vapor pressure and heat of sublimation.^{62,63} Thermal techniques are a primary source of data for determining the relative stability of polymorphs; they are used in conjunction with the measurement of polymorphic conversion, solubility or intrinsic dissolution rate to provide a comprehensive determination of the stability relationship between polymorphs (see below).

Physical characterization of polymorphic drug substances

In this section, the integrated characterization approach is explored for different polymorphs. The general elements of investigation – identification and quantitation, structures, properties and structure–property relationships – are illustrated in detail for true polymorphs, although the same approach is applicable to other types of polymorphs. For convenience, Table 1 summarizes the information provided by each technique for different types of polymorphs. From this summary, the inter-disciplinary nature of polymorph characterization is indicated clearly.

True polymorphs

The identification of true polymorphs begins with establishing the same chemical composition (e.g. by solution spectroscopy and elemental analysis) of different solid forms. Different physical methods are then used to confirm the difference in solid-state structures. For this purpose, all techniques discussed previously are used widely and technique selection is based largely on availability, compound-dependent sensitivity to specific techniques and the need for cross-validation.

The structures of polymorphs are determined most precisely by single-crystal x-ray diffraction. Besides basic crystallographic information (unit cell, molecular packing, bond lengths and angles, etc.), such structural features as absolute and relative configurations, hydrogen-bonding pattern, crystal disorder and conformational polymorphism^{55,64,65} may be obtained.

In addition to crystallography, solid-state spectroscopy also yields a wide range of structural information that can be related to the formation and physical properties of polymorphs. Of course, molecular structure, even with our liberal definition of polymorphism, is a constant among polymorphs. However, SSNMR spectroscopy has been used to show that different solid forms of a molecule are not polymorphs, but rather different solid forms of keto and enol tautomers^{66,67}. In addition, SSNMR has been used to identify conformational polymorphism^{65,68,69}, the crystallographic asymmetric unit, loss of molecular symmetry in a crystal, hydrogen-bonding interactions, and disorder⁷⁰. Similar structural information may be obtained using IR^{71,72} and Raman⁷³ spectroscopy. For example, frequency shifts of carbonyl stretching vibrations are often interpreted in terms of changes in hydrogen bonding. Band splittings can indicate changes in molecular or crystallographic symmetry. Centrosymmetry of hydrogen-bonded carboxylic acid dimers has been shown to be different among polymorphs by IR and Raman spectroscopy⁷⁴.

Perhaps the most important physical property for a polymorphic drug is the relative thermodynamic stability of polymorphs. This property, for example, influences the selection of the best crystal form for development. The relative stability of polymorphs is measured by their free energy difference, ΔG , which is given by $\Delta G = \Delta H - T\Delta S$. The enthalpy term (ΔH) results from the structural (lattice) energy difference between polymorphs, and the entropy term ($T\Delta S$) from the difference in lattice vibrations and disorder.

A practical approach to determining the stability relationship of polymorphs is to perform three, increasingly quantitative steps:

- Step 1. Distinguish qualitatively between monotropy (the stability order of polymorphs is the same at any temperature) and enantiotropy (the stability order changes with temperature).

- Step 2. Determine the enantiotropic transition temperature.
- Step 3. Obtain the quantitative ΔG vs. temperature curve.

Step 1. The heat of transition rule (HTR) and the heat of fusion rule (HFR)⁷⁵ can provide a relatively reliable prediction of the existence of monotropy and enantiotropy. These rules are based on the fact that an up-temperature transition (i.e. from a low-temperature form to a high-temperature form) must be endothermic ($\Delta H > 0$) at the equilibrium transition temperature, T_i (Ref. 76). Thus, if the ΔH and the direction of a polymorphic conversion are known at a temperature, T , it is possible to infer whether T_i lies below or above T . Specifically, HTR states that if an endothermic polymorphic conversion is observed at T , then a transition temperature T_i exists below T (enantiotropy); however, if an exothermic polymorphic conversion is observed at T , then no T_i exists below T (monotropy or enantiotropy with $T_i > T$). To apply HTR, ΔH can be obtained by DSC or solution calorimetry^{77,78} and the direction of polymorphic transitions from interconversion studies and the solubility order. As a special case of HTR, HFR states that if the lower melting form has a higher heat of fusion than the higher melting form, then the two forms are enantiotropic; otherwise, they are related monotropically. The abundance of melting data for organic polymorphs, a result of the 'reconstructive' and sluggish⁷⁶ solid-solid conversions that prevail in organic crystals, makes HFR suitable for a range of applications. Although HTR and HFR have been tested widely, it is best to confirm the predictions by selected polymorphic conversion experiments.

