International Union
of Pure and Applied Chemistry (IUPAC)

Handbook of
Pharmaceutical Salts
Properties, Selection, and Use

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Verlag Helvetica Chimica Acta · Zürich

WILEY-VCH

Weinheim · New York · Chichester
Brisbane · Singapore · Toronto

Foreword

The surprise with this very first book on Pharmaceutical Salts is that it has appeared so late. Problems concerning the physical form of drug substances have been with us for nearly 10 years at the interface between the disciplines essential to the development of new drugs: chemical process development, analytical chemistry, pharmaceutical sciences, pharmacokinetics, toxicology, and clinical studies. These problems have for many years figured prominently in the nightmares of industrial chemists and pharmacists, not to mention those of their quality assurers, regulatory writers, and project managers.

The answer to the question 'Why has this book appeared so late?' may perhaps have something to do with the fact that pharmaceutical crystal and powder engineering should be founded on crystal and powder science. But such a science does not yet exist as a single concept since knowledge in this field is scattered among different disciplines such as crystallogenesis, crystallography, the physical chemistry and thermodynamics of multiphase systems, powder flow characteristics and mechanics, piezo-electrostatics, the physics of complex micellar systems, *etc.*

Academics, whose vocation it is to edit this type of book, therefore, heard about the specific problems related to pharmaceutical crystal and powder engineering fairly late from industrial colleagues who are often reticent to air their difficulties in public. Thus, it is only now that efforts at unification have begun.

This book is perhaps an attempt to found such a science, but in the sense of a market-driven effort bringing together contributions from academics and industry. The book deals not only with the problems raised by salt selection strategies and process scale-up, but also with the industrial property and regulatory aspects at the heart of the highly regulated pharmaceutical industry.

I cannot end without emphasizing that further exploration is required in areas where theoretical and practical knowledge is still lacking. For instance, the mechanisms involved in crystallogenesis need to be elucidated since we still cannot predict the solubility of a given salt. Will it be oily or solid? Will it show several polymorphs? The crystal chemistry of crystalline surfaces – regulated by specific interactions between functional groups exposed on the surfaces and very small amounts of impurities – impacts with other factors on the preferential development of one face rather than another, but is still in limbo. We still know nothing precise about the factors governing the electrostatics of drug substances. We are still unable to predict the relations between crystalline forms and the compressibility of powders. I hope that the preliminary basis of an answer to some of these questions will be found in a future version of this book.

Prof. Bertrand Castro
Director of the Chemical Development
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Preface

The origin of this book goes back to a proposition made by one of us (*C. G. W.*) at a meeting of the *Medicinal Section of Division VII* of *IUPAC* to write useful handbooks for medicinal chemists. Among the topics suggested, the preparation of pharmaceutically acceptable salts was rapidly considered as important and timely. As a matter of fact, an estimated half of all drug molecules used in medicine are administered as salts. The salt formation of drug candidates has been recognized as an essential preformulation task, as the selection of a suitable salt prior to the initiation of dosage form development has become a decision point in the netplans of the Preclinical Phase of modern drug development. Surprisingly, however, a chemist in search of a book dealing with the preparation, significance, and selection of pharmaceutically active salts will fail to find one, and also the scientific literature on this topic is rather limited and scattered across many journals and patents. On the other hand, the majority of medicinal chemists working in the pharmaceutical industry are organic chemists whose main concern is to design and to synthesize novel compounds as future drug entities. While they focus on this challenging primary goal, salt formation is often restricted to a marginal activity with the short term aim of obtaining nicely crystalline material. Moreover, chemists are not explicitly trained in the various aspects of pharmaceutical salts and their inherent opportunities. By bringing together the necessary theoretical foundations and a lot of practical experience, the objective of the present book is to fill this long felt gap in the pharmaceutical bibliography.

A concise introduction reviewing the various objectives pursued in forming salts is followed by contributions presenting the theoretical background of salt formation: dissociation and ionic equilibria, solubility and dissolution (*Chapt. 1* and *2*), basics and the evaluation of solid-state properties (*Chapt. 3*), safety and biopharmaceutical as well as pharmaceutical-technological aspects (*Chapt. 4* and *5*). *Chapt. 6*, *7*, and *8* reflect the practice of salt formation in an industrial research and development environment. They describe salt selection strategies, industrial large scale aspects of salt production, and the significance of salt formation in industrial processing. The involvement of authorities is dealt with in *Chapt. 9* and *10*, which are devoted to patent and regulatory issues, respectively. Addressing the practitioners at the lab bench, the last chapters of the book feature practical examples of preparation of salts presented in the style of model procedures (*Chapt. 11*) and a comprehensive annotated compilation of the individual salt-forming acids and bases with their relevant properties (*Chapt. 12*), followed by an *Appendix* containing tables with the acids and bases sorted alphabetically, and by pK_a values and supplemented with other useful facts and data.

Altogether, these chapters reflect the multidisciplinary character of formation and selection of suitable salt forms of drug substances. An attempt is made to establish an up-to-date guide and source of information not only serving medicinal chemists, but also all the other scientists who are involved in the research and development of drugs and their pharmaceutical dosage forms.

A book dealing with such a truly interdisciplinary subject relies on contributions of a well-coordinated team of authors from industry and academia representing the various disciplines involved in the process of drug-salt formation and selection for pharmaceutical products in an industrial environment. The editors wish to thank all the authors for their engaged cooperation and their patience during the revision procedures that were necessary to arrive at this comprehensive and well-balanced handbook. Thanks are also due to *F. O. Ajayi*, *H. Asche*, and *C. Hoff*, who accepted to contribute to the book in the very last moment. The editors wish to acknowledge the smooth and excellent cooperation with *Verlag Helvetica Chimica Acta* in the preparation of the volume: *Thomas Kolitzus*, Assistant Editor, for his patient and attentive handling of all the practical details of the editorial process, and Dr. *M. Volkan Kisakürek*, Managing Director and Editor-in-Chief, for his inspiration and for his untiring scrutiny in bringing his considerable comprehensive knowledge into this project. Thanks are also expressed to *Larry Lesko* of the U.S. Food and Drug Administration for establishing helpful contacts. One of the editors (*P. H. S.*) gratefully acknowledges the support granted by *Novartis AG*, Basel, and the permission to use their Scientific Library facilities.

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Strasbourg and Freiburg, January 2002

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Introduction

by **Camille G. Wermuth** and **P. Heinrich Stahl**

When the first 'vegetable alkalis', those nitrogen-containing bases later termed alkaloids, were extracted from plant materials, they were isolated and purified as well-crystallizing salts. In contrast to the free bases, the salts were found to be water-soluble and also more stable. Such properties qualified the salts of these biologically highly active compounds as the preferred forms for use as therapeutic agents (morphine hydrochloride, atropine sulfate, quinine sulfate, pilocarpine nitrate, codeine phosphate, to name only a few of them). If we turn to endogenous biological agents, we see that almost all neurotransmitters, which are biogenetically derived from amino acids, are also nitrogenous bases able to form salts. Nitrogenous functional groups are present in many synthetic drugs that mime the neurotransmitters and account for the old adage 'no medicaments without nitrogen'. This assertion is certainly exaggerated as it excludes therapeutic agents such as the steroids, the prostaglandins and their derivatives, also the fibrates and acidic anti-inflammatory drugs like aspirin, diclofenac, and ibuprofen. Many of these classes of drugs contain a carboxylic function, and, therefore, salt formation can evidently also be considered.

An estimated half of all the drug molecules used in medicinal therapy are administered as salts, and salification of a drug substance has become an essential step in drug development. The solid-state properties of a drug, as well as its properties in solution, can be modified by salt formation. Therefore, the search for a suitable salt form is important, and salt selection may have far-reaching consequences and can open new opportunities. In modern pharmaceutical research and development, a variety of objectives are pursued in the formation of salts. The most important of these objectives and points to be considered, as they become significant along the pathway of the development of a new drug, are reviewed here.

Improving Solubility

Before undergoing pharmacological evaluation and other preclinical studies, synthetic or natural active principles must usually be dissolved. In the majority of cases, the objective is to render the compound water-soluble.

Sufficiently high solubility in H_2O eases molecular pharmacology screening for drug candidates. Thus *in-vitro* studies (receptor binding, enzyme inhibition, cell cultures) and studies with isolated organs are facilitated. The common procedure in testing practically insoluble compounds in such assays is to prepare stock solutions in an organic solvent (DMSO, polyethylene glycol, EtOH, *etc.*) and to proceed to appropriate aqueous dilutions. In doing so, there is often the risk that the compound can precipitate during dilution, and precipitation may even go unnoticed if the assay is performed in plastic tubes where the precipitate can adhere to the tube wall.

Most organic acids and bases are only poorly soluble in H_2O, whereas many of the corresponding salts render the drug substances ionized in H_2O, and, as a consequence, water-soluble. Salts that are soluble in H_2O are also ideally suited for the preparation of injectable sterile aqueous solutions. Fast dissolution of the active principle contained in solid dosage forms, *e.g.*, for immediate-release tablets and hard-gelatine capsules is also dependent on the aqueous solubility.

Considering *in-vivo* testing, solubility in H_2O facilitates all studies in which parenteral administration is required. In pharmacokinetics, reliable determination of absolute peroral bioavailability is possible in comparison with the amount administered intravenously, because a dose entering the system by this parenteral route is a precisely known reference. Aqueous solubility becomes particularly important in acute and in chronic toxicity studies where the gavage of the animal with an insoluble compound always leaves some doubts as to whether the molecule under study is non-toxic or just incompletely absorbed.

Finally, one has to remember that the pharmacological effects of hydrophilic compounds are much more comparable from one animal species to the other than those of lipophilic substances [1].

On the *therapeutic level*, the major interest of water-soluble drugs resides in the possibility of intravenous administration. Solubility in H_2O represents an indispensable requisite for drugs in emergency treatments permitting therapeutic plasma levels to be reached within one minute. This route is imposed when the oral route is excluded, as in patients undergoing surgery or lying in coma. Finally, several other pharmaceutical dosage forms are based on water-soluble active agents: Apart from parenteral injections and infusions, there are nasal drops and eye-drops, syrups for oral administration, *etc.* Water-soluble drug entities should *a priori* also be less toxic. Thanks to their easier renal clearance they have a lesser propensity for accumulation in the organism and thus avoid an overload of the hepatic microsomes responsible for phase-one and phase-two metabolism (*e.g.*, hydroxylation, conjugation).

However, one must keep in mind that making a drug molecule more water-soluble can also be a drawback. There is a general tendency that the more water-soluble a compound is, the more diffusible it is. This causes it to be less specific in its activity, and more liable to rapid elimination and, therefore, shorter acting.

It may also be pointed out here that the simultaneous presence of an ionized hydrophilic group on one end of a nonpolar lipophilic chain confers to the molecule an amphiphilic, 'soap-like' character. Such compounds can show a detergent behavior towards numerous membranes, and, in particular, they can induce hemolysis of erythrocytes.

Obtaining a Solid Aggregation State and Increasing Chemical Stability

Some of the bio-active bases are oily or low-melting solids and are liable to oxidation. Appropriate salt formation can yield products that are crystalline, easy to purify, more resistant towards oxidation, and, hence, generally have a longer shelf life.

Polymorphism

Selecting a salt suitable for a certain route of administration or a particular dosage form of a drug substance requires that all the relevant solid-state properties of the salt candidates be thoroughly investigated. Polymorphism and pseudopolymorphism are frequently critical points in determining preferences for one salt to another. Polymorphism is a widespread phenomenon observed in more than half of all drug substances [2]. The choice of the most appropriate solid-state form is of considerable importance. Here, the most prominent aspect to be considered is stability. First of all, this means thermodynamic stability of the solid-state form, but also chemical stability and reactivity (*e.g.*, compatibility, *i.e.*, the stability in the presence of excipients) may vary from one polymorph to the other. In most cases, the modification thermodynamically stable at room temperature is the most appropriate one. This is the solid-state form into which, sooner or later, all other forms will eventually transform. However, high-energy mechanical processes such as milling or compression can induce transformation to a form not stable at room temperature. Such transformation processes may lead to either another crystalline form or result in an amorphous material and do not necessarily run to completeness. Several techniques have been proposed and are applied to determine the thermodynamically stable form. These include measurement of solubility, equilibration of a mixture of forms in suspension and observing any changes of their mass ratio over time, thermoanalytical data such as the melting points of the pure polymorphs or the behavior of eutectic mixtures at reduced temperatures, and enthalpy–temperature diagrams [3]. A variety of techniques is at hand for characterizing and identifying polymorphs: X-ray powder diffraction, IR and *Raman* spectra, solid-state NMR, and various temperature scanning techniques.

Salt Formation as a Means to Industrial Processing

Salt formation is an established means for the isolation and purification of substances. This applies not only for the final step in the synthesis of a drug. Also, along a synthetic route, salt formation can afford an economic means to separate an intermediate from side products.

As with crystallization in general, also crystallization of salts is associated with the realm of polymorphism. Crystallizations in the pharmaceutical industry are mostly carried out batch-wise. The techniques used are cooling, evaporation, drowning-out, and reaction crystallization. Normally, the process will be carried out as unseeded crystallization, relying on spontaneous nucleation and the modification it entails. In a large number of cases, this will be an unstable modification, as is predicted by *Ostwald*'s rule of stages. However, an unstable form is prone to a phase transformation either while the product is still in suspension, during workup, or even during storage. The latter case is not acceptable, since this would question reproducible product properties.

The growing number of chiral drugs requires efficient methods for producing these compounds in an enantiomerically highly pure form. Despite the available alternative techniques, optical resolution *via* diastereoisomeric salt formation remains the most widely used method for preparing pure enantiomers. Enantiomers can be separated from racemic drug substances or intermediates along synthetic routes by fractional crystallization of suitable diastereoisomeric salts.

Adaptation to the Therapeutic Use and Pharmaceutical Dosage Form

For a new chemical entity considered for development as a drug candidate, it is important to achieve optimal physical and chemical stability. The form to be chosen must be chemically and physically compatible with excipients and adjuvants in a pharmaceutical formulation, it must be able to resist the micro-environmental and macro-environmental factors during processing and storage, and must have properties compatible with the technology applied in the manufacture of the corresponding dosage form.

Although a substantial aqueous solubility is generally a highly appreciated quality for a drug substance, there are certain circumstances in which liposolubility may be desirable. Highly ionized drug substances usually lack sufficient lipophilicity for good penetration of biological membranes. Formation of salts with lipophilic salt-forming counter-ions may be a means of obtaining better absorption of such drugs. The design of implants, sustained-release oral formulations, dermal and transdermal products can benefit from use of less soluble or more lipophilic salts.

Safety Aspects and Modification of Biological Properties

'*Nil nocere*' is one of the oldest and the topmost requirements for a therapeutic treatment. For this reason, the step next to the detection of a desired biological activity of a new chemical entity is to initiate toxicological and pharmacological investigations on the safety of a potential drug candidate. Because the salt form of an active compound may modify its biological performance *in vivo*, toxicological and safety considerations also play a role in salt selection.

Pharmacokinetic properties may be modified by choosing salts with different solubilities. Oral absorption may so be accelerated or retarded as compared to a reference form. Selection of a sparingly soluble salt can be an alternative to complicated release retardation by technological measures.

With proper choice of a pharmacodynamically active cation or anion as the counter-ion for an ionizable drug molecule, it is sometimes possible to achieve a synergistic effect to counteract side effects or to facilitate the detoxification of the main active principle.

Finally, salt formation sometimes offers solutions to biopharmaceutical problems such as suppression of pain on injection, avoidance of local irritation, taste-masking (bitterness *etc.*) or avoiding causticity (*e.g.*, corrosion of manufacturing equipment).

Extension of the Patent Protection

As already mentioned above, the salt form, as well as a particular solid-state form of a drug substance, can influence a variety of important properties, *e.g.*, the solubility and rate of dissolution, the chemical stability or compatibility with excipients, *etc.* A new salt of a drug substance already in use may, for example, allow a simpler manufacturing procedure of the dosage form or may be more stable than the salt hitherto in use; it may have a profile of properties that make it suitable for a new route of administration, or the new salt may even open a new field of therapeutic application. Any one of such advantages may, therefore, constitute new claims for an extension of proprietary rights. The same can apply for the detection of a new polymorph.

Regulatory Considerations

Along the route of a new drug product to the market, the final step is to obtain marketing approval from the regulatory authorities. Nevertheless, the regulatory aspects need to be taken into account right at the initiation of a development project involving a new salt. A new salt of an approved drug substance is, in principle, a new chemical entity which would require a full dossier to be submitted for marketing approval. However, the regulatory treatment of new salts of approved drugs may rely in some details on the facts already known about the active entity of the new salt within its prior therapeutic use.

Both, different polymorphs and different salts, and again any polymorphs of those, may alter the performance of a drug. For this reason, the regulatory authorities require an exhaustive search for polymorphic forms of a drug substance. The manufacturer is required to make a substantiated choice for one of the forms, or a defined mixture of forms. Changes in the polymorphic form of the batches produced are seen as indicative of changes in the production process, also requiring the reproducible crystallization of a certain solid-state form.

Salt Selection

Many aspects need to be considered when a salt of a drug substance is selected for the development of a drug candidate. Such a decision must be thoroughly prepared by well-timed and coordinated investigations followed by the intelligent weighting and comparison of the available alternatives. The points addressed above make it clear that all the various disciplines that are involved in the drug development process should likewise participate in the salt selection. Moreover, a rational strategy should be followed in order to guide the selection process in an economic way, and the final decision should be made transparent and acceptable to all units involved downstream the development path. The present-day situation of industrial drug development makes the salt-decision an almost irreversible one, because a change of the salt form during later stages of the development of a drug candidate entails high additional expenses and loss of valuable time to be spent for repeating preparative work and numerous costly investigations. This fact, in addition, underlines the importance of a careful selection of the most suitable drug salt.

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Chapter 3

Evaluation of Solid-State Properties of Salts

by **Danielle Giron*** and **David J. W. Grant**

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1. Introduction

The properties of the solid state are critical factors that determine the choice of an appropriate salt form of a drug molecule, especially because most pharmaceutical products are solids, in particular, tablets and capsules. A satisfactory salt form of a drug molecule must be technically feasible and suitable for full-scale production and its solid-state properties maintained batchwise as well as over time [1] [2]. These considerations add to, and do not replace, considerations of pH–solubility profiles that depend on the pK_a value(s) and the solubility of the unionized drug, as described in *Chapt. 2*, in guiding the choice of salt form. The present chapter focuses on those characteristics of the solid state that depend on the crystal structure. Within the crystal, the drug molecule, in ionized form(s), interacts with other drug ions, with the oppositely charged counter-ions, and with solvent molecules, if present in the crystal lattice [3 – 5].

Comparisons of the solid-state properties of different salt forms of a drug molecule may be quite complicated, especially when the salt form(s) exist as different solid phases. Different solid phases may arise during crystallization and pharmaceutical processing and include polymorphs, amorphous forms, and solvates (often termed pseudopolymorphs). Polymorphism is often defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice [3 – 6]. Amorphous solids, unlike polymorphs, are not crystalline [7] because the arrangement of the molecules is disordered. Solvates contain molecules of the solvent of crystallization in a definite crystal lattice [8]. Solvates, in which the solvent of crystallization is H_2O, are termed hydrates. Because H_2O is a constituent of the atmosphere, hydrates of drugs may be formed rather easily, especially with salts, on account of the dipolar interactions, co-ordination, and sometimes hydrogen-bonding between the H_2O molecules and the constituent ions. Many compounds can exist as crystals with different morphologies (habits, shapes) by preferential growth of certain crystal faces, the crystal lattice arrangement remaining unchanged. *Fig. 1* summarizes various possibilities of crystallization of a molecule, as stated by *Haleblian* [6].

Because effects associated with temperature, pressure, humidity (H_2O and its vapor), solvents, and excipients are involved in processing solid forms of the active drug molecule, it is important to understand the detailed parameters relevant in the choice of its appropriate salt form(s). Furthermore, in the manufacture of the drug substance, it is necessary to know the thermodynamic relationships between drug substance and solvent(s), and the factors that govern the final crystallization process for the reproducible manufacture of the required solid phase of the drug.

Different salt forms, polymorphs, and solvates have different values of virtually all the physico-chemical properties of the solid state [5 – 10] [18]. These properties have been classified as crystal packing, bulk thermodynamic, spectroscopic, kinetic, surface, and mechanical properties [9].

