REYES & REYES
A B O G A D O S

SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **EXPEDIENTE 04-016-758**

TÍTULO SOLICITADO: **"COMPOSICIÓN CRISTALINA QUE CONTIENE ESCITALOPRAM"**

PUBLICACIÓN: **Gaceta 556 de 30-09-2005, número de publicación 540, Página 454.**

PRIORIDAD: **DK PA200101164 (31/07/2001)**

SOLICITANTE: **H. LUNDBECK A/S**

APODERADO: **EMILIO FERRERO**

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 capitulo descriptivo y el capitulo reivindicatorio, presentadas el 12 de Marzo de 2008 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 capitulo reivindicatorio, se nota claramente que persiste la carencia de nivel inventivo al mantenerse, en esencia, las mismas características técnicas (partículas cristalinas de oxalato de escitalopram de tamaño medio de particula entre el rango de 50 a 20 micrómetros).

Entrando en materia, cualquier persona medianamente versada en la materia debe reconocer que la escogencia de formas cristalinas 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.

Refiriéndonos en especial a la obtención de formas cristalinas de los compuestos, cualquier persona medianamente versada en la materia debe reconocer que las sustancias tienen la capacidad intrínseca de manifestarse en ordenamientos cristalinos diversos[1], razón por la cual es predecible y obvia la posibilidad de que dichas sustancias se manifiesten en ordenamientos polimórficos. Es así como La publicación "Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates[2]" revela cerca de 600 casos de polimorfismo en principios farmacéuticos.

En otras palabras, en un polimorfo la estructura química molecular original no cambia, sino que presenta una acomodación diversa de su unidad repetitiva en el espacio, que le confiere una forma cristalina diferente[3]. De allí que cuando se habla de polimorfos de una molécula siempre se denominen en números romanos u orden alfabético (Por ejemplo, formas I, II, III, etc.) y en orden ascendente, en función de su descubrimiento. Nunca un polimorfo y/o solvato de una sustancia

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[1] "Quienes estudian el polimorfismo están llegando a la conclusión de que todos los compuestos, orgánicos e inorgánicos, pueden cristalizar en diferentes formas cristalinas o polimorfos. De hecho, cuanto más diligente sea el estudio de una entidad química, mayor será el número de polimorfos que se descubra." (Subrayado fuera de texto).- Giron, D., *Thermochimica acta 248-1-59*, Elsevier Science B.V., 1995. Páginas 3 a 11.

[2] Thermal Analysis and calorimetric methods in the characterisation of polymorphs and solvates – Thermochimica Acta 248 (1995) 1-59, D. Giron. Páginas 4 a 10.

[3] Pharmaceutical Dosage Forms. 2a Edición. 1989. Volumen 1. p 34

resulta ser una invención, ya que necesariamente dichos sistemas se manifiestan bajo alguno de los siete sistemas cristalinos conocidos: triclínico, monoclínico, ortorrómbico, tetragonal, trigonal, hexagonal y cúbico[4], sin que sea el caso de la presente solicitud, el que se este obteniendo otra forma de organización o sistema cristalino.

En cuanto la insistencia que hace el solicitante tanto en la respuesta al requerimiento en cuestión como en la radicada el 03 de Septiembre de 2009 en donde expresa que *"el objeto de la solicitud es proporcionar partículas cristalinas grandes de escitalopram, las cuales son apropiadas para la compresión directa de una forma de dosificación de farmacéutico sólido"* y que a su vez a través de las anterioridades que revela el examinador técnico *"una persona versada en la materia no sabe cuando puede obtener un producto cristalino con el tamaño medio de partícula deseado y mucho menos sabe como debe controlar el enfriamiento de la cristalización por lotes con el fin de obtener cristales con un tamaño medio de partícula deseado"* , se puede desvirtuar dicha premisa, con la que el solicitante busca argumentar el aparente nivel inventivo de la solicitud en cuestión.

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 fundido[5]. Dentro de estas técnicas, específicamente dentro de la del enfriamiento de una solución sobresaturada, encaja a la perfección el proceso descrito por la solicitud en cuestión, en donde ocurre un enfriamiento controlado de dicha solución sobresaturada de oxalato de Escitalopram.

Complementando lo anterior, podemos tomar algunos apartes de la publicación científica ***"Significance of Controlling Crystallization Mechanisms and Kinetics in Pharmaceutical Systems[6]"*** que nos pueden dar claridad acerca de lo rutinario y detalladamente estudiado que resulta ser el fenómeno de la cristalización, dada su importancia a nivel farmacéutico, veamos:

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[4] Giron, D., Journal of Thermal Analysis and Calorimetry. Vol. 64, Budapest – 2001, página 38
[5] http://es.wikipedia.org/wiki/Cristalizaci%C3%B3n

Because crystallization provides a way of reducing the free energy of metastable thermodynamic states, the extent to which metastable states can be maintained is determined by the crystallization mechanisms and kinetics.

(...)

Cases of unwanted or previously unknown nucleation events abound. Dunitz and Bernstein documented cases of "disappearing or elusive polymorphs" that provide evidence for the consequences of poor process control in crystallization of polymorphic systems. The recent shortage in the supply of capsules of the HIV protease inhibitor Norvir (indinavir), due to the sudden formation of a crystalline structure different from the one harvested for months, illustrates the decisive role that nucleation mechanisms and kinetics have on crystallization.

(...)

The critical role of crystallization kinetics in determining the appearance of crystalline modifications is also recognized by the FDA and described in the guidelines for the manufacture of drug substances:21 "Appropriate manufacturing and control procedures (including in-process testing when needed) should be established for the production of the desired solid-state form(s). It should be emphasized that the manufacturing process (or storage condition) is responsible for producing particular polymorphs or solvates; the control methods merely determine the outcome."

(...)

Desiraju and Gavezzotti have discussed the various methods for crystal structure and polymorphism prediction and the capabilities and shortcomings of the various computer simulation techniques. The main challenge lies in determining the relationships between the molecular aggregation pathways that cause some nuclei to grow and the structure and thermodynamics of the crystalline solids. Recent work from various groups highlight the importance of combining computer simulations with experimental methods to investigate the molecular events that lead to crystallization.

(...)

Experimental methods that can be employed to investigate the factors that regulate crystallization from solution will be presented.

(...)

For instance, compare the following two approaches to describe the processes for the selective crystallization of polymorphs: (1) form I obtained by cooling, form II obtained by evaporation, and (2) form I obtained at a supersaturation x, temperature y, and time z at which crystals were harvested after crystallization onset; form II obtained at supersaturation x', etc.

(...)

Knowledge of the driving force for crystallization is essential, not only to characterize the kinetics, but also to relate the crystallization outcomes to the parameters that regulate crystallization. The number of molecules necessary to achieve an effective nucleating cluster is inversely proportional to the supersaturation.

(...)

Supersaturation may be created by various methods that regulate the solute activity (concentration) or activity product. These include (a) solvent removal (evaporation or freezing), (b) addition of indifferent salts with ions that participate in

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[6] NAI´R RODRI´GUEZ-HORNEDO AND DENETTE MURPHY. Journal of Pharmaceutical Sciences. Vol. 88, No. 7, July 1999.

precipitation, and (c) dissolution of metastable solid phases. Supersaturation can also be created by methods that regulate the solute solubility, such as temperature change, pH change, and addition of a solvent that lowers the solubility of the solute.

(...)

Nucleation is often the decisive step in the crystallization process and is of practical importance in pharmaceutical systems.

(...)

Nucleation phenomena are equally important in the control of micromeritic properties and in the selective crystallization of a particular polymorph.

(...)

The boundaries of possible outcomes are represented by the following scenarios: (1) crystals of very small size (even in the nanometer range) are formed as a result of the high nucleation rates,60,61 or (2) a glass or amorphous solid is formed due to the low diffusion rates of molecules that inhibit the evolution of clusters to crystals within the time scale of the experiment.

(...)

The supramolecular assembly process can be controlled so that the precursor nuclei in solution adopt a structure that resembles the structure of the desired crystalline modification.29,89,90 This concept has been used in the design of nucleation inhibitors to prevent growth of the stable polymorph and enhance the growth of the metastable polymorph.13,15,16 Davey et al.14 have explained the solventdependent polymorph appearance of sulfathiazole by analyzing the intermolecular interactions in the various polymorphic structures and comparing them with the supramolecular assemblies that could exist in the different solvents. In this case, however, the solvent-dependent selective crystallization of a polymorph was not correlated with solubility.
Strategies used for the rational choice of additives to selectively inhibit nucleation or growth of the thermody namically stable modification are based on the work of Davey,Leiserowitz, and others. The main features of these strategies are as follows:

(1) identification of the fastest growing faces of the stable crystalline modification,
(2) characterization of intermolecular interactions along the crystallographic direction with fastest growth,
(3) selection of additives that can be incorporated in the crystalline structure along this direction, and
(4) development of experimental methods to investigate the effectiveness of the additive to kinetically stabilize the metastable modification. The selection of additives can be guided by molecular visualizations of the crystal structure based on geometric fits or binding energy calculations.

(...)

The morphological importance of a face (surface area) is inversely related to its growth rate. Based on these concepts, one of the standard methods used for identifying solvents or dissolved additives that influence nucleation and growth is to investigate the relation between crystal morphology and growth conditions.
A common approach is to compare the experimentally observed morphology with the theoretical morphology and to interpret differences on the basis of experimental growth parameters and assumptions of molecular modeling techniques.

(...)

Any one of the above steps may be rate-limiting depending on the growth conditions, such as the supersaturation, temperature, additives or solvent, and

hydrodynamics of the system. Consequently, crystal growth mechanisms fall into two main categories:41-44 volume diffusion control and surface integration control, and the goals of crystal growth theories are to determine the source of steps and the rate controlling step for crystal growth.

De la misma manera la publicación científica **"Model Identification And Control Of Solution Crystallization Processes : A Review[7]"** revela:

Abstarct: *The modeling of crystal quality (size, shape, and purity) is discussed. Numerical methods for the model solution are reviewed including collocation and Galerkin's method on finite elements. Measurement technologies for on-line crystal size distribution are presented. The difficulties with laser light scattering methods are discussed in detail. Parameter estimation is reviewed and new methods based on nonlinear optimization are presented. Sample calculations of parameters and their uncertainty from experimental data are included. The research literature covering control of continuous and batch crystallization is reviewed, and sample calculations of optimal cooling profiles for batch crystallizers are presented.*

Como se puede apreciar claramente, estas publicaciones científicas dejan en evidencia que con anterioridad se han establecido los parámetros y las técnicas para conocer las características que influyen en los procesos de cristalización, y de esta manera poder controlarlos. En otras palabras, dichas publicaciones científicas dejan en evidencia que una persona versada en la materia tiene a su alcance los conocimientos necesarios para generar estudios que conlleven a la expresión o conformación de alguna de las formas cristalinas que son inherentes a la naturaleza a un compuesto específico.