Step 2. The polymorphic transition temperature T_i can be determined in several ways. T_i can be bracketed by measuring polymorphic conversions at different temperatures. Teetsov and McCrone⁵⁴ determined the range of T_i values for the explosive HMX by lowering the eutectic melting points with different reference compounds. Variable-temperature solubility data have been used to estimate T_i (temperature of equal solubility) by extrapolation⁷⁹⁻⁸². Similarly, melting data have been used for estimating T_i with results consistent with the solubility method⁸³.

Step 3. The ΔG vs. T curve is the most complete and quantitative information on the stability relationship of polymorphs. Several techniques operating at different temperatures may be used for the determination of ΔG . Solubility or intrinsic dissolution rate data provide ΔG near room temperature (0–50°C)⁷⁹⁻⁸². The advantage of this technique is the possibility of making measurements at as many temperatures and in as many solvents as desired, thereby increasing confidence in the results. However, potential problems include solution-mediated conversion, solvate formation and large sample requirement. Melting data have been used to obtain ΔG and its temperature slope near the

melting points⁸³. Advantages of this method are the speed of data collection, small sample consumption and the abundance of melting data, whereas potential problems include thermal degradation and the need to extrapolate from high-temperature data. These shortcomings are overcome, in part, by the eutectic melting technique. By adapting Teetsov and McCrone's HSM method⁵⁴ to DSC, it is possible to obtain the value of ΔG (not just the sign) at temperatures well below the melting points⁸⁴. The combination of the melting and eutectic melting data can provide the ΔG vs. T curve over an approximately 100°C range. Finally, the ΔH data are also useful in this context because ΔH is the slope of the $\Delta G/T - 1/T$ plot.

The integration of different types of data provides the ΔG vs. T curve over a wide T range and also allows the consistency between techniques to be checked. Figure 3 shows that for sulphathiazole and gepirone the melting and solubility data correlate well with each other and provide the ΔG vs. T curve over an approximately 200°C range.

A good example of structure-property relationships is the close-packing principle⁸⁶, which states that, regardless of the details of molecular packing and conformation, the form with the highest packing coefficient is the most stable. Stated this way (i.e. in terms of thermodynamic stability or free energy), the close-packing principle has many exceptions because, in the main, it is incompatible with temperature-dependent relative stability (enantiotropy), which accounts for approximately 50% of organic polymorphs⁷⁵.

The generality of the close-packing principle is largely restored, however, if it is restated as follows: the form with the highest packing coefficient has the lowest lattice energy and entropy, but not necessarily the lowest free energy or greatest stability. This modified form is essentially Burger's Density Rule⁷⁵.

Another example of structure-property relationships is Burger's Infrared Rule⁷⁵, which states that for polymorphs predominated by hydrogen bonding, the polymorph having the first absorption band at the higher frequency will have higher entropy and be less stable at 0K. Because other intermolecular forces can outweigh hydrogen bonding and no distinction is made between inter- and intramolecular hydrogen bonds, exceptions^{75,87} to the IR Rule are not uncommon. Nonetheless, the IR Rule is a meaningful step towards predicting stability from structures. Other attempts have been made to correlate calculated and experimental lattice energies⁸⁵, hydrogen bonding pattern and crystal stability⁸⁸, molecular conformation and crystal color^{58,65}, and conformational stability and crystal stability⁶⁴.