The most relevant of these properties are molar volume, density, refractive index, color, conductivity, heat capacity, melting and sublimation temperatures, solubility, dissolution rate, hygroscopicity, stability, reactivity, crystal habit,

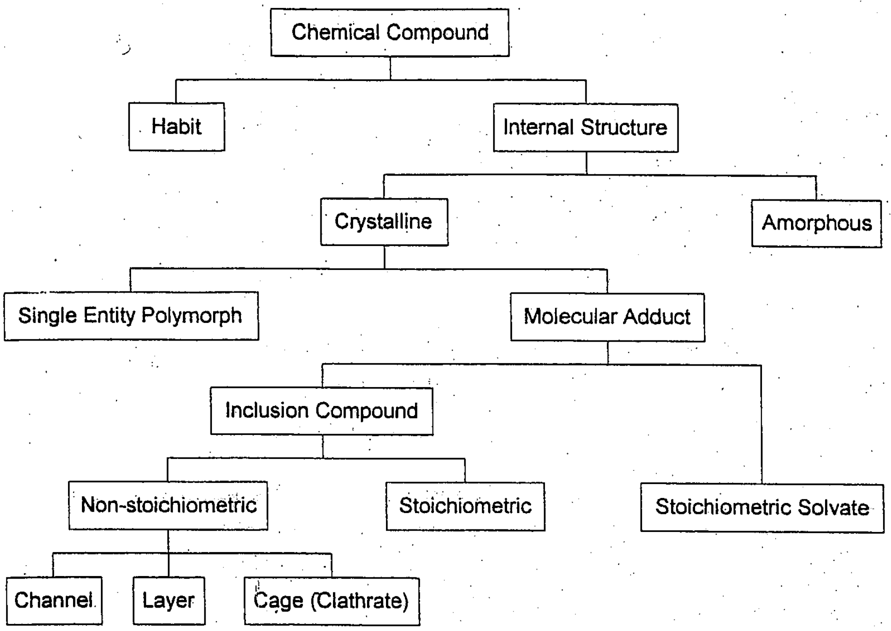
Chemical Compound
Habit
Internal Structure
Crystalline
Amorphous
Single Entity Polymorph
Molecular Adduct
Inclusion Compound
Non-stoichiometric
Stoichiometric
Stoichiometric Solvate
Channel
Layer
Cage (Clathrate)

Fig. 1. *Possible solid phases of a chemical compound according to* Haleblian (modified [6])

crystal hardness, and compactibility. Of major concern are the influences of salt form, polymorphism and pseudopolymorphism on therapeutic efficacy, toxicity, and bioavailability [5] [6] [10–13] and on pharmaceutical processing [14] [15] of pharmaceutical products. Polymorphism and pseudopolymorphism are known to influence every stage in the manufacture and storage of pharmaceuticals. The *International Conference on Harmonization* (*ICH*) requires investigations and analytical procedures for new drug substances and pharmaceutical products according to a decision tree [16] [17]. The polymorphism and pseudopolymorphism of many pharmaceuticals have been reviewed [18–20].

2. Thermodynamic Background

2.1. Phase Diagram of a Single Component Exhibiting Polymorphism

Polymorphism, as defined above, recognizes that the polymorphs (often referred as crystal modifications) of a given substance possess different crystal structures and are therefore distinct phases of that substance, which constitutes a single component. In the liquid state (*i.e.*, melt or solution) or gaseous state, polymorphic differences disappear, because the structure of the solid state no longer exists. In the solid state, the atoms, molecules, or ions may be arranged in one of the fundamental crystal systems: triclinic, monoclinic, orthorhombic, tetragonal, trigonal, hexagonal, or cubic. Each crystal system is characterized by unique relationships existing among the crystal axes and the angles between them. The most widely known example of polymorphism is the element carbon, which can exist in the form of graphite (hexagonal), diamond (cubic), or as fullerenes (C_{60} and C_{70}). Among the different forms of paracetamol, one is a monoclinic polymorph and another is an orthorhombic polymorph. Three forms of cortisone acetate are orthorhombic and two forms are monoclinic.

The relationships between different phases, *e.g.*, polymorphs, of a substance are governed by *Gibbs*' phase rule:

$$P + F = C + 2 \tag{1}$$

where C is the number of components, P is the number of phases that exist in equilibrium, and F is the number of degrees of freedom, *i.e.*, the variance, of the system. The integer, 2, in *Eqn. 1* recognizes that two of the variables, namely temperature and pressure, are not associated with the relative amounts of the components, in contrast to the other variables, termed concentrations, which do reflect the relative amounts.

In the case of a single substance, such as a drug, exhibiting polymorphism, C equals unity. If one phase, *i.e.*, one polymorph, is present, $P = 1$; therefore, $F = 2$. *Eqn. 1* reveals that the variance, $F = 2$, meaning that both temperature and pressure may be varied without changing the number of phases. If two phases, *i.e.*, two polymorphs, are in equilibrium, $P = 2$, in which case the variance $F = 1$, meaning that, at a chosen pressure, usually atmospheric pressure, the temperature of the system is fixed at the so-called transition temperature, T_t. The conclusion from the phase rule is that only one phase can exist at any given temperature and pressure, except at the transition temperature at a defined pressure, usually atmospheric, in which case two phases, *e.g.*, polymorphs, exist in equilibrium.

The process of transformation of one polymorph into another is a phase transition, which, according to the phase rule, may occur at a given pressure by changing the temperature. If the phase transition is reversible, the two polymorphs are *enantiotropes*, and the energy of the transition on heating is endothermic. If the phase transition is irreversible, the two polymorphs are *monotropes*, in which case only one form is stable whatever the temperature, and the transformation of the unstable form to the stable one is exothermic. For kinetic reasons, an unstable form may exist for a time outside the region assigned by the phase diagram and the phase rule, and is then termed a *metastable* form. *Fig. 2* presents the two types of phase diagram of a single component with polymorphic behavior, *a*) representing enantiotropy, and *b*) representing monotropy.

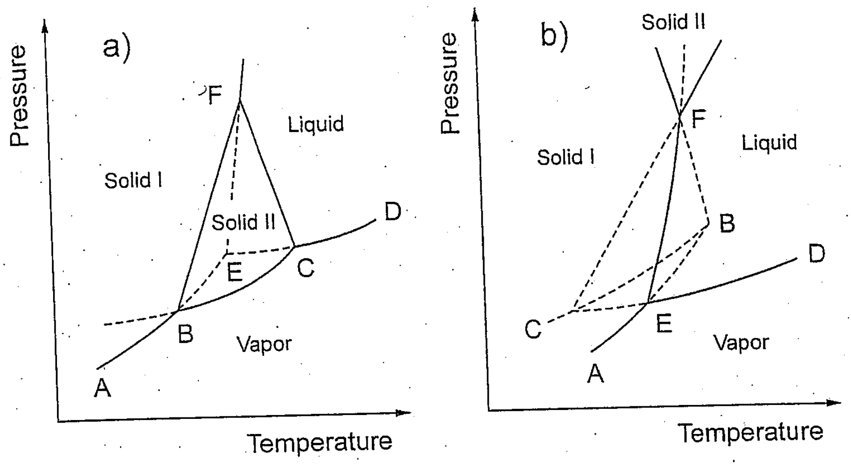
Pressure
a)
F
Liquid
Solid I
Solid II
D
E
C
B
Vapor
A
Temperature
Pressure
b)
Solid II
F
Solid I
Liquid
B
D
C
E
Vapor
A
Temperature

Fig. 2. *Phase diagram of pressure* vs. *temperature for a single compound, showing* a) *enantiotropy, and* b) *monotropy* (after S. C. Wallwork, D. J. W. Grant, 'Physical Chemistry for Students of Pharmacy and Biology', 3rd edn., Longman, London, U. K., 1977, p. 42)

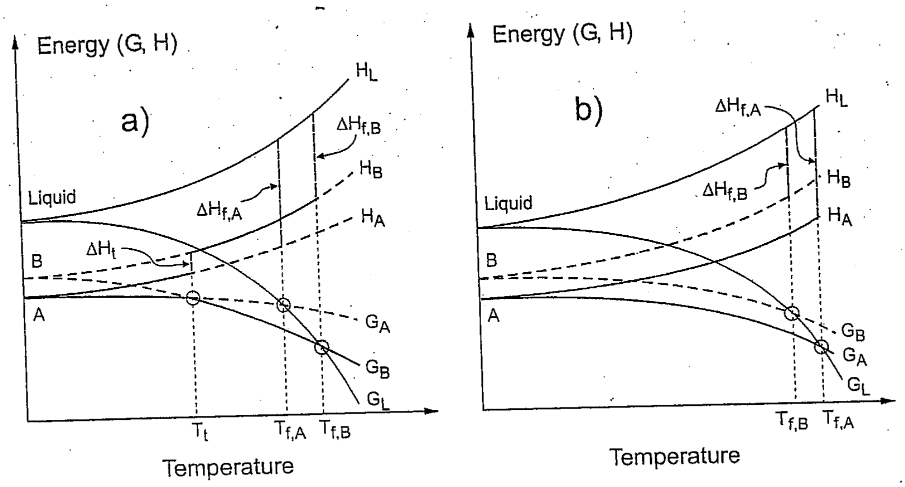
Energy (G, H)
a)
H_L
$\Delta H_{f,B}$
H_B
H_A
Liquid
$\Delta H_{f,A}$
ΔH_t
B
A
G_A
G_B
G_L
T_t
$T_{f,A}$
$T_{f,B}$
Temperature
Energy (G, H)
b)
$\Delta H_{f,A}$
H_L
$\Delta H_{f,B}$
H_B
H_A
Liquid
B
A
G_B
G_A
G_L
$T_{f,B}$
$T_{f,A}$
Temperature

Fig. 3. *Energy diagrams showing plots of enthalpy,* H, *and* Gibbs *free energy,* G, vs. *temperature,* T, *for the solid and liquid phases of a single compound, showing* a) *enantiotropy, and* b) *monotropy* (after [22])

The ability of a system to perform work and to undergo a spontaneous change at constant pressure is measured by the *Gibbs* free energy, G, which is given by

$$G = H - TS \tag{2}$$

In general, the thermodynamic relationship between two polymorphic phases is represented by plotting the *Gibbs* free energy as a function of temperature for each form (*Fig. 3*). If the two curves intersect below the melting point of each polymorph, a reversible transition occurs at the temperature T_t of the intersection. At temperatures below T_t, polymorph A has the lower free energy and is, therefore, the thermodynamically stable form, while at temperatures above T_t polymorph B is stable. In the case of monotropy, the higher melting form is always the thermodynamically stable form.

Burger [21–23] proposed to plot energy diagrams (*Fig. 3*) showing the free energy and the enthalpy as functions of temperature. As shown in *Figs. 3,a* and *b*, a notable difference between enantiotropy and monotropy is the melting enthalpy of the higher melting form. In the case of enantiotropy, the *higher*-melting form has the *lower*-melting enthalpy. In the case of monotropy, the *higher*-melting form has the *higher*-melting enthalpy. A detailed discussion of phase diagrams has been presented by *Toscani* [24].

2.2. Phase Diagrams of Binary Mixtures

Solvates show interesting contrasts, because there are two components, the host and the solvent. The phases to be considered are the solvate, the unsolvated host, and the solvent. In the more complex cases of several solvates, the different phases with different compositions have their respective domains of stability. *Fig. 4* shows some typical phase diagrams of binary mixtures. When manufacturing salts, the possible occurrence of such phase diagrams needs to be considered. Besides the pure compound (*i.e.*, the salt), eutectic mixtures between the acidic and basic components can result. Congruent or incongruent melting of the solvate (or of the salt) may be observed (*Fig. 4,d* and *e*), leading to a mixture of the two components after melting. For example, the eutectic between the anhydrous form and the hydrated form of terpin has been described [25]. Furthermore, polymorphism can occur between solvated forms [18].

Several hydrates of a substance may be possible and stable at ambient conditions. For example, ouabaine was obtained as an anhydrous form, dihydrate, trihydrate, tetrahydrate, octahydrate, and even as a nonahydrate, depending on the conditions of manufacture [6].

Because drug substances are usually dried before analysis, the crystallization of a solvated form is often ignored or overlooked, especially if the crystals had been obtained by fast cooling. In this respect, the water activity in organic solvents is the critical parameter for the formation of hydrates [26–28]. By drying hydrates or other solvates, metastable forms are frequently obtained. Because process development aims at a robust process, it is mandatory to evaluate the tendency of solvate formation during the crystallization procedure. If solvent mixtures, *e.g.*, aqueous alcohols, are used, the formation of the anhydrous salt, a solvate, and hydrate(s) have to be con-

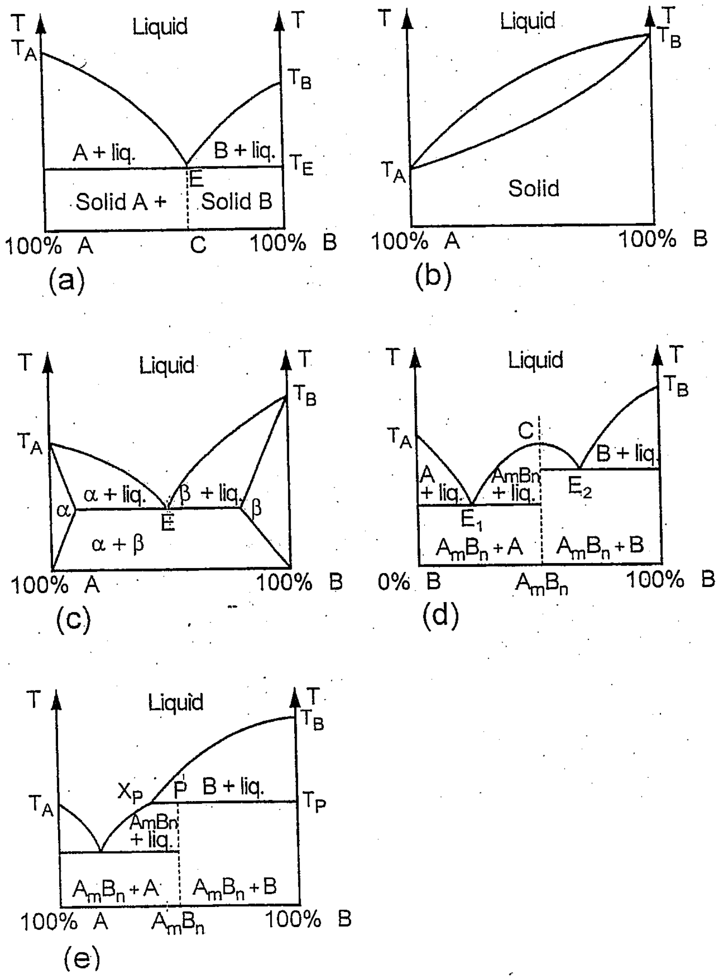
T
Liquid
T
T_A
T_B
A + liq.
B + liq.
T_E
E
Solid A +
Solid B
100% A
C
100% B
(a)
T
Liquid
T
T_B
T_A
Solid
100% A
100% B
(b)
T
Liquid
T
T_B
T_A
α + liq.
β + liq.
α
β
E
α + β
100% A
100% B
(c)
T
Liquid
T
T_B
T_A
C
A + liq.
A_mB_n + liq.
B + liq.
E_2
E_1
A_mB_n + A
A_mB_n + B
0% B
A_mB_n
100% B
(d)
T
Liquid
T
T_B
T_A
X_P
P
B + liq.
T_P
A_mB_n + liq.
A_mB_n + A
A_mB_n + B
100% A
A_mB_n
100% B
(e)

Fig. 4. *Phase diagrams of binary mixtures of temperature* vs. *composition* (*e.g.*, mole fraction) *of two chemical compounds, A and B, showing the following behavior:* a) *simple eutectic, with negligible miscibility in the solid state,* b) *continuous range of solid solutions* (miscibility in the solid state as well as in the liquid state), c) *eutectic with partial miscibility in the solid state,* d) *formation of a compound with a congruent melting point at C,* e) *formation of a compound with an incongruent melting point at P*

sidered, as well as the formation of various salts or the crystallization of the free acid or base. In addition, the stability zones, with respect to temperature and solvent composition, have to be determined.

As mentioned above, the formation of multiple hydrates of a given compound frequently occurs. If the temperature is varied over a wide range, a series of equilibria will be observed. *Soustelle* [29] discussed the implication of water vapor pressure on the system comprising the hydrates of copper(II) sulfate as illustrated in *Fig. 5,a*.

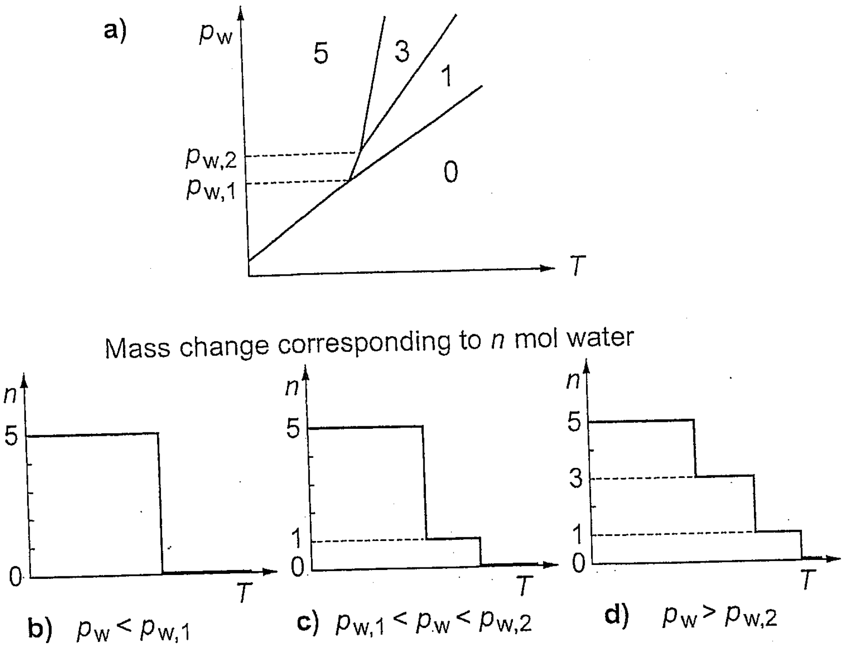

Fig. 5. *Influence of pressure and temperature on the composition of the stable phases formed between copper(II) sulfate and water,* $CuSO_4 \cdot nH_2O$ [29]. Phase diagram of pressure vs. temperature, *a)* showing the equilibrium curves of the anhydrate ($n = 0$), monohydrate ($n = 1$), trihydrate ($n = 3$), and pentahydrate ($n = 5$), and thermogravimetric curve obtained at different values of water vapor partial pressure (p_w): *b)* below $p_{w,1}$; *c)* between $p_{w,1}$ and $p_{w,2}$; d) p_w above $p_{w,2}$.

- At pressures below $p_{w,1}$, only one equilibrium is possible, that between the pentahydrate and the anhydrate. The corresponding curve representing the water content as a function of the temperature, determined by thermogravimetry, is shown in *Fig. 5,b*. A mass loss of 36.05% corresponding to 5 mol H_2O occurs.
- At pressures between $p_{w,1}$ and $p_{w,2}$, the corresponding thermogravimetric curve shown in *Fig. 5,c*, involves the phase transformation from the pentahydrate to the monohydrate, followed by the transformation of the monohydrate to the anhydrate with the corresponding mass loss of 28.84% and of 7.21% referring to the pentahydrate. At the triple point at the pressure level of $p_{w,1}$, both equilibria occur simultaneously.
- At pressures above $p_{w,2}$, the thermogravimetric curve corresponds to the three successive monovariant transformations, pentahydrate → trihydrate → monohydrate → anhydrate, (*Fig. 5,d*) with the mass loss of 14.42, 14.42, and 7.21%, respectively.

2.3. Amorphous State

The amorphous state is characterized by solidification in a disordered, random manner, structurally similar to the liquid state. If a physical property of a crystalline substance is plotted against temperature, a sharp discontinuity occurs at the melting point. For amorphous substances, there is no melting point, and a change of slope occurs at the so-called glass transition temperature T_g. The glass transition is characterized by a change of heat capacity. Below this temperature, the amorphous phase has certain properties of a crystalline solid (*e.g.*, plastic deformation) and is termed 'glassy'. Above this temperature, the substance retains some of the properties of a liquid, *e.g.*, molecular mobility, and is termed 'rubbery'. Above this temperature, the increase in molecular mobility facilitates spontaneous crystallization into the crystalline form with an exothermic enthalpy change after the glass transition. The use of amorphous forms is attractive, particularly for sparingly soluble compounds because of the enhanced solubility and dissolution rate over the crystalline state leading to increased bioavailability. However, the amorphous state is thermodynamically unstable. The glass transition temperature, T_g, is lowered by H_2O or other additives, facilitating conversion to the rubbery state and hence facilitating crystallization [30]. Moreover, uncontrolled crystallization can occur at any time, and is accelerated by the presence of H_2O. The effect of additives on T_g can be described by a modified *Gordon-Taylor* equation (*Eqn. 3*) where

$$T_{g,\,mix} = (w_1 T_{g1} + K \cdot w_2 T_{g2}) / (w_1 + K \cdot w_2) \tag{3}$$

where $T_{g,\,mix}$ is the glass transition temperature of the blend, w_1 and w_2 are the weight fractions of the components 1 and 2, and K can be calculated from the densities ϱ and the glass transition temperatures of the components:

$$K = (T_{g1} \cdot \varrho_1) / (T_{g2} \cdot \varrho_2) \tag{4}$$

3. Physicochemical Properties

As mentioned above, the fundamental physico-chemical properties are consequences of the underlying crystal structure. In contrast, properties modified by milling are related to reductions of crystallinity and particle size, while properties modified by manipulating the crystal habit are related to the nature of the crystal faces that are expressed. Methods for characterizing polymorphs and solvates have been recently reviewed [31].

3.1. Melting Point

The melting point of a new organic substance is one of the first properties measured. A number of techniques are available, from immediate melting to the capillary method described in the various pharmacopoeias, in which the substance is heated and the transition to the liquid phase is observed visually or by hot-stage microscopy. *Kuhnert-Brandstätter* studied the melting behavior of many drugs, including their eutectic melting with several reference substances for identification purposes [32]. If fusion is reversible, the equilibrium is monovariant (*i.e.*, $F = 1$), and the enthalpy change accompanying fusion (formerly termed the latent heat of fusion) is positive, because fusion is endothermic. Fusion can be accompanied by dissociation or by decomposition. The vapor pressure of H_2O plays an important role in the dissociation of hydrates [33]. Differential scanning calorimetry (DSC) allows the change of enthalpy during melting to be followed and the thermal processes involved to be determined quantitatively. Because processing and milling involve the evolution of heat, the melting point is an important property in the choice of the salt candidate. As discussed by *Wells* [2], the counter-ion plays a dominant role in determining the melting point of the salt. For example, small counter-ions such as chloride increase the melting point, because of their large charge density. This situation is illustrated by various salts formed by a basic chemical entity of melting point 98 °C; the melting points and enthalpies of the crystalline salts are listed in *Table 1* [41].

