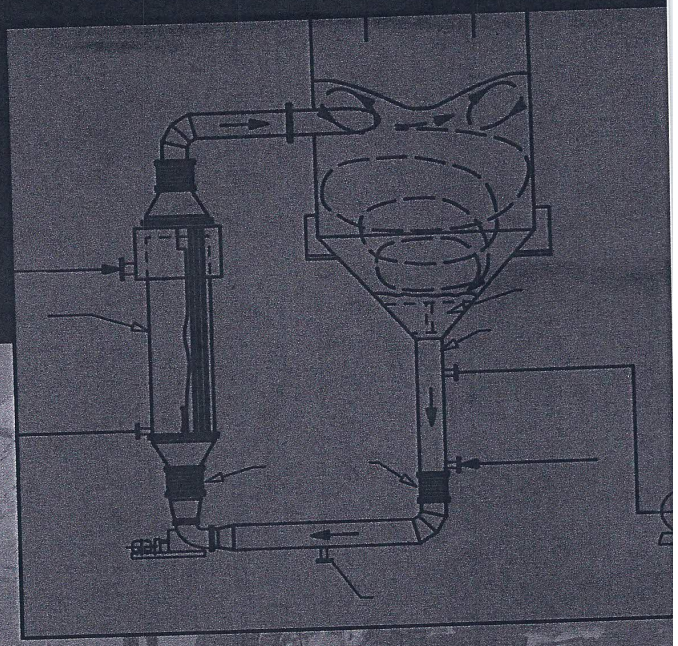
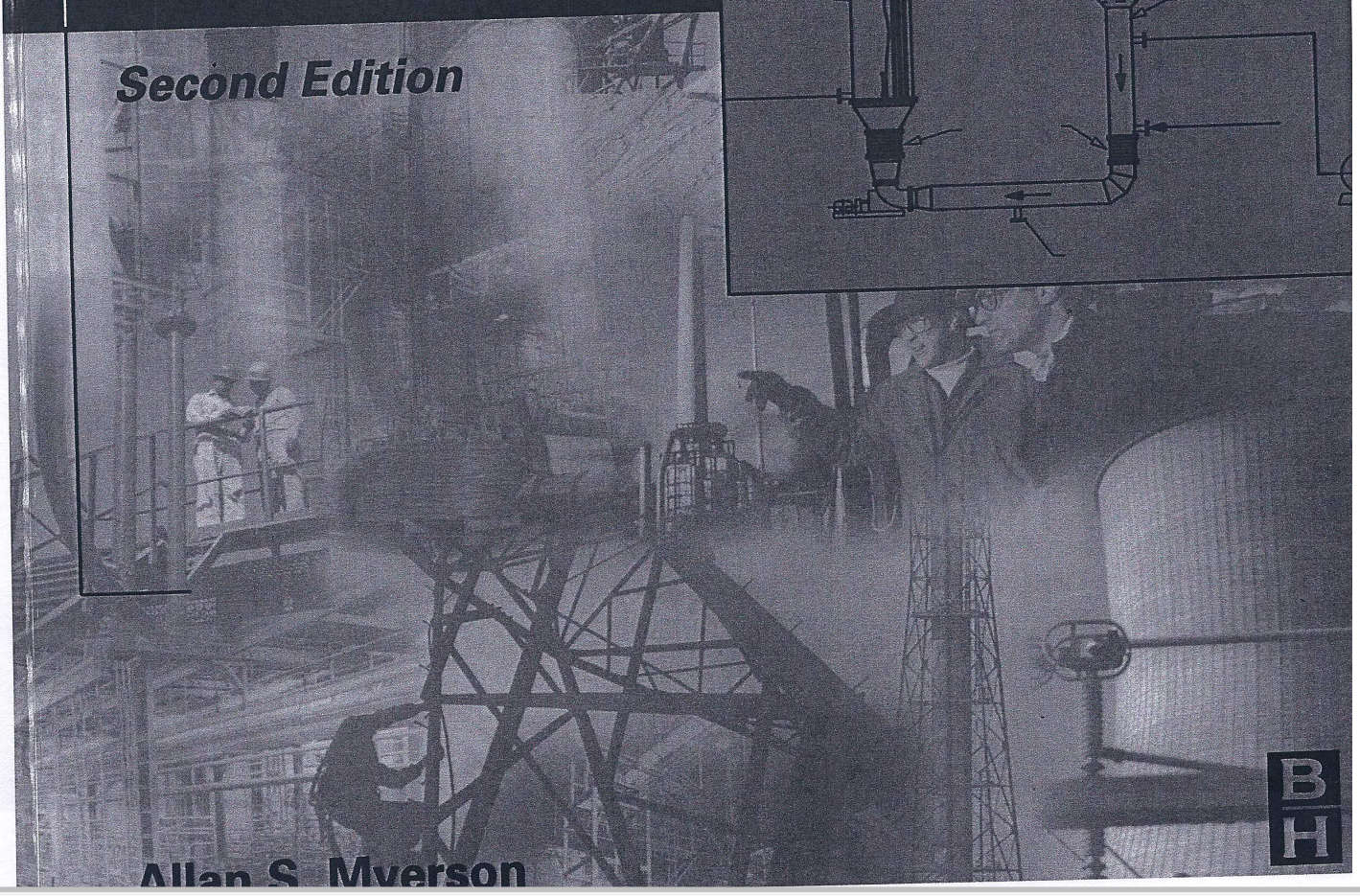
Handbook of Industrial Crystallization



