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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE 06-019-211

TÍTULO SOLICITADO:

“Proceso para controlar una estructura cristalina de Risedronato”

PUBLICACIÓN:

Gaceta 566 de 31-07-2006, número de publicación 304

PRIORIDAD :

US 60/491,222 de julio 30 de 2003

SOLICITANTE:

THE PROCTER & GAMBLE COMPANY

APODERADO:

JIMENA ESCOBAR URIBE

TRÁMITE:

REMISIÓN DE INFORMACIÓN.

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, dentro del trámite de la referencia, por medio del presente escrito, procedo a presentar argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario:

I. REMISION DE INFORMACIÓN.

En primer lugar, es importante señalar que las modificaciones presentadas en al capítulo descriptivo y el capítulo reivindicatorio, presentadas el 09 de Septiembre de 2010 por parte del solicitante, corresponden a un simple cambio de forma, que



por esa condición, no logran superar los argumentos planteados en contra por el suscrito, ni aquellos formulados por el examinador técnico.

Es así como al revisar dicho nuevo capítulo reivindicatorio, se nota claramente que persiste la carencia de nivel inventivo al mantenerse, en esencia, las mismas características técnicas (un proceso para la obtención de una sal del ácido 3-piridil-1-hidroxietileno-1,1-bifosfónico en la forma cristalina hemipentahidratada).

Entrando en materia, cualquier persona medianamente versada en la materia debe reconocer que hay muchas sustancias medicamentosas que pueden tener dentro de su red cristalina disolvente atrapado en una cantidad estequiométrica, lo que origina los denominados solvatos o hidratos, si ese disolvente es el agua. Cualquier persona medianamente versada en la materia debe reconocer además que la escogencia de una forma cristalina o aducto molecular (hidratos y/o solvatos) de cualquier principio activo que va a ser incluido en un medicamento, no se realiza de manera aleatoria, sino que, dependiendo de las características predefinidas para la formulación farmacéutica, la escogencia de dichas características debe estar sustentada por los respectivos ensayos de preformulación y formulación de rutina.

En otras palabras, nunca un polimorfo y/o solvato de una sustancia resulta ser una invención, ya que necesariamente dichos sistemas se manifiestan bajo alguno de los siete sistemas cristalinos conocidos: triclinico, monoclinico, ortorrómbico, tetragonal, trigonal, hexagonal y cúbico¹, sin que sea el caso de la presente solicitud, el que se este obteniendo otra forma de organización o sistema cristalino.

Siendo aun más específicos, y enfocándonos en los solvatos y/o hidratos, cualquier persona medianamente versada en la materia debe reconocer que a través de los respectivos estudios de preformulación y formulación se deben establecer ensayos que permitan conocer a cabalidad la posible creación de solvatos y/o hidratos del principio activo en alguna de las etapas de producción, o en su defecto, escogerse alguna de estas formas solvatadas si sus características (por ejemplo solubilidad) corresponden a las necesidades de la formulación y/o al

¹ Giron, D., Journal of Thermal Analysis and Calorimetry. Vol. 64, Budapest – 2001, página 38

proceso de formulación. Una de las estrategias que un formulador puede emplear para tomar decisiones respecto a un principio activo durante su proceso de formulación es el siguiente²:

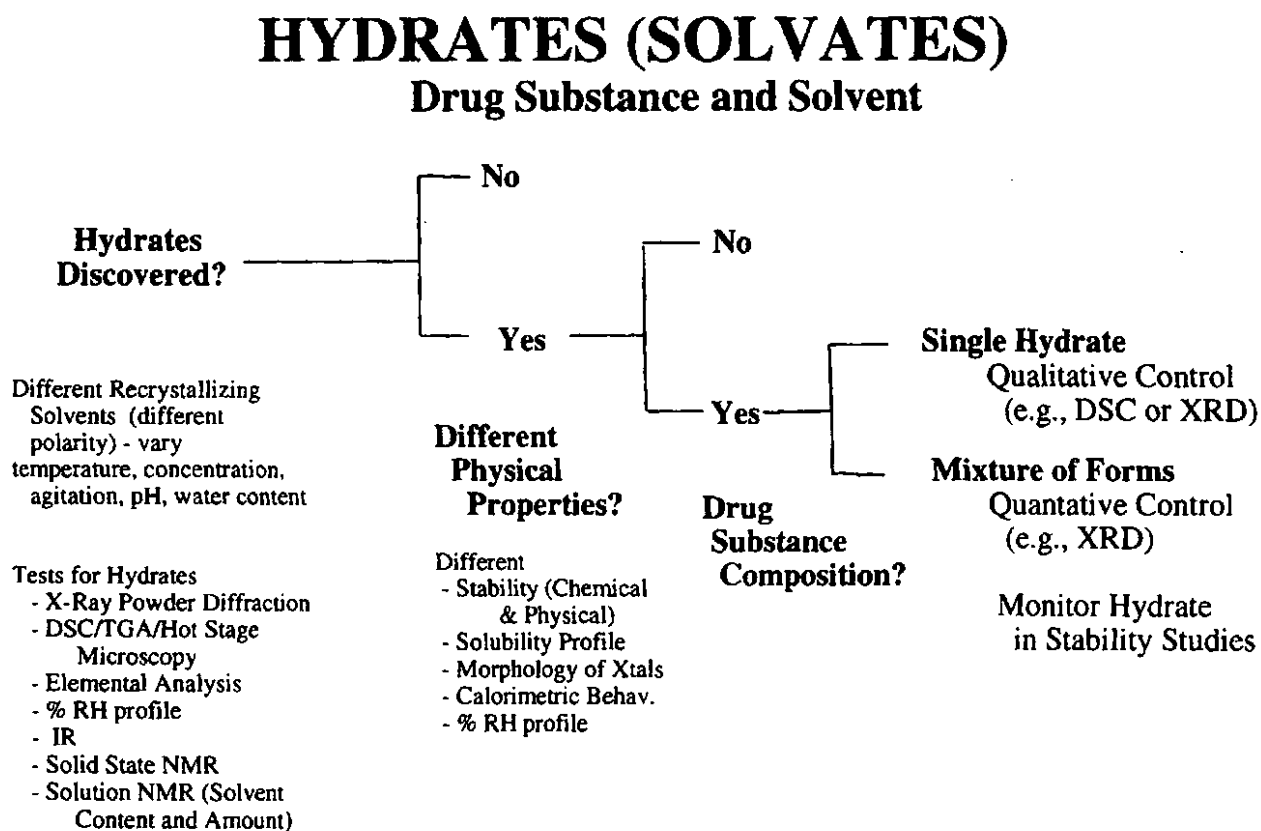


Figure 6. Flow chart for solvates or hydrates.

Como se puede apreciar, la manipulación de cualquier principio activo a través de recristalizaciones en diferentes solventes, para la obtención y caracterización de posibles solvatos y/o hidratos que se puedan dar en dicho compuesto, resulta una practica rutinaria en la industria farmacéutica, y el resultado arrojado es un simple reporte de las características inherentes a las potenciales conformaciones estructurales del compuesto que se evalúa.

Esta misma caracterización de los compuestos en estado sólido (formas solvatadas y/o hidratadas de fármacos) no es únicamente parte de la rutina dentro de los procesos de formulación farmacéutica, sino que además existen documentos que evidencian que es un tema que se estudia a profundidad para poner en práctica en procesos de formación de partículas en la industria farmacéutica , en especial a lo relacionado con materiales para compresión

² Byrn S, Pfeiffer R, Ganey M, Hoiberg C, Poochikian G. Pharm Res. 1995 Jul;12(7):945-54.

directa, formación de formas amorfas, solvatos y polimorfos, separación quiral de fármacos, producción de materiales para vía inhalatoria e inyectables³. De la misma manera se reconoce que son frecuentes las investigaciones respecto a la transformación y la predicción de la formación de solvatos y/o hidratos⁴.