No siendo suficiente, también existen libros que dedican exclusivamente su contenido a los sistemas cristalinos y a los procesos que los involucran. Es el caso, por ejemplo del libro **"Crystallization Technology Handbook[8]"** en donde se profundizan absolutamente todos los aspectos relacionados con la cristalización, entre estos, lo relacionado al crecimiento cristalino, al tamaño de partícula y balance poblacional, al diseño de cristalizadores y operación de equipos cristalizadores, entre otros. En cuanto a este último aspecto, cualquier persona medianamente versada en la materia debe reconocer que una forma de clasificar los aparatos de cristalización se basa en el método utilizado para crear la sobresaturación[9]:

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[7] James B. Rawlings, Stephen M. Miller, Walter R. Witkowski. Ind. Eng. Chem. Res., 1993, 32 (7), pp 1275–1296.
[8] Alfons Mersmann – 1995 (1° edición). Ed. Marcell Decker, Ink.
[9] http://www.textoscientificos.com/quimica/cristales/cristalizadores

1. Sobresaturación producida por enfriamiento sin evaporación apreciable, por ejemplo, cristalizadores de tanque.

2. Sobresaturación producida por evaporación, con enfriamiento apreciable, por ejemplo, evaporadores de cristalización, cristalizadores-evaporadores.

3. Evaporación combinada con enfriamiento adiabático: cristalizadores al vacío.

Siendo algunos de los equipos de cristalización más comunes[10]:

5.3. Equipment Types
- **5.3.1. Batch Crystallizers**
- **5.3.2. Fluidized Suspension Crystallizer**
- **5.3.3. Forced-Circulation Crystallizer**
- **5.3.4. Draft Tube Baffle (DTB) Crystallizer**
- **5.3.5. Surface-Cooled Crystallizers**
- **5.3.6. Direct-Contact Refrigeration Crystallizers**
- **5.3.7. Teflon Tube Crystallizer**
- **5.3.8. Spray Crystallization**
- **5.3.9. General Characteristics**

Con lo anterior queremos hacer énfasis que no sólo se conoce la información necesaria para establecer ensayos que permiten regular el tamaño de partícula de los cristales de un compuesto específico, sino que además se cuenta con equipos comerciales para realizar dichos procedimientos.

Adicionalmente, y como contrapunto al hecho que el solicitante también insista en que dicho tamaño de los cristales obtenidos para el oxalato de escitalopram pueden sustentar la invención al ser útiles para un proceso de compactación directa, la publicación científica **"Crystal Engineering And Particle Design For The Powder Compaction Process[11]"** revela:

Abstract: *The historical background to the subject of crystal engineering of pharmaceuticals is briefly reviewed with reference to materials as diverse as insulin and direct compression tablet excipients. In the light of the limited scientific and practical information available on the topic two questions are posed:*

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[10] http://books.google.com.co/books?id=gJ7KNvbMtREC&printsec=frontcover&dq=handbook+crystallization&hl=es&ei=pCYRTaL7LYK8lQeut13lCw&sa=X&oi=book_result&ct=result&resnum=2&ved=0CCoQ6AEwAQ#v=onepage&q&f=false

[11] Peter York. 1992, Vol. 18, No. 6-7 , Pages 677-721. Drug Development and Industrial Pharmacy.

Is it possible to prepare 'designer' materials with preferred processing, specifically compressive, properties giving optimised product characteristics?

How can such materials be efficiently manufactured?

In order to consider these questions, several important elements of data-base requirements are regarded as essential. These include knowledge of the crystalline phases of pharmaceutical solids, full understanding of the fundamental mechanical constants and moduli of particulate solids, and the relationships describing the influence of crystallographic structure on the mechanical properties of crystals and powders. At the same time the effects of preparation, pretreatment and processing effects on crystal structure, crystallinity and thermodynamic properties of powdered solids must be established.

The topics of material based compaction problems, property groupings of pharmaceutical powders with particular emphasis on crystal structure and mechanical properties are discussed. The review then considers recent and current research work examining the compaction behaviour of modified or engineered materials, prepared using alternative crystallisation conditions and the incorporation of low level additives. Specific examples include modern direct compression excipients, 'spherical' drug particle production and high purity lubricant (magnesium stearate) powders.

In conclusion, the future potential of the concepts of crystal engineering and particle design is considered in terms of predicting mechanical and processing properties from fundamental molecular and structural information.

De la misma manera la publicación científica **"Crystallization Processes In Pharmaceutical Technology And Drug Delivery Design[12]"** revela:

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.*

Como se puede apreciar, en estas dos publicaciones científicas se hace evidente la relación entre la forma cristalina de los compuestos y la compresión directa, así como la necesidad de tener en cuenta este tipo de relaciones para ensayos rutinarios de preformulación y formulación que se deben realizar en todo proceso de fabricación de medicamentos. En otras palabras, la relación entre una forma

[12] Shekunov BY, York P. Journal of Crystal Growth, Vol.211, No.1-4, 122-136, 2000.

cristalina de un compuesto, característica inherente a dicho compuesto, y su utilidad para un proceso de compactación directa no comprenden una invención, sino un simple reporte de caracteristicas indispensables en un proceso de formulación que requiera precisamente de estas características para formular una composición que se pueda compactar de manera directa.

Finalmente también es importante resaltar el hecho que, desvirtuado el nivel inventivo de los cristales de oxalato de escitalopram de tamaño de partícula especifico, su inclusión junto a otros excipientes convencionales en las formulaciones farmacéuticas sólidas obtenidas a través de compresión directa (reivindicaciones 13 a 25), tampoco puede sustentar nivel inventivo alguno.

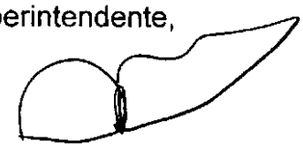
En conclusión, las modificaciones y los argumentos expuestos por el solicitante no logran solventar la evidente ausencia de nivel inventivo de la solicitud de cuestión, principalmente porque dichas modificaciones y argumentos se refieren a características inherentes a todos los compuestos, como los son las formas cristalinas, y además hace referencia a procesos de cristalización, cuya tecnología y conocimientos están lo suficientemente descritos con anterioridad en el estado de la técnica, como para que cualquier persona medianamente versada en la materia plantee ensayos relacionados y reporte dichas características en cualquier principio activo o excipiente, que se requieran incluir en una formulación para compactación directa.

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.

11

Cristalización

De Wikipedia, la enciclopedia libre

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 liquida 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

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 KNO_3. 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 cristalizacion puede ser fisica o qiumica tenemos que dar ejemplos de este tema

Cambio de disolvente

Preparando una disolución concentrada de un 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

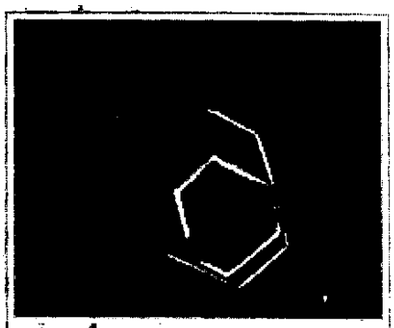
En algunos compuestos la presión de vapor de un sólido puede llegar a ser lo bastante elevada como para evaporar cantidades notables de este compuesto sin alcanzar su punto de fusión (sublimación). Los vapores formados condensan en zonas más frías ofrecidas por ejemplo en forma de un "dedo frío", pasando 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.



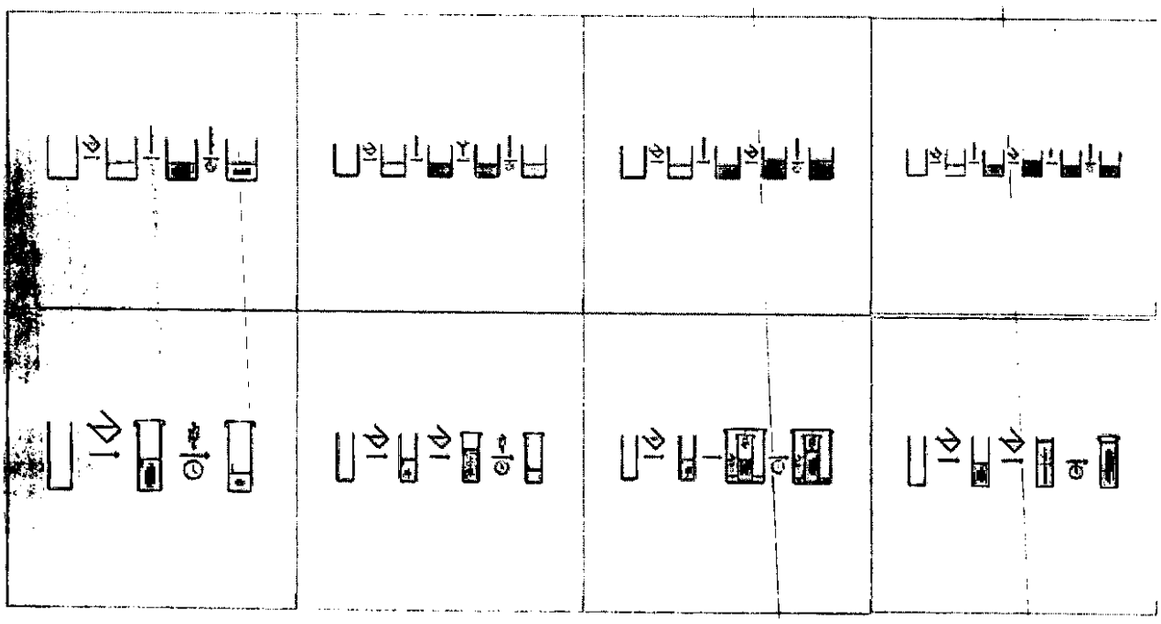
Monocristal de lizosima para estudio por difracción de rayos X.

La forma y el tamaño de los cristales pueden ser influenciados a aparte 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



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Obtenido de "http://es.wikipedia.org/wiki/Cristalizaci%C3%B3n"
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A publication of the **American Pharmaceutical Association** and the **American Chemical Society**

JOURNAL OF
Pharmaceutical Sciences

July 1999
Volume 88, Number 7

MINIREVIEW

Significance of Controlling Crystallization Mechanisms and Kinetics in Pharmaceutical Systems

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Received December 23, 1998. Final revised manuscript received April 8, 1999.
Accepted for publication April 12, 1999.

Introduction

Metastable thermodynamic states are frequently encountered in pharmaceutical systems, in the intentional or unintentional creation of supersaturation, in the crystallization of desired solid-state modifications, and in the control of solid-phase conversions during isolation, manufacturing, storage, and dissolution.[1-4] Some examples in which metastable states are encountered include solid solutions, freeze-concentrated solutions, solutions of weak acids or bases exposed to a pH change, solutions prepared by dissolving a solid-state modification with a higher solubility (higher free energy), and residual solutions during filtration, granulation, and drying. Because crystallization provides a way of reducing the free energy of metastable thermodynamic states, the extent to which metastable states can be maintained is determined by the crystallization mechanisms and kinetics.[5-16] What is surprising, however, is that despite the important role that crystallization has in process control and in determining solid-phase outcomes, crystallization phenomena are often neglected in the pharmaceutical industry until a problem is encountered.

While emphasis is often given to the knowledge of equilibrium phase diagrams with the purpose of identifying the concentration and temperature regions of thermodynamic stability of solid phases, information on crystallization processes can only be obtained by combining studies of thermodynamic properties with kinetic measurements. Cases of unwanted or previously unknown nucleation events abound. Dunitz and Bernstein[17] documented cases of "disappearing or elusive polymorphs" that provide evidence for the consequences of poor process control in crystallization of polymorphic systems. The recent shortage in the supply of capsules of the HIV protease inhibitor Norvir (indinavir), due to the sudden formation of a crystalline structure different from the one harvested for months,[18] illustrates the decisive role that nucleation mechanisms and kinetics have on crystallization. Nichols and Frampton[19] have reported considerable efforts that failed to crystallize the metastable polymorph of paracetamol as described in the initial publication of the crystal structure.[20] The critical role of crystallization kinetics in determining the appearance of crystalline modifications is also recognized by the FDA and described in the guidelines for the manufacture of drug substances:[21] "Appropriate manufacturing and control procedures (including in-process testing when needed) should be established for the production of the desired solid-state form(s). It should be emphasized that the manufacturing process (or storage condition) is responsible for producing particular polymorphs or solvates; the control methods merely determine the outcome."