Table 1. *Melting Points and Enthalpies of Fusion of Some Salts of a Drug Candidate* [41]

Salt form	**Melting point** [°C]	**Enthalpy of fusion** ΔH_f [cal/g]
Base	98	16
Hydrogen fumarate	196	24
Hydrogen maleate	161	17
Hydrogen tartrate	122	16
Hydrogen malonate	72	3
Hydrochloride	251	61

3.2. Solubility

The process of dissolution involves the breaking of interionic and/or intermolecular interactions in the solid solute, the separation of the solvent molecules from each other to provide space for the solute, and the formation of interactions between the solvent molecules and the solute molecules or ions. The intermolecular bonding forces in solids include *Van der Waals* forces, H-bonds, and ionic interactions. *Van der Waals* forces include dipole-dipole forces, dipole-induced dipole forces, and induced dipole-induced dipole forces (*i.e.*, *London* dispersion forces). H-Bonding is the most directional of the intermolecular interactions. The polarity of a molecule can be expressed in terms of its dipole moment. In general, the solubility of a substance in H_2O increases with increasing dipole moment, other factors, such as melting point, being equal. If the solute in a solution consists of molecules with a small or zero dipole moment, it is said to be nonpolar and the interaction between solute and solvent is dominated by dipole-induced dipole forces and *London* dispersion forces.

In the case of a salt, the attractive force, F, between oppositely charged particles or ions is expressed by *Coulomb*'s law:

$$F = q^+ \cdot q^- / D \cdot d^2 \tag{5}$$

where q^+ and q^- represent the electric charges on the particles or ions, d is the distance between them and D is the dielectric constant of the surrounding medium with respect to vacuum for which $D = 1$.

The ion-dipole interaction is the force that dominates the dissolution of salts in polar solvents. In aqueous solution, the ions are surrounded by (*i.e.*, hydrated by) as many H_2O molecules as possible. The amount of H_2O of crystallization affects the heat of solution. In a crystal hydrate, the ions are already largely hydrated in the crystal lattice and, consequently, the ion-dipole interaction energy liberated on dissolution is considerably less than that of the anhydrous solute during the dissolution process. More considerations of solubility are discussed in *Chapt. 2*.

In the case of a solid salt, for which the stoichiometry is represented by A_mB_n, dissolution may be accompanied by dissociation of the ions which causes the ions to separate; thus:

$$A_m B_n \rightleftharpoons m\,A^{n+} + n\,B^{m-}$$

The apparent, concentration-based, solubility product, K_s, is given by:

$$K_s = [A]^m\,[B]^n \tag{6}$$

In the absence of added ions, the solubility of the solid, defined as the ionic molarity, *i.e.*, the number of moles of electronic charges of each ion dissolved per unit volume of solution is:

$$C = n[\mathrm{A}] = m[\mathrm{B}] = (K_s)^{1/(m+n)} \cdot m^{n/(m+n)} \cdot n^{m/(m+n)} \quad (7)$$

If dissolution occurs without dissociation, the solubility, c_s, is directly given by the concentration of the undissociated species, thus,

$$c_s = [\mathrm{A}_m \mathrm{B}_n] \quad (8)$$

The changes in the energy of the interactions as a solute dissolves is manifested as the enthalpy of solution, ΔH_{sol}, while the standard free energy change, ΔG^{θ}, is related to the solubility c_s.

$$\Delta G^{\theta}_{\text{sol}} = -RT \ln c_s \quad (9)$$

where R is the gas constant and T is the absolute temperature. According to the *van't Hoff* equation, the logarithm of the equilibrium constant (*e.g.*, solubility product) is a linear function of the reciprocal of the absolute temperature, as follows,

$$\ln K_s = \ln K_0 - \Delta H_{\text{sol}} / RT$$

or

$$\text{or} \quad K_s = K_0 \cdot \mathrm{e}^{-\frac{\Delta H_{\text{sol}}}{RT}} \quad (10)$$

The solubility of polymorphs is related to their thermodynamic activity, to the escaping tendency of their molecules, and hence to their melting point. For riboflavin [2] a linear relation was found between the log of the solubilities and the melting points of the three polymorphic forms. The thermodynamically stable form at a given temperature and pressure is the form with the lowest free energy and the poorest solubility.

For each polymorph, we may apply the *van't Hoff Eqn. 10* in the form:

$$\ln c_s = -\Delta H_{\text{sol}} / RT + c \quad (11)$$

where c is a constant and the other quantities have been defined above. The solubility curves obtained are shown in *Fig. 6*. In the case of enantiotropy, there is a transition point at which the solubility of the two polymorphs is identical. In the case of monotropy, the curves do not intersect. However, if a solvent-mediated transition occurs, it would result in spontaneous precipitation of the thermodynamically stable form. Plotting ln c_s *vs.* $1/T$ for each modification (polymorph or solvate) allows the determination of the transition point and the calculation of ΔH_{sol} for each modification. The difference of ΔH_{sol} between two forms is the transition enthalpy. The same applies to the transition between a solvate and an unsolvated form. In the case of different hydrates, different transition points can be observed (*Fig. 7*). This solubility *vs.* temperature approach is frequently applied for determining the re-

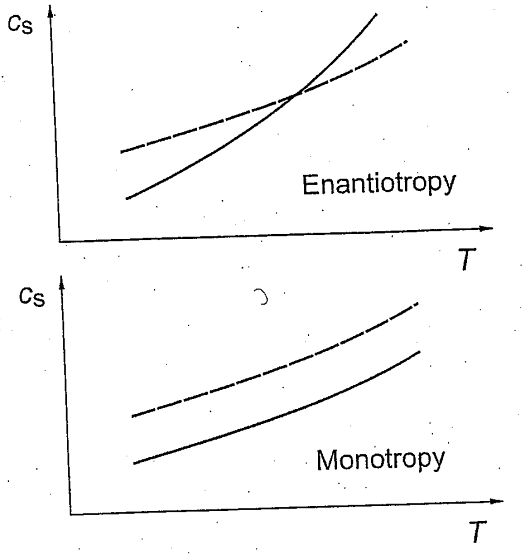

Fig. 6. *Plots of solubility* c_s vs. *temperature* T (solubility curves) *for enantiotropic and monotropic systems*

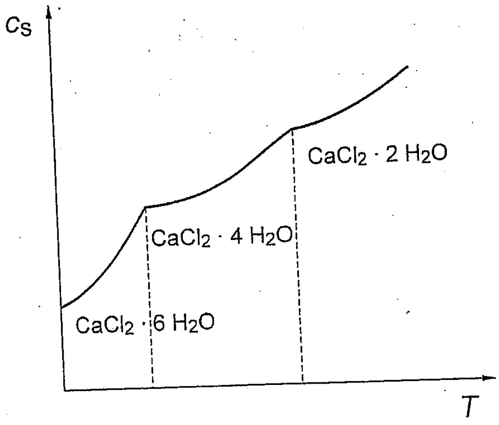

Fig. 7. *Solubility curves of solvates, exemplified by the dihydrate, tetrahydrate and hexahydrate of calcium chloride*

lationship between the polymorphs of anhydrous forms and even for solvates or hydrates [33].

When comparing the solubilities of salts, the impact of polymorphism has to be taken into account as for nonelectrolytes. Dissolved concentrations should be measured as a function of time when determining the solubility of the different forms because transformation during the measurement may occur. Furthermore, for proper interpretation of the results of solubility measurements, the temperature has to be maintained constant and accurately defined.

Solubility can be measured by phase solubility analysis, where an excess of the solid remains in equilibrium with the saturated solution [34–37]. The solution is analyzed by gravimetry, high performance liquid chromatography (HPLC), or spectroscopy. High throughput methods of solubility determination have been developed based on the measurement of the appearance of the solid phase by nephelometry or by ultraviolet spectrophotometry [38] [39]. In all solubility determinations, soluble impurities can significantly influence the measured solubility. For example, in the case of a single-point measurement on a supersaturated solution, if the relative amount of a drug substance of 98% purity is 20 mg/ml in the suspension, 0.4 mg of the impurity may be dissolved. If the solubility of the drug substance is 1.0 mg/ml, an apparent solubility equal to $1.0 + 0.4 = 1.4$ mg/ml will be found, whereas, if the solubility of the drug substance is 0.5 mg/ml, the apparent solubility will be $0.5 + 0.4 = 0.9$ mg/ml. This discussion highlights the relevance of the conditions used by comparing solubilities. *Figs. 8* and *9* emphasize the influence of both impurities and polymorphism [35].

In the case of salts, the relationships are more complex because a salt may be partially dissociated. By measuring the solubility in buffers, the possibility of the salting-out effect (and less frequently, the salting-in effect) must also be considered. For polybases or polyacids, there are pH domains of stability for each species, and the pH–solubility profiles should be measured. The pH profile of a base or an acid may be calculated on the basis of the

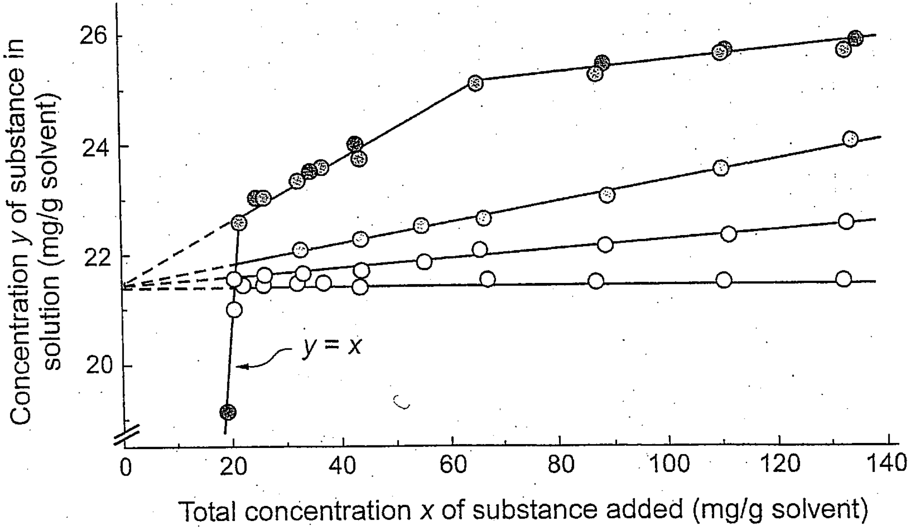

Fig. 8. *Phase solubility analysis of 7-(2-hydroxypropyl)theophylline in AcOEt, showing the influence of impurities in increasing the total solubility.* Increasing impurity content of the five samples used in the study is indicated by the increasing gray intensity of the data points. Below saturation, the data points lie on line $y = x$ indicating complete dissolution of the sample added to the solvent (redrawn from [35]).

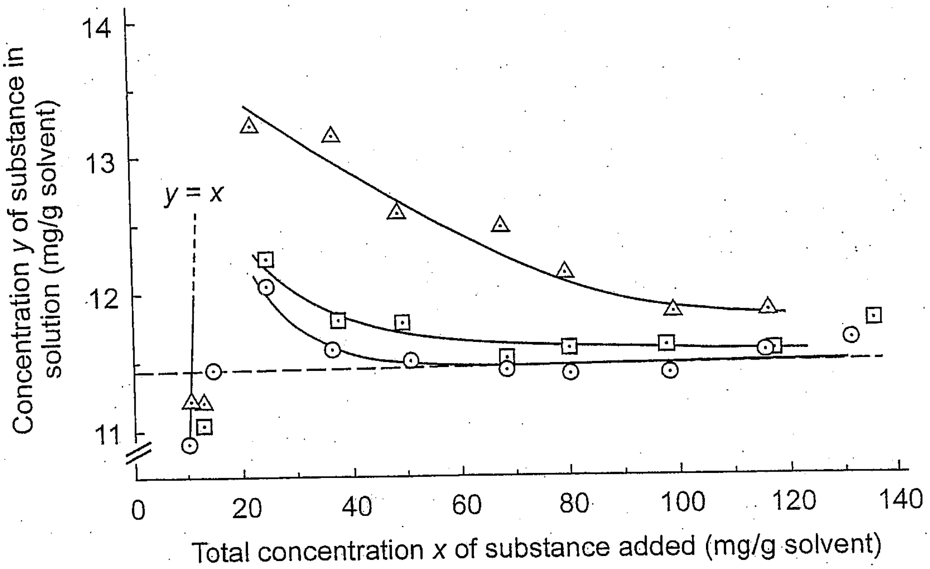

Fig. 9. *Phase solubility analysis: transformation of a higher soluble into a less soluble form depending on the time allowed for equilibration.* △: 20 h; □: 63 h; ○: 115 h (redrawn from [35]).

known intrinsic solubility (the solubility of the undissociated species) and the pK_a (see *Chapt. 1* and 2) [38] [39]. By means of recently introduced automated titration methods, the pH profile of the solubility can be obtained quite fast (see *Chapt. 2*). The pH domains of stability, mentioned above, are different in H_2O or in water + liquid media used as pharmaceutical formulations, as well as in the solvent(s) of crystallization as defined by the phase diagrams of each species with the solvent. Here again, polymorphism and pseudopolymorphism must also be taken into account. Generally, the solubility in H_2O increases in the rank order: hydrate < anhydrate < solvated form, but exceptions exist, especially when the transition temperature lies below the ambient temperature. In organic media, *e.g.*, in alcohols, a hydrated form is usually more soluble than the anhydrous form. For nedocromil magnesium, the rank order of the pentahydrate, the heptahydrate, and the decahydrate was not exactly the same for the solubility and intrinsic dissolution rate (IDR) [40], because the metastable higher hydrates transform to the stable pentahydrate during contact with H_2O in the solubility measurements.

3.3. Dissolution Rate

The dissolution rate of powders is often measured by the flow-through cell method as described in *Chapt. 2*. When comparing different salts, this

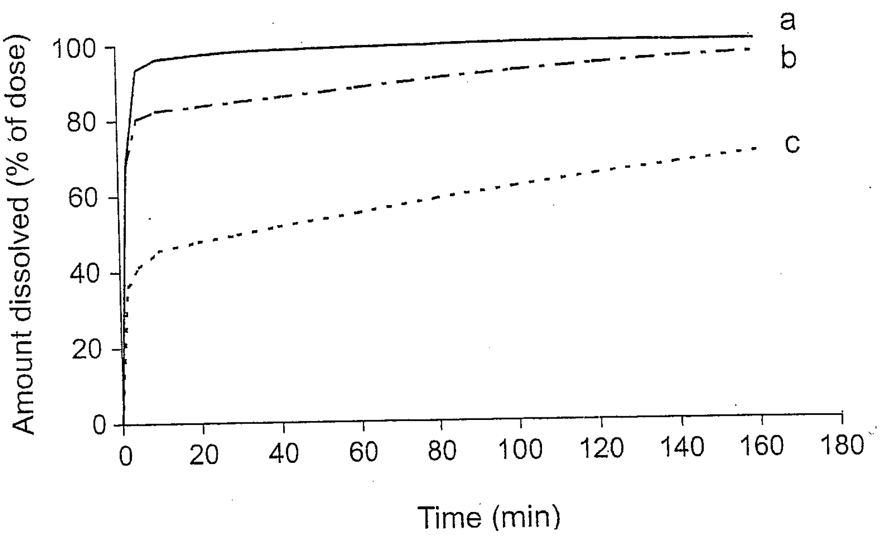

Fig. 10. *Influence of particle size on the dissolution process of reserpine hydrochloride in 0.1*M *HCl. a)* Particle size: 99% <49 µm, 90% <40 µm; *b)* particle size: 99% <67 µm, 90% <52 µm; *c)* particle size: 99% <158 µm, 90% <120 µm.

method has the disadvantage that the dissolution rate depends on the particle size. On the other hand, this dependency is utilized for a given form to evaluate the effect of particle size, as demonstrated in *Fig. 10* [41]. As for solubility measurements, the pH of measurement and the salt effect of the buffer have to be taken into consideration.

The transformation of an anhydrous form into a hydrated form and the transformation of a salt into the free base or acid is often observed. *Fig. 11* is an example of the observed dissolution rates in the case of transitions during the course of the experiment:

I: The anhydrous form dissolves without change;
II: the anhydrous form transforms into a hydrate;
III: instantaneous change of the anhydrous form into the hydrate and dissolution of the less soluble hydrate.

The difference, *b*, between the curves *II* and *III* results from the concurrence of the dissolution process and the transformation process.

Fig. 12 deals with a drug substance with polymorphic behavior [41]. The dissolution rate of two samples of the drug substance, representing two polymorphs of almost the same particle size, is reflected in the dissolution rate of the drug product as capsules.

The dissolution rate per unit surface area, termed the intrinsic dissolution rate (IDR; see *Chapt. 2*) is independent of the particle size. In the 'disc' meth-

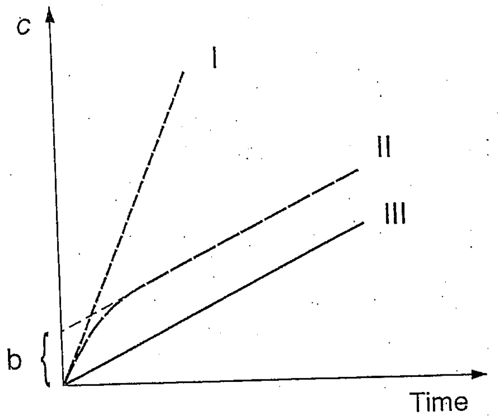

Fig. 11. *Plots of the dissolution of a compound that forms an anhydrate and a hydrate. I*) Anhydrate dissolves without phase change; *II*) anhydrate dissolves followed by phase change into the hydrate; the hydrate, being less soluble, dissolves more slowly; *III*) instantaneous phase change into the (less soluble) hydrate occurs, followed by the dissolution of the hydrate.

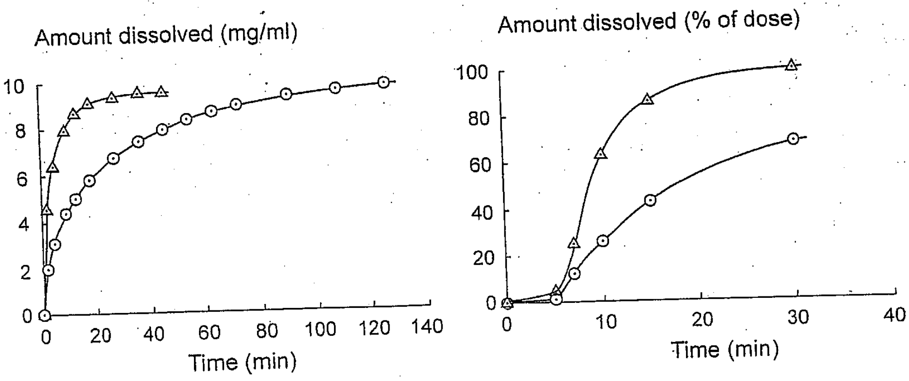

Fig. 12. *Dissolution curves* (left) *of two crystalline modifications* (A and B) *of a drug substance and the corresponding curves* (right) *the drug products* (capsules). △: polymorph A; ○: polymorph B.

od, the powder is compressed by a punch in a die to produce a compact disc or tablet. Instruments are now commercially available for this purpose [42]. Only one face of the disc is exposed to the dissolution medium, and the cumulative amount dissolved per unit surface area is determined by ultraviolet spectrophotometry until 10% of the solid is dissolved. The slope of the plot of mass dissolved per unit surface area *vs.* time gives the IDR in appropriate units, *e.g.*, mg/min/cm^2. If a change in the slope is observed during the course of the experiment, then a change in the solid phase exposed to the solvent occurs during the experiment. A solid phase with different state of ionization (*e.g.*, the unionized form) as well as a polymorphic change can occur. For example, the initial dissolution rate for a drug substance was 0.05 mg/min/cm^2.

After several minutes, the dissolution slowed down in order to continue with the lower rate of 0.01 mg/min/cm^2, resulting from the formation of a hydrate. A separate measurement of the IDR of the hydrate indeed reproduced the same rate of 0.01 mg/min/cm^2.

3.4. Heat of Solution

The enthalpy of the solution process, *i.e.*, the heat of solution, ΔH_{sol}, can be calculated from the temperature dependence of the solubility as discussed in *Sect. 3.2*. This method has been widely used, for example, for etoxadrol base and its hydrochloride [43]. However, *Hollenbeck* [44] and *Burger* [23] consider that the slope of the linear relation predicted by *Eqn. 10* is too variable, and is subject to systematic errors of several percent due to nonideality of the saturated solution, resulting in inaccurate determination of both the heat of solution and the transition point of two forms. The heat of solution of substances can be measured directly by solution calorimetry, which clearly provides more significant values [18] [45]. The difference between the heats of solution of the two polymorphs is equal to the transition enthalpy of the polymorphs at temperatures close to ambient. The results provide an alternative to DSC for the discrimination between enantiotropy and monotropy, when the substance decomposes upon melting. Quantitative analysis of polymorphs, solvates, and amorphous forms in mixtures has been performed using solution calorimetry. Studies of polymorphism by solution calorimetry have been reviewed [18].