En cuanto la insistencia que hace el solicitante en dicha respuesta al requerimiento en cuestión, radicada el 29 de Septiembre de 2010, en donde expresa que *“la existencia de un proceso para la obtención de una forma cristalina, no anula automáticamente cualquier variación sobre dicho proceso que resulte ser más eficiente o selectiva”* y que a diferencia de las anterioridades que revela el examinador técnico (US 2002002282 o D1) *“el risedronato se disuelve primero en una mezcla de isopropanol y agua (...) Debido a la presencia inicial de isopropanol en el presente caso, el pH debe ajustarse a un valor mayor que el D1 con el fin de obtener una solución, algo que no se anticipa en D1 y no es obvio para el técnico en la materia”*, que otra diferencia es que *“la temperatura a la que inicia la nucleación en la presente invención también es menor (50-60°C) comparado con los ejemplos de D1 (60-75°C)”* y que finalmente *“La nucleación se inicia por el ajuste del pH y no por la adición del anti-solvente, como sucede en D1, puestos que este ya se encuentra presente en la solución del proceso en estudio.”*; todas estas premisas con las que el solicitante busca argumentar el nivel inventivo de un proceso de obtención de hemipentahidrato de risedronato que claramente esta estrechamente relacionado al que se describe con anterioridad en D1.

Cualquier persona medianamente versada en la materia debe reconocer que existen diversas técnicas para la cristalización de compuestos. Dentro de estas técnicas podemos encontrar el enfriamiento de una solución sobresaturada, cambio del medio disolvente, evaporación del disolvente, sublimación y enfriamiento selectivo de un sólido fundido⁵. Dentro de estas técnicas, encaja a la perfección el proceso descrito por la solicitud en cuestión, en donde ocurre una variación en la solubilidad por manipulación del pH y adición de un antisolvente,

³ B. Yu. Shekunov Corresponding Author Contact Information, a and P. York. Crystallization processes in pharmaceutical technology and drug delivery design. Journal of Crystal Growth. Volume 211, Issues 1-4, 1 April 2000, Pages 122-136.

⁴ Sudha R. Vippaguntaa, Harry G. Brittainb and David J. W. Crystalline solids. Advanced Drug Delivery Reviews. Volume 48, Issue 1, 16 May 2001, Pages 3-26. Characterization of the Solid State.

⁵ <http://es.wikipedia.org/wiki/Cristalizaci%C3%B3n>

así como un enfriamiento controlado de dicha solución de ácido 3-piridil-1-hidroxietilideno-1,1-bifosfónico.

También es importante indicar que varios de los compuestos que son útiles como fármacos, resultan ser ácidos o bases débiles. Es el caso del ácido 3-piridil-1-hidroxietileno-1,1-bifosfónico. El solicitante indica que en la anterioridad D1 no se anticipaba el hecho de incluir una primera parte del antisolvente (alcohol isopropílico) y un ajuste de pH inicial para lograr la disolución completa del ácido 3-piridil-1-hidroxietileno-1,1-bifosfónico. Sin embargo, para cualquier persona medianamente versada en la materia es evidente la influencia que tiene el pH en la solubilidad de este tipo de compuestos con características acidas o básicas débiles, que se comportan como electrolitos. Es claro para cualquier persona medianamente versada en la materia que al estar presente el antisolvente el ácido 3-piridil-1-hidroxietileno-1,1-bifosfónico se encuentra menos soluble y que por lo tanto una de las alternativas más evidentes para aumentar dicha solubilidad es modificando el pH hacia valores que favorezcan las especies disociadas mas solubles en agua. En otras palabras, ésta modificación no puede sustentar nivel inventivo alguno, dado que el pH es uno de los principales factores que influyen en la solubilidad de cualquier sustancia ionizable⁶, y la modificación del mismo en el medio donde se encuentra disuelto un electrolito, resulta mas que obvio para cualquier persona medianamente versada en la materia que requiera aumentar la solubilidad de un ácido débil como lo es el ácido 3-piridil-1-hidroxietileno-1,1-bifosfónico.

Teniendo en cuenta lo anterior, insistimos en el hecho que el proceso revelado en el ejemplo 1 de la patente americana US 2002/0002282 afecta el nivel inventivo de la presente solicitud de invención en cuanto a que:

- ✓ En ambos casos se genera una solución de ácido Risedrónico sódico en agua y en isopropanol;
- ✓ En los dos procesos se adiciona una base orgánica o NaOH para ajustar pH o proporcionar un pH determinado;
- ✓ En los procesos comparados la solución debe calentarse a más o menos 60°C;

⁶ Vila Jato, J.L. Tecnología Farmacéutica. Volumen 1. Páginas 158 y 159.

- ✓ En ambos casos coinciden las etapas de enfriamiento y filtración.
- ✓ En los dos procesos el pH ajustado está alrededor de 4.5 y 5.0;
- ✓ Por supuesto, en ambos casos se obtiene el mismo resultado, es decir, el Hemipentahidrato de Ácido Risedrónico.

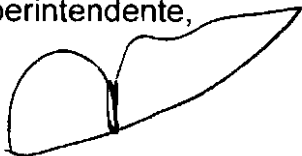
En conclusión, una persona medianamente versada en la materia técnica respectiva, conociendo la materia revelada en la tantas veces citada publicación US 2002/0002282 A1, fácilmente podría adaptar algunas condiciones, como las modificadas en la presente solicitud en trámite, para obtener el mismo tipo de hidrato de la sal de ácido 3-piridil-1-hidroxietileno-1,1-bifosfónico, como por ejemplo, la manipulación del pH, para mantener unas condiciones mas homogéneas, para así evitar las fluctuaciones o variaciones de temperatura en el medio que puedan modificar las condiciones requeridas y descritas por la anterioridad revelada, para la obtención del hemipentahidrato correspondiente.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS.

- ❖ Copia de todas las publicaciones mencionadas en el acápite de Remisión de información.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

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T.P. 44655 del C. S de la J.

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 Poochikian²

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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⁴ To whom correspondence should be addressed.

appropriate analytical controls. One should also note that it is the responsibility of the industry to select the appropriate test or tests to identify the phase of the solid and determine its relevant pharmaceutical properties. This approach is superior to simply performing a broad range of tests without regard to their relevance.

We should point out that, from a regulatory standpoint, if a company can establish a specification/test to ensure production of a well defined solid form of the drug substance, then it is not necessary to do all of the physical/chemical testing outlined in the decision trees. From a scientific standpoint, however, such an approach is risky since new forms may appear unpredictably during various stages of the development process. The appearance of these new forms usually slows the drug approval process and makes planning difficult.

Four decision trees are described in the sections that follow: Polymorphs; Hydrates (Solvates); Desolvated Solvates; and Amorphous Forms. Polymorphs exist when the drug substance crystallizes in different crystal packing arrangements all of which have the same elemental composition (Note that hydrates can exist in polymorphs). Hydrates exist when the drug substance incorporates water in the crystal lattice in either stoichiometric or non-stoichiometric amounts. Desolvated solvates are produced when a solvate is desolvated (either knowingly or unknowingly) and the crystal retains the structure of the solvate. Amorphous forms exist when a solid with no long range order and thus no crystallinity is produced. It is apparent that the appropriate flow chart can only be determined after the solid has been characterized using some of the tests described in the first decision point of the decision trees/flow charts (i.e. X-ray powder diffraction, elemental analysis, etc.). If there is no interest in marketing or producing an amorphous form or desolvated solvate at any stage in the process, then the corresponding flow charts do not need to be addressed. As already mentioned, it is advisable to investigate the drug substance for the existence of polymorphs and hydrates since these may be encountered at any stage of the drug manufacturing process or upon storage of the drug substance or dosage form.

All of the flow charts end (see for example Figure 1) with an indication of the types of controls which will be required based on whether a single morphic form or a mixture will be produced as the drug substance. Although this ending provides a simplistic view of a very complicated process of selecting appropriate controls, it is included to illustrate the consequence of the decisions made with regard to the drug substance. The reader should realize that the actual selection of the appropriate control could be the subject of another review which might contain another set of flow charts or decision trees.

POLYMORPHS

The flow chart/decision tree for polymorphs is shown in Figure 1. It outlines investigations of the formation of polymorphs, the analytical tests available for identifying polymorphs, studies of the physical properties of polymorphs and the controls needed to ensure the integrity of drug substance containing either a single morphic form or a mixture.