Second Edition



Allan S. Myerson

Butterworth–Heinemann supports the efforts of American Forests and the Global ReLeaf program in its campaign for the betterment of trees, forests, and our environment.

Library of Congress Cataloging-in-Publication Data

Handbook of industrial crystallization / edited by Allan S. Myerson.—2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-1239-0804-3 (alk. paper)
1. Crystallization—Industrial applications. I. Myerson, Allan S., 1952-

TP156.C7 H36 2001
660'.284298—dc21 2001037405

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

The publisher offers special discounts on bulk orders of this book. For information, please contact:

Manager of Special Sales
Butterworth–Heinemann
225 Wildwood Avenue
Woburn, MA 01801–2041
Tel: 781-904-2500
Fax: 781-904-2620

For information on all Butterworth–Heinemann publications available, contact our World Wide Web home page at: http://www.bh.com

10 9 8 7 6 5 4 3 2 1

Printed in the United States of America

11

CRYSTALLIZATION IN THE PHARMACEUTICAL AND BIOPROCESSING INDUSTRIES

D.J. Kirwan and C.J. Orella

11.1. THE ROLE OF CRYSTALLIZATION IN BIOPROCESSES

The application of crystallization in the pharmaceutical industry directly parallels crystallization in other industries. There is a need to control particle size distribution through control of crystal growth versus nucleation and to control the purification achieved through crystallization. The latter requirement often requires different approaches and operating conditions than those for optimizing yield. Precipitation is commonly used in the pharmaceutical industry. [In this chapter, we shall use the term precipitation to mean the creation of a solid phase (crystalline or not) by the addition of an agent. Precipitation historically often referred to reactions resulting in the formation of a solid phase.] What is unique in the pharmaceutical industry is the chemical complexity of the entities that are crystallized. This complexity and chemical diversity impacts the thermodynamics (solubility and crystal structure) as well as the kinetics of crystallization. Several examples of the chemical diversity of products crystallized in the pharmaceutical industry are shown in Figure 11.1. In this chapter we will focus on low molecular weight pharmaceutical compounds while protein crystallization is discussed in Chapter 12.

The majority of these pharmaceutical compounds are between 100 and 1000 daltons, and exhibit a great diversity of functional groups ranging from ionic moieties to very lipophilic or hydrophobic groups. Thus, their interactions with one another, with solvents or anti-solvents, and with co-solutes and impurities in solution are very diverse. The solid phases (including polymorphs and various solvates) formed by such molecules are very poorly understood. The transformation rate between such solid phases may be kinetically limited. Therefore, solids of differing characteristics or even immiscible liquid phases, "oiling out," might be obtained from different modes of crystallization. This complexity is compounded by the limited experimental studies on such compounds from which generalizations can be made.