3.5. Interaction with Water Vapor

Water vapor is an omnipresent component of the atmosphere. The vapor pressure of H_2O at different temperatures has been tabulated. At a given temperature, the ratio, actual water vapor pressure/saturated water vapor pressure at that temperature is termed the *relative humidity* (r.h.), given as percentage of saturation. The environmental humidity depends on the weather and climatic zone and may vary from 10 to more than 75%. This variability has to be taken into account when determining the storage conditions of a salt candidate.

When a solid is exposed to a gas, some of the gas molecules, termed the *adsorbate*, become attached to the surface of the solid, termed the *adsorbent*. This process, which is divariant, is called *adsorption*. When water vapor is adsorbed, the H_2O molecules may undergo any type of interaction (*Van der Waals*, ion-dipole, and specific H-bonding interactions) with the functional groups on the surface of the adsorbent; they may cause swelling of hydro-

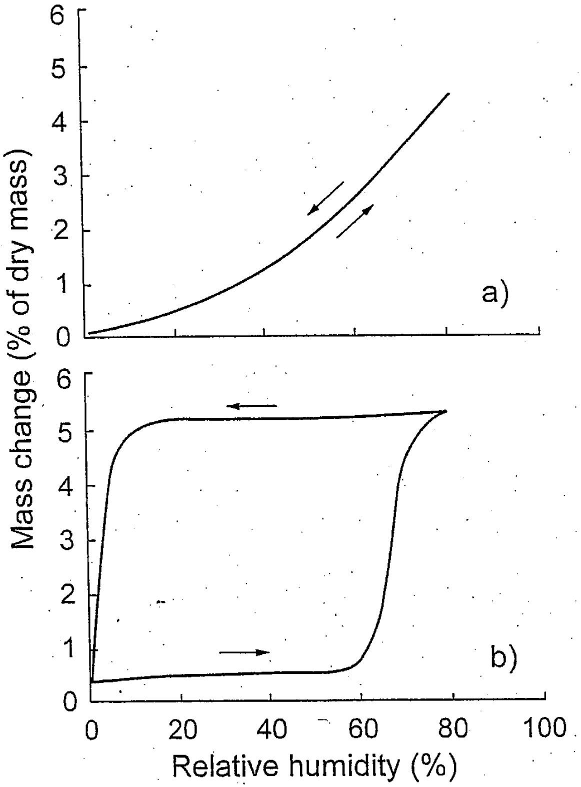

Fig. 13. *Examples of water sorption/desorption isotherms. a*) Sorption/desorption is reversible; *b*) Desorption exhibits hysteresis.

philic polymers, may induce a phase transformation of the adsorbent to form a solid hydrate, or may cause a hygroscopic adsorbent to form a pool of saturated solution by the process known as *deliquescence*. Water sorption and desorption isotherms of drug substances should be determined, especially if the solid undergoes a phase change. Hygroscopicity and sorption kinetics have been reviewed [46] [47], and the use of water sorption isotherms for comparison of salt candidates has been discussed [48].

In the case of certain drugs and excipients as adsorbents for water vapor, the sorption and desorption isotherms may not coincide, giving rise to hysteresis as illustrated in *Fig. 13*. Limiting the sorption of water vapor from ambient air is crucial for maintaining the quality of some pharmaceuticals during their manufacture. The behavior of drug substances at different temperatures and humidities for different climates is generally studied by gravimetry. The humidity for gravimetric studies of water sorption and desorption can be controlled by saturated salt solutions [49] or by humidification of a stream of air or N_2 to which the solid sample is exposed. In the so-called 'dy-

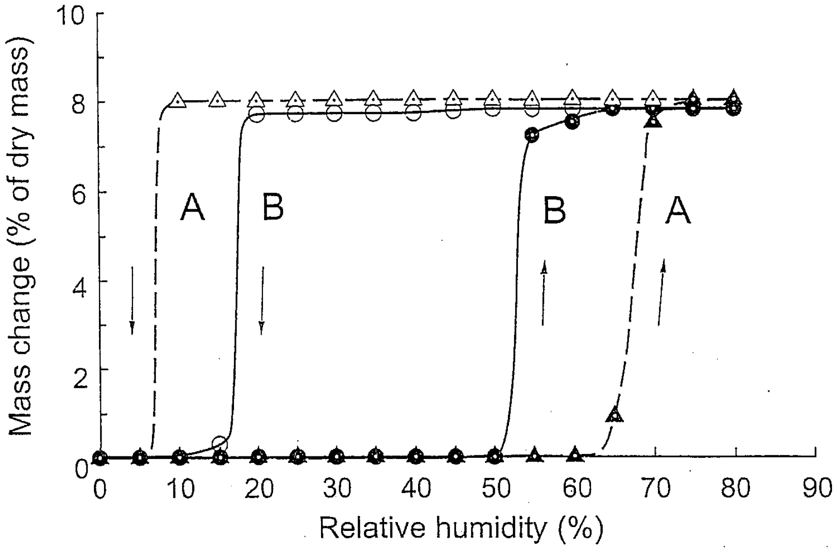

Fig. 14. *Two polymorphs* (A and B) *transforming into the same hydrated form.* The metastable form B takes up H_2O at lower relative humidity than the stable form A. The hydrate form loses H_2O at r.h. values below 20%.

namic water sorption' system [50], the sample is placed on a microbalance and exposed to a continuous flow of air or N_2 with constant, predetermined relative humidity. By these methods, samples as small as 1 mg can be accurately studied.

Solid-state hydration may occur leading to the formation of hydrates. X-ray diffractometers may be equipped with special sample cells for exposing the sample to controlled temperature and humidity. The structural changes in the solid can be monitored, and the extent of their reversibility can be studied. The powder X-ray diffraction patterns collected during heating allow dehydration steps, or other desolvation steps, to be followed efficiently. Because sorption and desorption phenomena are accompanied by heat exchange, microcalorimetric techniques are valuable for monitoring purposes [51] [52].

Fig. 14 shows the sorption isotherms of two crystalline modifications of a drug substance both of which transform into a hydrated form at 25 °C [53]. Under ambient conditions, the thermodynamically stable form is less hygroscopic. The critical humidity at which the mass changes abruptly, corresponding to the humidity at which the formation of hydrate begins, depends upon the temperature. The higher the temperature the lower is the critical humidity. The formation of theophylline monohydrate at the surface of tablets containing anhydrous theophylline is an example that has been thoroughly studied [54–56].

Different polymorphs usually behave differently [18]. A metastable polymorph may transform into a crystalline hydrate, whereas the stable polymorph may not (*e.g.*, see *Table 3*). Solvates may transform into hydrates by direct displacement of a solvent guest by H_2O. This process suggests a method for obtaining hydrates that cannot otherwise be manufactured [57]. When several hydrates are formed, the kinetics of the dehydration processes may be different from the kinetics of the hydration step, as in the case of nafragel hydrochloride [58] for which the sorption of H_2O occurs in two steps *via* the hemihydrate. The resulting monohydrate loses H_2O in one step yielding the anhydrate. Due to the different kinetics of their transformations, the anhydrate, hemihydrate, and monohydrate can co-exist for an appreciable period of time. Hydrates have been the subject of several reviews (*e.g.*, [59]).

Fig. 15 illustrates the complexity of hydration and dehydration processes in the water-sorption isotherms of three salts of a basic drug [41]. The hydrogen malonate salt takes up moisture reversibly corresponding to a weight change that exceeds 22% at saturation. The hydrogen tartrate salt is also hygroscopic exhibiting a slight hysteresis. For the hydrochloride salt, a strong hysteresis is observed due to the formation of a stable hydrate. The base and the hydrogen maleate salt were not at all hygroscopic. This example illustrates the importance of the study of the hygroscopicity of salt candidates.

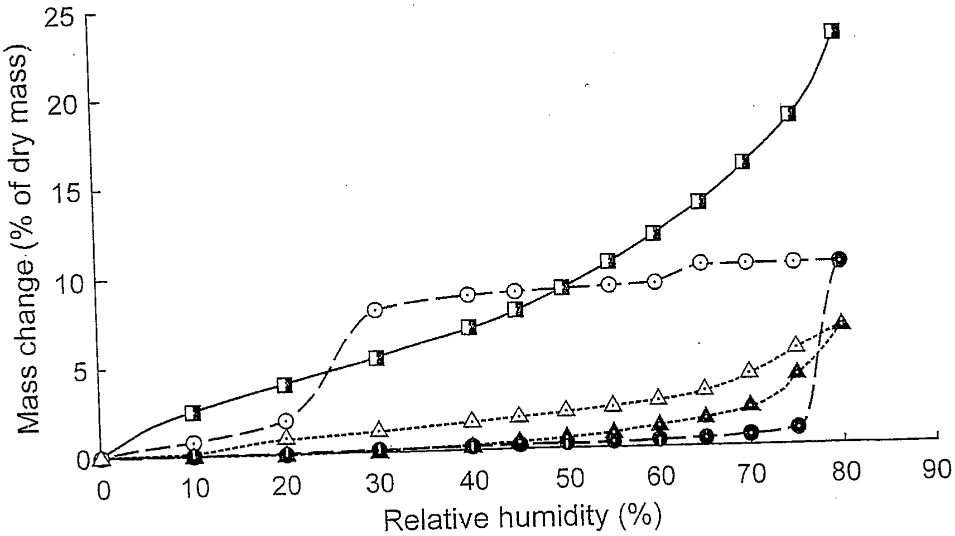

Fig. 15. *Water vapor sorption isotherms of three salts of a basic investigational compound.* O: Hydrochloride, △: hydrogen tartrate, □: hydrogen malonate (sorption and desorption without hysteresis); black symbols: adsorption; empty symbols: desorption.

3.6. Density

For solids, different expressions of density have been defined and are considered to be of practical importance for powdered solids. The *tapped density* and the *bulk density* (also called *poured density*) describe the bulking properties of a powder and are an indirect measure of the flow properties of the powder resulting from the distributions of particle size, shape, and surface area. On the other hand, the *true density* as a theoretically derived parameter depends on the packing of the molecules in the crystal structure. It is determined by the volume of the unit cell, the number of molecules contained therein, and the molecular weight. Thus, the true density can be calculated if the crystal structure has been determined by X-ray analysis. Experimentally, the true density is measured in a gas pycnometer with He as displacement gas, as described in USP XXIV. According to one of the four thermodynamic rules for polymorphs established by *Burger* [23], under the conditions of measurement the more densely packed form is the more stable form at 0 K. For example, the densities of three crystalline modifications of the purine derivative, MKS 492, are 1.422, 1.411, and 1.400 g/cm^3 [60]. A complete study of the polymorphic behavior of MKS 492 demonstrated that two less dense forms are monotropic in relation to the crystalline modification with the highest density. However, while the density rule is obeyed by MKS 492, it fails for some polymorphic systems. Of the four thermodynamic rules, the heat of fusion rule and the heat of transition rule are found to be more reliable.

3.7. Morphology

Crystal morphology is an important consideration when selecting a salt form. Generally, needle-shape crystals are not desirable because of their poor flow properties [61]. Therefore, it is usual to examine and to compare the crystals under a magnifying glass, light microscope, or scanning electron microscope (SEM). The microscopic techniques have been augmented by image analysis for comparing the morphology of different salts [62] [63]. Morphology of anisotropic crystals may be modified by the conditions of crystallization (crystal engineering) [65].

4. Kinetic Aspects

If phase transformations were based solely on thermodynamic rules, stable crystal forms should be obtained quite easily. However, kinetic factors cause metastable states to be encountered. A considerable activation energy barrier may have to be overcome in moving from a metastable state to a stable state. The activation energy, E, is related to the rate constant, k, of the transformation by the well-known *Arrhenius* equation:

$$k = A\,e^{-E/RT} \tag{12}$$

where A is the frequency factor, which is related to the entropy of activation according to *Eyring* and *Polanyi*, and R and T have been defined previously (*Eqn. 9*). The activation-energy barrier may be reduced by catalysts, impurities, and/or crystal defects. Most transformation processes in the solid state involve nucleation, progression of a growth zone, and regression of an unreacted core. When comparing the stability of solids during storage, many factors play a role, such as temperature, particle size, the presence of seed nuclei of the product, activation energy for the change, and diffusion of the molecules.

The influence of nuclei (seed crystals) of the stable form in a sample of a metastable form is demonstrated in the following example. For the substance exemplified in *Fig. 12*, two batches of the metastable form were stored under different conditions for stability testing. The DSC scans showed that the second batch contained traces of the stable form, whereas no stable form could be detected in the first batch. After 5 years, the second batch had transformed to the stable form at a rate that depended on the temperature, whereas no transformation of the metastable form to the stable form was observed in the first batch at all storage temperatures. After storage of the second batch for 3 years at 30 °C, 50% of the stable form was found by X-ray diffractometry and by IR spectroscopy [41] [64]. However, no trace of the stable form was found by X-ray diffractometry in all samples of the first batch. Samples of the second batch, when stored in a deep-freezer for 5 years, contained *ca.* 5% of the stable form (estimated by X-ray diffractometry). The different behavior of the batches is explained by the presence of the small amount of seed nuclei of the stable form in the second batch. This example emphasizes the need for sensitive methods to differentiate and to detect polymorphs in mixtures.

Transformations may be accelerated by the presence of a solvent, such as H_2O. *Solvent-mediated transformations* occur by a continuous dissolution–crystallization process. This type of transformation may occur during crystallization or granulation. Hydrates may be formed by this process in mixtures involving moisture. Solvent-mediated transformations may occur when measuring solubilities, such that, after some time, recrystallization of a more stable state may be complete (*Fig. 16*).

Table 2 summarizes solubility measurements on four forms, A, B, C, and D, of MKS 492 as functions of time and at different temperatures [60]. After

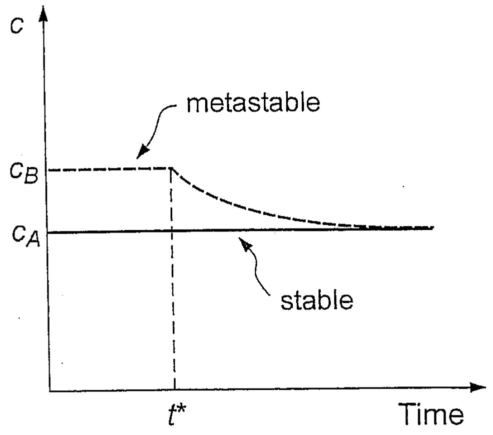

Fig. 16. *Concentration* vs. *time plots showing the possible solubility behavior of stable* (A) *and metastable* (B) *polymorphs or pseudopolymorphs, respectively.* At the time indicated t^*, the saturated solution of the metastable form, which is supersaturated with reference to the stable form, starts to crystallize, thereby approaching the concentration of the lower solubility of the stable form. Crystallization may occur by spontaneous nucleation or can be induced by seeding with the stable form.

Table 2. *Solubility Measurements of MKS 492 Polymorphs, and of Mixtures of Each Polymorph with the Stable Form B, in H_2O* [60]

		Polymorphs				**Mixtures**		
Temperature [°C]	**Time** [min]	**A**	**B**	**C**	**D**	**A + B**	**C + B**	**D + B**
20	10	2.71	1.71	2.16	1.77	1.57	1.67	2.15
	20	2.76	1.62	2.02	1.76	1.55	1.60	2.00
	40	2.77	1.68	2.07	1.87	1.60	1.67	1.65
30	10	2.96	1.76	3.03	2.21	1.86	1.77	2.22
	20	2.98	1.58	2.76	2.34	1.70	1.59	2.04
	40	3.00	1.59	2.82	2.26	1.68	1.66	1.96
40	10	3.56	1.61	4.51	2.36	1.69	1.58	1.60
	20	3.61	–	4.31	–	–	–	–
	40	3.58	–	4.63	–	–	–	–

equilibration, the aqueous phase was analyzed. Form B is the least soluble form and is, therefore, the most stable form. After 10 min or 40 min, no obvious differences were observed among the measurements. The same experiment was repeated with forms A, C, and D, each containing some of the less soluble form B. The decreases in the solubilities demonstrate the influence

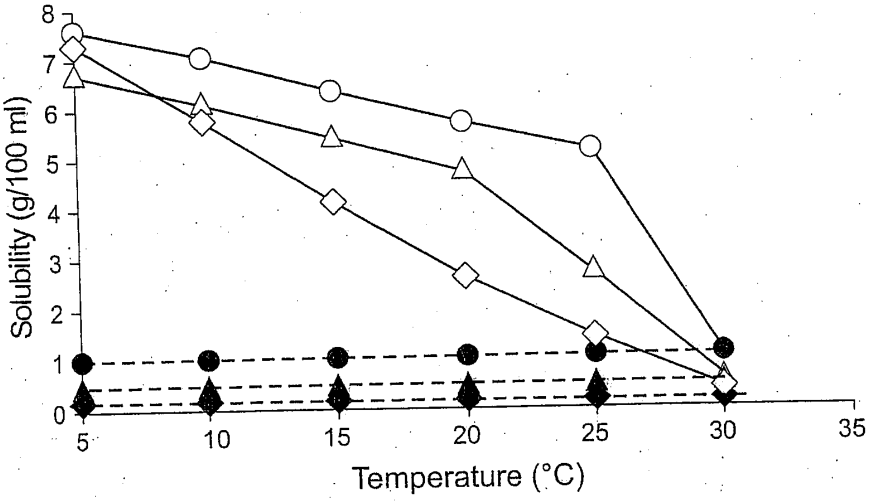

Fig. 17. *Influence of temperature on the kinetics of a solvent-mediated transformation in formulations of an investigational drug substance in two crystalline modifications, monitored by the concentration of dissolved substance after one day of storage.* Full symbols and broken lines: stable form; hollow symbols and full lines: metastable form; solvents: ○: Miglyol 812, ◇: soybean oil, △: mixture of equal parts of Miglyol 812 and soybean oil.

of seeds of the stable form, which accelerate the solvent-mediated transformation [60].

The influence of temperature on the phase transformation is demonstrated by the example shown in *Fig. 17* for an investigational drug of which the stable crystalline form was obtained for the first time only after storage of liquid formulations [41]. A great difference in solubility between the stable and the metastable forms has been observed in this case. In suspensions prepared with the three solvents, it was found that the higher the storage temperature is, the faster the solubility decreases, departing from the initially high value of the metastable form. The rate of transformation is accelerated by increasing the temperature. The transformation is almost complete after one day in suspensions held at 30 °C, whereupon the concentrations of substance in solution remain unchanged after a further week of equilibration. This example illustrates that the identification of the stable form of a drug substance and the knowledge of its solubility facilitate the prediction of the physical stability of a pharmaceutical formulation.

There is a metastable zone of supersaturation with respect to the stable polymorphic form, which is important in crystallization processes driven by cooling (*Fig. 18*). If the solubility curve of a metastable form is in the metastable zone, the first crystal obtained will be the metastable form. Thus, this metastable form will crystallize, and the stable form will not appear, if the

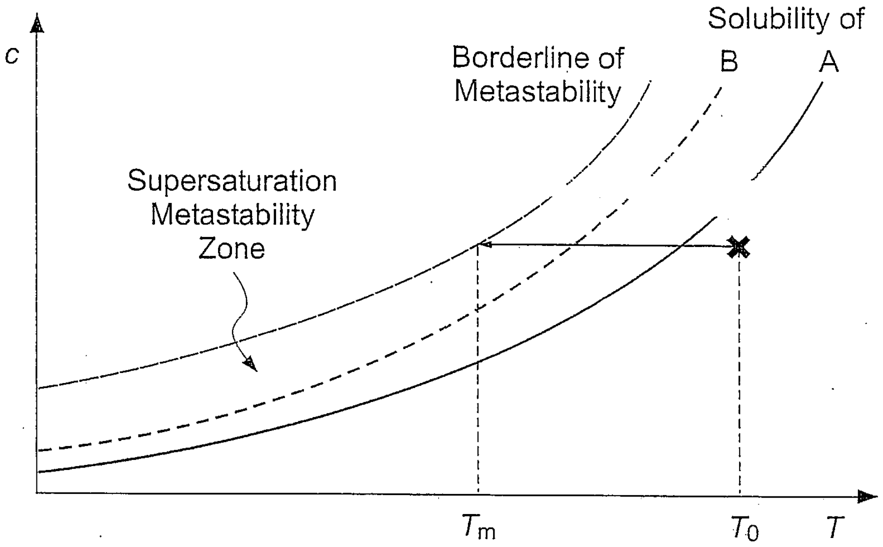

Fig. 18. *Crystallization from supersaturated solution by cooling.* Plots of solubility c_s *vs.* temperature of two polymorphs, stable A and metastable B with the solubility curve of form B located within the crystallization metastability zone. Cooling starts at ✖.

transformation into the stable form is limited by the kinetics of dissolution and growth [65] [66]. Difficulties in obtaining crystals of a particular form, which were obtained at an earlier time are discussed by *Dunitz* and *Bernstein* [67].

Amorphous or partially amorphous solids may result from very rapid precipitation, drying, milling, freeze drying, or shock cooling from the melt. Often, the presence of seeds of a crystalline form in the amorphous bulk represent a 'memory' of the crystalline state especially after drying solvated forms. Amorphous substances are generally hygroscopic; they have high solubility and bioavailability, and good tableting properties, but are difficult to mill. Amorphous forms are usually less stable chemically and physically due to their molecular mobility; they tend to transform into crystalline forms upon storage, humidification, and heating.