A. Formation of Polymorphs—Have Polymorphs Been Discovered?

The first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question: Are polymorphs possible? Solvents should include those used in the final crystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate. New crystal forms can often be obtained by cooling hot saturated solutions or partly evaporating clear saturated solutions. The solids produced are analyzed using X-ray diffraction and at least one of the other methods. In these analyses, care must be taken to show that the method of sample preparation (i.e. drying, grinding) has not affected the solid form. If the analyses show that the solids obtained are identical (e.g. have the same X-ray diffraction patterns and IR spectra) then the answer to the question "Are polymorphs possible?" is "No",

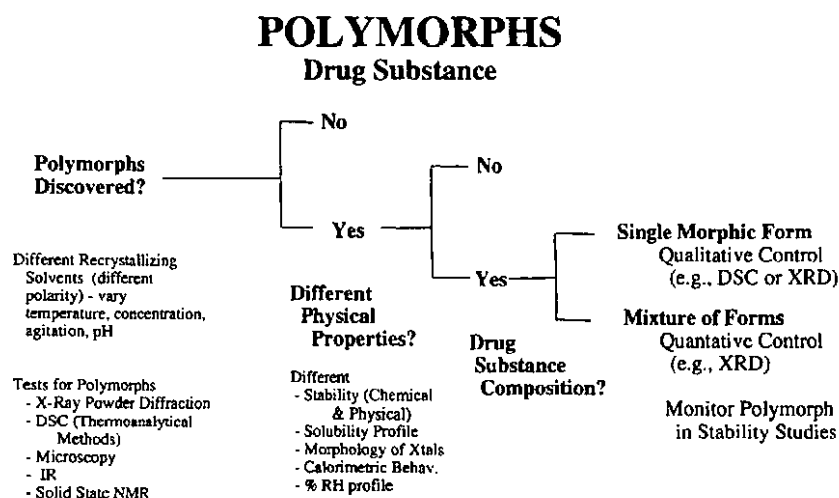


Figure 1. Flow chart/decision tree for polymorphs.

and further research is not needed. The work of Miyamae *et al.* serves as a good example of solid state studies of a drug substance which exists as polymorphs (1). Powder diffraction showed that there were two crystal forms (see Figure 2).

These workers also carried out single crystal analysis of the two crystal forms of the compound. The structures are shown in Figure 3. While such studies are not required, and indeed sometimes not possible, they provide an unequivocal confirmation of the existence of polymorphs. Moreover, once the single crystal structure of a phase has been determined, it is possible to calculate the corresponding X-ray powder pattern. This provides an irrefutable standard for identifying the phase by that method.

The DSC thermal curves of the two forms are slightly different, as shown in Figure 4 and thus may not be the preferred way of differentiating these polymorphs.

The IR spectra of the two polymorphs are quite similar(1), and IR does not appear to be a powerful method for differentiating the crystal forms in this case. Thus, for 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-a]pyridine, powder diffraction appears to be the best method for differentiating the two forms.

Solid-state NMR is another powerful technique for analyzing different crystal forms (2,3). Figure 5 shows the solid-state C-13 NMR spectra of Forms I and II of prednisolone. Differences in the positions of the two resonances in the 120 ppm range clearly differentiate the two forms. In principle, solid state NMR is an absolute technique in which the signal intensity is proportional to the number of nuclei provided appropriate conditions are met. In addition, solid state NMR is a bulk technique which is not very sensitive to surface changes. This method appears to be very sensitive and will undoubtedly be used more often in the future as a tool to detect different crystal forms. However, with present technology, errors in solid-state quantitative studies may be rather large.

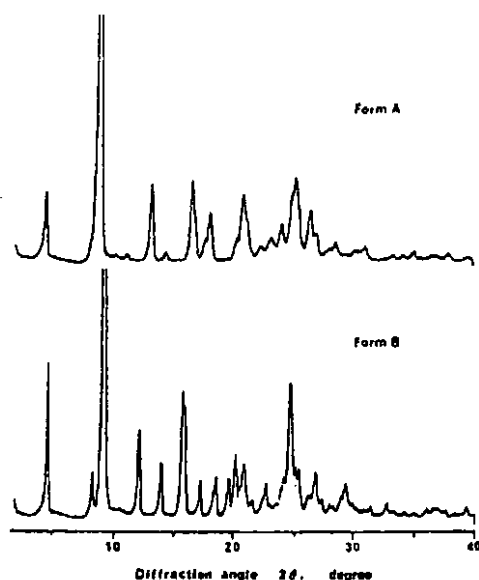


Figure 2. Powder X-ray diffraction patterns of the polymorphs of 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-a]pyridine (1).

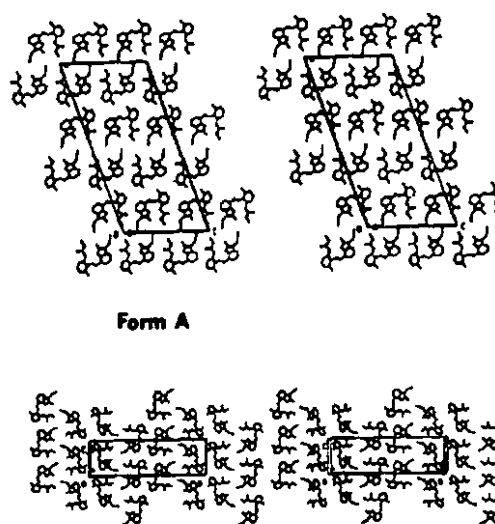


Figure 3. Stereoscopic drawings of the crystal packing of both polymorphs of 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-a]pyridine viewed along the shortest axis (Form A, b-axis; Form B, a-axis) (1).

B. Do the Polymorphs Have Different Physical Properties?

If polymorphs exist then it is necessary to examine the physical properties of the different polymorphs that can affect dosage form performance (bioavailability and stability) or manufacturing reproducibility. The properties of interest are solubility profile (intrinsic dissolution rate, equilibrium solubility), stability (chemical and physical), and crystal morphology (including both shape and particle size), calorimetric behavior, and %RH profile. If there are no discernible differences between these physico-chemical properties, then the answer to the second question in the decision tree, "Different physical properties?" is "No."

The variable physical properties of several drugs with different polymorphs are reported in the literature. For example, the dissolution profiles of the polymorphs of chloramphenicol are significantly different (4). In addition, van't Hoff solubility analysis has been used to elucidate the dif-

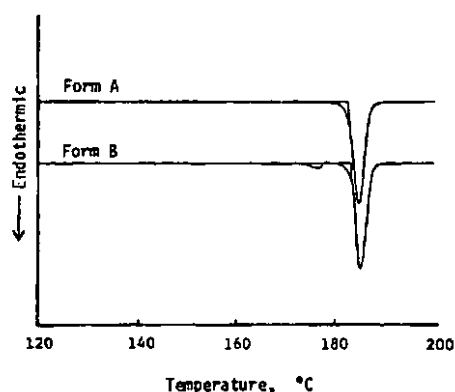


Figure 4. DSC thermal curves of the polymorphs of 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-a]pyridine (1). These curves show that Form A melts whereas Form B undergoes a small endothermic transition and then melts at the same temperature as Form A.