Owing to the final use of such compounds, strict control is required on their purity, crystal form and morphology, and particle size distribution (PSD). All of these characteristics are governed by the crystallization process. Obviously, control of purity is of great importance for products intended for human medicinal use in order to minimize exposure to anything other than the intended therapeutic agent. But, equally important is the PSD, which can dramatically impact the in-vivo dissolution of a drug, especially one that is hydrophobic and has limited solubility in aqueous solutions. This "bioavailability" can be strongly hindered if many larger particles are present, and is enhanced by the presence of predominantly smaller particles. Less obvious is that a change in crystal morphology (shape) or crystal structure can impact the bioavailability. In addition, these same properties of the crystals can play a dramatic role in the stability of the product; and, therefore, its purity at time of use. Whereas small particle size is generally good for bioavailability, it is a disadvantage to crystals subject to oxidation during processing or storage because of the greater surface area per crystal mass.

Crystallization also is employed as an intermediate purification step in many processes because of good separation factors per stage and its effectiveness at low temperatures for thermally labile compounds. Particle size and habit are important in these steps as well because of their effect on filtration or centrifugation rates. The influence of crystallization conditions on morphology and PSD, and, therefore, on the "de-liquoring" characteristics is often overlooked when laboratory work is conducted. However, this becomes much more important in pilot- or full-scale manufacturing where slow "de-liquoring" can result in low productivity and reduced stability.

There are several common problems encountered in the use of crystallization in the pharmaceutical industry; (1) the control of supersaturation (and PSD) in a batch crystallizer; (2) the effective use of seed; (3) efficient measurement of solubilities in multiple solvent systems to maximize purification and yield; and (4) identification and retention of the most stable polymorphic form.

As stated above, control of the crystallization or precipitation process is essential to obtain crystals of biochemical compounds having appropriate properties. The phenomena, techniques, and analysis discussed in many of the previous chapters: solubility and supersaturation, nucleation and growth kinetics, population balance methods, batch and continuous crystallizers, and factors governing crystal purity, habit and morphology are all relevant to the discussion of the crystallization of pharmaceuticals. We shall analyze the crystallization/precipitation of biomolecules in terms of these concepts.

11.2. SOLUBILITY AND THE CREATION OF SUPERSATURATION

Crystallization obviously requires the creation of a condition where the equilibrium solubility value is below that of the concentration of solute in the solution. Both growth and nucleation rates are dependent upon the departure of the solution conditions from equilibrium values. Further, the single-step yield achieved in a given crystallization is directly related to the equilibrium amount of solute remaining in solution, after nucleation and growth have relieved supersaturation. Crystallization can be accomplished by reducing the temperature as in a cooling crystallizer, by removing solvent as in an evaporative crystallizer, or by altering the composition of the solution by the addition of acid, base, miscible anti-solvents, or salts as in a precipitating crystallizer. These techniques also can be used in concert to accomplish the desired solubility reduction. While solubility is a thermodynamic variable not influenced by the mode of crystallizing; in precipitation crystallization, the mode of addition in a batch crystallizer can be used to create very different transient conditions of solubility and supersaturation.