Even when the parameters that regulate crystallization phenomena are neglected, the illusion of process control is motivated by a crystallization process that yields the desired product—solid phase modification, shape, or size distribution—and by the robust analytical methods used for solid state characterization. This situation is greatly complicated by the recent emphasis on an exclusively

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10.1021/js980490h CCC: $18.00
Published on Web 05/19/1999

structural approach due to the availability of commercial software for the prediction of crystal structure from molecular structure (ab initio predictions) while kinetic processes are scarcely investigated. Desiraju[22–24] and Gavezzotti[25–29] have discussed the various methods for crystal structure and polymorphism prediction and the capabilities and shortcomings of the various computer simulation techniques. The main challenge lies in determining the relationships between the molecular aggregation pathways that cause some nuclei to grow and the structure and thermodynamics of the crystalline solids. Recent work from various groups[14,30–40] highlight the importance of combining computer simulations with experimental methods to investigate the molecular events that lead to crystallization.

The purpose of this review is to describe ways in which crystal structure, morphology, and crystallization kinetics can be utilized to reproducibly maintain metastable states and control solid-state outcomes. Experimental methods that can be employed to investigate the factors that regulate crystallization from solution will be presented.

Crystallization

A crystalline phase is created as a consequence of molecular aggregation processes in solution that lead to the formation of nuclei (with a configuration compatible with the crystal structure), which achieve a certain size for a sufficient time to enable growth into macroscopic crystals. The rate and mechanisms by which crystals are formed in liquid solutions is determined by the solubility, supersaturation, rate at which supersaturation is created, diffusivity, temperature, and the reactivity of surfaces toward nucleation.[41–45]

Transferability of crystallization microtechniques to larger scale processes that are reproducible requires identification of crystallization mechanisms and kinetics. While operationally useful variables that describe crystallization methods are often related to crystallization outcomes, this approach lacks meaningful information for developing a process that yields reliable outcomes, since the factors that determine the crystallization kinetics and outcomes are not explicitly considered. For instance, compare the following two approaches to describe the processes for the selective crystallization of polymorphs: (1) form I obtained by cooling, form II obtained by evaporation, and (2) form I obtained at a supersaturation x, temperature y, and time z at which crystals were harvested after crystallization onset; form II obtained at supersaturation x', etc. While the former approach is at best anecdotal, the latter employs the causative factors and leads to relationships between the crystallization kinetic parameters and the outcomes.

Control of the processes of nucleation and crystal growth is possible as long as the required information is available. Dunitz and Bernstein[17] have explained the mystery of disappearing polymorphs by considering various examples and the relevant questions that were left unanswered. They state that "once a particular polymorph has been obtained, it is always possible to obtain it again; it is only a matter of finding the right experimental conditions."

Supersaturation

Knowledge of the driving force for crystallization is essential, not only to characterize the kinetics, but also to relate the crystallization outcomes to the parameters that regulate crystallization. The number of molecules necessary to achieve an effective nucleating cluster is inversely proportional to the supersaturation. Therefore, as the supersaturation is increased the probability of nucleation increases. However, nucleation is energetically more demanding than crystal growth, and there are supersaturation regions in which crystal growth proceeds while nucleation is suppressed.[41,42,44]

The driving force for nucleation and growth is the difference in chemical potential of the solute in a supersaturated solution, μ_1, and in a saturated solution, μ_{eq}:

$$\Delta\mu = (\mu_1 - \mu_{eq}) \tag{1}$$

Since $\mu = \mu^\circ + RT \ln a$, then

$$\Delta\mu = \mathrm{RT} \ln (a_1/a_{eq}) = \mathrm{RT} \ln (\gamma_1 c_1/\gamma_{eq} c_{eq}) \tag{2}$$

and the supersaturation is

$$\sigma = \Delta\mu/\mathrm{RT} = \ln (a_1/a_{eq}) = \ln (\gamma_1 c_1/\gamma_{eq} c_{eq}) \tag{3}$$

If the activity coefficient, γ, is independent of concentration, in the given concentration regime, then $\gamma_1 = \gamma_{eq}$ and the supersaturation becomes

$$\sigma = \ln (c_1/c_{eq}) = \ln (c/s) \tag{4}$$

where c is the concentration of the crystallizing substance in the supersaturated solution and s is the solubility. (This notation is adopted to avoid the use of subscripts.) A frequently used definition for the supersaturation is

$$\sigma \cong (c - s)/s \tag{5}$$

For c/s values smaller than 1.15,

$$\sigma = \ln (c/s) \approx (c - s)/s \tag{6}$$

Supersaturation may be created by various methods that regulate the solute activity (concentration) or activity product. These include (a) solvent removal (evaporation or freezing), (b) addition of indifferent salts with ions that participate in precipitation, and (c) dissolution of metastable solid phases. Supersaturation can also be created by methods that regulate the solute solubility, such as temperature change, pH change, and addition of a solvent that lowers the solubility of the solute.

Nucleation

Nucleation is often the decisive step in the crystallization process and is of practical importance in pharmaceutical systems. For instance, questions regarding the concentration threshold above which crystallization is observed at times shorter than the desired product shelf life, or dilution rates and concentrations above which precipitation occurs upon injection, are related to the kinetic stability of supersaturated solutions and are regulated by the nucleation mechanisms and kinetics. Nucleation phenomena are equally important in the control of micromeritic properties and in the selective crystallization of a particular polymorph.

In general, nucleation mechanisms can be divided into two main categories: homogeneous and surface or interface catalyzed.[42–44,46] Homogeneous nucleation rarely occurs in large volumes (greater than 100 μl) since solutions contain random impurities which may induce nucleation.[47,48] This type of nucleation is referred to as heterogeneous. A surface or an interface of different composition than the crystallizing solute may serve as a nucleation substrate, by decreasing the energy barrier for the formation of nuclei that can grow into mature crystals. Nucleation that is promoted by crystals of the crystallizing solute is known

as secondary nucleation. These mechanisms are thoroughly discussed by Mullin,[42] Myerson,[44] and Zettlemoyer.[46]

Homogeneous Nucleation—Thermodynamic considerations for nucleation are based on the work of Gibbs,[49] Volmer [50] and others, where the free energy change for an aggregate undergoing a phase transition ΔG is given by

$$\Delta G = \Delta G_v + \Delta G_s \tag{7}$$

where ΔG_s is the surface free energy change associated with the formation of the aggregate (a positive quantity), and ΔG_v is the volume free energy change associated with the phase transition (a negative quantity). For homogeneous or heterogeneous nucleation

$$\Delta G_v = -\alpha l^3 v k_B T \ln\left(\frac{c}{s}\right) \tag{8}$$

where α is the volume-shape factor, l is the characteristic length, v is the molecular volume of the crystallizing solute, k_B is Boltzmann's constant, and T is temperature. For homogeneous nucleation

$$\Delta G_s = \beta l^2 \gamma_{12} \tag{9}$$

where β is the area shape factor and γ is the interfacial energy per unit area between the crystallization medium, 1, and the nucleating cluster, 2. Consequently, the overall free energy change for nucleation is decreased by a large supersaturation ratio (c/s) and by a low interfacial energy.

The factors that regulate nucleation are best appreciated by considering the equation for the rate of homogeneous nucleation from solutions:

$$J = N_o \nu \exp\left(\frac{-\Delta G^*}{k_B T}\right) = N_o \nu \exp\left(\frac{-4\beta^3 v^2 \gamma_{12}^3}{27\alpha^2 (k_B T)^3 \left[\ln\left(\frac{c}{s}\right)\right]^2}\right) \tag{10}$$

J is the number of nuclei formed per unit time per unit volume, N_o is the number of molecules of the crystallizing phase in a unit volume, ν is the frequency of atomic or molecular transport at the nucleus–liquid interface, and ΔG^* is the maximum in the Gibbs free energy change for the formation of clusters, at a certain critical size, l^*. The nucleation rate was initially derived for condensation in vapors by Becker and Döring,[51] where the preexponential factor is related to the gas kinetic collision frequency. In the case of nucleation from condensed phases, the frequency factor is related to the diffusion process.[52] The value of l^* can be obtained by minimizing the free energy function with respect to the characteristic length

$$l^* = \frac{2\beta v \gamma_{12}}{3\alpha k_B T \ln\left(\frac{c}{s}\right)} \tag{11}$$

For spherical clusters, $\alpha = 4\pi/3$ and $\beta = 4\pi$ based on the cluster radius. Therefore,

$$r^* = \frac{2v\gamma_{12}}{k_B T \ln\left(\frac{c}{s}\right)} \tag{12}$$

Considering these geometric factors, the rate for homogeneous nucleation of spherical clusters is

$$J = N_o \nu \exp\left(\frac{-16\pi v^2 \gamma_{12}^3}{3(k_B T)^3 \left[\ln\left(\frac{c}{s}\right)\right]^2}\right) \tag{13}$$

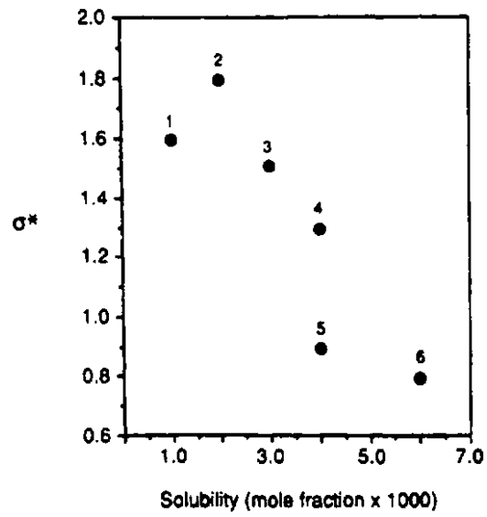

Figure 1—Dependence of the critical supersaturation for nucleation on solubility of nitrofurantoin in (1) formic acid, (2) formic acid:water (4:1), (3) formic acid:ethanol (2:1), (4) formic acid:dioxane (2:1), (5) formic acid:methanol (2:1), (6) formic acid:water (2:1). Data from ref 55.

While the classical theory of nucleation is limited by the implicit assumptions in its derivation (described in detail in ref 41) it successfully predicts the nucleation behavior of a system.[42–44,46,53] Inspection of the equation above clearly suggests that the nucleation rate can be experimentally controlled by the following parameters: molecular or ionic transport, viscosity, supersaturation, solubility, solid–liquid interfacial tension, and temperature.

Nucleation kinetics are experimentally determined from measurements of nucleation rates, induction times and metastability zone widths (the supersaturation or undercooling necessary for spontaneous nucleation) as a function of initial supersaturation.[41–43,54] The nucleation rate will increase by increasing the supersaturation while all other variables are constant. However, at constant supersaturation the nucleation rate will increase with increasing solubility. Solubility affects the pre-exponential factor and the probability of intermolecular collisions. Furthermore, when changes in solvent or solution composition lead to increases in solubility, the interfacial energy decreases since the affinity between crystallizing medium and crystal increases.[41] Consequently, the supersaturation required for spontaneous nucleation decreases with increasing solubility,[55] as shown in Figure 1.