Solvates (pseudopolymorphs)

Solvates are often detected by low-temperature weight loss by TGA and loss of translucency under certain temperature/humidity conditions⁸⁹. Again, single-crystal x-ray diffraction provides

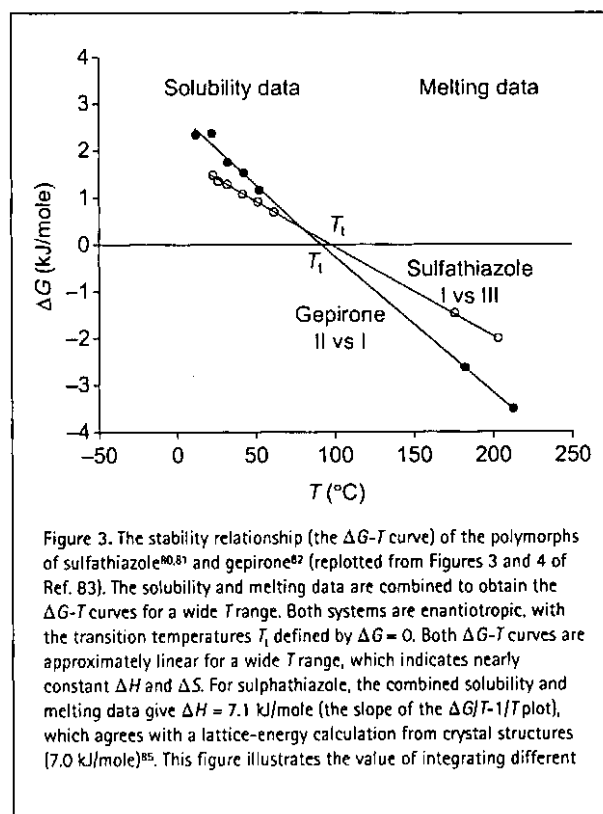


Figure 3. The stability relationship (the ΔG - T curve) of the polymorphs of sulphathiazole^{80,81} and gepirone⁸² (replotted from Figures 3 and 4 of Ref. 83). The solubility and melting data are combined to obtain the ΔG - T curves for a wide T range. Both systems are enantiotropic, with the transition temperatures T_i defined by $\Delta G = 0$. Both ΔG - T curves are approximately linear for a wide T range, which indicates nearly constant ΔH and ΔS . For sulphathiazole, the combined solubility and melting data give $\Delta H = 7.1$ kJ/mole (the slope of the $\Delta G/T - 1/T$ plot), which agrees with a lattice-energy calculation from crystal structures (7.0 kJ/mole)⁸⁵. This figure illustrates the value of integrating different

the most definitive evidence for solvates. In the absence of single-crystal data, however, solvate characterization must begin with the identification of solvent(s) of crystallization. Solvents may be identified and drug-solvent stoichiometry determined by vibrational and solution ¹H NMR spectroscopy, TGA (with the aid of an evolved gas analyser), and Karl Fischer titration (for water). Organic solvents can usually be detected by ¹³C SSNMR spectroscopy, however, water is observed only indirectly by its influence on the ¹³C environments of the drug.

Once the solvents and the stoichiometry are identified, the next step in solvate characterization is to determine the nature of solvent molecules in the host crystal. Whereas solvent molecules located in discrete crystal sites are usually bound (e.g. by hydrogen bonding) and relatively immobile, solvents trapped in open cavities are highly mobile or similar to liquid⁹⁰. Such loosely bound solvent molecules (eg. in inclusion compounds and clathrates) can lead to nonstoichiometric solvates. The nature of solvent molecules determines the appropriate characterization technique(s). For example, bound solvent molecules produce sharp resonances in SSNMR spectra, whereas highly mobile solvents may not be observable by this technique. However, x-ray powder diffraction is usually unaffected by the state of solvent molecules and sensitive only to the difference in crystal structures. Thermal analysis is also informative about the

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nature of solvent molecules: strongly bound solvates may melt prior to solvent evaporation, whereas weakly bound solvates tend to desolvate before melting.

For 'isostructural' solvates, for which x-ray powder patterns are nearly indistinguishable from those of the nonsolvated crystals, solid-state spectroscopy can be valuable. FTIR⁸⁷ and SSNMR⁹¹ have been used to differentiate isostructural solvates. Usually drug-solvent interactions will shift slightly the spectra of both. However, if the solvent does not interact specifically with the drug to render its electronic environments inequivalent among isomorphous materials, isomorphism can be difficult to assign from SSNMR spectra alone.

Desolvated solvates

Desolvation of a solvate can lead to several types of solid forms. In addition to solvent-free crystal and amorphous solids, there exists a third possibility: isomorphic desolvates⁹²⁻⁹⁴. An isomorphic desolvate retains the same overall molecular packing as the 'parent' solvate. Thus, even though the solid composition changes during desolvation, the same or only subtly shifted x-ray powder patterns are observed. In this case, solid-state spectroscopy may

prove effective for distinguishing desolvates from the parent solvates, through loss of solvent peaks, shift of drug peaks and shift of low-frequency lattice (phonon) vibrations. TGA and DSC can also be used to determine the degree of desolvation.