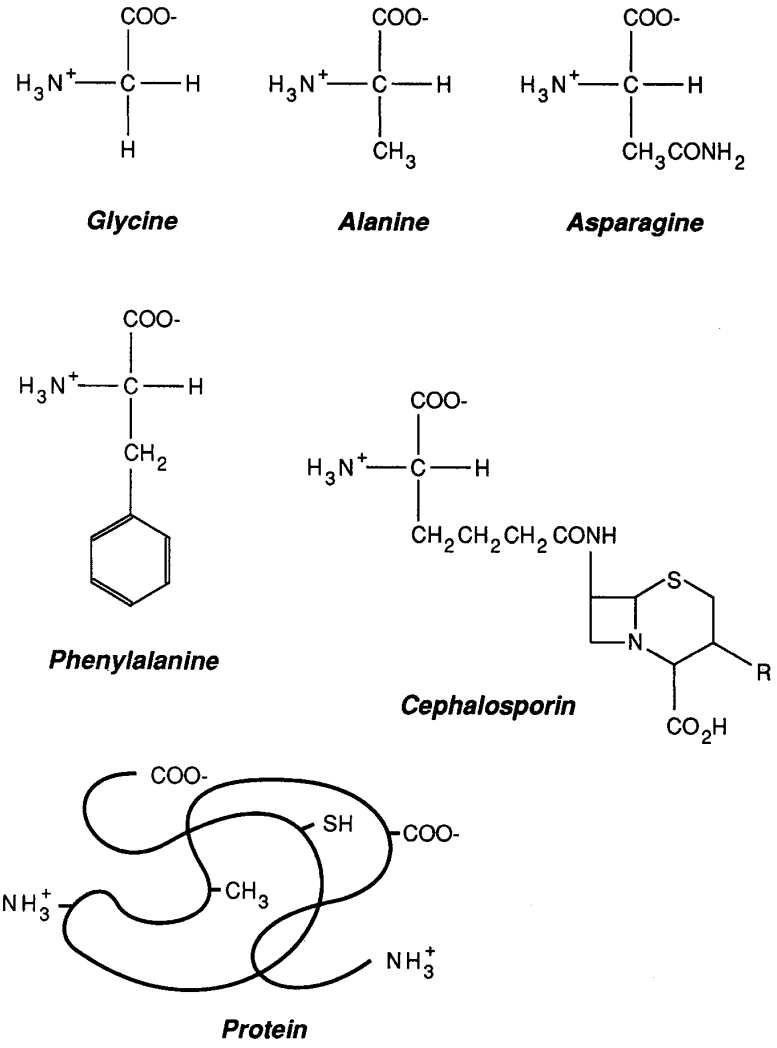


Figure 11.1 Molecular structures of various biochemicals.

That is, adding nonsolvent to the solute in solution is very different from the "reverse addition" of solution to nonsolvent and both are different from a rapid in-line blending to the final proportions.

11.2.1. TEMPERATURE EFFECTS ON SOLUBILITY

Most solutes, whether biological in nature or not, exhibit increasing solubility with increasing temperature. For example, Figure 11.2 shows the solubilities of citric acid and glutamic acid in water as a function of temperature. There can be complicating factors in the solubility behavior related to the actual form of the solute in the crystal phase and in solution as evidenced by the various forms of glutamic acid. For the case of citric acid a monohydrate exists below about 37 °C and the anhydrous form at higher temperatures. Although it can be useful to raise the temperature to increase the amount of material in solution for low molecular weight solutes prior to a crystallization step, such a practice may not be acceptable for temperature sensitive materials subject to thermal degradation. The operational temperature range is limited, therefore, by the freezing point of the solvent (solution) at low temperatures and by thermal degradation of the solute at higher temperatures. Low temperatures generally minimize solubility and favor stability but slow kinetics. As with citric acid anhydrous forms can only exist above some temperature. The particular form may greatly affect kinetics as well as solid stability and morphology.

11.2.2. pH EFFECTS ON SOLUBILITY

The acidic and basic salts of glutamic acid exhibit very different solubility behavior as can be seen in Figure 11.2b. The solubility of amphoteric compounds such as amino acids or antibiotics are strongly pH dependent because the predominant form existing in solution changes with the hydrogen ion concentration. Acid/base solution equilibria for a compound having one acidic and one basic group could be represented as