The dependence of nucleation rate on solubility is also consistent with Ostwald's law of stages[56] regarding the preferential formation of a metastable solid phase, that states the following: "when leaving an unstable state, a system does not seek out the most stable state, rather the nearest metastable state which can be reached with loss of free energy". This indicates that if the unstable solid-state modification (the system with highest solubility) precipitates before more thermodinamically stable solid phases, it must have higher nucleation and growth rates than solid states of lower solubility. However, Ostwald's law of stages is not universally valid because the appearance and evolution of solid phases are determined by the kinetics of nucleation and growth under the specific experimental conditions.[5,6,13]

Accounts of nucleation inhibition in the pharmaceutical literature are sometimes confusing because the dependence of the nucleation event (nucleation rate, metastability zone width, or induction time) on supersaturation is not considered. In search for additives that inhibit nucleation,

Table 1—Comparison of Crystallization Behavior of Disodium Phosphate during Far-from-Equilibrium Freezing of Buffer Solutions

crystallization behavior of $Na_2HPO_4 \cdot 12H_2O$		$C_{Na_2HPO_4}$[a] (mM)
reference	observation	
Murase and Franks[63,64]	crystallization begins to decrease	≤200
	does not crystallize	≤10
Cavatur and Suryanarayanan[65]	readily crystallizes	190
	crystallization is inhibited by $C_{NaH_2PO_4}$[b] ≥ 730 mM	190
Gómez[66]	crystallization begins to decrease	≤15
	crystallization readily occurs	≥0.3
	crystallization is not inhibited at $C_{NaH_2PO_4} \leq 94$ mM	6

[a] $C_{Na_2HPO_4}$ = initial disodium phosphate concentration in solution at 25 °C. [b] $C_{NaH_2PO_4}$ = initial monosodium phosphate concentration in solution at 25 °C.

induction times are often measured as a function of additive concentration while the dependence of the nucleation event on supersaturation is neglected. Results from such studies possibly lead to the erroneous conclusion that the additive inhibited nucleation[57,58] when indeed the additive decreased the supersaturation, and frequently led to an undersaturated state. Hence, the system is under *thermodynamic* control instead of *kinetic* control.

An important factor contributing to the nucleation mechanism and kinetics is the volume of solution in which nucleation occurs. The dispersal of a bulk liquid into a collection of small droplets has been shown to be an effective way of achieving large supersaturations or undercoolings.[47,48] Precipitation and solidification in small volumes (droplets) involving emulsions have been used to study homogeneous nucleation processes,[59] and to control purity, particle size, and morphology.[60,61] Dispersing a solution into small volumes isolates heterogeneous nucleants within a fraction of the drops and makes nucleation more difficult. Consequently, larger supersaturations need to be reached for nucleation to occur. The boundaries of possible outcomes are represented by the following scenarios: (1) crystals of very small size (even in the nanometer range) are formed as a result of the high nucleation rates,[60,61] or (2) a glass or amorphous solid is formed due to the low diffusion rates of molecules that inhibit the evolution of clusters to crystals within the time scale of the experiment.[62]

Nucleation outcomes from solutions with initially the *same composition* may vary as a consequence of impurities, rates at which supersaturation was created, thermal histories, experimental techniques employed to detect precipitation, and solution volumes in which nucleation occurred. An important factor contributing to the changes in pH during freezing of buffer solutions is the selective crystallization of buffer components.[63–66] The salt and buffer concentrations for precipitation of disodium phosphate during freezing of sodium phosphate buffer solutions among various laboratories are shown in Table 1. Murase et al.[63,64] report higher initial buffer and disodium phosphate concentrations for the precipitation of disodium phosphate, compared to results from our laboratory.[66] The fraction of disodium phosphate precipitated was observed to decrease with decreasing the initial buffer concentration below 500 mM, at 200 mM disodium phosphate concentration, versus an initial buffer concentration below 8 mM, at 0.3 mM disodium phosphate concentration in our studies;[66] furthermore, disodium phosphate did not precipitate at initial disodium salt concentrations below 10 mM[63,64]

Table 2—Experimental Conditions and Methods of Measuring Progress of Sodium Phosphate Crystallization during Freezing

reference	vol of solution (μL)	cooling rate (°C/min)	temp (°C)	method
Murase and Franks[63,64]	2–5	0.62	−52	DSC, SEM
Cavatur and Suryanarayanan[65]	300[a]	15	−40	XRPD
Gómez[66]	25×10^3	0.3–0.5	−10	pH

[a] Personal communication.

while our studies show that precipitation occurs at salt concentrations as low as 0.3 mM.[66] Inspection of the experimental conditions under which these studies were done (Table 2) shows a trend toward slower salt precipitation rates with decreasing volume of solutions from 25 mL to 3 μl and increasing rates of cooling to lower temperatures.

Neglecting the factors that regulate nucleation leads to misleading generalizations when developing guidelines to control precipitation by the addition of noncrystallizing additives. Consider, for example, the conflicting interpretation of additive effects on nucleation when these are expressed in terms of concentration ratios (additive to crystallizing solute) while ignoring other parameters. Data in Table 1 indicates that disodium phosphate precipitation is inhibited at $(H_2PO_4^-/HPO_4^{2-}) = 4$ (0.73 M/0.19 M)[65] while it is not inhibited at $(H_2PO_4^-/HPO_4^{2-}) = 16$ (0.094 M/0.006 M).[66] Compared to the systems we studied,[66] the buffers studied by Cavatur and Suryanarayana[65] have much higher concentrations of monosodium phosphate (which increase the viscosity of solutions), smaller solution volumes, and faster rates of cooling to lower temperatures. All these factors contribute to delaying salt precipitation.

The effect of the viscosity of the crystallization medium on the nucleation rate has been described by Turnbull and Fisher.[52] The frequency of atomic or molecular transport at the nucleus–liquid interface can be related to the bulk viscosity, η, with the Stokes–Einstein relation:

$$\nu \approx \frac{kT}{3\pi a_o^3 \eta(T)} \tag{14}$$

where a_o is the mean effective diameter of the diffusing species. If the viscosity dependence on temperature is described by Arrhenius behavior, then

$$J = \frac{K}{\eta_o} \exp\left(\frac{-\Delta G^* - \Delta G_a}{k_B T}\right) \tag{15}$$

where ΔG_a is the activation energy for transport across the nucleus–liquid interface. Thus, the nucleation rate may go through a maximum when an increase in undercooling or supersaturation is accompanied by an increase in viscosity. This behavior has been observed in the nucleation of citric acid in aqueous solutions,[67] and the crystallization of ice.[68]

Heterogeneous Nucleation—Heterogeneous nucleation processes are of fundamental and practical importance in pharmaceutical systems since unintentionally or intentionally added surfaces or interfaces may promote nucleation. The reactivity of crystals surfaces as heterogeneous nucleants has significant consequences in the isolation of the desired solid-state modification and in the control of conversions between these modifications, since the free energy required for the formation of two-dimensional nuclei is lowered by the presence of an appropriate substrate. Quantitatively this is described by the following equation:[69,70]

$$\Delta G_s = \gamma_{12}A_{12} + (\gamma_{23} - \gamma_{13})A_{23} \quad (16)$$

where γ is the interaction energy per area, A is the surface area of the interfaces, and the subscript 3 represents the substrate. The total change in surface free energy will be lowered by favorable surface interactions between the aggregate and the substrate and unfavorable interactions between the crystallization medium and the substrate, due to the negative value of the second term in eq 16. Consequently, nucleation will be enhanced by increasing the surface area of the substrate.

The effectiveness of crystal seeding in controlling crystallization outcomes relies on the potential of crystal surfaces to promote heterogeneous or secondary nucleation,[42,43] while avoiding heterogeneous nucleation mediated by unknown contaminants. A review by Ward[71] on the structure, properties, and reactivity of organic crystal surfaces is recommended to develop strategies for the choice of surfaces that promote nucleation. Various studies[8,72–75] have demonstrated the influence of substrate topography, lattice parameters, crystallographic symmetry and intermolecular interactions on surface-directed nucleation.

Heterogeneous nucleation mechanisms can significantly affect dissolution of metastable solid phases, because this form of nucleation can occur at low driving forces. While the choice of a metastable solid phase with a solubility higher than other crystalline modifications is motivated by the expectation of faster dissolution rates, achievement of faster dissolution rates and higher concentrations in solutions is jeopardized by surface-mediated nucleation events. We have reported[8] that the surface of the metastable phase of theophylline promoted the nucleation of the stable monohydrate crystals. The observed oriented growth of monohydrate crystals on the anhydrous surface is consistent with a close lattice match between the *b* and *c* crystallographic axes.[8] Other studies on the dissolution of metastable solids such as anhydrous theophylline[76] and anhydrous carbamazepine[77–79] have shown that crystallization of the stable phase occurs during dissolution, Figure 2. It is unfortunate that in view of the important influence that nucleation mechanisms have on dissolution of metastable solid phases, very seldom are studies carried out to identify the potential of substrate-mediated nucleation by the metastable modification. The information gained from this type of study can be used in the design of methods to regulate crystallization during dissolution as well as during isolation of the desired solid form.

Carter and Ward[70] have identified a surface-mediated nucleation mechanism that involves a geometric shape match between planes of a ledge site on the substrate and planes of prenucleation aggregates. They have applied these concepts to the directed nucleation of polymorphs.[72,74] This work provides us with the attractive possibility that "a library of organic seeds can be used to control polymorphism, or to search for unknown polymorphs".[71] Molecular interpretations based on this approach are experimentally more accessible than those based on solvent-selective polymorph crystallization.

Experimental and Computational Strategies—While nucleation phenomena have their origin at the molecular level, they are often described in terms of macroscopic properties due to the scarcity of experimental techniques that allow for monitoring events at the molecular level. Nevertheless, information about molecular association processes in supersaturated systems obtained by laser Raman spectroscopy and laser light scattering has been used to identify prenucleation clusters and growth units under well-defined experimental conditions. Methods that measure cluster size distributions are more appropriate for studying crystallization of macromolecules[80–84] due to the large sizes of prenucleation clusters, while Raman and fluorescence spectroscopic techniques are capable of providing information about the solution structure or the species present in solution.[85–88] The implications for crystallization pathways are examined by comparing the solution and crystal structures at a molecular level, and by combining information obtained from macroscopic analysis with results from molecular simulations.[14,31–40]

Figure 2—Nucleation and growth of dihydrate carbamazepine on crystal faces of anhydrous monoclinic carbamazepine in aqueous solutions of sodium lauryl sulfate (17.3 mM, 0.5%), supersaturation ratio of 1.15 at 25 °C. From ref 79.

Desiraju[22–24] and Gavezzotti[26–29] have described crystal engineering strategies to understand the molecular aggregation processes involved in crystallization and to elucidate the supramolecular motifs in organic crystals. In this context, crystals are viewed as solid-state supermolecules assembled by intermolecular interactions, with the basic approach of establishing a relation between molecular interactions and supramolecular structure. Recent studies by Gavezzotti[29] show how molecular dynamics calculations allow for simulation of solvent and kinetic effects on molecular aggregation.