Crystallization of an amorphous solid proceeds generally fast at temperatures above the glass transition temperature, which is depressed by the presence of H_2O. The amorphous form may crystallize into one or another of different polymorphs depending on the temperature and humidity, as was observed in the case of indomethacin [7] [68]. The amorphous content of micronized solids is important, because recrystallization produces agglomerates and consequently increases the particle size, as demonstrated by *Otsuka* [69]. The hygroscopicity of brequinar sodium is related to the amorphous content [70].

Dehydration and hydration processes largely depend on kinetic factors, such as diffusion of H_2O molecules, as well as diffusion and transformation in the solid state, and, therefore, depend on the particle size [71]. Processes involving a high input of mechanical energy, such as the shear created during milling and the pressure applied during tableting [73], are capable of inducing or accelerating phase transformations. As demonstrated by *Takahashi* for fostedil [72], the types of mill employed and the added excipients greatly influence the transformation.

5. Study of Transitions between Solid Phases

The solid-state properties of the drug substance, its salt forms, polymorphs, and solvates, such as the solid-solid, solid-liquid, liquid-liquid, and solid-gas equilibria and transformations, are derived from the thermodynamic phase diagrams, which express the influence of temperature and pressure. Expeditious product development requires rapid recognition of the form that is thermodynamically stable under a range of relevant temperatures and water vapor pressures. The characterization and study of polymorphs and pseudo-polymorphs is quite complex. It is usually important to know whether the solid under study is a mixture of phases, a metastable form, or a stable form at the temperature and other conditions of interest. However, the kinetic factors in solid-solid transformations complicate the interpretations. Therefore, several methods should be applied to the study of solid phases and their transitions. These methods have been described in *Sect. 3*. Chemical analysis after transformation avoids misleading interpretations that could arise from isomerization, dimerization, and/or decomposition. Thermal analytical methods in which a physical property, such as the flow of heat energy or weight, is measured as a function of temperature, or as function of time, while the substance is subjected to a temperature program, are especially valuable for the study of polymorphism and pseudo-polymorphism [18] [53] [74] [75].

Differential scanning calorimetry (DSC) measures the heat flow, d*q*/d*t*, into and out of a sample cell relative to a reference cell in a controlled atmosphere over a defined temperature range within an available range between –50 to >300 °C. *Fig. 19* shows typical events in DSC, *i.e.*, change of heat capacity at glass transition, and changes in enthalpy, namely exothermic crystallization, endothermic melting, and exothermic decomposition. Every DSC study should include scans at different heating rates because DSC is a dynamic method, and solid-state transformations, while being thermodynamically driven, are kinetically controlled. The DSC scans will differ if the sample under study is stable or metastable at ambient temperature, as shown in

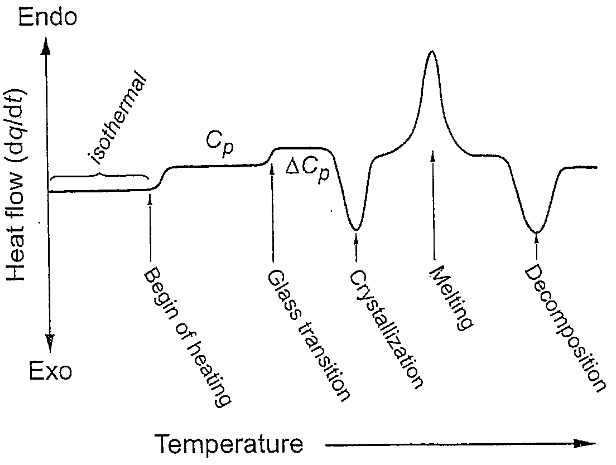

Fig. 19. *Theoretical DSC scans.* Following a period of isothermal equilibration, the temperature, T, is increased at a constant rate dT/dt. The heat flow output, dq/dt, is plotted *vs.* temperature.

Figs. 20,a and *b* [77]. The scans illustrate the polymorphic relationship of two forms A and B.

Case of enantiotropy (*Fig. 20,a*)

Scan 1. The sample studied is the stable form A, which gives the endothermic solid phase transition A → B (see *Fig. 3,a*), followed by the melting endotherm of form B.

Scan 2. The sample studied is the stable form A, but, for kinetic reasons, the solid transformation A → B does not occur. Instead, form A melts.

Scan 3. The sample studied is the stable form A which melts. Form B crystallizes from the melt with an exothermic peak, and form B melts at a higher temperature.

Scan 4. The sample studied is the metastable form B, which becomes stable at a higher temperature above the transition temperature. An exothermic peak corresponds to the solid transformation B → A, followed by successive transformation A → B and melting of B.

Scan 5. The sample studied is the metastable form B. The DSC scan shows its melting endotherm.

Case of monotropy (*Fig. 20,b*)

Scan 1. The sample studied is the stable form A, and its melting endotherm is observed.

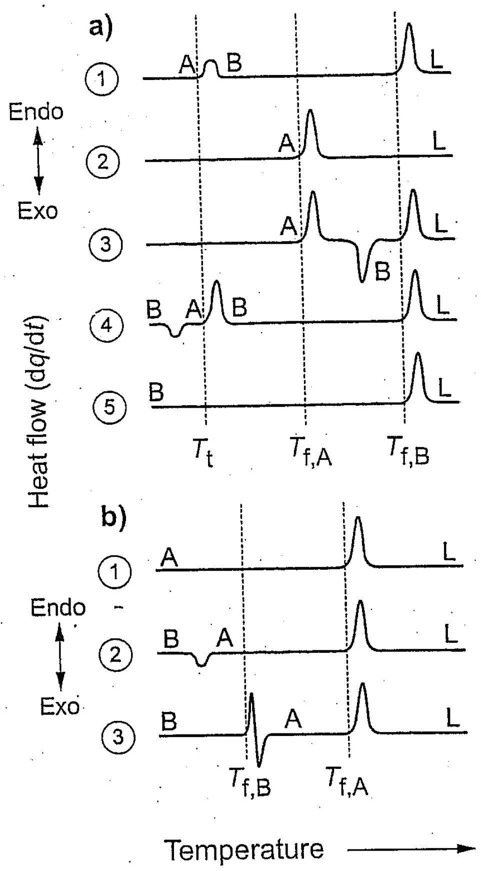

Fig. 20. *Theoretical DSC curves of polymorphs:* a) *enantiotropically-related polymorphs;* b) *monotropically-related polymorphs.* For details, see text.

Scan 2. The sample studied is the metastable form B, which transforms exothermically in the solid state into the stable form A. Form A melts at a higher temperature.

Scan 3. The sample studied is the metastable form B, which does not transform into A but melts endothermically. From the melt, the stable crystalline form A appears with an exothermic peak. Then, A melts at a higher temperature.

Similar interpretations apply to all methods that involve heating (*e.g.*, hot-stage optical microscopy, hot-stage IR or *Raman* microscopy, temperature-resolved or variable-temperature X-ray diffractometry).

Fig. 21 shows an example of a DSC curve, which is observed in the case of enantiotropy. This is not the case for the hydrochloride salt of a drug candidate presented in *Fig. 22*. The form A melts, and various other forms grow

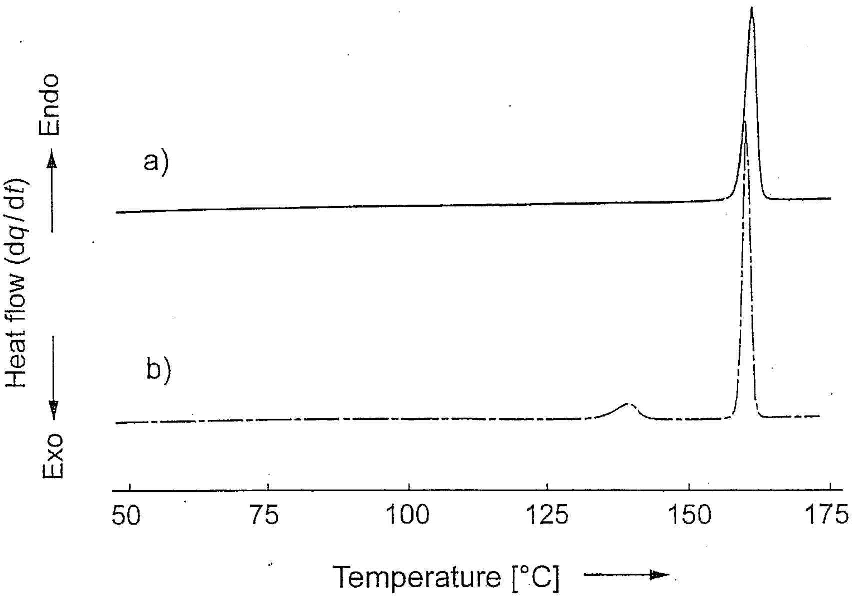

Fig. 21. *DSC Curves of two polymorphs, A* (a) *and B* (b), *of oxybuprocaine* [18]. Polymorph B undergoes an enantiotropic transition to polymorph A at 140–150 °C.

from the melt, although they may not be present in the original solid samples studied as resulting from the X-ray diffraction analysis.

It is difficult to distinguish between monotropy and enantiotropy in the case of *Fig. 20,a*, Scan 5, and *Fig. 20,b*, Scan 1, as well as *Fig. 20,a*, Scan 3 and *Fig. 20,b*, Scan 3. The interpretation of the DSC curves is facilitated by the *Burger*'s enthalpy of fusion rule [21]: if the higher-melting form has the lower melting enthalpy, both forms are related enantiotropically. As demonstrated in *Table 3*, for a benzisoquinoline hydrochloride [18], the melting enthalpy of the higher-melting form B is lower than the melting enthalpy of A. Therefore, the two forms are enantiotropically related, with form A stable below the transition point. Modification B is hygroscopic and undergoes a solvent-mediated transition to A in alcohols at ambient temperature.

In thermogravimetry (TG, TGA) the change of the mass of a sample is determined in a thermobalance as a function of temperature and/or time. Most instruments record the percentage of mass change and the derivative curve (DTG), which shows the rate of the mass change with respect to temperature or time. *Fig. 23* shows the DSC and TG scans of a salt obtained as hydrate or as an EtOH solvate depending on the ratio EtOH/H_2O in the solvent and on the temperature of crystallization.

Solution microcalorimetry and isothermal microcalorimetry are complementary techniques. The larger volumes of the sample cells and the higher

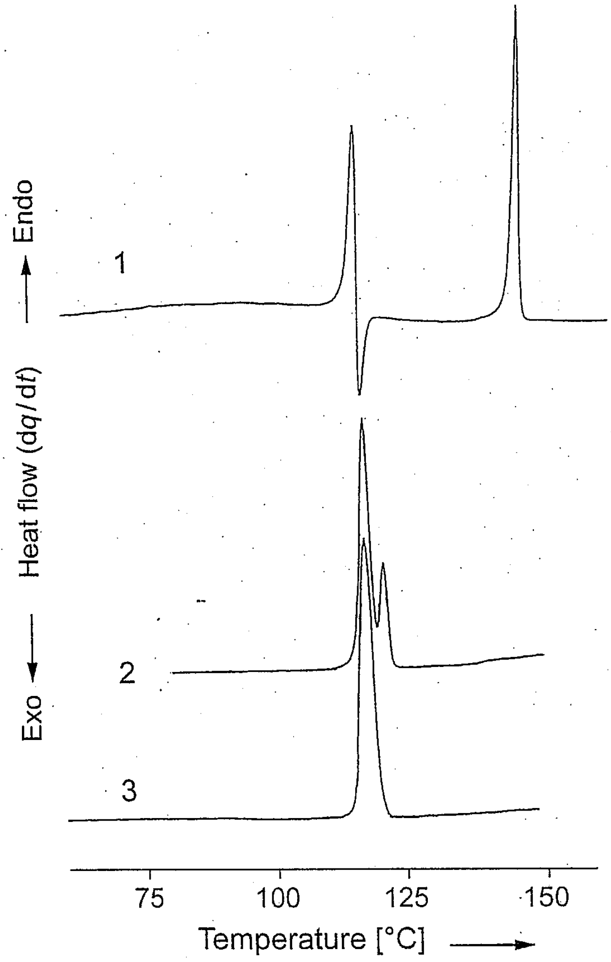

Fig. 22. *DSC Scans of three batches of a drug candidate, Code 205-397 hydrochloride, of similar quality according to powder X-ray diffraction* (form A) *but showing different behavior following melting* [18]. *1*) After melting of form A, the enantiotropic form C is obtained from the melt; *2*) a metastable form B, monotropic to the stable form A, is obtained from the melt; *3*) only the melting peak of the form A is observed.

sensitivities of the instruments facilitate the study of phenomena with changes in energy much smaller than can be measured by DSC. Calorimetric analysis of different polymorphs permits the determination of the enthalpies of transformation. By this technique, the form with the lowest enthalpy can be identified [18] (see *Sect. 3.4*).

Modern DSC and TG instruments are sensitive and can be equipped with robotics for rapid and accurate output. However, both of these techniques are relatively unspecific. Therefore, DSC instruments may now be coupled to other analyzing instruments, such as FTIR and *Raman* spectrometers, and mi-

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Table 3. *Some Physical Properties of Two Crystalline Forms of a Benzisoquinoline Hydrochloride That Are Enantiotropically Related* [18]

Property	**Form A**	**Form B**
M.p. [°C]	304	311
Melting enthalpy [kcal/mol]	12	11
Water uptake after 1 day at 92% r.h.	0%	3.2% (= Hydrate)
Transformation in alcohols	A	B → A

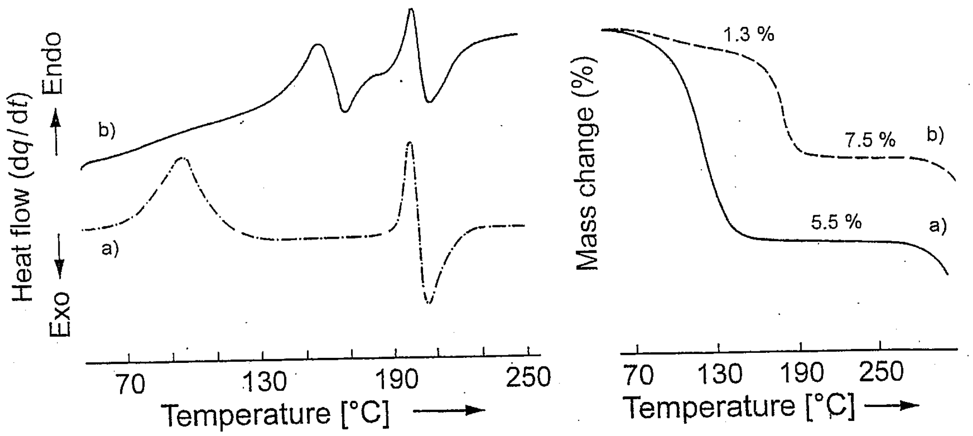

Fig. 23. Left: *DSC curve of a hydrate* (curve a) *and a solvate* (curve b). Right: *the corresponding TG curves, enabling the position of the dehydration and desolvation peaks to be compared* [18].

croscopes, and to temperature-resolved X-ray powder diffractometers, for increasing specificity and easing the interpretation of results. The instruments may be combined, or the sample may be studied in a temperature-programmable cell within the spectrometer. TG Instruments may also be interfaced with similar instruments such as DSC or with a gas chromatograph (GC), mass spectrometer (MS), or IR spectrometer. Optical thermomicroscopy (hot-stage microscopy) with a videorecorder provides a visual study of melting, desolvation, crystallization, and dissolution. *Fig. 24* shows the DSC trace and the X-ray diffraction patterns obtained by temperature-resolved powder X-ray diffractometry, of two polymorphs involved in a reversible enantiotropic transition [18] [60].

The equilibration of saturated solutions of the polymorphs in different solvents, by the slurry techniques, offers the advantage of accelerating solvent-mediated transformations. If a mixture of two forms is equilibrated with

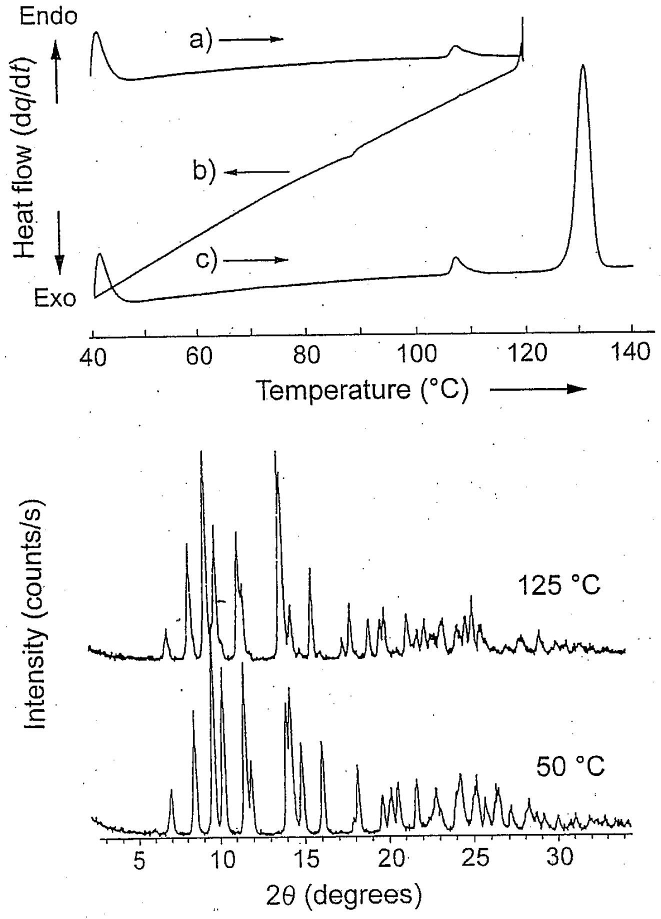

Fig. 24. *DSC Curves and temperature resolved X-ray diffractograms of the purine derivative MKS 492*

a solvent, careful observation of the remaining solid is a direct and efficient way to study the phase transformation. However, as emphasized by *Byrn et al.* [76], the clearest indication of the existence of polymorphs and solvates is derived from X-ray crystallographic examination of single crystals.

Studies of hydrate formation with water-sorption isotherms have been discussed in *Sect. 3.5*. The example given in *Fig. 25* for tetracaine hydrochloride illustrates the complexity of investigations of polymorphism. To obtain the relationships between six polymorphs, a tetrahydrate, a monohydrate, and a hemihydrate of tetracaine hydrochloride [78], several techniques were necessary: DSC, TG, IR spectroscopy, regular and temperature resolved X-ray diffractometry, and solubility studies in different solvents. No polymorphism was observed for the tetracaine base itself.

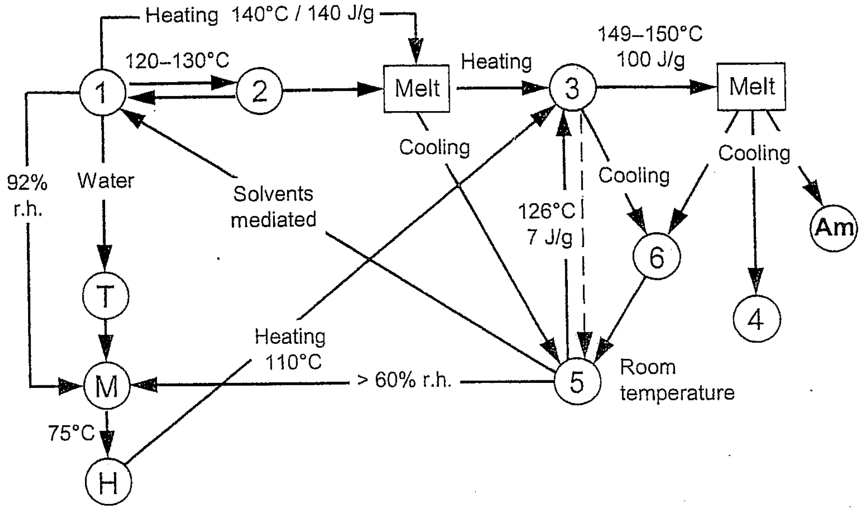

Fig. 25. *Relationships between six crystalline forms, an amorphous form, and three hydrated forms of tetracaine hydrochloride.* Am: amorphous form, T: tetrahydrate, M: monohydrate, H: hemihydrate.

X-Ray diffraction, DSC, and TG are very useful when deciding upon a salt form. By these techniques typical questions, which can be answered by suitable investigations, are: is the solvent retained or released under certain conditions; are the salts equally crystalline; are they hygroscopic; are they stable during storage; what is their polymorphic behavior; is the manufactured salt a true salt or a eutectic mixture; does the salt remain undissociated in the solid state in the pharmaceutical formulation? [53]. The experiments described for the study of polymorphs allow to establish the relationships between several salts to be studied. *Fig. 26* shows DSC curves of two salts, 3:2 and 1:1, formed by a drug base candidate with fumaric acid. Both salts could be crystallized from the same solvents, depending upon the conditions of crystallization. Equilibration of 1:1 mixtures of the two salts in EtOH or i-PrOH showed the preferential crystallization of the 1:1 fumarate salt [53].