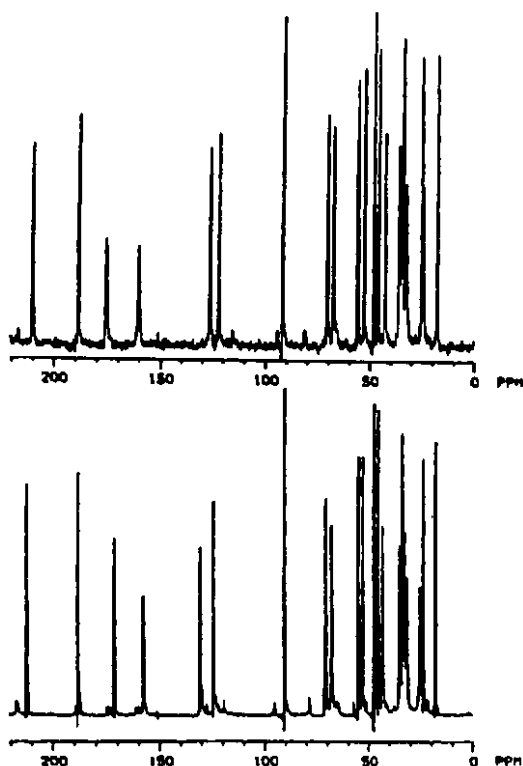


Figure 5. Solid state NMR of the two Crystal Forms of Prednisolone (2).

ferent solubilities of two polymorphs of methyl prednisolone(5). This method involves determining the equilibrium solubility of each polymorph at various temperatures. The log of the equilibrium solubility is then plotted vs $1/T$. This should give straight lines for each polymorph and the temperature at which the curves intersect is the transition temperature. This technique does not work if the polymorphs interconvert.

For balance, it is important to point out that there are also cases where polymorphs exist but they have virtually identical dissolution properties(6).

C. Drug Substance Control

The important question lies in the properties that differ among polymorphs and whether those properties affect the dosage form performance (i.e., quality or bioavailability). If they do then from a regulatory standpoint it is appropriate to establish a specification/test (e.g. powder X-ray diffraction or IR) to ensure the proper form is produced. From a production standpoint, it is important to develop a process that reproducibly produces the desired polymorph.

If mixtures of forms cannot be avoided, then quantitative control is needed to ensure that a fixed proportion of forms is obtained. Furthermore, the method of analyzing for the proportion of forms would have to be validated. Also, the proportion of forms would have to remain within stated limits through the retest date of the drug substance and potentially throughout the shelf life of the product; a difficult requirement if the forms interconvert. Thus, the way to avoid a substantial amount of work in this area is to select a single

solid form for production. Usually, this would be the most physically stable form when their bioavailabilities are not significantly different. Selection of the most stable from would, of course, insure that it there would be no conversion into other forms.

Powder diffraction is often a useful method to determine the percentages of polymorphs in a mixture; however, the detection limit is variable from case to case and can be as high as 15%. Matsuda (7) carried out a mixture analysis of phenylbutazone polymorphs. Diffraction lines disappear and appear as the ratio of the crystal forms change. Some of these calibration curves developed from this analysis are almost horizontal, meaning that any given mixture gives the same line intensity in this mixture range. However, other calibration curves are sloped and would appear to allow a reasonable analysis. It is fair (although Matsuda did not carry out an estimate) to estimate the errors in this analysis as $\pm 15\%$.

Tanninen and Ylirussi (8) used computer curve fitting to carry out a mixture analysis of prazosin. In this particular case, they reported a highly accurate analysis, and, in fact, showed a calibration curve that could detect 0.5% of one form in another. This is obviously a highly accurate mixture analysis by powder diffraction and shows the power of this method for some applications. However, this analysis required extreme care in sample preparation and may be more difficult to carry out in a production setting where particle size may not be controlled. Similar comments apply to the analysis of mixtures by IR, where the accuracy and precision may also vary considerably from case to case. Given the analytical problems in dealing with mixtures of forms, it may generally be simpler to develop a method to prepare only one crystal form.

In summary, it is important to determine whether polymorphs are present and to solve any problems before pivotal clinical studies are initiated.

D. Determination of the Polymorph Present in the Drug Product

In cases where stability or bioavailability issues exist, the solid form present in the drug product should be investigated, if possible.

For bulk drug substances, X-ray powder diffraction and other techniques can identify the polymorph; however, solid state NMR appears to be the best method for the study of the drug substance in the dosage form (2, 3). Solid-state NMR study of three commercial products containing prednisolone showed that the products A and B contain Form I, whereas product C contains Form II. This analysis was possible even though these tablets contain approximately 95 mg of excipients and 5 mg of drug. There are numerous cases, often involving complex mixtures or low dose products, where solid state NMR (and, in fact, any technique) will not be sensitive enough to identify the polymorph present in the drug product. However, the safety and efficacy is, of course, controlled by the potency assays and by the physical tests (e.g., dissolution).

HYDRATES (SOLVATES)

The flow chart/decision tree for hydrates (solvates) is shown in Figure 6. It outlines investigations of the formation

HYDRATES (SOLVATES)

Drug Substance and Solvent

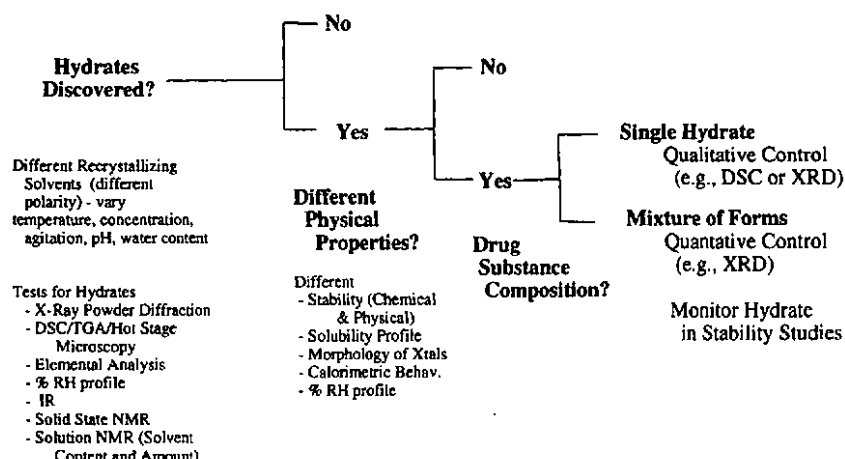


Figure 6. Flow chart for solvates or hydrates.

of hydrates (solvates), the analytical tests available for hydrates (solvates), studies of the physical properties of hydrates (solvates) and the controls needed to ensure the integrity of drug substance containing either a single morphic form or a mixture.

A. Have Hydrates (Solvates) Been Discovered?

The flow chart for hydrates (solvates) (Figure 7) is applied after the preliminary crystallizations have been completed. These are essentially the same as in the polymorph decision tree but, in addition, should include solvent-water mixtures in order to maximize the chance for hydrate formation. These experiments can be guided by the moisture uptake (% RH) studies. Any solids that indicate a significant change in water content as indicated by the % RH-moisture profile should also be examined. The resulting solid phases are preferably characterized by a combination of methods—two for phase identity and two to reveal composition and stoichiometry.

With a very few exceptions, the structural solvent contained in marketed crystalline drug products is water. It is nevertheless often desirable to characterize other solvated crystalline forms of a drug for several reasons: they may be the penultimate form used to crystallize the final product and thus require controlled characterization; they may form if the final crystallization from solvents, especially mixed solvents, is not well controlled; they may be the actual crystallized form of a final product that is desolvated during a final drying step; they may be the form used in recovery for subsequent rework. The relevance of these points will vary from case to case, but for the present discussion we shall treat the subject of solvates in its broadest form.

Examples taken from the literature serve to illustrate the kind of data that proves useful in characterizing solvated crystal forms. For example, a recent report from our laboratory showed that IR and solid state NMR was useful for the identification of the different crystal forms of dirithromycin(9). TGA is another powerful method for the analysis

of solvates. For example, one early study showed that TGA could differentiate three different hydrated salts of fenopropfen(10). Combined with IR or other methods, TGA is an unequivocal method for the verification of the existence of solvates. In addition, TGA is a good method for looking at mixtures of solvated and unsolvated crystal forms, and probably can be developed into an analytical method for determining the ratios of solvated and unsolvated forms.