The supramolecular assembly process can be controlled so that the precursor nuclei in solution adopt a structure that resembles the structure of the desired crystalline modification.[29,89,90] This concept has been used in the design of nucleation inhibitors to prevent growth of the stable polymorph and enhance the growth of the metastable polymorph.[13,15,16] Davey et al.[14] have explained the solvent-dependent polymorph appearance of sulfathiazole by analyzing the intermolecular interactions in the various polymorphic structures and comparing them with the supramolecular assemblies that could exist in the different solvents. In this case, however, the solvent-dependent selective crystallization of a polymorph was not correlated with solubility.[14,91]

Strategies used for the rational choice of additives to selectively inhibit nucleation or growth of the thermody-

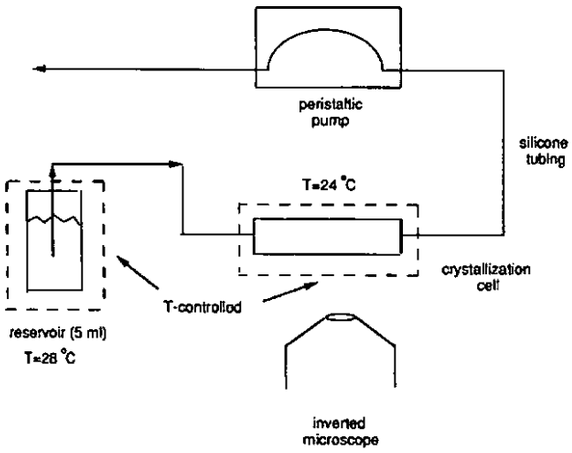

Figure 3—Schematic diagram of a flow system used to measure growth rates of crystal faces. The volume of the crystallization cell is 300 to 500 μL.

namically stable modification are based on the work of Davey.[12–14,92] Leiserowitz,[15,16] and others.[40,93,94] The main features of these strategies are as follows:

(1) identification of the fastest growing faces of the stable crystalline modification,
(2) characterization of intermolecular interactions along the crystallographic direction with fastest growth,
(3) selection of additives that can be incorporated in the crystalline structure along this direction, and
(4) development of experimental methods to investigate the effectiveness of the additive to kinetically stabilize the metastable modification.

The selection of additives can be guided by molecular visualizations of the crystal structure based on geometric fits[13,95] or binding energy calculations.[36,96]

Growth Mechanisms and Kinetics

Once the nucleation step has been overcome, nuclei grow into macroscopic crystals. This stage of the crystallization process is known as crystal growth. The nucleation and growth processes compete for solute in terms of their respective dependence on supersaturation, and their relative rates will determine the crystal size distribution.

Crystal growth is governed by both internal and external factors. Internal factors such as the three-dimensional crystal structure and crystal defects will determine the nature and strength of the intermolecular interactions between the crystal surface and the solution, whereas external factors such as temperature, supersaturation, solvent, and the presence of impurities will affect the type of interactions at the solid–liquid interface.

Depending on the objectives and applications of growth rate measurements, the growth rate may be expressed as (1) overall linear growth rate which is the rate of change of the volume equivalent diameter with time, (2) linear growth rate of a face which is the rate of displacement of a crystal face in a direction perpendicular to the face, and (3) velocity, height, and spacing of growth steps spreading across a crystal surface. The linear growth rate of a face can be expressed in terms of the step velocity, the step height, and the step spacing. Techniques used for in-situ measurement of crystal growth rates as a function of supersaturation include (1) monitoring the crystal population by methods that measure particle size and number,[97,98] (2) monitoring the growth rates of individual crystal faces by optical microscopy with the use of a flow cell system shown in Figure 3,[39,95,99–101] and (3) monitoring the development of surface morphology at the molecular level by atomic force microscopy (AFM)[101–105] and interferometric microscopy.[37,38]

The external shape or morphology of a crystal is a consequence of the relative growth rates of the faces and reveals the molecular events occurring at the crystal face–liquid interfaces during growth. Even when morphology does not play a significant role in quality control, studying it is essential to understand the kinetics of crystallization.[106] The morphological importance of a face (surface area) is inversely related to its growth rate. Based on these concepts, one of the standard methods used for identifying solvents or dissolved additives that influence nucleation and growth is to investigate the relation between crystal morphology and growth conditions.[13,95,107] A common approach is to compare the experimentally observed morphology with the theoretical morphology and to interpret differences on the basis of experimental growth parameters and assumptions of molecular modeling techniques.[37–39]

Batch-to-batch differences in crystal morphology may result from small but significant changes in growth conditions during the crystallization process. For instance, the presence of a small amount of impurity can have a significant effect on the crystal habit. The most potent inhibitors of growth are impurities which are structurally similar to the host molecule (i.e., tailor-made additives and synthetic impurities). For example, the growth of L-alanine in the presence of hydrophobic L-amino acids at concentrations as low as 0.02 m (0.3 g additive/100 g solvent or 0.18 g additive/100 g L-alanine) results in a change in crystal morphology from prismatic to needle-shaped.[95,101] The supersaturation at which crystal growth occurs can also significantly affect growth rates along different crystallographic axes and crystal habit. Growth of phenytoin crystals along the *a* crystallographic axis has a stronger dependence on supersaturation than growth along the *c* axis.[39]

The process of crystal growth consists of several stages through which growth units pass. These include (a) transport from the bulk solution to a site at the crystal surface, (b) adsorption of the growth unit onto the impingement site, or (c) diffusion from the impingement site to a growth site, and (d) incorporation into the crystal lattice. Desolvation can take place in steps b–d; however, the solvent has the possibility of being adsorbed.

Any one of the above steps may be rate-limiting depending on the growth conditions, such as the supersaturation, temperature, additives or solvent, and hydrodynamics of the system. Consequently, crystal growth mechanisms fall into two main categories:[41–44] volume diffusion control and surface integration control, and the goals of crystal growth theories are to determine the source of steps and the rate-controlling step for crystal growth.

As a crystal grows from a supersaturated solution, the solute concentration is depleted in the region of the crystal–solution interface. If diffusion of solute from the bulk solution to the crystal surface is rate limiting, growth is *volume-diffusion controlled*. A diffusion-controlled process is not applicable if there is no dependence of growth rate on hydrodynamic conditions such as flow rate or stirring rate. In practice it is difficult to completely eliminate volume diffusion resistance, and experimental growth kinetics can be misinterpreted as being purely surface-integration controlled when in fact diffusive resistance is still present. Garside has defined an effectiveness factor that is a measure of the relative importance of diffusion and surface integration as the rate-controlling factors for crystal growth.[108]

If incorporation into a crystal lattice is the slowest process, growth is *surface-integration controlled*. Many

crystallization studies involving proteins, small organic electrolytes, and nonelectrolytes have reported growth controlled by surface integration.[37–39,95,99–105] Depending on the roughness of the crystal surface, layer growth or continuous growth may result. If the crystal–solution interface at the molecular level is rough, there are many potential kink (growth) sites. In this case, *continuous or normal growth* models apply. Growth proceeds isotropically resulting in nonfaceted crystals and responds to very small gradients in the growth driving chemical potential (temperature, concentration, etc.). If the interface is smooth, growth proceeds through a *layer growth* model. Kink sites are only found on the edges of two-dimensional nuclei or steps; hence, surface diffusion and surface topography become more important.

Layer growth models describe the formation of steps by two mechanisms: screw dislocation and two-dimensional nucleation. Details of the derivation of these models can be found in the literature.[42,44,109–111]

The spiral growth mechanism or screw dislocation model was first described by Burton, Cabrera, and Frank (BCF).[112] Bennema[111,113,114] modified this theory for crystals growing from aqueous solution. Flat crystal surfaces have a high energy barrier for nucleation at low supersaturations, and the presence of screw dislocations provides a source of steps for the addition of growth units in an infinite sequence of equidistant and parallel steps. In the simplest case, these steps will develop as a spiral which rotates about its axis during growth.

Two-dimensional nucleation requires the formation of clusters above a critical size for growth of layers. The same concepts discussed in the nucleation section apply to the nucleation of a two-dimensional cluster above a critical size. This model accounts for crystal growth at high supersaturations. These models were developed by Volmer[115] and Stranski.[116] Variations in the mode that nuclei spread after being formed lead to the various two-dimensional nucleation models: mononuclear, polynuclear, and birth and spread.

Each crystal growth model describes the growth rate dependence on supersaturation, temperature, and face area. Although the various models can be used to identify the growth mechanism by fitting the various equations to the experimentally measured face-growth rate dependence on supersaturation, it may be difficult to discriminate between models.[39,101,117] This approach is often combined with observations of surface topography to confirm the growth mechanism.

Surface microtopographic observations can reveal growth mechanisms of crystal faces under different growth conditions, as shown for human insulin crystals in Figure 4. Monitoring the development of surface topography and transport processes during crystal growth will reveal events that are not evident from morphology studies. Interactions of growth units and additives with different crystal planes exposed on a surface may be deduced from the shape of two-dimensional nuclei, and the kinetic anisotropy of the growth steps along crystallographic directions. These techniques have been successfully applied for identifying the crystal growth mechanisms and kinetics of small molecules[37,38,101] and proteins.[102–105,118]

Solution-Mediated Transformations

Knowledge of the propensity of a metastable solid phase to dissolve in a liquid phase from which a stable solid phase nucleates and grows is crucial in many stages of pharmaceutical development, because pharmaceutical solids are designed to be dissolved and to come in contact with solvents since the early stages of development (isolated by

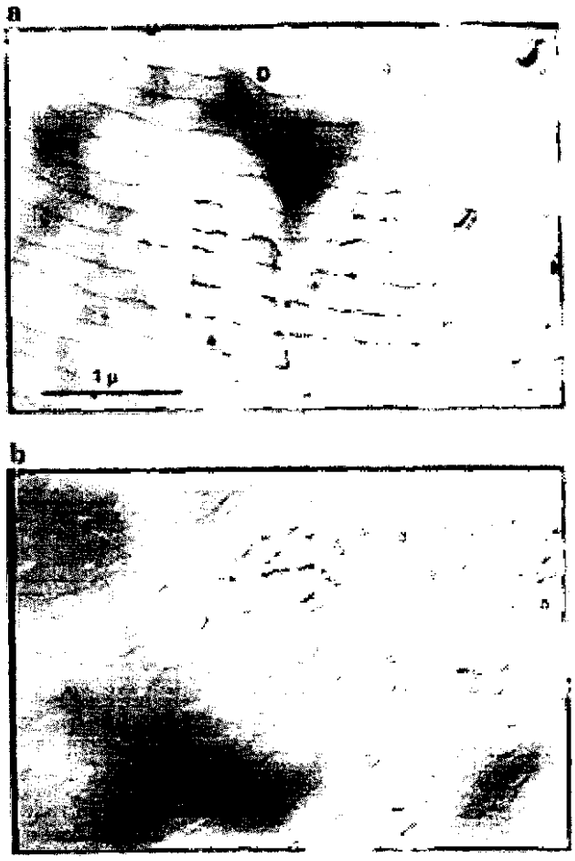

Figure 4—Micrographs of human insulin crystals showing that steps arise by different mechanisms depending on supersaturation. (a) At low supersaturation, steps are created by screw dislocations, D. (b) At high supersaturation, d/s >10, steps occur at the edges of islands as a consequence of two-dimensional nucleation.

crystallization from solution) and during processing (wet granulation, spray-drying, freeze-drying, etc.). Given that the sudden disappearance or appearance of a crystalline modification can threaten process development, characterization of the kinetics and mechanisms of solvent-mediated transformations is of practical importance. It will provide answers to questions such as the following: What is the relation between processing conditions and the solid-state modification manufactured? Is there a correlation between dissolution conditions, solid phase(s) dissolving, and concentration of drug dissolved?