6. Stability Behavior

Solid-state reactions fall into three categories: solid-solid reaction, solid-gas reactions, and solid transformations. Solid transformations have been discussed in *Sect. 5*. For example, tolbutamide can undergo an enantiotropic transition at 40 °C [75]. If the chosen polymorphic form is sensitive to a change of temperature, pressure, or moisture, methods for quantification of

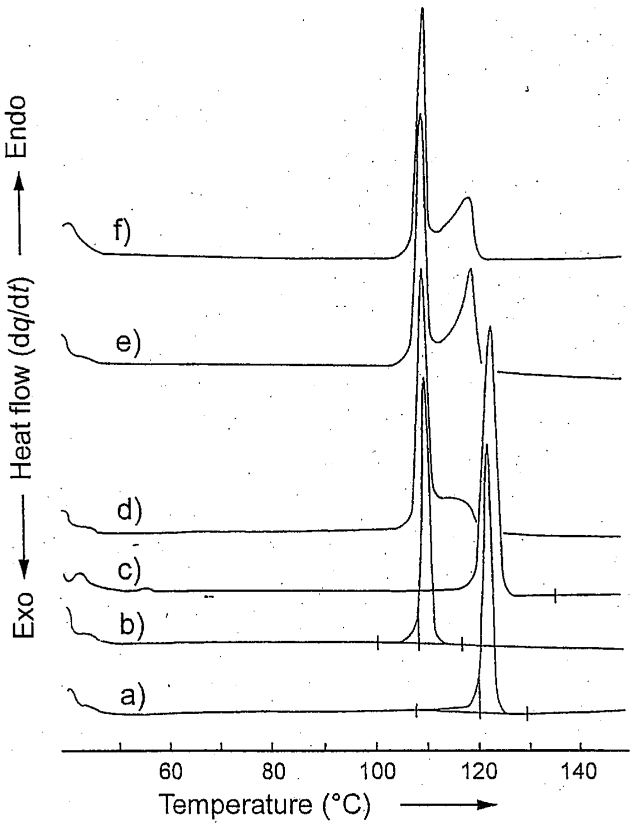

Fig. 26. *DSC Curves of mixtures of two different fumarate salts of a basic investigational drug substance. a)* Fumarate salt A (base/acid 1:1); *b)* fumarate salt B (base/acid 3:2); *c)* 1:1 mixture of A and B, equilibrated in EtOH or i-PrOH; *d)* 1:1 mixture of A and B, ground; *e)* 1:1 mixture of A and B, placed directly in the sample pan; *f)* 1:1 mixture of A and B, equilibrated in AcOEt.

the changes need to be developed. For this purpose, phase-pure modifications have to be produced. Valuable methods for quantitative analysis are powder X-ray diffractometry [79] [64], *Raman* spectroscopy [80], diffuse reflectance IR spectroscopy [80] or attenuated reflectance spectroscopy [82], solid-state ^{13}C-NMR spectroscopy with high-power proton decoupling, cross-polarization (CP) and magic angle spinning (MAS) [76] [83] [84]. The limits of detection and the quality of the results obtained depend largely on the sensitivity and on the selectivity of the signal assigned to each form. For all methods, the preparation of the samples is a critical factor. It should be ascertained that the prepared forms are phase-pure and stable enough, if metastable, to survive the experimental conditions employed. The methods used should take into consideration the availability of suitable references, such as the individual polymorphic forms, internal references, external references, or peak ratios. Powder X-ray diffraction is the technique most often employed and its limit of detection (LOD) can attain 1% or lower [64] [79]. Powder X-ray diffraction patterns, calculated from the known crystal structure, may be used for purity analysis of samples. Furthermore, diffraction patterns obtained at higher temperatures can be used for the detection of higher-melting enantiotropic forms in samples of lower-melting forms. Thermogravimetry is quite useful for the determination of the amounts of hydrates in solid samples. The amorphous content of a solid sample may be determined by X-ray diffraction, DSC, or microcalorimetry. Determination of the amorphous content by X-ray diffraction is generally based on the deviation from the baseline, termed the 'halo' of the amorphous fraction [85] [86]. The DSC method is based on the crystallization peak observed after the glass transition. The microcalorimetric method is based on the measurement of the exothermic crystallization peak of the amorphous form accelerated by the presence of humidity [86] [87]. X-Ray diffraction and microcalorimetry give comparable results, but the microcalorimetric method is more sensitive and provides reproducible results in the 1% range of amorphous content [86]. Solution calorimetry is also useful but is less sensitive [18]. Analysis of the stability of the drug product is less easy and depends on the excipient matrix and on the dose strength.

The salt form may influence the chemical stability of the solid state. *Walkling* [88] studied the solid-state stability of four salts and the free base of xilobam and observed a salt dependent stability behavior. The counter-ion can react chemically with the molecule of the drug substance by esterification, amidation, and/or the *Michael* reaction. For a drug substance candidate sensitive to epimerization, a correlation was found between the stability in the presence of moisture and the pH of the salt [41]. Furthermore, if the salt form is very soluble, dissociation, and variations in the localized micro-pH with the excipients can occur in the formulation, resulting in variations in stability behavior with the excipients. When comparing salt candidates, it is advisable to compare the pH of solutions or suspensions of the salt forms, taking into account the influence of pH of the stability profile of the compound (stability–pH profile).

Chemical reactivity in the solid state is correlated with the nature of the crystalline modifications. *Walkling et al.* [89] found that the two crystalline modifications of fenretinide behave quite differently. After 4 weeks at 25 °C, the stable form showed no detectable degradation, whereas the unstable form showed 8% degradation. In a serious example, the hydrolysis of an investigational compound led to a toxic degradation product for which one solid form was much less stable than the other [90].

The amorphous state is very reactive. According to *Zografi* [7] [30], the chemical reactivity in the liquid state should enable us to predict that of the

Table 4. *Influence of Temperature, Light, and Humidity on the Stability of the Amorphous and Crystalline Forms of a Peptide Drug Candidate*

Stress condition	**Amorphous**	**Crystalline**
	Degradation [%]	
1 week at 70 °C	79	10
Light: 300 k lx · h	38	2
	Uptake of moisture [%]	
1 day at 92% r.h.	9.0	1.3

amorphous state. *Table 4* illustrates the difference of reactivity between the crystalline and amorphous states of a peptide drug candidate. In the amorphous state, both the base and its hydrochloride were very unstable. However, the base could be obtained as a crystalline material with a substantial gain in stability [41].

When performing accelerated or stressed stability tests on a drug, it is common to employ chromatography as a stability-indicating and purity-indicating assay of the drug, after isothermal exposure of samples to elevated temperatures with or without an elevated humidity. If solid-phase transformations occur under such conditions, the results may not reflect the behavior under real storage conditions. For example, at a high temperature and high humidity, a transformation of an amorphous form to a crystalline form may result in erroneous evaluation of the chemical stability of the amorphous form. If the temperature is too high, melting can occur leading to reaction in liquid state at a higher rate than in the solid state. Microcalorimetry may be used to examine the different stability behaviors at moderate temperatures [91] [92].

The stability of polymorphs under the influence of light can be different as demonstrated for chloroquine diphosphate [93]. Even for ethoxycinnamic acid, different photolytic degradation products were obtained for each crystalline modification; the α-form gave one degradation product, whereas the β-form gave a second degradation product. No degradation product was found in the γ-form [94]. The above examples emphasize that the stability behavior of salt candidates in the solid state needs to be carefully evaluated.

7. Molecular Modelling and Solid-State Prediction

Molecular modelling by computational techniques plays an increasingly important role, not only in the design of drug substances but also in the study of their solid-state properties. The objective of these predictive methods is to reduce significantly the otherwise increasing amount of experimental efforts required. While prediction of crystal structures and their thermodynamic stability remains the long-term goal [95] [96], a brief summary of the present status of this rapidly developing field is given here.

Different types of intermolecular forces are present in the various structures adopted by molecules in the solid state. These intermolecular forces include: *Van der Waals* attractive interactions, H-bonds, electrostatic interactions, non-classical CH ⋯ OH-bonding, and short directional contacts representing the repulsive forces. The lattice energy, or crystal binding energy, is calculated assuming that the interaction energy between two molecules is the sum of the interaction energies between the constituent atom pairs. The calculated lattice energy can be broken down into the specific interactions along particular directions and further partitioned into the atom-atom contributions. The calculated intermolecular interactions can be further examined using the vast amount of data available in the *Cambridge Structural Database* (*CSD*). It is possible to interpret solid-state properties in terms of packing and intermolecular interactions. Attachment and slice energies can be calculated from the single-crystal structure, and the crystal morphology can thereby be predicted. By indexing the different faces of the crystal, morphological manipulations, based on the growth of defined faces, can be predicted for the choice of solvent or for the choice of additives in the final crystallization. From the single-crystal structure, powder X-ray diffraction pattern may be calculated and compared with the experimental pattern. The use of *Rietveld* and *MonteCarlo* algorithms with suitable software can provide the generation of approximate crystal structures. *Polymorph Predictor* is a module of the *Cerius* software package offered by *Accelerys* (formerly *Molecular Simulations Inc.*, *MSI*). Predictions of this type are based on lattice energy, and ignore the entropy component. The thermodynamic stability is, of course, determined by the *Gibbs* free energy, which depends on both the lattice energy and entropy. Predictions of the relative stability of polymorphs are, therefore, expected to be more accurate when the entropy relationships are included in the calculations. Molecular dynamics may provide a useful method for determining lattice entropies. *MSI* presented the commercial software package 'PowderSolve' at the *International Union of Crystallography* (*IUCr*) in Glasgow, August 1999. This software is designed to determine the crystal structures of flexible molecules or complex crystals, such as salts or hydrates, from the powder X-ray diffraction pattern [97]. Software of this type should facilitate comparisons of the solid-state structures of salts. The short time allowed for today's drug development requires the use of advanced tools which enable fast and well-founded decisions.

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Chapter 6

Salt-Selection Strategies

by **Abu T. M. Serajuddin*** and **Madhu Pudipeddi**

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   REFERENCES

1. Introduction

Because of the introduction of combinatorial chemistry and high-throughput screening (HTS) during the past ten years, the pharmaceutical industry is going through a revolutionary change in the way it has been discovering and developing drugs [1]. Larger, more lipophilic, and less water-soluble leads are being selected as a result of the quest for more potent and highly specific molecules. The widespread use of dimethyl sulfoxide (DMSO) in HTS also favors the selection of lipophilic, water-insoluble compounds, which are easily solubilized in this solvent. Since some of the attributes of newer drug molecules are unfavorable to their development as dosage forms, the 'developability' is becoming a critical consideration for the transition of a chemical entity from the discovery phase to the development phase [2] [3]. There is now a greater collaboration between discovery and development scientists in evaluating such developability criteria as solubility, dissolution rate, stability, permeability, and so forth, for the selection of optimal-development candidates. Since, as mentioned in *Chapt.* 2, salt formation can improve solubility and dissolution rate of basic and acidic drugs, thus increasing their absorption rate and bioavailability, we will present in this chapter various strategies for the selection of optimal salt forms for new drug candidates. The physicochemical principles to be described in this chapter will also be helpful in identifying acidic or basic drug candidates that can form more developable salts.

The salt selection should be viewed as a part of the overall objective of selecting the 'optimal form' of a drug candidate for development. When one refers to the optimal form, it involves both chemical and physical forms. A new chemical entity can be an acid, a base, or a neutral species. If it is a neutral species, there are no options for chemical manipulation to make it more developable other than possibly preparing prodrugs. On the other hand, if it is an acid or a base, one can select the free acid or base form, or, alternatively, one can select a salt form. In the selection of free *vs.* salt form, questions that need to be answered are: Is the acid or base form preferred because of biopharmaceutical considerations? Is the salt form more suitable? Is the preparation of stable salt forms feasible? Among various potential salt forms of a particular drug candidate, which has the most desirable physicochemical and biopharmaceutical properties?

Along with the evaluation of chemical form, the strategy for the selection of physical form must also be considered. One needs to determine whether the compound exists in crystalline or amorphous form, and, if crystalline, whether it exhibits polymorphism. One also needs to investigate: Does the compound exist in hydrate or solvate form? If so, how is such a form affected by temperature and moisture? How stable is a particular form in solid state and in solution? The ultimate selection of the 'optimal form' of a new drug candidate for development depends on a balance among the physicochemical properties of its various available chemical and physical forms.

Another critical element of a salt-selection process in any drug-development program is the timing. Here, the critical questions are: When does one start salt selection? Should a new drug candidate be selected after consideration of its feasibility for salt formation? Or should any such consideration be postponed, until the new candidate has been selected and forwarded to the development stage? How can the salt selection be integrated in the development process such that it does not become a rate-limiting step or does not extend development time?

The success of a salt-selection program also depends on how various disciplines within drug discovery and development interact and collaborate. The composition of a salt-selection team and the responsibilities of individual team members may have profound effects on time and resources spent on a salt-selection program.

Based on the above considerations, salt-selection strategies for new drug candidates may have the following components:

i) selection of chemical forms of salts,
ii) selection of physical forms of salts,
iii) salt-selection timing,
iv) composition of salt-selection team

In the present chapter, strategies for the selection of chemical forms of salts will be described in detail. Strategies for the selection of physical forms will be discussed in less detail, since *Chapt. 3* and *7* will also cover several aspects of these strategies. Salt-selection timing and composition of salt-selection teams will be discussed only briefly, since no clear picture of how these are practiced in various drug companies has emerged yet.

2. Selection of Chemical Forms of Salts

At the outset of any salt-selection program, it is important to determine whether a particular acid or base is amenable to salt formation. If the salt formation appears to be feasible, the question then arises is which one of the many available counter-ions would be most suitable for the purpose. Some of these issues will be addressed in this section.

2.1. Feasibility Assessment for Salt Formation

No predictive procedure to determine whether a particular acidic or basic drug would form a salt with a particular counter-ion has been reported in the literature. *Anderson* and *Flora* [4] reported that successful salt formation generally requires that the pK_a value of a conjugate acid should be smaller than the pK_a value of the conjugate base to ensure sufficient proton transfer from the acidic to the basic species. Thus, relatively stronger acids like HBr, HCl, H_2SO_4, or one of the sulfonic acids ($pK_a < 2.0$) would be suitable for the preparation of salts of weakly basic amines having $pK_a < 4$. Other investigators also provided similar but rather general guidelines for the selection of counter-ions. *Wells* [5], and also *Tong* and *Whitesell* [6] recommended that, for the preparation of salt forms of a basic drug, the pK_a of the acid used should be at least 2 pH units lower than the pK_a of the drug. Although these are valuable guidelines, a more predictive method for assessing the feasibility of salt formation would be necessary to minimize trials and errors in a salt-selection program.

As described in *Chapt. 2*, the pH–solubility interrelationship and the location of pH_{max} in the pH scale play critical roles in determining which salt, if any, can be synthesized for a particular free acid or base. *Dittert et al.* [7] reported as early as in 1964, although not for the specific purpose of salt selection, that whether a basic drug would exist as the free base or as a salt under certain pH conditions can be determined by studying its solubility *vs.* pH relationship. Later, *Kramer* and *Flynn* [8] demonstrated that the pH–solubility relationship of a basic drug could be expressed by two independent curves, and the point where the two curves intersected was the pH_{max}, the pH of maximum solubility. This is shown in *Fig. 1*, and the relevant equations are given below:

$$\text{At pH} > \text{pH}_{max}: \quad S_T = [BH^+] + [B]_s = [B]_s \cdot (1 + [H_3O^+]/K_a) \qquad (1)$$

$$\text{At pH} < \text{pH}_{max}: \quad S_T = [BH^+]_s + [B] = [BH^+]_s \cdot (1 + K_a/[H_3O^+]) \qquad (2)$$

In both *Eqns. 1* and *2*, S_T is the total or equilibrium solubility under a particular pH condition, [B] and [BH^+] are concentrations of free and protonated species of the base, respectively, and the subscript s represents the concentration in equilibrium with the solid phase. *Fig. 1* essentially illustrates that a salt would not be formed in an aqueous medium, unless the pH of the saturated solution of a basic drug is not lowered below the pH_{max}, and any salt formed would be reconverted to its free base form, if the pH of a saturated salt solution is raised above the pH_{max}. In other words, solid phases that remain in equilibrium with solutions at pH below and above pH_{max} are a salt and the free base, respectively.

Similar pH–solubility relationship also exists for acidic drugs [9] [10]. As illustrated in *Fig. 2*, for a monoprotic acid, the free acid would be the equilibrium species at a pH below the pH_{max}, and a salt would be formed only if the pH is raised above the pH_{max} by using suitable counter-ions. The relevant

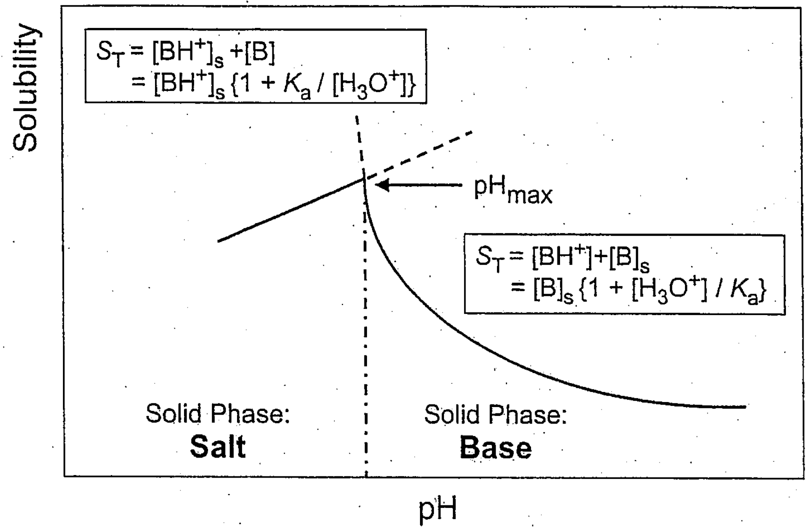


Fig. 1. *Schematic representation of the pH–solubility profile of a monobasic compound, showing that solubilities of base and salt can be expressed by two independent curves corresponding to two independent equations.* The point where the two curves intersect is the pH$_{max}$.

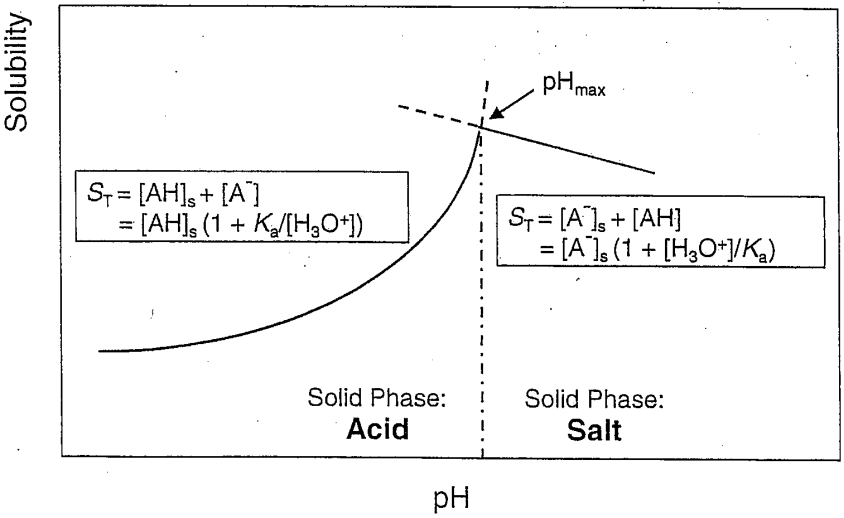


Fig. 2. *pH–Solubility profile analogous to* Fig. 1 *of a monoprotic acid*

equations are given below:

At pH < pH$_{max}$:
$$S_T = [AH]_s + [A^-] = [AH]_s \cdot (1 + K_a/[H_3O^+]) \quad (3)$$

At pH > pH$_{max}$:
$$S_T = [A^-]_s + [AH] = [A^-]_s \cdot (1 + [H_3O^+]/K_a) \quad (4)$$

In *Eqns. 3* and *4*, S_T is again the total solubility under a particular pH condition, [AH] and [A^-] are concentrations of free and ionized species of the acid, respectively, and the subscript s represents the concentration in equilibrium with the solid phase.

Solubilities of salts, as described by *Eqns.* 2 and 4, can be influenced by excess counter-ions present in solution. However, counter-ions influence solubilities through solubility products only after salts are formed and, therefore, might not adversely affect the feasibility of salt formation. The issue of solubility product on the salt-selection strategy will be discussed in a later section of this chapter.

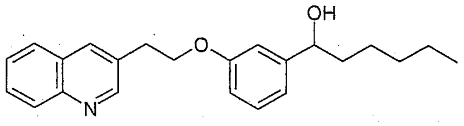
Serajuddin and co-workers [10 – 14], and numerous other authors [8] [9] [15 – 18] confirmed the application of the above-mentioned pH–solubility relationships in determining under which pH conditions salts of particular acidic and basic drugs can be formed.

2.2. Application of pH–Solubility Relationship: Case Histories

The application of pH–solubility relationships in determining the feasibility of salt formation can be explained by a few case histories.