Isomorphic desolvates are unstable structures. They tend to resorb the lost solvent or pick up ambient moisture (extremely hygroscopic). In the absence of solvent or moisture, they can undergo lattice relaxation, which leads to decreased unit cell volume and increased packing efficiency⁹⁵. Lattice relaxation can also result in heat dissipation, which can be measured by isothermal calorimetry⁹⁵. Despite quantifiable structural changes, isomorphic structures created by the relaxation process should probably be considered to be related structures of the same crystal form, rather than different polymorphs.

Amorphous solids

The relative importance of amorphous solids (glasses) to crystalline solids increases in proportion to molecular size and complexity. Thus, polymers and proteins are familiar glass-formers, even though glasses of small-molecule organics are by no means uncommon. Indeed, normal pharmaceutical processes

Table 1. Information obtained from different physical techniques for each type of polymorphs

Types of polymorphs	Single crystal x-ray crystallography	X-ray powder diffraction	IR/Raman spectroscopy	Solid-state NMR spectroscopy	Thermal methods	Microscopy
True polymorphs	Same chemical composition. Unique unit cell parameters molecular conformation and packing.	Unique diffraction peaks. Useful for determination of phase purity and % crystallinity.	Characteristic spectra. Sensitive to H bonding.	Unique chemical shifts. Useful for determining phase purity, molecular mobility.	Unique mp, heat capacity, heats of fusion/transition, solubility. Useful for determining relative stability of forms.	Characteristic indices of refraction, birefringence, dispersion color and crystal habit.
Solvates	Same as true polymorphs	Same as true polymorphs	Unique solvent bands. Shifted drug bands. Sensitive to H.	Unique solvent resonances. Shifted drug resonances. Solvent mobility can be determined.	Low-temperature transitions due to desolvation (TGA loss).	Same as true polymorphs. Desolvation observable by HSM.
Isomorphic desolvates	NA	Diffraction pattern only slightly changed from parents solvates.	Solvent bands disappear. Drug bands shifted.	Solvent resonances disappear. Drug resonances shift.	Low-temperature desolvation absent. Events due to crystallization or lattice relaxation.	Birefringent microcrystalline domains, with cracks and fissures.
Amorphous solids	NA	No diffraction peaks	Broadened spectra	Broadened spectra	Glass transition seen. Often followed by crystallization and melting. 'Fragility' related to width of T_g .	No birefringence, irregular particle shape.
Polymorphic mixtures	NA	Composite pattern of crystalline components	Composite spectrum of all components	Nuclei-specific composite spectrum of all components	Thermal behavior indicative of phase diagram (e.g. mp-depression, eutectic melting, dissolution).	Composite of distinct crystalline and amorphous particles

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(freeze drying, spray drying, solid dispersions and milling, etc.) are capable of producing amorphous solids, which are generally less stable physically and chemically, less dense, more soluble, faster dissolving/subliming and more hygroscopic than their crystalline counterparts.

An amorphous material can be identified by DSC (glass transition, perhaps followed by crystallization and then melt), x-ray diffraction (no sharp diffraction peaks), light microscopy (no birefringence and crystal habit) and spectroscopy [spectral broadening and lack of discrete low-frequency ($< 200 \text{ cm}^{-1}$) lattice-vibrations].

The structures of amorphous solids, or lack thereof, are the subject of recent studies and debates. Such terms as 'energy landscape', 'ideal glasses' and 'polyamorphism' are new theoretical proposals concerning amorphous solids⁹⁶. Pikal has discussed possible effects of polyamorphism on the stability of freeze dried formulations⁹⁷. However, the fundamental relevance of the 'structures' of amorphous solids in drug development is poorly understood.

It is informative to measure the properties of amorphous solids against the crystalline counterparts and express them as 'excess properties'. The excess enthalpy is obtained from heats of solution⁹⁸ or crystallization. The excess free energy, in principle, can be obtained from the solubility or vapor pressure data, in a similar manner as outlined for true polymorphs. The excess entropy is obtained indirectly from the excess energy and free energy ($G = H - TS$) or estimated from the entropy of melting and the excess heat capacity of supercooled liquids.