The importance of phase transition kinetics, molecular interpretations, and process implications are emphasized by several investigators.[5–9,12–14,119] Cardew and Davey[5] developed a theoretical framework to investigate solvent-mediated transformations in terms of dissolution kinetics of one phase and growth of a second phase. The model represents the time development of the supersaturation with respect to the stable phase, or solute concentration in solution, and solid phase composition during the transformation. The experimental approach involves saturating the solution with respect to the metastable phase under consideration and to monitor both solution concentration and solid phase composition in the presence of the metastable phase, under constant external conditions. More useful information is obtained from the concentration or supersaturation profiles than from the solid phase composition profiles with time. Since the former is related to the

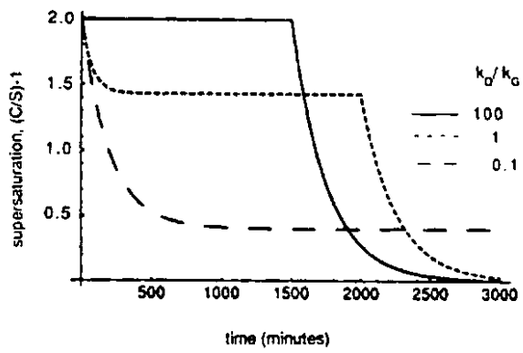

Figure 5—Numerical simulation of the supersaturation–time profiles, as a function of the relative rates of dissolution and crystallization during a solution-mediated transformation. Generated from a kinetic model developed by Cardew and Davey,[5] assuming that both dissolution and growth rates are linearly dependent on their respective driving forces.

Table 3—Information on Crystallization Kinetics and Mechanisms Provided by Various Experimental Techniques

techniques	information
optical microscopy (inverted microscope)	- study crystallization processes *in situ* - monitor transformations in suspensions - determine transformation times - screen and characterize additive/solvent interactions with specific crystal faces - identify nucleation mechanisms - measure crystal growth rates
electron microscopy	- characterize additive/solvent interactions with specific crystal faces - identify nucleation and growth mechanisms - measure crystal growth rates
atomic force microscopy interferometric microscopy	- study crystallization processes *in situ* - examine surface topography - identify nucleation and growth mechanisms - measure crystal growth rates
Raman spectroscopy	- monitor molecular association processes that direct nucleation and crystal growth
spectrophotometry chromatography	- monitor concentration of solute in solution and supersaturation
diffraction calorimetry spectroscopy	- monitor solid phase composition

driving forces that regulate the transformation rate and can be used to identify the rate-controlling process: dissolution or growth. A calculated supersaturation profile with growth-limited and dissolution-limited regimes is shown in Figure 5, for the case in which dissolution and growth are linearly dependent on supersaturation.[5,6] Experimental studies of the phase transitions of organic crystals have shown this model to be applicable to explain the solution-mediated transformation kinetics of polymorphs[5,6,119] and solvates,[8] and to be applicable to process development.[119] Some useful experimental techniques for studying small and large scale crystallization and solution-mediated transformations are summarized in Table 3.

Summary

In this review we have presented the significance of crystallization mechanisms and kinetics in directing crystallization pathways. Given the recent advances in computational and analytical techniques that provide access to the molecular events that direct nucleation and crystal growth, there is no reason for the development of ill-defined crystallization processes even when the desired product is obtained. Understanding the thermodynamic and kinetic behavior of the system is vital for the design of reliable processes; thus, at least a holistic approach that identifies the relevant experimental parameters is required. While the objectives of formulation or process development may not explicitly include interpretations at the molecular level, the information concealed in the interfaces present during the process, the structure of the solution, and the solids harvested (crystal structure, morphology, particle size and number) can be significant in the identification of nucleation and growth mechanisms, and will reveal molecular events associated with crystallization. Although the significance of crystallization mechanisms and kinetics has been underestimated in the pharmaceutical industry, we hope that the recent developments in crystallization engineering and techniques will inspire interest in the application of this field to pharmaceutical systems.

References and Notes

1. Marshall, P. V.; York, P. Crystallization Solvent Induced Solid State and Particulate Modifications of Nitrofurantoin. *Int. J. Pharm.* **1989**, *55*, 257–263.
2. Ludlambrown, I.; York, P. The Crystalline Modification of Succinic Acid by Variations in Crystallization Conditions. *J. Phys. D: Appl. Phys.* **1993**, *26*, B60–B65.
3. Byrn, S. R.; Pfeiffer, R. R.; Stephenson, G.; Grant, D. J. W.; Gleason, W. B. Solid-State Pharmaceutical Chemistry. *Chem. Mater.* **1994**, *6*, 1148–1158.
4. Byrn, S.; Pfeiffer, R.; Ganey, M.; Hoiberg, C.; Poochiklan, G. Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations. *Pharm. Res.* **1995**, *12*, 945–954.
5. Cardew, P. T.; Davey, R. J. The Kinetics of Solvent-Mediated Phase Transformations. *Proc. R. Soc. London* **1985**, *A 398*, 415–428.
6. Davey, R. J.; Cardew, P. T.; Mcewan, D.; Sadler, D. E. Rate Controlling Processes in Solvent-Mediated Phase Transformations. *J. Cryst. Growth* **1986**, *79*, 648–653.
7. Boylan, J. C.; Swarbrick, J. *Crystallization and the Properties of Crystals*; Rodriguez-Hornedo, N., Ed.; Marcel Dekker Inc.: New York, 1991; Vol. 3, pp pp 399–434.
8. Rodríguez-Hornedo, N.; Lechuga-Ballesteros, D.; Wu, H. J. Phase Transition and Heterogeneous Epitaxial Nucleation of Hydrated and Anhydrous Theophylline Crystals. *Int. J. Pharm.* **1992**, *85*, 149–162.
9. Boylan, J. C.; Swarbrick, J. *Hydrates*; Morris, K., Rodríguez-Hornedo, N., Eds.; 1993; Vol. 7, pp 393–440.
10. Zhu, H. J.; Grant, D. J. W. Influence of Water Activity in Organic Solvent Plus Water Mixtures on the Nature of the Crystallizing Drug Phase. 2. Ampicillin. *Int. J. Pharm.* **1996**, *139*, 33–43.
11. Zhu, H. J.; Yuen, C. M.; Grant, D. J. W. Influence of Water Activity in Organic Solvent Plus Water Mixtures on the Nature of the Crystallizing Drug Phase. 1. Theophylline. *Int. J. Pharm.* **1996**, *135*, 151–160.
12. Davey, R. J.; Black, S. N.; Goodwin, A. D.; Mackerron, D.; Maginn, S. J.; Miller, E. J. Crystallisation in Polymer Films: Control of Morphology and Kinetics of an Organic Dye in a Polysilicone Matrix. *J. Mater. Chem.* **1997**, *7*, 237–241.
13. Davey, R. J.; Blagden, N.; Potts, G. D.; Docherty, R. Polymorphism in Molecular Crystals: Stabilization of a Metastable Form by Conformational Mimicry. *J. Am. Chem. Soc.* **1997**, *119*, 1767–1772.
14. Blagden, N.; Davey, R. J.; Lieberman, H. F.; Williams, L.; Payne, R.; Roberts, R.; Rowe, R.; Docherty, R. Crystal Chemistry and Solvent Effects in Polymorphic Systems –Sulfathiazole. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 1035–1044.
15. Weissbuch, I.; Leisorowitz, L.; Lahav, M. Tailor-Made and Charge-Transfer Auxiliaries for the Control of the Crystal Polymorphism of Glycine. *Adv. Mat.* **1994**, *6*, 952–956.
16. Weissbuch, I.; Zbaida, D.; Addadi, L.; Leiserowitz, L.; Lahav, M. Design of Polymeric Inhibitors for the Control of Crystal Polymorphism – Induced Enantiomeric Resolution of Racemic Histidine by Crystallization at 25 °C. *J. Am. Chem. Soc.* **1987**, *109*, 1869–1871.
17. Dunitz, J. D.; Bernstein, J. Disappearing Polymorphs. *Acc. Chem. Res.* **1995**, *28*, 193–200.

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Model identification and control of solution crystallization processes : a review

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Résumé / Abstract

The modeling of crystal quality (size, shape, and purity) is discussed. Numerical methods for the model solution are reviewed including collocation and Galerkin's method on finite elements. Measurement technologies for on-line crystal size distribution are presented. The difficulties with laser light scattering methods are discussed in detail. Parameter estimation is reviewed and new methods based on nonlinear optimization are presented. Sample calculations of parameters and their uncertainty from experimental data are included. The research literature covering control of continuous and batch crystallization is reviewed, and sample calculations of optimal cooling profiles for batch crystallizers are presented

Revue / Journal Title

Industrial & engineering chemistry research ISSN 0888-5885 CODEN IECRED

Source / Source

1993, vol. 32, n°7, pp. 1275-1296 (3 p.3/4)

Langue / Language

Anglais

Editeur / Publisher

American Chemical Society, Washington, DC, ETATS-UNIS (1987) (Revue)

Mots-clés anglais / English Keywords

Crystallization ; Modeling ; Identification ; Numerical simulation ; Process control ; Measurement method ; Parameter estimation ; State of the art ;

Mots-clés français / French Keywords

Cristallisation ; Modélisation ; Identification ; Simulation numérique ; Commande processus ; Méthode mesure ; Estimation paramètre ; Etat actuel ;

Mots-clés espagnols / Spanish Keywords

Cristalización ; Modelización ; Identificación ; Simulación numérica ; Control proceso ; Método medida ; Estimación parámetro ; Estado actual ;

Localisation / Location

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Second Edition
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edited by
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Contents

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Cristalizadores

El hecho de que se le de a un recipiente el nombre de cristalizador depende primordialmente de los criterios utilizados para determinar su tamaño. En un cristalizador, la clasificación por tamaños se realiza normalmente sobre la base del volumen necesario para la cristalización o de las características especiales que se requieren para obtener tamaños apropiados de productos. Sin embargo, en su aspecto exterior, los recipientes pueden ser idénticos.

Los cristalizadores comerciales pueden operara de forma continua o por cargas, excepto para algunas aplicaciones especiales, es preferible la operación continua. La primera condición que debe de cumplir un cristalizador es crear una solución sobresaturada, ya que la cristalización no se puede producir sin sobresaturación. El medio utilizado para producir la sobresaturación depende esencialmente de la curva de solubilidad del soluto. Algunos solutos como la sal común, tiene solubilidades que son prácticamente independientes de la temperatura, mientras que otros, como el sulfato sódico anhidro y el carbonato sodico monohidratado, poseen curvas de solubilidad invertida y se hacen mas solubles a medida que la temperatura disminuye. Para cristalizar estos materiales se precisa crear la sobresaturación mediante evaporación. En los casos intermedios resulta útil la combinación de evaporación y de enfriamiento.