2.2.1. *Case History 1: REV5901*

To determine the feasibility of salt formation for REV-5901 (*Fig. 3*), a base with the pK_a value 3.7, *Serajuddin et al.* [14] determined its pH–solubility profile as shown in *Fig. 4*. An identical profile was obtained, when either the free base or the hydrochloride salt was used as the starting solid phase. The pH_{max} of the compound was 1, indicating, as mentioned above, a salt form would exist only at pH below 1.0. Indeed, only two salts, a hydrochloride salt and a sulfate salt, could be prepared for REV-5901, since only strong acids like HCl and H_2SO_4 could lower the pH of a saturated solution below the pH_{max} of 1. A salt formation with relatively weaker acids like phosphoric acid, acetic acid, lactic acid, tartaric acid, and so forth, would not be feasible, since such acids would be unable to lower the pH below 1.0. Thus, just from the pH–solubility relationship, one can narrow down the type and the number of salts that can be prepared, saving much efforts and resources that could otherwise be wasted in attempting to synthesize many different salt forms. Based on *Fig. 4*, one would even question the suitability of hydrochloride and sulfate salts for development, because such salts would be converted to the free base form, when the microenvironmental pH in presence of moisture rises above 1.0. It was, indeed, observed that both of these salts



$pK_a = 3.6$
$S_0 = 0.002$ mg/ml

Fig. 3. *Chemical structure of REV5901, the compound used in* Case History 1

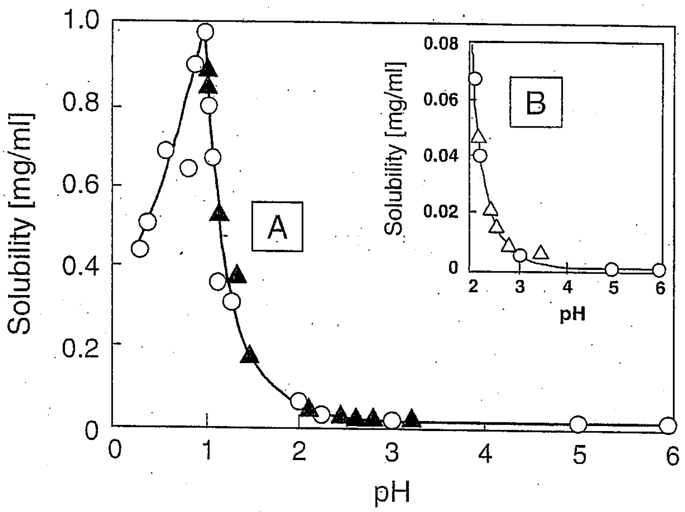


Fig. 4. *pH–Solubility profile of REV5901* (A), *where triangles represent the solubility obtained with the free base and circles the data obtained with the hydrochloride salt. In the insert* (B), *the solubility is shown on an expanded scale.* Either HCl or NaOH was used to adjust pH.

did not have acceptable properties for development, and the free base form of REV-5901 was ultimately selected.

2.2.2. *Case History 2: GW1818*

Tong and *Whitesell* [6] studied the feasibility of salt formation of a basic drug GW1818, which had the pK_a value of 8.0 and the intrinsic free base solubility of 0.0044 mg/ml. For this compound, the pH_{max} was *ca.* 5, and, as a result, the formation of stable salts with both strong and weak counter-ions, such as hydrochloride, methanesulfonate, phosphate, and succinate, was feasible. This is because all of these counter-ions could lower the pH below 5.

2.2.3. *Case History 3: Phenytoin*

The feasibility of salt formation for an acidic drug can be illustrated by the pH–solubility profile of phenytoin (*Fig. 5*), a compound with a pK_a value of 8.4 and the intrinsic free acid solubility of 0.02 mg/ml at 37 °C [19]. The sodium salt is the commercially available salt form for phenytoin, and there are numerous reports in the literature demonstrating that the free acid form of phenytoin precipitate out of salt solutions depending on pH. There is also the propensity for the conversion of salt to free acid in solid dosage form. It is apparent from *Fig. 5* that the salt formation for phenytoin is feasible only with strong alkalis like NaOH because it can raise the pH above the pH_{max} value of 11. Since relatively weaker bases like $Mg(OH)_2$, $Ca(OH)_2$, *etc.*, and the commonly used amine bases like arginine, lysine, *etc.*, would not raise the pH of an aqueous solution above 11, they will not form salts with phenytoin. *Fig. 5* also indicates that any salt formed would be converted to the free acid if the microenvironmental pH were below 11. If, unlike phenytoin, the pH_{max} of an acid were, for example, around 8, there would be a much better option for salt formation, because the pH could be raised above 8 by using a larger selection of alkalis and bases.

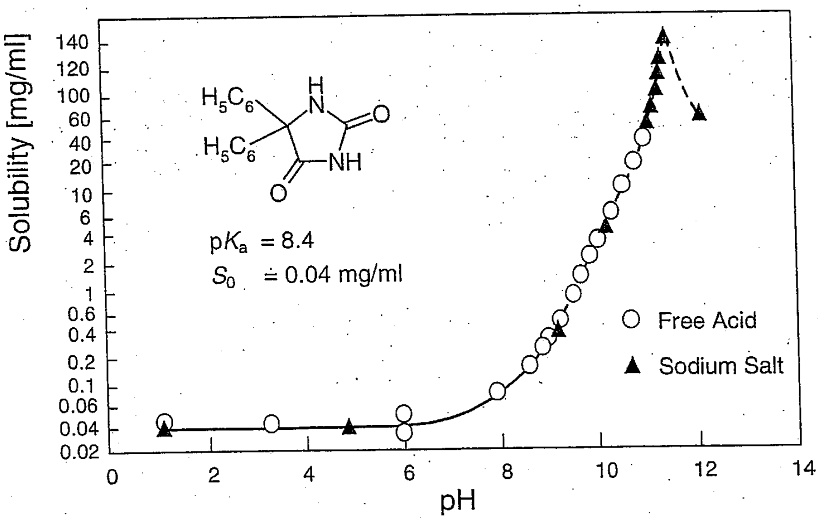


Fig. 5. *pH–Solubility profile of phenytoin at 37 °C indicating* pH_{max} *at 11.* Identical profiles were obtained when either free acid or the sodium salt of the drug substance was used. pH was adjusted using either NaOH or HCl.

2.3. Theoretical Modeling of pH–Solubility Relationship

In the case histories mentioned above, pH–solubility profiles, which were determined experimentally, have been used to identify the pH_{max} and to determine the feasibility of salt formation. However, at drug discovery and early development stages, when the supply of drug substances is limited, it might not be practical to determine pH–solubility profiles experimentally. In such a situation, the pH–solubility relationships corresponding to *Eqns. 1* and *3* for basic and acidic drugs, respectively, can be generated theoretically, if pK_a and S_0 values are available. Then, an estimate of pH_{max} values can be made by assuming certain values for salt solubilities.

Fig. 6 shows pH–solubility profiles of a basic compound generated theoretically according to *Eqn. 1* by using a fixed pK_a value of 8.0 and various S_0 values ranging from 0.0001 to 10 mg/ml. In this case, solubilities of salt forms corresponding to various theoretical curves are unknown. Any particular value for the salt solubility can be assumed for the purpose of estimating pH_{max} values. If, for example, a salt solubility of 20 mg/ml is assumed corresponding to each curve in *Fig. 5*, the estimated pH_{max} values corresponding to S_0 values of 0.0001, 0.001, 0.01, 0.1, 1, and 10 mg/ml would be 3, 4, 5, 6, 7, and 8, respectively. The pH_{max} values would not differ much even if the solubility of salt form somewhat differs, because, as mentioned in *Chapt. 2*, for a ten-fold difference in salt solubility, the pH_{max} differs by one unit only. Thus, from the theoretical analysis of pH–solubility relationships in *Fig. 6*, it may be concluded that the salt formation of a base with the pK_a value of 8.0 might be feasible with most commonly used acids when S_0 val-

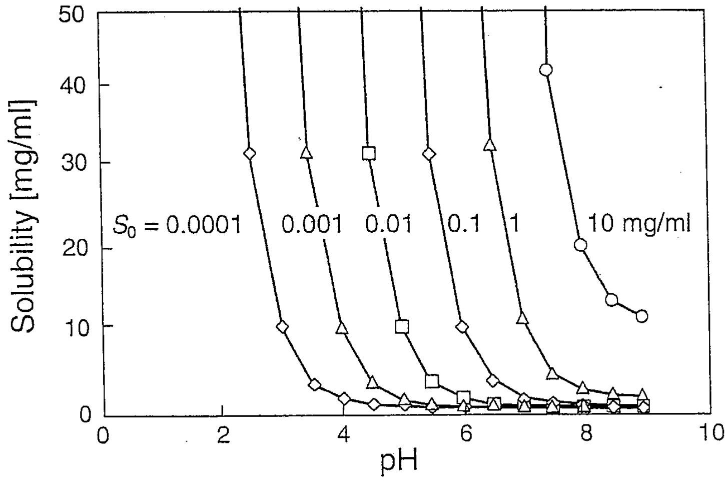
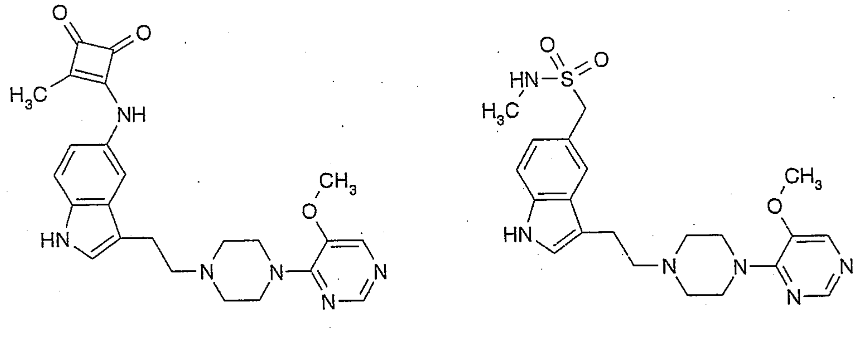


Fig. 6. *Theoretical pH–solubility profiles demonstrating the effect of intrinsic solubility* (S_0) *ranging from 0.0001 to 10 mg/ml of a basic drug with the* $pK_a = 8.0$

ues are *ca.* 0.01 mg/ml and higher. This is because pH_{max} values in these cases would be around 5 and higher. For S_0 values of 0.001 and 0.0001 mg/ml, however, relatively stronger acids would be required to form salts because pH_{max} values would be *ca.* 4 and *ca.* 3, respectively.

The theoretical analysis in *Fig. 6* will change if the pK_a value of a basic drug is lower. As shown in *Chapt. 2*, there is a direct relationship between pK_a and pH_{max}; the pH_{max} decreases by 1 for each unit decrease in the pK_a value. Thus, if the pK_a value in *Fig. 6* would be 4.0 instead of 8.0, the pH_{max} would be 3 and lower for S_0 values of 1 mg/ml and lower. In such a situation, the possibility of salt formation becomes limited, because only relatively stronger acids like HCl, methanesulfonic acid, ethanesulfonic acid, *etc.*, can lower the pH of saturated solutions below 3. The salt formation may not at all be feasible if the S_0 is below 0.01 mg/ml because the pH_{max} in this case would be less than 1.

A confirmation of the validity of above theoretical analysis may be obtained from the work of *Lakkaraju et al.* [20], where the authors studied pH–solubility relationships of two structurally similar compounds, avitriptan and BMS-181885 (*Fig. 7*). The compounds were dibasic in nature, each of them with pK_a values of 8.0 and 3.6. However, the S_0 values of the compounds differed; they were 0.006 and 0.0007 mg/ml for avitriptan and BMS-181885, respectively. Because of this difference in S_0 values, the pH_{max} values, due to the effect of the higher pK_a (8.0), were *ca.* 5 for avitriptan and *ca.* 4 for BMS-181885. As a consequence, salts with many different counterions, including acetate, lactate, succinate, and tartrate, could be synthesized for avitriptan. But, with BMS-181885, it was not possible to lower the pH of a saturated solution below 4 by using acetic acid, lactic acid, succinic acid,



Avitriptan
$pK_{a,1} = 8.0$; $pK_{a,2} = 3.6$
$S_0 = 0.006$ mg/ml

BMS-181885
$pK_{a,1} = 8.0$; $pK_{a,2} = 3.6$
$S_0 = 0.0007$ mg/ml

Fig. 7. *Chemical structures of avitriptan and BMS-181885*

or tartaric acid, and, therefore, the salt formation with any of these counter-ions was not feasible for this compound. However, BMS-181885 formed salts with stronger acids like H_3PO_4 and HCl.

It should be noted here that self-association of drug molecules in solutions may sometimes lead to deviations in pH–solubility profiles predicted from pK_a and solubility. Nevertheless, the theoretical modeling can still serve as a useful method of predicting the feasibility of salt formation because a pH_{max} value may be estimated within a reasonable range. Also, the self-association often shifts pH_{max} in favor of salt formation.

2.4. Feasibility of Disalt Formation

Eqns. 1–4 are applicable to compounds with only one pK_a value, and, therefore, the discussion in this chapter has so far focused primarily around the feasibility of salt formation for bases with one protonatable moiety and acids with one ionizable species. Such compounds can form only mono-salts (*e.g.*, mono-hydrochloride, mono-sodium, *etc.*). In addition, a compound may have both basic and acidic moieties. Such a compound can also be classified as one forming a mono-salt, because only one of these groups can be used at one time for salt formation. In contrast, drugs can also be polybasic or polyprotic, which might be able to form poly-salts. Examples of disalts, such as dihydrochloride, disodium, *etc.*, are common in the literature. Some of the questions that arise for compounds with multiple basic moieties or multiple acidic moieties are: Should mono- or poly-salt be synthesized for such compounds? Is the formation of poly-salt feasible? If the synthesis of both forms of salts is feasible, which one is preferred for a particular drug candidate? Some of these issues are addressed below.

2.4.1. *Feasibility of Salt Formation for Dibasic Compounds*

Serajuddin and co-workers [20] [21] have demonstrated that the feasibility of salt formation for a dibasic compound can also be predicted from its pH–solubility relationship. As illustrated schematically in *Fig. 8*, the solubility of a free base increases with a decrease in pH, and, after the first pH_{max} (or $pH_{max,1}$) is reached, a mono-salt might be formed. The solubility of the mono-salt formed then increases because of the protonation of the second basic moiety, thus reaching $pH_{max,2}$. Below $pH_{max,2}$, a disalt could be formed. Depending on pH and counter-ions used to prepare salts, there could be three distinct solid phases (free base, mono-salt, and disalt) in equilibrium with aqueous solutions. The equations corresponding to solubilities of these three

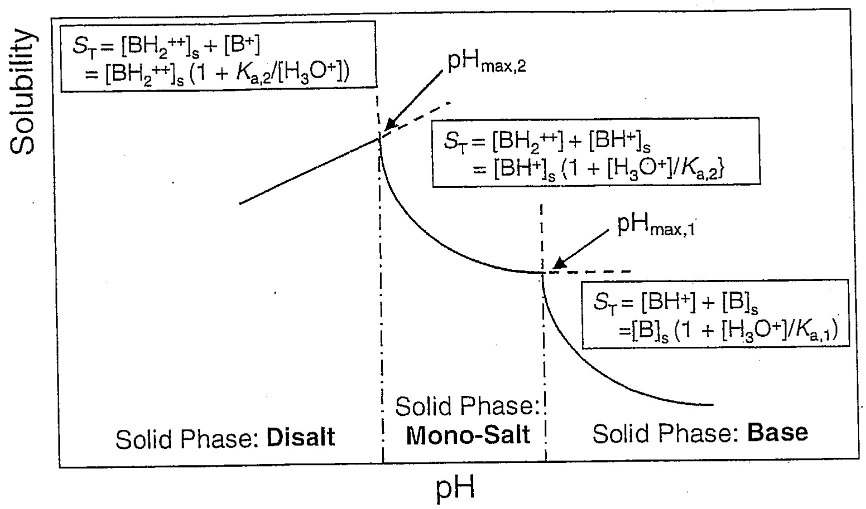


Fig. 8. *A schematic representation of the pH–solubility profile of a dibasic compound, showing that solubilities of the base and its mono- and disalt forms can be expressed by three independent curves corresponding to three independent equations.* The profile indicates that two pH_{max} values, $pH_{max,1}$ and $pH_{max,2}$, may exist for such a compound.

phases are given below:

At $pH > pH_{max,1}$:
$$S_T = [BH^+] + [B]_s = [B]_s \cdot (1 + [H_3O^+]/K_{a,1}) \quad (5)$$

At $pH < pH_{max,1}$ and $> pH_{max,2}$:
$$S_T = [BH_2^{++}] + [BH^+]_s = [BH^+]_s \cdot (1 + [H_3O^+]/K_{a,2}) \quad (6)$$

At $pH < pH_{max,2}$:
$$S_T = [BH_2^{++}]_s + [B^+] = [BH_2^{++}]_s \cdot (1 + K_{a,2}/[H_3O^+]) \quad (7)$$

For the sake of simplicity, no consideration of the common-ion effect and the solubility product was made in deriving the above equations. It should also be mentioned here that distinct regions in the pH–solubility profile corresponding to mono- and disalt forms may not be obtained if pK_a and/or pH_{max} values of the compound are not far apart (*ca.* 2 units). If two pH_{max} values are indistinguishable, only the disalt may be isolated in pure form.

Avitriptan (*Fig. 7*), a dibasic compound, was used as the test compound for salt formation. As shown in *Fig. 9*, protonation of the piperazine N-atom and the pyrimidine N-atom was responsible for pK_a values of 8.0 and 3.6, respectively, for the compound. By using HCl to adjust pH, it was established that the compound could have two pH_{max} values, one at pH 5 ($pH_{max,1}$) and the other at pH *ca.* 2 ($pH_{max,2}$). This is shown in *Fig. 10*. It is evident from

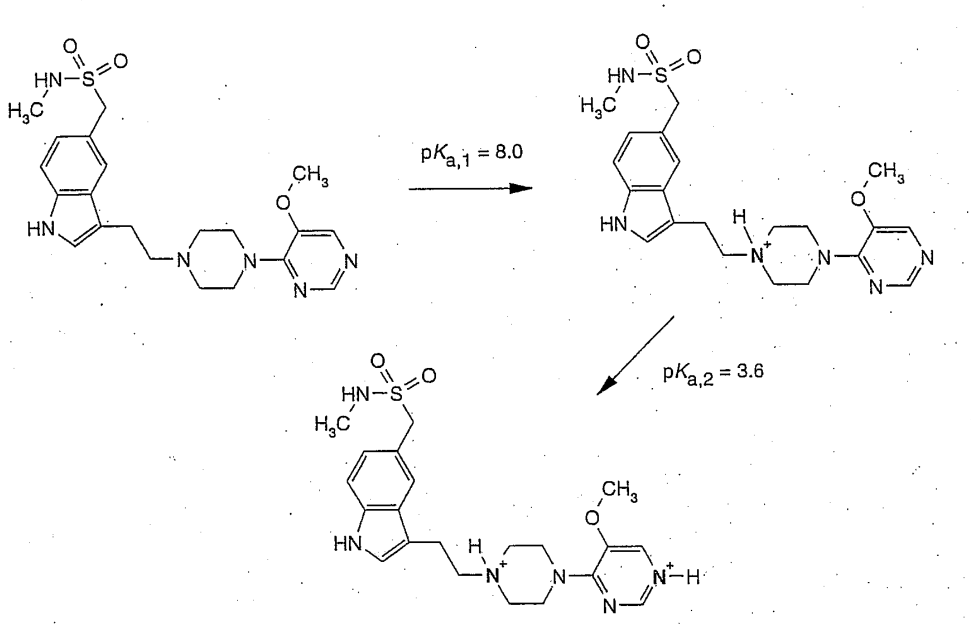


Fig. 9. *Protonation of avitriptan corresponding to its two* pK_a *values*

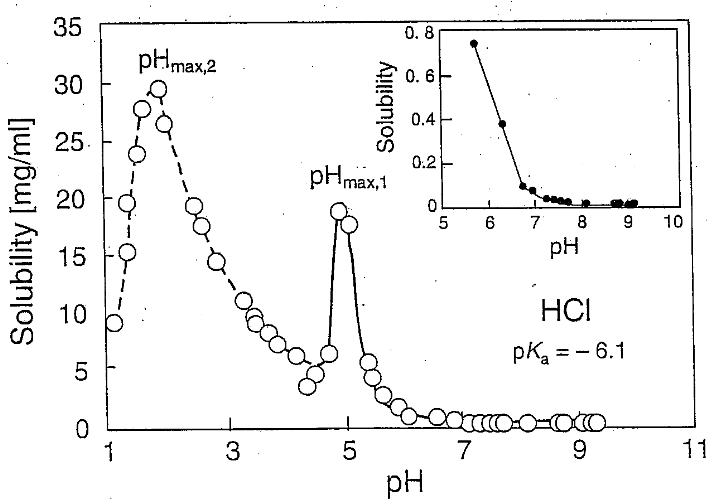


Fig. 10. *pH–Solubility profile of avitriptan at 25 °C where HCl was used to adjust pH, indicating two* pH_{max} *values. Solubility profile at pH above 5 is shown in the inset.*

Fig. 10 that both mono- and dihydrochloride salts can possibly be prepared for avitriptan; the monohydrochloride salt would be the equilibrium species at pH between 2 and 5, and the dihydrochloride salt would be the equilibrium species at pH below 2. Among various acids used by *Lakkaraju et al.* [20] to form salts with avitriptan, only HCl could lower the pH of a saturated av-

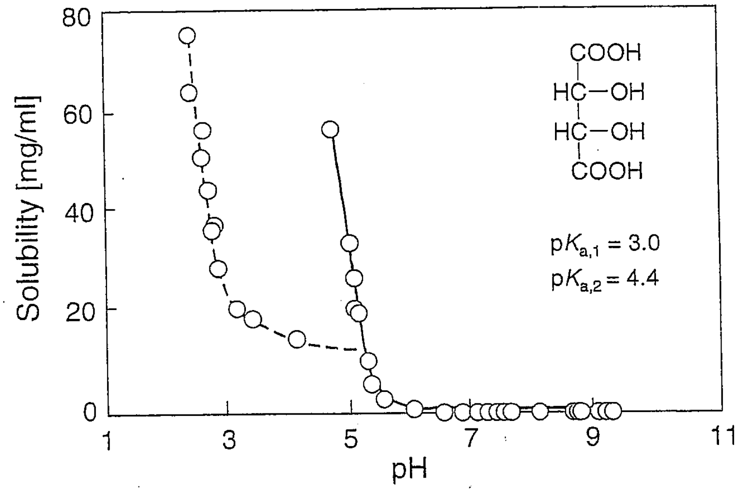


Fig. 11. *pH–Solubility profile of avitriptan at 25 °C where tartaric acid was used to adjust pH, indicating the presence of only one pH$_{max}$ value*

itriptan solution below 2 and thus could form a disalt. The pH of an avitriptan solution could be lowered below 5 (pH$_{max,1}$) but not below 2 (pH$_{max,2}$), when methanesulfonic acid, acetic acid, lactic acid, tartaric acid, and succinic acid were used, indicating that these acids would form only mono-salts with avitriptan. As a typical example, the pH–solubility profile of avitriptan in presence of tartaric acid is shown in *Fig. 11*, where the pH could not be lowered below 2.5 by adding excess amount of tartaric acid. In agreement with these pH–solubility considerations, the salt-selection program of avitriptan yielded mono-salts for all counter-ions used except for hydrochloride, although the existence of two basic moieties in the molecule intuitively suggested that attempts for the synthesis of disalts using various counter-ions should be made. Thus, conducting a feasibility analysis based on pH–solubility relationships can save considerable time and efforts in a salt-synthesis program.