DSC is also a good method for detecting solvates since there is usually heat change involved in desolvation, especially for hydrates(11). Specifically, DSC by itself does not prove the existence of a solvate, but once other analytical

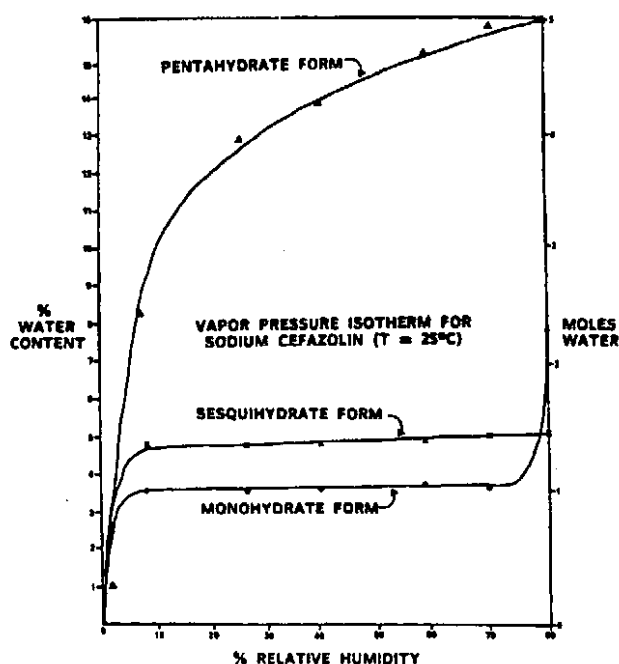


Figure 7. Water uptake vs percent relative humidity for sodium cefazolin.

data from TGA, NMR, etc. are available, DSC becomes a good method for analyzing solvates and determining a percentage of solvates present.

The three solvates of ethynylestradiol (0.5 acetonitrile, 1.0 methanol, 0.5 water) provides another interesting example (12). These solvates have different cell parameters and are crystallographically completely distinct materials. The hemihydrate was obtained from an organic solvent which is not completely miscible with water but was saturated with water. In fact, it is known that crystallization from water-immiscible solvents containing small but slightly different proportions of water can produce different hydrates of a substance.

The DSC/TGA of the three ethynylestradiol solvates(12) are unique and in this case it may be possible to develop DSC/TGA into an analytical procedure for determining the proportions of each solvate. The DSC in some of these traces appears to show a melt and recrystallization corresponding to the loss of solvent of crystallization. However, the exact interpretation of this is not possible without either a DSC microscope or interrupting the tracing to analyze the sample at various temperatures. The methanolate appears to lose solvent in two equal steps, indicating that there may also be a hemimethanolate of this compound. Again, confirmation of this would require interrupting the heating and analyzing the substance after the first solvent loss has occurred. In addition, the DSC/TGA traces suggest that all of the forms are converted to an anhydrous form which then melts at a higher temperature. Thus, interrupting any one of these thermal curves just prior to the final melt could reveal a new form that gives the powder pattern for the anhydrate. Unfortunately, no data of this type is provided in the case cited.

DSC analysis of solvates should be carried out using either an open pan or a pan with a pin-prick; otherwise, unusual and variable results will be obtained because the solvent is not provided a way of escape from the pan. One advantage of using an open pan for DSC is that it reproduces the conditions under which the TGA is performed.

Comparison of the ethynylestradiol powder diffraction patterns clearly establishes that these solvates are different crystal forms as would be expected from the single crystal data(12). In summary, DSC, TGA, and powder diffraction are all good methods for analysis of the different crystal forms of ethynylestradiol.

Figure 7 shows a percent relative humidity versus water uptake study of the type recommended by the USP committee on water(13) In this case, there are two hydrates which are relatively well behaved insofar as they are completely hydrated at about 10% relative humidity and remain uniformly hydrated throughout a wide humidity range. On the other hand, the so-called pentahydrate, which really is only a pentahydrate at very high humidity, changes water content considerably as the relative humidity is changed. The USP committee on moisture specifications recommended that moisture uptake vs relative humidity studies should be routinely performed on all drug substances and excipients (13).

B. Do the Hydrates (Solvates) Have Different Physical Properties?

The physical properties of hydrates are often quite different from the anhydrate form. Figure 8 shows the dissolu-

tion profile of theophylline hydrate and anhydrate. This figure shows that the anhydrate reaches a much higher solubility in water, and on extended exposure recrystallizes to the less soluble hydrate. Such differences must be further examined for possible effects on bioavailability.

In our laboratory we have described the different crystal forms of hydrocortisone-21-tertiary butylacetate(14). Our studies showed that the nonstoichiometric ethanolate is oxygen-sensitive and, of course, would show different physical properties from the stoichiometric ethanolate and the other solvates. Prednisolone tertiary-butylacetate also exists as a nonstoichiometric hydrate which is oxygen sensitive(15). Thus, these are cases where different crystal forms have different chemical stability, although there may be no significant differences in solubility.

C. Mixtures of Polymorphs and Hydrates

Other drug substances exist as both polymorphs and solvates. For example, furosemide exists in two polymorphs, two solvates, and an amorphous form (16, 17). The polymorphs are enantiotropically related, which means that at one temperature one polymorph is more stable, but at a different temperature the other polymorph is physically more stable. That is, plots of solubility versus temperature cross for the two polymorphs. In addition, the different crystal forms have different photostability (chemical stability in light) and moreover have different dissolution rates. Thus, there are significant differences in both chemical and physical properties.

The five different forms, or modifications of furosemide, give clearly different powder patterns. Thus, powder diffraction is a good method for analysis of these different forms. There are similarities between the IR spectra of the five different forms but there are also some significant differences, and expansion and careful analysis could lead to an FT/IR method for analysis of these different forms. IR would probably be a useful method for analysis at least for pairs of these compounds. However, it is not clear whether IR could be used to determine the percentages of several different forms in a more complex mixture. The DSC and TGA of the different forms are significantly different. As expected, the solvates show weight loss in the TGA.

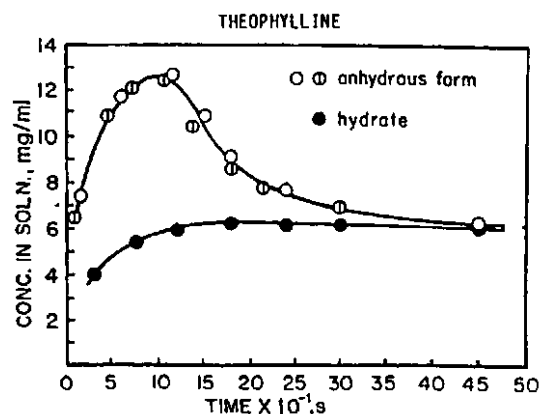


Figure 8. The dissolution-time curves for anhydrous and hydrated theophylline in water at 25°. The two types of open circles represent successive experiments (18).

The interconversion of the different forms of furosemide have been analyzed and a diagram constructed. Such a diagram can be experimentally difficult when so many pairs of crystal forms must be studied for possible interconversions and under different conditions. It is clear from this diagram that many of the forms of furosemide can be converted to form I. This study is one of the most complete reports of solvates and polymorphs available in the literature and serves as a model for studies of such systems for regulatory submissions.

D. Determination of the Hydrate Present in the Drug Product

Another important area is the analysis of the material which is produced after wet granulation of a substance which can form hydrates. We are aware of cases where the bulk drug substance is manufactured and stored as the anhydrate. However, upon wet granulation, there is a conversion (either partial or complete) to a hydrate. Subsequent drying is sometimes not adequate to convert the substance back to the anhydrate, and a hydrate or a mixture of hydrate and anhydrate remain. The formation of a hydrate and its subsequent drying can result in a change in particle size of the drug substance (19). It may also be possible to cause transformations during other processing steps. It is thus recommended that if wet granulation or processing that subjects the drug to even brief changes in temperature or pressure (e.g. milling or compression) is contemplated, then extensive studies of the ability to convert the drug substance to a new crystal form be carried out by mimicking the processing step in the laboratory.