Una forma de clasificar los aparatos de cristalización se basa en el método utilizado para crear la sobresaturación:

1. Sobresaturación producida por enfriamiento sin evaporación apreciable, por ejemplo, cristalizadores de tanque.
2. Sobresaturación producida por evaporación, con enfriamiento apreciable, por ejemplo, evaporadores de cristalización, cristalizadores-evaporadores.
3. Evaporación combinada con enfriamiento adiabático: cristalizadores al vacío.

Cristalizadores de suspensión mezclada y de retiro de productos combinados

Este tipo de equipo, llamado a veces cristalizador de magma circulante, es el más importante de los que se utilizan en la actualidad. En la mayor parte de los equipos

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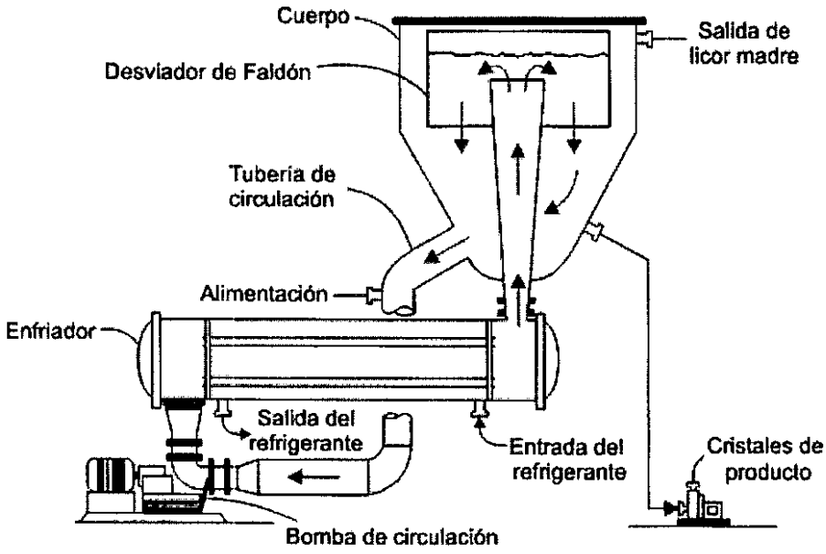
comerciales de este tipo, la uniformidad de la suspensión de los sólidos del producto en el cuerpo del cristalizador es suficiente para que se pueda aplicar la teoría. Aun cuando se incluyen ciertas características y variedades diferentes en esta clasificación, el equipo que funciona a la capacidad mas elevada es del tipo en que se produce por lo común la vaporización de un disolvente, casi siempre agua.

Cristalizador de enfriamiento superficial

Para algunos materiales, como el clorato de potasio, es posible utilizar un intercambiador de tubo y coraza de circulación forzada, en combinación directa con un cuerpo de cristallzador de tubo de extracción.

Es preciso prestar una atención cuidadosa a la diferencia de temperatura entre el medio enfriador y la lechada que circula por los tubos del intercambiador.



Cristalizador de enfriamiento superficial

Además la trayectoria y la velocidad de flujo de la lechada dentro del cuerpo del cristalizador deben ser de tal índole que el volumen contenido en el cuerpo sea activo. Esto quiere decir que puede haber cristales suspendidos dentro del cuerpo debido a la turbulencia y que son eficaces para aliviar la sobresaturación creada por la reducción de temperatura de la lechada, al pasar por el intercambiador. Evidentemente la bomba de circulación es parte del sistema de cristalización y es preciso prestar atención cuidadosa a este tipo y sus parámetros operacionales para evitar influencias indebidas de la nucleación. Este tipo de equipo produce cristales en la gama de malla de 30 a 100. El diseño se basa en las velocidades admisibles de intercambio de calor y la retención que se requiere para el crecimiento de los cristales de producto.

Cristalizador de evaporación de circulación forzada

La lechada que sale del cuerpo se bombea a través de una tubería de circulación y por un intercambiador de calor de coraza, donde su temperatura se eleva de 2 a 6 °C. puesto que este calentamiento se realiza sin vaporización, los materiales de solubilidad normal no deberán producir sedimentación en los tubos. El licor calentado, que regresa al cuerpo mediante una línea de recirculación, se mezcla con la lechada y eleva su temperatura localmente, cerca del punto de entrada, lo que provoca la ebullición en la superficie del líquido. Durante el enfriamiento subsiguiente y la vaporización para alcanzar el equilibrio entre el líquido y el vapor, la sobresaturación que se crea provoca sedimentaciones en el cuerpo de remolino de los cristales suspendidos, hasta que vuelven a alejarse por la tubería de circulación. La cantidad y la velocidad de la recirculación, el tamaño del cuerpo y el tipo y la velocidad de la bomba de circulación son conceptos críticos de diseño, para poder obtener resultados

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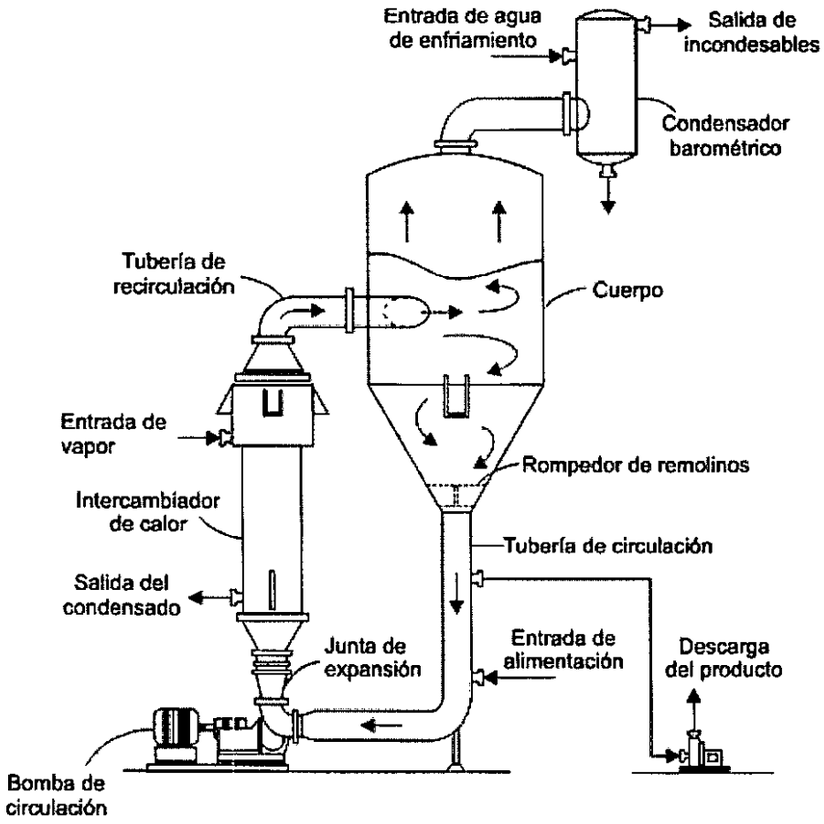
predecibles. Si el cristalizador no es del tipo de evaporación y depende sólo del enfriamiento adiabático de evaporación para lograr un buen rendimiento, se omitirá el elemento calentador. La alimentación se admite a la línea de circulación, después de retirar la lechada, en un punto situado suficientemente por debajo de la superficie libre del líquido, para evitar la vaporización instantánea durante el proceso de mezclado.



Cristalizador de evaporación de circulación forzada

Cristalizador evaporador de desviador y tubo de extracción (DTB).

Puesto que la circulación mecánica influye considerablemente en el nivel de nucleación dentro del cristalizador, se han desarrollado muchos diseños que utilizan circuladotes situados dentro del cuerpo del cristalizador, reduciendo en esta forma la carga de bombeo que s ejerce sobre el circulador. Esta técnica reduce el consumo de potencia y la velocidad de punta del circulador y, por ende, la rapidez de nucleación.

La suspensión de los cristales de productos se mantiene mediante una hélice grande y de movimiento lento, rodeada por un tubo de extracción dentro del cuerpo. La hélice dirige la lechada hacia la superficie del líquido, para evitar que lo sólidos pongan en cortocircuito la zona de sobresaturación mas intensa.

La lechada enfriada regresa al fondo del recipiente y vuelve a recircular a través de la hélice.

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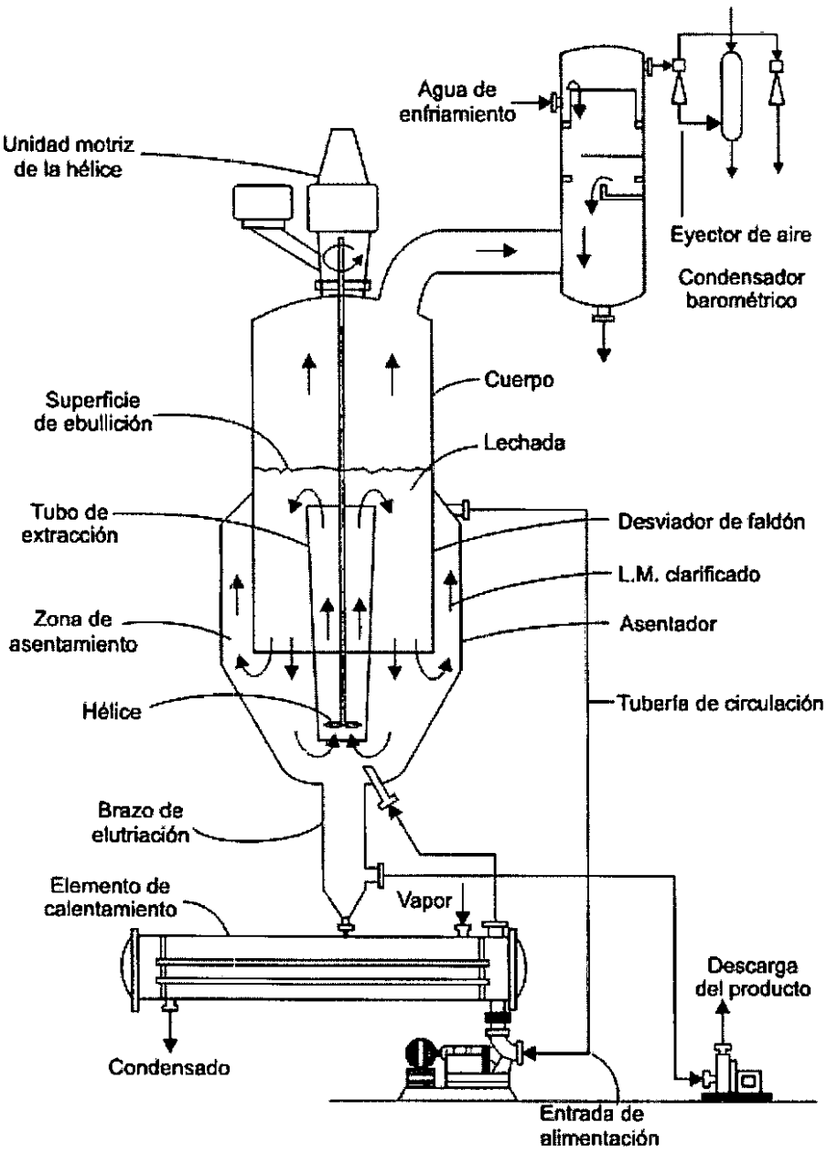


Cristalizador evaporador de desviador y tubo de extracción

En esta última, la solución calentada se mezcla con la lechada de recirculación. Este diseño consta de una característica de destrucción de partículas finas que comprende la zona de asentamiento que rodea al cuerpo del cristalizador, la bomba de circulación y el elemento calentador. Este último proporciona suficiente calor para satisfacer los requisitos de evaporación y elevan la temperatura de la solución retirada del asentador, con el fin de destruir todas las partículas cristalinas pequeñas que se retiran. Los cristales gruesos se separan de las partículas finas en la zona de asentamiento por sedimentación gravitacional.