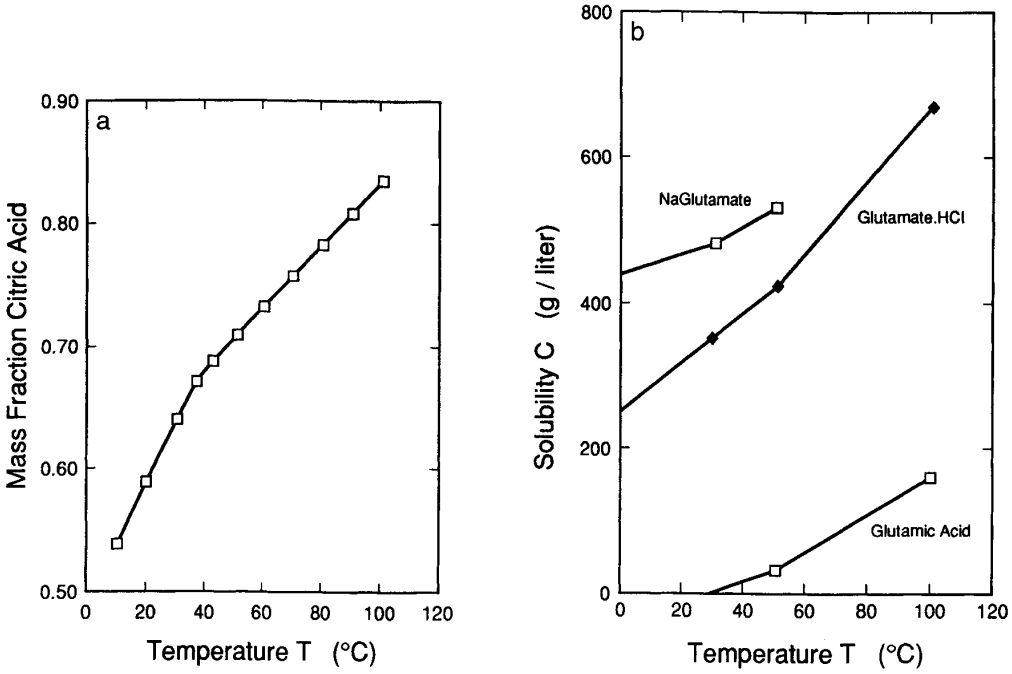


Figure 11.2 Temperature dependence of the aqueous solubility of (a) citric acid; and (b) glutamic acid. (Data from Samejima 1972.)

$$H_2A^+ \overset{K_1}{=} HA^{\pm} + H^+ \overset{K_2}{=} A^- + 2H^+ \tag{11.1}$$

The crystal-solution equilibrium relates to that between a particular form of the solute in solution and the same form in the crystalline phase. The isoelectric (zwitterionic) form usually exists in the crystalline phase over most of the pH range. Such compounds usually exhibit the lowest *apparent* solubility at their isoelectric pH since at other pH's some fraction of the solute exists in solution in the acid or base form. However, at very high acid or base concentrations, a salt, e.g., $H_2A^+Cl^-$, could be the crystalline form.

Figure 11.3 shows the solubilities (defined as total solute dissolved) of some β-lactam antibiotics as a function of pH. All of these compounds exhibit a minimum in their solubility, C^*_0, at the isoelectric point of the compound. At a pH significantly removed from the isoelectric point, the total (apparent) solubility is increased. The U-shape of the apparent solubility versus pH curve can be described by taking into account the acid-base equilibria of the antibiotic solute and assuming that the solute in the crystal is in the zwitterionic (isoelectric) form.

$$C^* = C^*_0\left(1 + \frac{k_1}{a_{H^+}} + \frac{a_{H^+}}{K_2}\right) \tag{11.2}$$

In Eq. (11.2) a_{H^+} is the hydrogen ion activity.

Further complications arise when the concentrations of salts formed at low or high pH exceed their solubility limit. Such an instance is shown in Figure 11.4 for *L*-isoleucine. At pH values above 2, the zwitterion is the dominant species in solution and in the crystalline phase. Upon addition of acid the solubility reaches a maximum at pH = 1 corresponding to the formation of the chloride salt. When the chloride ion is further increased whether from HCl or a chloride salt, precipitation of the chloride salt of leucine occurs (common ion effect.)

11.2.3. REDUCTION OF SOLUBILITY WITH ANTI-SOLVENTS

The use of miscible anti-solvent liquids to precipitate low molecular weight compounds is quite common in pharmaceutical processing as it often can rapidly create higher supersaturations as compared to cooling or evaporation. For example, aliphatic alcohols such as isopropanol can be added to aqueous solutions of amino acids to reduce their solubility by orders-of-magnitude. Of course, this results in dilution of the stream. For compounds soluble in organic liquids, water or an alkane (heptane) may be the precipitating agent. The precipitating agent usually can be recovered by distillation for re-use in these processes.

In Figure 11.5 are shown the solubilities of various amino acids at their isoelectric point as a function of isopropanol concentration (Orella and Kirwan 1989). Simple theories suggest that the effect of the alcohol is to reduce the dielectric constant and thereby reduce solubility (Kirkwood 1936). In fact, the solubility behavior is much more complex and significantly influenced by the nature of the amino acid side chain. For example, compare the behavior of phenylalanine (hydrophobic side chain) and asparagine (hydrophilic side chain) in Figure 11.5. Both hydrophobic and polar interactions between the mixed solvent and the various groups present on the molecule can occur. Correlation of the solubility behavior in these solutions using Margules, NRTL, or Wilson activity coefficient equations can be successful (Orella and

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.