DESOLVATED SOLVATES

The term "desolvated solvates" refers to compounds that are crystallized as solvates but undergo desolvation prior to analysis. Often these "desolvated solvates" retain

the structure of the solvate with relatively small changes in the lattice parameters and atomic coordinates, but no longer contain the solvent. In addition, desolvated solvates are apt to be less ordered than their crystalline counterparts. These forms are particularly difficult to characterize properly since analytical studies indicate that they are unsolvated materials (anhydrous crystal forms) when, in fact, they have the structure of the solvated crystal form from which they were derived. Several observations may give clues that one is dealing with a desolvated form: (1) The form can be obtained from only one solvent; (2) On heating, the form converts to a structure known to be unsolvated; and (3) The form has a particularly low density compared to other forms of the same substance. Experiments that help to clarify whether an apparently solvent free modification is a desolvated form or a true anhydrate include: (1) Single crystal X-ray structure determination in the presence of mother liquor from the crystallization; (2) comparison of the X-ray powder diffraction patterns and solid state NMR spectra of the solvated and desolvated crystal forms; and (3) determination of the vapor pressure isotherm by varying the vapor pressure of the specific solvent involved. A desolvated form will often take up stoichiometric amounts of the relevant solvent. In addition, crystals of the form directly isolated from the crystallizing medium will show a plateau in their isotherm as the vapor pressure of the solvent is reduced.

Figure 9 shows the flow chart used to address regulatory issues involving desolvated solvates. It is similar to the polymorphs flow chart except that the first question involves determining whether a solvate was formed initially and then desolvated, perhaps by "air drying." The remaining questions are identical to the polymorphs flow chart.

Figure 10 shows the behavior of three different crystal forms of the same antibiotic. One crystal form takes up about two waters of hydration and further analysis indicated that it was the dimethanolate which had been desolvated by drying. The second crystal form takes up approximately one water and was originally the monomethanolate which had been desolvated by drying. The third crystal form also takes up

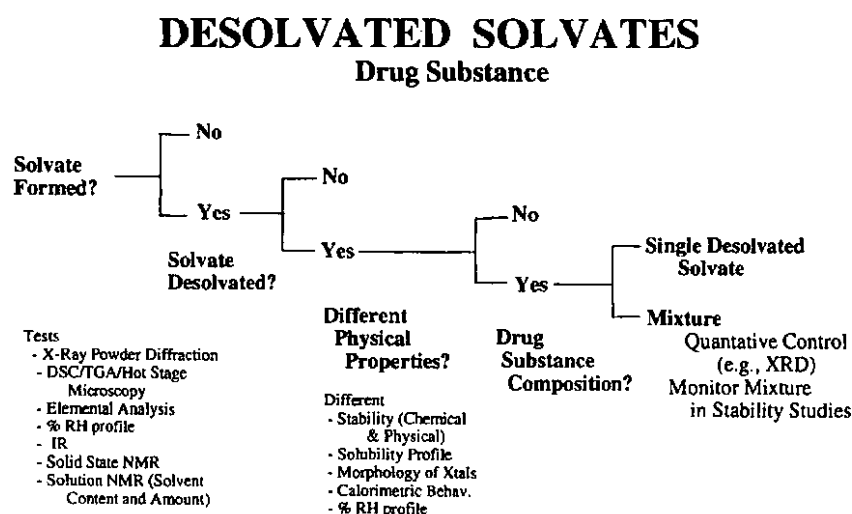


Figure 9. Flow chart for desolvated solvates.

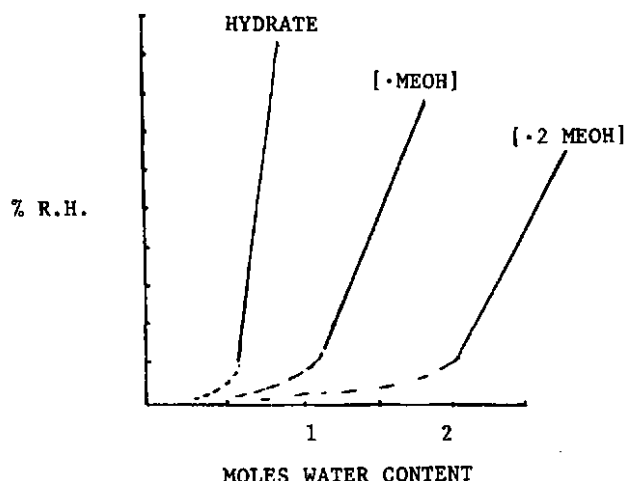


Figure 10. Water sorption by three crystal forms of cephaloridine. The brackets indicate the crystal form produced by desolvating the designated methanolate.

about one molecule of water and is the 0.75 hydrate typically obtained from water solution.

AMORPHOUS FORMS

Amorphous forms are of substantial interest because they usually are much more soluble than their crystalline counterparts. Indeed, there are cases where the amorphous form is the only solid form that has adequate bioavailability. The initial question with this flow chart (Figure 11) is similar to the previous ones: "Are amorphous forms possible?" Amorphous forms can be prepared in different ways, for example, by spray drying or by freeze drying. One can test whether an amorphous form has been produced by using one of the methods listed. X-ray powder diffraction and microscopy are the two primary methods for determining whether an amorphous form has been produced. Powder diffraction is an

excellent method for determining the existence of an amorphous form since they usually exhibit a broad hump between 2 and 20° 2θ. An amorphous form is expected to have no peaks in the powder diffraction pattern. The USP test for the presence of an amorphous form involves determining, by microscopy, whether the material lacks birefringence. IR and solid-state NMR may be useful for detecting amorphous forms since the amorphous nature of the solid sometimes results in broad lines, or in NMR, altered relaxation times. The next question on the flow chart is: "Do the amorphous forms have different physical properties?" The answer to this question will almost certainly be "Yes." Three differences from crystalline forms may generally be expected: 1) Amorphous forms would have greater solubility, 2) Amorphous forms take up water more extensively, and 3) Amorphous forms are sometimes less chemically stable. Another key question for an amorphous form is: "Does it crystallize, and how and when?" This question is very important since inadvertent crystallization can greatly affect the solubility and dissolution rate, and lead to other failures in formulation. Attempts to purposely cause amorphous forms to crystallize can provide information on the parameters involved in crystallization of amorphous forms. Specific questions include: (1) "Does the amorphous form crystallize upon exposure to heat and/or humidity?," and (2) "What other factors (e.g. mechanical pressure and seeding) can lead to the crystallization of the amorphous forms?"

The amorphous form of any substance can be partly characterized by the glass transition temperature, T_g (11). When heated to a temperature above T_g , the solid transforms from a glassy state to a more fluid-like rubbery state. The corresponding increased molecular mobility greatly raises the likelihood of two adverse events: (1) Crystallization and subsequent decreased solubility; and (2) Reduced chemical stability in the more reactive amorphous solid. Amorphous solids are also often prone to absorb moisture and this water sorption reduces the glass transition temperature further. The weight of water required to reduce the glass transition

AMORPHOUS FORMS

Drug Substance

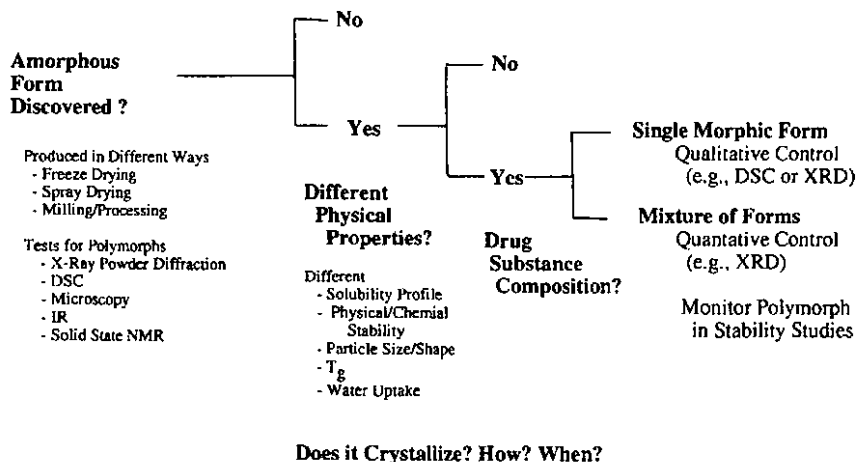


Figure 11. Flow chart for amorphous solids.

temperature to room temperature is of obvious interest and is termed W_g . Table I shows a series of interesting studies on amorphous forms of some common pharmaceuticals.