The excess entropy, a somewhat obscure property, is essential for the characterization of amorphous solids. In the Adam-Gibbs model⁹⁹, this property is related to the characteristic relaxation time ('mobility') in amorphous solids. The 'fragility' parameter of Angell⁹⁶ is a measure of how fast the excess entropy – the 'lifeblood' of amorphous solids (Angell) – diminishes with declining temperature: 'fragile' liquids (most small-molecule organics) do so rapidly, whereas 'strong' liquids (typical proteins and peptides) do so slowly. The temperature at which the excess entropy vanishes is the temperature of 'zero' mobility, T_0 . The difference between T_0 and T_g (glass transition temperature) is directly related to fragility and may have some significance in deciding the 'safe' storage temperatures for amorphous drug formulations and the selection of excipients¹⁰⁰. Based on the results of several studies^{101,102}, Pikal suggested the possibility of estimating the fragility and T_0 from the width of the glass transition¹⁰³, which has been performed for several systems with some success^{100,104,105}.

Molecular mobility in amorphous solids has been assessed from the measurement of viscosity, enthalpy relaxation, frequency-dependent shear modulus¹⁰⁶ and SSNMR relaxation times. Characterization of glass mobility below T_g has been

motivated by observations that sub- T_g mobility is not zero, but sufficient to induce physical and chemical changes¹⁰⁷, and by the affinity of amorphous solids for water, a potent plasticizer and mobility enhancer¹⁰⁸.

Polymorphic mixtures and drug formulations

Polymorphic mixtures can result from a range of pharmaceutical processes: milling, desolvation, polymorphic conversion, crystallization of amorphous solids, 'accelerated' storage and uncontrolled crystallization. X-ray powder diffraction is a powerful tool for the quantitation of crystalline mixtures. Although preferred orientation can cause observed peaks to be more or less intense than calculated values, the existence of symmetry-forbidden peaks provides unambiguous evidence for phase impurity. The detection limit of this method, particularly due to the ability to find non-overlapping peaks, can be as low as 1% w/w. Solid-state spectroscopy is also effective for crystalline mixtures, with its importance increasing for the analysis of crystalline-amorphous mixtures. Solid-state NMR, for example, is useful for quantitating components of heterogeneous mixtures with correct selection of relaxation, or contact and dipolar dephasing times¹⁰⁹. The degree of crystallinity has been assessed from the signal-to-noise ratio of ^{13}C SSNMR spectra¹¹⁰ and NIR has also seen recent applications¹¹¹⁻¹¹³. Finally, crystalline-amorphous mixtures can be quantitated from the heat of solution, heat of crystallization and hygroscopicity.

Future directions

The accumulation of structure and property data for organic polymorphs makes systematic investigations of structure-property relationships ever more urgent. Without some understanding of the structure-property relationships, there will always be the cynical view that the book of organic polymorphism has as many chapters as there are molecules. The close-packing principle and the IR Rule are qualitative attempts to establish structure-property relationships. The current crystal-modeling efforts have the potential of producing more quantitative tools for bridging structures and properties. Theoretical predictions of lattice energies, entropies, morphologies and even polymorphs themselves should stimulate experimental activities and vice versa. The idea of utilizing structure-property relationships to create solid forms with desired properties is extremely appealing. Recent attempts in crystal engineering¹¹⁴, selective nucleation and growth of polymorphs⁷ and polymorph prediction represent an optimism in our ability to understand, control and utilize the phenomenon of polymorphism.

Conclusions

The widespread existence of polymorphic drugs underscores the importance of an efficient and consistent characterization

strategy. The potential impact of changing crystal forms during late-stage development in terms of cost and product delay justifies the systematic and early characterization of polymorphism. A thorough understanding of polymorph characteristics also allows the selection of the best form to market. We have described a characterization approach that is based on recognizing the distinct elements in polymorphism investigations, namely identification and quantitation, structures, properties and structure-property relationships. The scope of these investigations necessitates an integrated characterization approach, involving both microscopic and macroscopic techniques. By clearly defining questions relevant to each class of polymorphs, the selection of techniques will become more straightforward, which should help eliminate redundancy, inadequacy or inconsistency in the physical characterization of polymorphs.

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