Cristalizador de refrigeración de contacto directo.

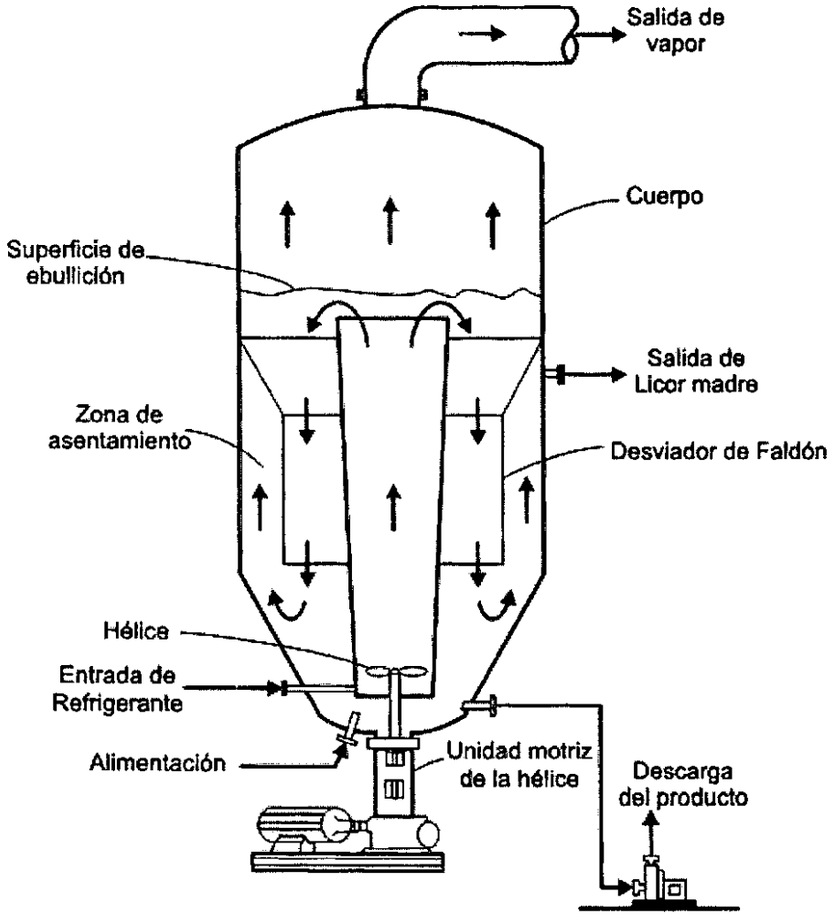
Para algunas aplicaciones, como la obtención de hielo a partir de agua de mar, es necesario a llegar a temperaturas tan bajas que hagan que el enfriamiento mediante el empleo de refrigerantes sea la única solución económica. En estos sistemas, a veces no resulta práctico emplear equipos de enfriamiento superficial, porque la diferencia admisible de temperaturas es tan baja (menos de 3°C), que la superficie de intercambio de calor se hace excesiva o porque la viscosidad es tan elevada que le energía mecánica aplicada por el sistema de circulación mayor que el que se puede

obtener con diferencias razonables de temperatura. En estos sistemas, es conveniente mezclar el refrigerante con la lechada que se enfría en el cristalizador, de modo que el calor de vaporización del refrigerante del refrigerante sea relativamente inmiscible con el licor madre y capaz de sufrir separación, compresión, condensación y un reciclaje subsiguiente en el sistema de cristalización. Las presiones operacionales y las temperaturas escogidas tienen una influencia importante sobre el consumo de potencia. Esta técnica resulto muy adecuada para reducir los problemas que se asocian con la acumulación de sólidos sobre una superficie de enfriamiento. El empleo de la refrigeración de contacto directo reduce también las necesidades generales de energía del proceso, puesto que es un proceso de refrigeración que incluye dos fluidos se requiere una diferencia mayor de temperaturas, sobre una base general, cuando el refrigerante debe enfriar primeramente alguna solución intermedia, como la salmuera de cloruro de calcio, y esa solución, a su vez, enfría al licor madre en el cristalizador. Los equipos de este tipo han funcionado adecuadamente a temperaturas tan bajas como -59°C (-75°F).

Cristalizador de tubo de extracción (DT).

Este cristalizador se puede emplear en sistemas en que no se desea ni se necesita la destrucción de las partículas finas. En esos casos se omite el desviador y se determina el tamaño del circulador interno para que tenga una influencia mínima de nucleación sobre la suspensión.

En los cristalizadores DT y DBT, la velocidad de circulación que se alcanza suele ser mucho mayor que la que se obtiene en un cristalizador similar de circulación forzada. Por tanto, el equipo se aplica cuando sea necesario hacer circular grandes cantidades de lechada, para minimizar los niveles de sobresaturación dentro del equipo.



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Cristalizador de tubo de extracción

En general, método se requiere para tener ciclos operacionales prolongados con materiales capaces de crecer en las paredes del cristalizador. Los diseños de tubo de extracción y desviador se utilizan comúnmente para la producción de materiales granulares, de malla 8 a la 30, como el sulfato de amonio, cloruro de potasio y otros cristales inorgánicos y orgánicos.

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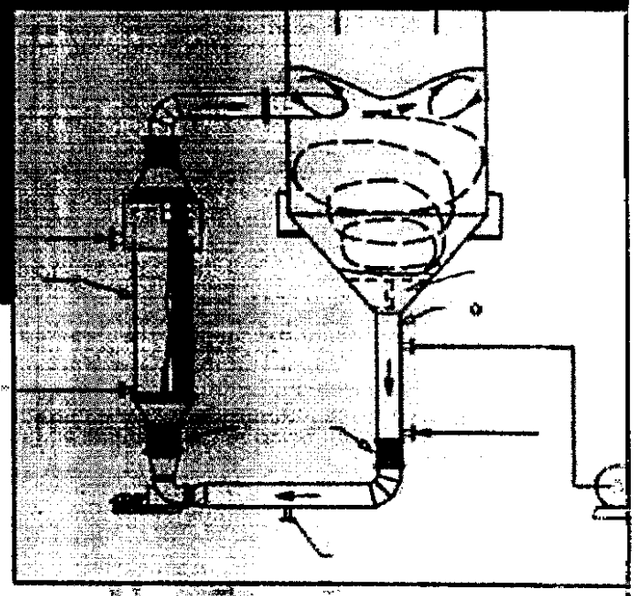

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Crystal Engineering and Particle Design for the Powder Compaction Process

1992, Vol. 18, No. 6-7 , Pages 677-721 (doi:10.3109/03639049209058558)

Peter York

Pharmaceutical Technology, School of Pharmacy University of Bradford, Bradford, BD7 1DP, UK

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Abstract

The historical background to the subject of crystal engineering of pharmaceuticals is briefly reviewed with reference to materials as diverse as insulin and direct compression tablet excipients. In the light of the limited scientific and practical information available on the topic two questions are posed -

Is it possible to prepare 'designer' materials with preferred processing, specifically compressive, properties giving optimised product characteristics?

How can such materials be efficiently manufactured?

In order to consider these questions, several important elements of data-base requirements are regarded as essential. These include knowledge of the crystalline phases of pharmaceutical solids, full understanding of the fundamental mechanical constants and moduli of particulate solids, and the relationships describing the influence of crystallographic structure on the mechanical properties of crystals and powders. At the same time the effects of preparation, pretreatment and processing effects on crystal structure, crystallinity and thermodynamic properties of powdered solids must be established.

The topics of material based compaction problems, property groupings of pharmaceutical powders with particular emphasis on crystal structure and mechanical properties are discussed. The review then considers recent and current research work examining the compaction behaviour of modified or engineered materials, prepared using alternative crystallisation conditions and the incorporation of low level additives. Specific examples include modern direct compression excipients, 'spherical' drug particle production and high purity lubricant (magnesium stearate) powders.

In conclusion, the future potential of the concepts of crystal engineering and particle design is considered in terms of predicting mechanical and processing properties from fundamental molecular and structural information.

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doi:10.1016/S0022-0248(99)00819-2 | How to Cite or Link Using DOI

Crystallization processes in pharmaceutical technology and drug delivery design

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Available online 21 April 2000.

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

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Corresponding author

Journal of Crystal Growth
Volume 211, Issues 1-4, 1 April 2000, Pages 122-136

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'organic fine chemical products as measured *in situ* using ultrasonic attenuation spectroscopy

J. Acoust. Soc. Am. Volume 109, Issue 1, pp. 274-282 (January 2001)

Issue Date: January 2001

Titre du document / Document title

Model identification and control of solution crystallization processes : a review

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Résumé / Abstract

The modeling of crystal quality (size, shape, and purity) is discussed. Numerical methods for the model solution are reviewed including collocation and Galerkin's method on finite elements. Measurement technologies for on-line crystal size distribution are presented. The difficulties with laser light scattering methods are discussed in detail. Parameter estimation is reviewed and new methods based on nonlinear optimization are presented. Sample calculations of parameters and their uncertainty from experimental data are included. The research literature covering control of continuous and batch crystallization is reviewed, and sample calculations of optimal cooling profiles for batch crystallizers are presented

Revue / Journal Title

Industrial & engineering chemistry research ISSN 0888-5885 CODEN IECRED

Source / Source

1993, vol. 32, n°7, pp. 1275-1296 (3 p.3/4)

Langue / Language

Anglais

Editeur / Publisher

American Chemical Society, Washington, DC, ETATS-UNIS (1987) (Revue)

Mots-clés anglais / English Keywords

Crystallization ; Modeling ; Identification ; Numerical simulation ; Process control ; Measurement method ; Parameter estimation ; State of the art ;

Mots-clés français / French Keywords

Cristallisation ; Modélisation ; Identification ; Simulation numérique ; Commande processus ; Méthode mesure ; Estimation paramètre ; Etat actuel ;

Mots-clés espagnols / Spanish Keywords

Cristalización ; Modelización ; Identificación ; Simulación numérica ; Control proceso ; Método medida ; Estimación parámetro ; Estado actual ;

Localisation / Location

INIST-CNRS, Cote INIST : 120 F, 35400003455970.0020

N° notice refdoc (ud4) : 4823593

Organic Process Research & Development

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Technical Note

Control of the Physical Form of Salmeterol Xinafoate

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Org. Proc. Res. Dev., 1999, *3* (5), pp 370-376
DOI: 10.1021/op990160z
Publication Date (Web): August 12, 1999

Abstract

Two approaches to the generation of particles of the phenethanolamine, salmeterol xinafoate, are discussed. To produce particles with good flow properties a fast cooling crystallisation process was developed which delivered salmeterol xinafoate as spherical agglomerates of microcrystals which had good powder flow characteristics and could be micronised efficiently in a fluid energy mill. In a radically different approach, salmeterol xinafoate was crystallised using supercritical carbon dioxide in the SEDS (solution enhanced dispersion by supercritical fluids) process. By means of this technique the solid state form, crystal habit, and particle size of salmeterol xinafoate could be effectively controlled.

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Crystal Growth & Design
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December 21, 1998.

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