The table compares the glass transition temperatures (T_g) of a number of pharmaceutical solids with the melting temperatures (T_m). It is interesting that the average ratio of the glass transition temperature to the melting temperature is about 0.70. This table provides a simple rule of thumb which allows the prediction of the glass transition temperature of pharmaceuticals from the known melting point. Crystallization and other solid-state phenomena, such as degradation reactions, as we have said, would be more likely to occur at temperatures above the glass transition temperature. For stability, one might, therefore, wish to prepare amorphous forms only for drugs which have a T_g well above room temperature.

Amorphous indomethacin crystallizes upon standing at room temperature (Figure 12). Obviously, formulations containing amorphous indomethacin are at significant risk to crystallize and thus become less soluble. This has to some extent hampered preparing more bioavailable indomethacin dosage forms.

Quantitative analysis of mixtures of amorphous and crystalline forms provides some challenges. Cefixamine trihydrate is the subject of some early research in this area. This antibiotic, upon grinding, became a mixture of crystalline and amorphous forms. A calibration curve based upon analyzing the height of a selected powder X-ray peak was constructed and used to determine the crystallinity versus grinding time for this system. It is clear that powder diffraction provides a way to estimate the amount of amorphous cefiximine. These studies show that milling and other similar processing steps can create amorphous material and that this process may be detectable. As with wet granulation where transitions to hydrated forms can occur, processing of the drug substance can promote the formation of amorphous drug.

Pikal has compared the analysis of mixtures of crystalline and amorphous forms of several antibiotics by powder diffraction and calorimetry (20). His studies indicate that calorimetry can be a more accurate method for analysis of percent crystallinity but are complicated by water sorption. Zografis and co-workers (unpublished results) have developed a powerful method for the determination of low per-

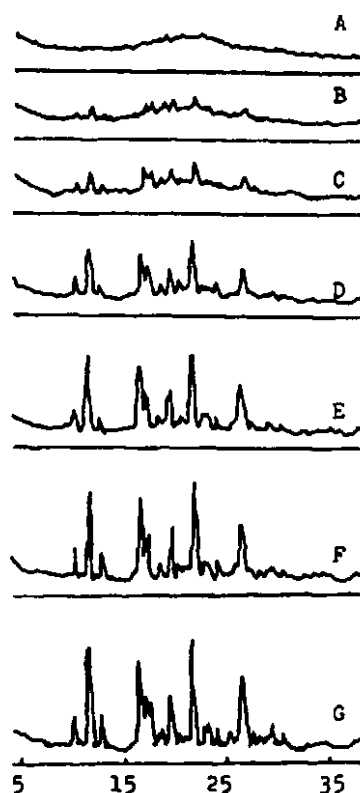


Figure 12. Behavior of amorphous indomethacin upon standing: A, at start; B 24 h; C, 48 h; D, 7d; E, 14d; F, 30d; G, 67d (22).

centages of amorphous material based on the general propensity of amorphous materials to sorb moisture.

SUMMARY

Four flow charts which describe approaches to regulatory issues involving pharmaceutical solids have been developed. These flow charts are for the different types of solids generally encountered (polymorphs, solvates, desolvated solvates, and amorphous forms). It is hoped that these flow charts will guide the solid-state research needed to prepare a comprehensive regulatory submission on the physicochemical properties of a pharmaceutical. It is also hoped that this review has provided enough information to allow the generation of results and information necessary to prepare a drug substance submission that will be quickly approved.

ACKNOWLEDGMENTS

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REFERENCES

1. A. Miyamac, S. Koda, S. Kitamura, Y. Okamoto, and Y. Morimoto. X-ray crystallographic characterization of two poly-

Table I. Pharmaceuticals Forming Glasses Above Room Temperature (21)

Pharmaceutical	T_g (K)	T_m (K)	T_g/T_m
Cholecalciferol	296	352	0.84
Sulfisoxazole	306	460	0.67
Stilbestrol	308	439	0.70
Phenobarbital	321	443	0.72
Quinidine	326	445	0.73
Salicin	333	466	0.71
Sulfathiazole	334	471	0.71
Sulfadimethoxine	339	465	0.73
Dehydrocholic acid	348	502	0.69
17 β -Estradiol	351	445	0.80



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Crystallization processes in pharmaceutical technology and drug delivery design

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Abstract

Crystallization is a major technological process for particle formation in pharmaceutical industry and, in addition, plays an important role in defining the stability and drug release properties of the final dosage forms. Industrial and regulatory aspects of crystallization are briefly reviewed with reference to solid-state properties of pharmaceuticals. Crystallization, incorporating wider definition to include precipitation and solid-state transitions, is considered in terms of preparation of materials for direct compression, formation of amorphous, solvated and polymorphic forms, chiral separation of drugs, production of materials for inhalation drug delivery and injections. Finally, recent developments in supercritical fluid particle technology is considered in relationship to the areas discussed.

Author Keywords: Particle technology; Crystallization and precipitation; Pharmaceuticals; Solid drugs and excipients; Supercritical carbon dioxide

Article Outline

1. Introduction
2. Regulatory aspect
3. Crystallization process and design of solid dosage forms
 - 3.1. Crystal properties and direct compression
 - 3.2. Amorphous and partly crystalline substances
 - 3.3. Polymorphs and solvates
 - 3.4. Chiral drugs
 - 3.5. Drug-carrier systems
 - 3.6. Particles for inhalation devices
 - 3.7. Solid drug nanoparticles
 - 3.8. Precipitation and stability of protein solutions

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4. Production of particulate materials using supercritical fluids

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Crystalline solids

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Abstract

Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling during the various stages of drug development. Crystalline solids can exist in the form of polymorphs, solvates or hydrates. Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development. The current focus of research in the solid-state area is to understand the origins of polymorphism at the molecular level, and to predict and prepare the most stable polymorph of a drug. The recent advances in computational tools allow the prediction of possible polymorphs of the drug from its molecular structure. Sensitive analytical methods are being developed to understand the nature of polymorphism and to characterize the various crystalline forms of a drug in its dosage form. The aim of this review is to emphasize the recent advances made in the area of prediction and characterization of polymorphs and solvates, to address the current challenges faced by pharmaceutical scientists and to anticipate future developments.

Author Keywords: Crystallinity; Polymorphs; Hydrates; Solvates; Formulation; Drug substance; Phase transformation; Characterization

Article Outline

1. Introduction
2. Recent advances in the identification, prediction and characterization of polymorphs
 - 2.1. Types of polymorphism
 - 2.2. Packing polymorphism
 - 2.3. Conformational polymorphism
 - 2.4. Phase transformations in the solid state
 - 2.5. Prediction of polymorphs

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Cristalización

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La **cristalización** es el proceso por el cual se forma un sólido cristalino, ya sea a partir de un gas, un líquido o una disolución. La cristalización es un proceso en donde los iones, átomos o moléculas que constituyen la red cristalina crean enlaces hasta formar cristales, que se emplea en química con bastante frecuencia para purificar una sustancia sólida. La operación de cristalización es aquella por medio de la cual se separa un componente de una solución líquida transfiriéndolo a la fase sólida en forma de cristales que precipitan. Es una operación necesaria para todo producto químico que se presenta comercialmente en forma de polvos o cristales, ya sea el azúcar o sacarosa, la sal común o cloruro de sodio.

Se han desarrollado diferentes técnicas al respecto:

Contenido

- 1 Enfriamiento de una disolución de concentración baja
- 2 Cambio de disolvente
- 3 Evaporación del disolvente
- 4 Sublimación
- 5 Enfriamiento selectivo de un sólido fundido
- 6 Crecimiento cristalino
- 7 Recristalización

Enfriamiento de una disolución de concentración baja

Si se prepara una disolución concentrada a alta temperatura y se enfría, se forma una disolución sobresaturada, que es aquella que tiene, momentáneamente, más soluto disuelto que el admisible por la disolución a esa temperatura en condiciones de equilibrio. Posteriormente, se puede conseguir que la disolución cristalice mediante un enfriamiento controlado. Esencialmente cristaliza el compuesto principal, y las aguas madre se enriquecen con las impurezas presentes en la mezcla inicial al no alcanzar su límite de solubilidad.

Para que se pueda emplear este método de purificación debe haber una variación importante de la solubilidad con la temperatura, lo que no siempre es el caso. La sal marina (NaCl), por ejemplo, tiene una solubilidad de unos 35 g /100 ml en el intervalo de temperaturas comprendido entre 0 y 100 °C, lo que hace que la cristalización por cambio de temperatura sea poco importante, no así en otras sales, como KNO₃. Cuanto mayor sea la diferencia de solubilidad con la temperatura, se pueden obtener mayores rendimientos. A escala industrial, estas operaciones pueden además incluir procesos de purificación complementarios como el filtrado, la decantación de impurezas, etc. Luego de hacer este procedimiento el material queda totalmente puro

El método de purificación debe hacer una variación de la solubilidad con la temperatura lo que siempre es el caso. la cristalización puede ser física o química tenemos que dar ejemplos de este tema

Cambio de disolvente

Preparando una disolución concentrada de una sustancia en un buen disolvente y añadiendo un disolvente peor que es miscible con el primero, el principal del sólido disuelto empieza a precipitar, y las aguas madres se enriquecen relativamente en las impurezas. Por ejemplo, puede separarse ácido benzoico de una disolución de éste en acetona agregando agua.

Evaporación del disolvente

De manera análoga, evaporando el disolvente de una disolución se puede conseguir que empiecen a cristalizar los sólidos que estaban disueltos cuando se alcanzan los límites de sus solubilidades. Este método ha sido utilizado durante milenios en la fabricación de sal a partir de salmuera o agua marina.

Sublimación

En algunos compuestos la presión de vapor de un sólido puede llegar a ser lo bastante elevada como para evaporar cantidades notables de este compuesto sin alcanzar su punto de fusión (sublimación). Los vapores formados condensan en zonas más frías ofrecidas por ejemplo en forma de un "dedo frío", pasando habitualmente directamente del estado gaseoso al sólido, (sublimación regresiva) separándose, de esta manera, de las posibles impurezas. Siguiendo este procedimiento se pueden obtener sólidos puros de sustancias que subliman con facilidad como la cafeína, el azufre elemental, el ácido salicílico, el yodo, etc.

Enfriamiento selectivo de un sólido fundido

Para purificar un sólido cristalino éste puede fundirse. Del líquido obtenido cristaliza, en primer lugar, el sólido puro, enriqueciéndose, la fase líquida, de las impurezas presentes en el sólido original. Por ejemplo, este es el método que se utiliza en la obtención de silicio ultrapuro para la fabricación de sustratos u obleas en la industria de los semiconductores. Al material sólido (silicio sin purificar que se obtiene previamente en un horno eléctrico de inducción) se le da forma cilíndrica. Luego se lleva a cabo una fusión por zonas sobre el cilindro. Se comienza fundiendo una franja o sección del cilindro por un extremo y se desplaza dicha zona a lo largo de este hasta llegar al otro extremo. Como las impurezas son solubles en el fundido se van separando del sólido y arrastrándose hacia el otro extremo. Este proceso de fusión zonal puede hacerse varias veces para asegurarse que el grado de pureza sea el deseado. Finalmente se corta el extremo en el que se han acumulado las impurezas y se separa del resto. La ventaja de este proceso es que controlando adecuadamente la temperatura y la velocidad a la que la franja de fundido se desplaza por la pieza cilíndrica, se puede obtener un material que es un monocristal de silicio que presenta las caras de la red cristalina orientadas en la manera deseada.

Crecimiento cristalino

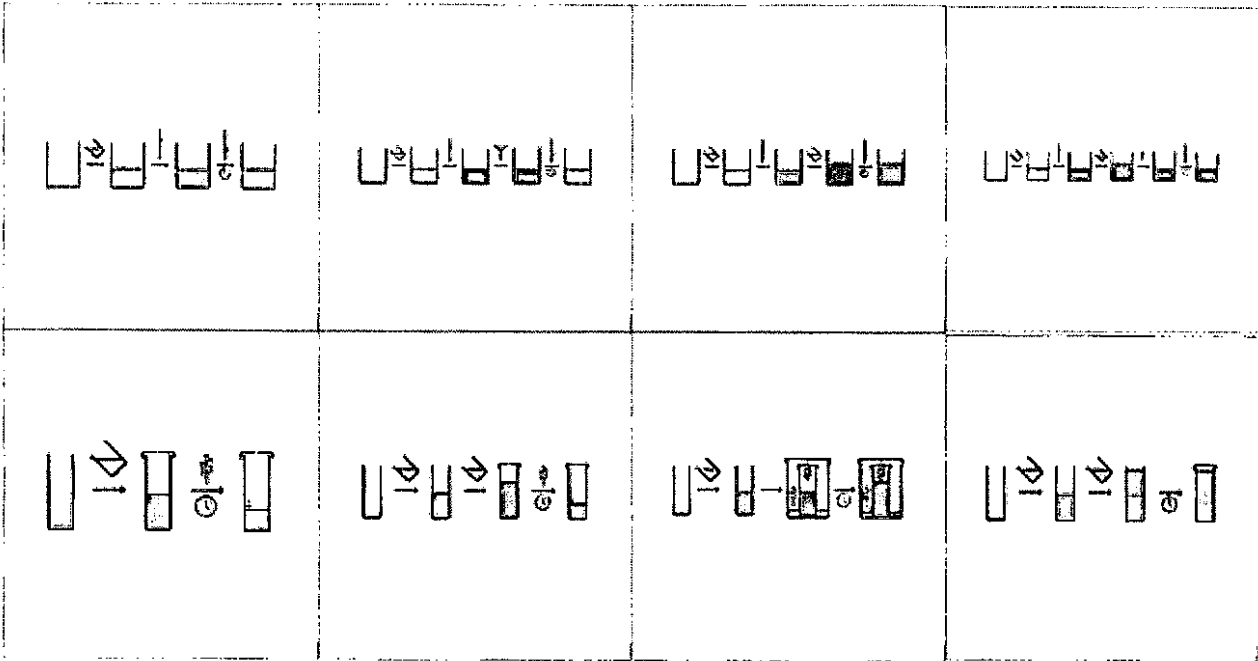
Para obtener cristales grandes de productos poco solubles se han desarrollado otras técnicas. Por ejemplo, se puede hacer difundir dos compuestos de partida en una matriz gelatinosa. Así el compuesto se forma lentamente dando lugar a cristales mayores. Sin embargo, por lo general, cuanto más lento es el proceso de cristalización tanto mejor suele ser el resultado con respecto a la limpieza de los productos de partida y tanto mayor suelen ser los cristales formados.

La forma y el tamaño de los cristales pueden ser influenciados a parte por condicionantes como el disolvente o la concentración de los compuestos, añadiendo trazas de otros componentes como proteínas (esta es la manera con que los moluscos, las diatomeas, los corales, etc... consiguen depositar sus conchas o esqueletos de calcita o cuarzo en la forma deseada.)

La teoría más aceptada para este fenómeno es que el crecimiento cristalino se realiza formando capas monomoleculares alrededor de germen de cristalización o de un cristalito inicial. Nuevas moléculas se adhieren preferentemente en la cara donde su adhesión libera más energía. Las diferencias energéticas suelen ser pequeñas y pueden ser modificadas por la presencia de dichas impurezas o cambiando las condiciones de cristalización.

En multitud de aplicaciones se puede necesitar la obtención de cristales con una determinada forma y/o tamaño como: la determinación de la estructura química mediante difracción de rayos X, la nanotecnología, la obtención de películas especialmente sensibles constituidas por cristales de sales de plata planos orientados perpendicularmente a la luz de incidencia, la preparación de los principios activos de los fármacos, etc...

Recristalización



Monocristal de lizosima para estudio por difracción de rayos X.



Obtenido de "http://es.wikipedia.org/wiki/Cristalizaci%C3%B3n"
Categorías: Procesos químicos | Operaciones de separación | Procesos de separación | Técnicas de laboratorio

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