2.4.2. *Feasibility of Salt Formation for Diprotic Acids*

Equations analogous to *Eqns. 5–7* above can also be derived for acids with two ionizable groups in order to study the feasibility of mono- or disalt formation. For such a compound, the solubility of the acid initially increases with an increase in pH due to the ionization of the first ionizable group (*i.e.*, the stronger ionizable group with lower pK_a value). At a certain pH, the first pH$_{max}$ (pH$_{max,1}$) will be reached, and above that a mono-salt will form.

With a further increase in pH, the solubility of the mono-salt will increase due to the ionization of the second ionizable group in the molecule, and the second pH_{max} ($pH_{max,2}$) will be reached. A disalt will be formed above $pH_{max,2}$. The relevant equations are given below:

$$\text{At } pH < pH_{max,1}: \quad S_T = [AH]_s + [A^-] = [AH]_s \cdot (1 + K_{a,1}/[H_3O^+]) \tag{8}$$

$$\text{At } pH > pH_{max,1} \text{ but} < pH_{max,2}: \quad S_T = [A^-]_s + [A^{--}] = [A^-]_s \cdot (1 + [H_3O^+]/K_{a,1}) \tag{9}$$

$$\text{At } pH > pH_{max,2}: \quad S_T = [A^{--}]_s + [A^-] = [A^{--}]_s \cdot (1 + [H_3O^+]/K_{a,2}) \tag{10}$$

In any salt-screening program for diprotic acids, the pH-solubility relationships can be studied either experimentally or by theoretical considerations using *Eqns. 8* and *9*. Then, whether a compound will at all form a salt, and, if it forms a salt, whether it will form a mono- or disalt can be ascertained by studying the effect of counter-ion on the pH of a saturated solution. If the pH of a saturated solution cannot be raised above $pH_{max,1}$ by adding a particular counter-ion, a salt would not be formed. If the pH remains between $pH_{max,1}$ and $pH_{max,2}$, a mono-salt would be formed. A disalt would be formed only if the pH rises above $pH_{max,2}$. In other instances, when pK_a values of two acidic moieties are closer, and, as a consequence, $pH_{max,1}$ and $pH_{max,2}$ are also closer or indistinguishable, it might be difficult to isolate mono-salts in pure forms; either a disalt or a mixture of mono- and disalts might be formed. Under such a situation, the preparation of only disalts may be considered, and, if acceptable disalts are not available, due consideration to the free form of the drug should be given.

2.5. Effect of Counter-Ions on Salt Solubility

It has been reported extensively in the literature that aqueous solubilities of different salt forms of a compound may vary depending on counter-ions used [9] [16] [17] [22–25]. *Streng et al.* [16] attributed the difference in aqueous solubilities of lactic acid, methanesulfonic acid, HCl, and H_3PO_4 salts of terfenadine on the difference in their K_{sp} values with different counter-ions. *Anderson* and *Flora* [4] reviewed the literature for this aspect of salt formation; however, no predictive relationship emerged. It is often difficult to predict *a priori* how solubilities of different salt forms of a particular drug will differ from each other. The reported differences in salt solubilities could sometimes be due to artifacts; some possible difficulties in the determination of accurate salt solubility have been discussed in *Chapt. 2* of this volume and also by *Anderson* and *Flora* [4]. It is possible that, for a particular salt, the excess solid present in equilibrium with a saturated solution during the solubility determination may not be a salt, because the salt may dissociate into its free form, and thus the 'apparent solubility' may not reflect the true solubility of the salt form. This can lead to an inaccurate and misleading solubility value. Other factors such as crystal lattice energy, solvation energy, common-ion effect, hydrated state of crystals, and so forth, could also be responsible for differences in solubilities of different salt forms of a particular compound. *Anderson* and *Flora* [4] noted that contributions of salt-forming counter-ions on salt solubility must be considered in terms of their separate contributions to crystal-lattice and solvation energies. Since crystal-lattice and hydration energies increase with an increase in cation or anion charges and decrease with an increase in ionic radius, the overall effect of a change in salt form on water solubility will depend on which term, the ionic charge or the ionic radius, is most sensitive to the change in structure. *Lakkaraju et al.* [20] reported that aqueous solubilities of mono-salt forms of avitriptan with five counter-ions, namely, acetate, lactate, methanesulfonate, succinate, and tartrate, were similar and ranged from 14.7 to 16.5 mg/ml, while the solubility of the monohydrochloride salt was 3.4 mg/ml. However, no analysis of contributing factors leading to the similarity in solubilities of certain salts and the difference with another was made.

2.5.1. *Common-Ion Effect on Salt Solubility and Dissolution*

When a basic drug forms a salt with a relatively strong acid, namely, HCl, the aqueous solubility of the salt is strongly influenced by the common-ion effect [11–16]. In such a case, *Eqn. 2*, which depicts the solubility of such a salt, becomes

$$S_T = (1 + K_a/[H_3O^+])\sqrt{K_{sp}} \qquad (11)$$

where, for a hydrochloride salt, the solubility product, K_{sp}, is defined by

$$K_{sp} = [BH^+]_s \cdot [Cl^-].$$

It is evident from *Eqn. 11* that as the chloride ion concentration increases with a decrease in pH, the solubility of the salt would decrease due to the common-ion effect and in accordance with the K_{sp} value. This fact should carefully be considered in selecting a hydrochloride salt for development, because, under the acidic pH condition of stomach in the gastro-intestinal tract, the solubility and the dissolution rate of the salt will decrease. The common-ion effect due to a decrease in pH is relatively less pronounced in case of salts of basic drugs with relatively weak acids, such as acetic acid, lactic acid, *etc.*, because the ionization of such acids decreases with the lowering of pH.

Solubilities of alkali salts of acidic drugs are also governed by the solubility product (K_{sp}) and decrease with an increase in common-ion. *Serajuddin et al.* [26] reported that the solubility of the sodium salt of an experimental drug REV3164 decreased from 7.8 mg/ml in distilled water to 1.1 mg/ml in a 0.1 M NaCl solution. This common-ion effect on solubility adversely influenced the development of REV3164 as a solution dosage form. Such an effect of K_{sp} on the solubility of the salt form of an acidic drug can be studied using the following equation:

$$S_T = (1 + [H_3O^+]/K_a)\sqrt{K_{sp}} \tag{12}$$

where, for a sodium salt, $K_{sp} = [Na^+]\,[A^-]$. The possible effect of K_{sp} on salt solubility and its influence on dosage form design should, therefore, be carefully analyzed during the salt-form selection for acidic drugs. Although no systematic study has been reported in the literature, it is usually assumed that organic counter-ions (*e.g.*, amines) exert relatively less effects on solubility as compared to the inorganic ones.

The use of counter-ions other than hydrochloride may also provide higher dissolution rates for salts of a basic drug as compared to its hydrochloride salt form in the gastric fluid where the presence of chloride ions is prevalent. Indeed, *Bogardus* and *Blackwood* [27] reported that the dissolution rate of doxycycline hydrochloride in 0.1M HCl was adversely influenced by the chloride-ion concentration, whereas a hyclate salt was not similarly affected. Unless the non-hydrochloride salt forms of a particular drug are converted to the crystalline hydrochloride salt during dissolution, no common-ion effect on the dissolution rate is expected. Since the dissolution is a dynamic process, the hydrochloride salt may not readily form on surfaces of dissolving non-hydrochloride salts. Also, any dissolved drug may not crystallize out in the gastric fluid as the hydrochloride salt, unless the solubility of the hydrochloride salt is extremely low. When solubilities of different salt forms for a particular drug are relatively low, such a lack of common-ion effect on the dissolution rate may result in higher bioavailability for a non-hydrochloride salt. Recently, *Engel et al.* [28] reported that the methanesulfonate salts of two basic drugs had 2.6 and 5 times higher bioavailability in dogs than their corresponding hydrochloride salts.

2.5.2. in-situ *Screening of Counter-Ion Effects on Salt Solubility*

Since salts with different aqueous solubilities can be produced for a particular compound by using different counter-ions, *Shanker et al.* [29] reported a method whereby salt solubilities can be screened *in situ* using small amounts of drug substances. In this method, small volumes of concentrated drug solutions using different counter-ions are prepared, and the solutions are then set aside for the crystallization of salts. In such solutions, the counter-ion concentrations are usually in stoichiometric ratios (or slightly in excess of stoichiometric ratios) with drugs. Once the crystals are formed and equilibria are established, drug concentrations in the solutions are measured. *Tong* and *Whitesell* [6] later used this method for the *in-situ* screening of salt solubilities for a basic drug having a pK_a value of 8.02 and the free base solubility of 0.0044 mg/ml. However, care must be taken in any routine use of this method for determining solubility and assessing the feasibility of salt formation. Supersaturated solutions with pH around the pH_{max} are often formed, when a free acid or base and its counter-ions are mixed together [10] [12] [13] [18]. Unless crystal forms of salts are produced and equilibria are reached, any measurement of drug concentration may lead to erroneous conclusions regarding salt solubility. It is also difficult during the initial set-up of such experiments to ascertain whether adequate amounts of drugs and counter-ions have been added. A salt would not crystallize, unless the drug concentration is adequate and the pH of solution is favorable for salt formation (for example, its position with respect to pH_{max} in the pH–solubility profile).

One should also keep in mind that a negative result with respect to crystallization during *in-situ* screening in aqueous media does not necessarily mean that a salt would not be formed. When salts are not produced in aqueous media, it might still be possible to crystallize them from organic solvents or water/organic cosolvent systems. For this reason, there is a recent trend where multiple counter-ions and multiple solvent systems are used in an attempt to prepare salts for a particular compound. In addition to a greater effort in salt synthesis, this makes the number of samples for subsequent physicochemical characterization very large. For example, if 10 counter-ions are tested for a compound, and for each counter-ion 10 solvent systems are used, the total number of samples generated would be 100. Salt-selection strategies based on pH–solubility principles, as reported in the present chapter, may greatly reduce the number of such samples and thus accelerate the salt-selection process.

2.6. Effect of Organic Solvents on Salt Formation

The pH–solubility relationships in aqueous media and their influences on the salt formation of acidic and basic drugs have been the primary focus of this chapter. However, organic solvents or water/organic cosolvent systems are frequently used for the preparation of salts. Although not much has been reported in the literature, it has been the experience of present authors that pH–solubility theories may also be applied in assessing the feasibility of salt formation from organic systems.

An organic solvent may influence the solubility of a compound in several ways: *i*) increase solubility of unionized species, *ii*) decrease protonation or ionization of the molecule, and *iii*) decrease solubility of salt formed. *Kramer* and *Flynn* [8] postulated that the pH_{max} of a basic drug can increase due to an increase in S_0 value in a cosolvent system. Similarly, the pH_{max} of an acidic drug may decrease because of an increase in S_0 value in the medium. As indicated in *Figs. 1* and *2*, such an effect may favor salt formation. However, this will be true only if the ionization behavior, that is, the pK_a value, of the compound remains unchanged. It has been extensively reported in the literature that an organic solvent may adversely influence the ionization of drug due to a decrease in dielectric constant as compared to H_2O [30 – 32]. For example, alcohols weaken both acids and bases. *Albert* and *Serjeant* [30] noted that the pK_a value of an acid was raised by *ca.* 1 and that of a base is lowered by *ca.* 0.5 in 60% MeOH in H_2O. A greater depression in ionization or protonation can be observed in mixtures of acetone, dioxane, *etc.*, with H_2O. Thus, any positive effect of an organic solvent on pH_{max} due to an increase in S_0 of a drug molecule may be negated by the depression of its ionization. The net effect might be such that the pH_{max} of the molecule becomes even less favorable to salt formation. The most positive effect of organic solvents on salt formation is the decrease in salt solubility, when suitable organic solvents with relatively low dielectric constants are used [33]. This favors crystallization and isolation of salts.

While assessing the influence of organic solvents on the salt formation of drugs, one should also consider their effects on the ionization of counter-ion species used. For example, in forming salt of a basic drug with a carboxylic acid, the organic solvent may not only decrease the pK_a of the base, it may also increase the pK_a of the conjugate acid as compared to its value in H_2O. This will have a negative impact on salt formation.

Thus, due to conflicting effects of organic solvents on S_0, pK_a, pH_{max}, salt solubility, *etc.*, the study of pH–solubility relationships of drugs in aqueous media remains the most useful tool in assessing the feasibility of salt formation. Organic solvents may, however, be conveniently be used to isolate salts. If, under certain circumstances, a salt is obtained from an organic solvent despite an unfavorable pH–solubility relationship in an aqueous medium, one should keep in mind that such a salt would be prone to disproportionation in presence of H_2O or moisture to produce its free acid or base form. Therefore the salt may not be optimal for dosage form development.

3. Selection of Physical Form

In the above section, we discussed how a rational strategy for the selection of chemical forms of salts can be developed based on the application of pH–solubility principles. Whether certain counter-ions have potentials for salt formation with a particular drug can be determined from a pH–solubility profile of the drug and the location of pH_{max} values in the solubility profile. If it becomes obvious from such an analysis that a stable salt would not form, no attempt should be made to synthesize such a salt, thus saving time and efforts in the salt-selection program. However, many drugs can still form multiple salts, and the number of potential salts depends on pK_a and S_0 values. When the synthesis of multiple salts is feasible, it is important to narrow down the number of salts and ultimately select the optimal salt form based on physicochemical characterization of solids.

3.1. A Multi-Tier Approach

Morris et al. [34] reported a multi-tier approach whereby salts can be screened for their optimal physical form. An updated version of this approach is shown schematically in *Fig. 12*. In this approach, certain physicochemical properties of salts are studied at each tier, and critical 'Go/No Go' decisions are made based on the results of those studies. The number of tiers usually

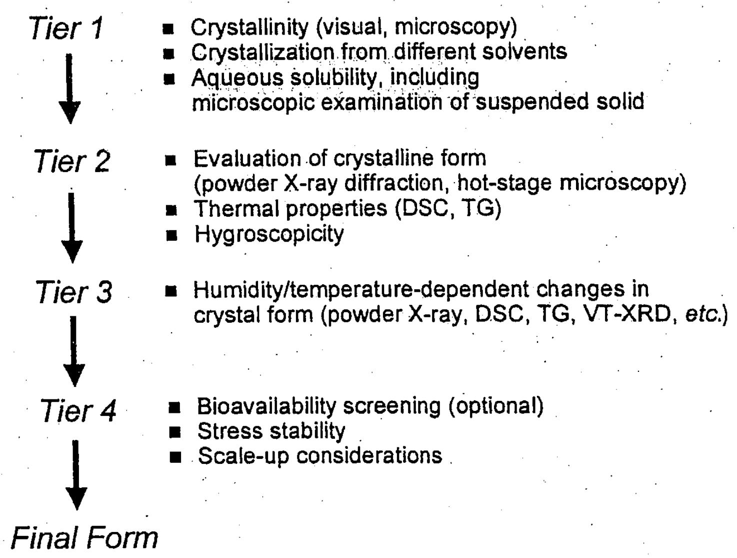

Tier 1
■ Crystallinity (visual, microscopy)
■ Crystallization from different solvents
■ Aqueous solubility, including microscopic examination of suspended solid
Tier 2
■ Evaluation of crystalline form (powder X-ray diffraction, hot-stage microscopy)
■ Thermal properties (DSC, TG)
■ Hygroscopicity
Tier 3
■ Humidity/temperature-dependent changes in crystal form (powder X-ray, DSC, TG, VT-XRD, etc.)
Tier 4
■ Bioavailability screening (optional)
■ Stress stability
■ Scale-up considerations
Final Form

Fig. 12. *Schematic representation of a multi-tier approach for the selection of optimal salt form for a drug*

depends on the number of salt forms available for a compound. Various methods for the characterization of physicochemical properties of salts have been described in *Chapt. 3* which can be applied in a systematic manner in the salt-selection process as discussed here.

In *Tier 1*, the crystallinity of salts is examined by simple visual or microscopic method. If the results of visual and microscopic examinations are inconclusive, powder X-ray diffraction may be used. Equipment is now available for the use of relatively small sample in powder X-ray diffraction studies. If a particular salt is found to be noncrystalline, attempts are made to crystallize it from alternate solvents. In many cases, more than one solvent is tried for the crystallization of drugs. Aqueous solubilities are then determined for those salts that are found to be crystalline. During the determination of aqueous solubility, excess solids in equilibrium with solutions are examined to determine any change in crystal form. Based on these studies, salts that are deemed to have acceptable crystallinity and aqueous solubility are elevated to *Tier 2*. Which aqueous solubility is acceptable for a particular drug often depends on the scope of the drug-development project. If a salt needs to be administered as a solution, a certain minimum solubility might be necessary depending on the dose. For a salt designed specifically for oral administration as a solid dosage form, it is not necessary that a salt with the highest aqueous solubility must be chosen; a salt with a relatively low solubility can also provide adequate dissolution rate for the product. Since many salts and their solid forms may possibly be produced at this stage, any attempt to conduct full physicochemical characterization of all those forms should be restricted at this time, because the results would be useless if the salts are not elevated to the next higher tier. For this reason, the microscopic examination of salts is recommended in *Tier 1*, and powder X-ray diffraction should be used only if microscopic studies are inconclusive. It should also be mentioned that an amorphous form of drug should be elevated to *Tier 2* only in exceptional situations.

In *Tier 2*, an in-depth characterization of crystal properties are conducted by using such techniques as powder X-ray diffraction, hot-stage microscopy, differential scanning calorimetry, thermal gravimetric study, and so forth. Hygroscopicity of salts as a function of relative humidity is also studied in this tier. Based on crystal properties and hygroscopicity, certain salts are then elevated to the next higher tier. If any salt selected in *Tier 2* is found to exist as a hydrate or solvate, or if it is found to be hygroscopic, further studies in *Tier 3* are conducted to determine the effect of temperature and humidity on the crystal form. In this way, the number of salts elevated to *Tier 4* can be minimized.

Salts selected in *Tier 3* are subjected to accelerated stability testing in *Tier 4*. Effects of temperature, humidity, and light are usually studied. If necessary, any potential incompatibility of salts with selected excipients and the effect of processing conditions on salt properties may also be studied at this tier. Since the stress stability testing of salts is labor-intensive and require much time, conducting this study in *Tier 4* with a limited number of salts avoids the generation of unnecessary data with other salt forms. Screening for the polymorphism of salts may also be conducted in *Tier 4* by crystallization from different solvent systems. Again, time and effort are saved by conducting polymorphism screening in this tier rather than with a larger number of chemical forms at an earlier tier.

Salts are usually prepared in test tubes and beakers during salt screening. However, prior to selecting a salt for development, appropriate consideration must be given in *Tier 4* whether the manufacturing process can be scaled up, and what would be the relative ease or difficulty in the scale-up of different salts studied in this tier. In many cases, bioavailability testing of different salt and acid/base forms of drugs in animal models is also conducted at this stage. A dog model is commonly used. However, to save developmental time and resources, one must be judicious in determining whether the bioavailability test should be conducted or not. The salt formation is an additional step in the manufacture of a drug substance. If a free acid or base has acceptable physicochemical properties and has comparable bioavailability to its salt forms, the free form of the compound might be preferred for development. Prior to reaching such a decision, a comparative bioavailability testing between a salt and the free form might be necessary. However, if the physicochemical properties clearly indicate that a salt form would have superior bioavailability (for example, the free form is extremely water-insoluble), a comparative bioavailability testing will not be necessary for the selection of a salt form. Similarly, a comparative bioavailability testing of different salt forms would not be necessary if the salts have acceptable dissolution rates, even though their aqueous solubilities might differ to a considerable extent.

Morris et al. [34] applied the above multi-tier approach for selecting the optimal salt form for an HMG-CoA reductase inhibitor containing a carboxylic group as the acidic functionality. Seven crystalline salt forms, namely, sodium, potassium, calcium, zinc, magnesium, arginine, and lysine, were synthesized and the arginine salt form was ultimately selected for development. The authors suggested that with such a systematic approach the entire salt-selection process can be completed in 4–6 weeks. *Engel et al.* [28] has recently adopted this multi-tier approach in selecting the methanesulfonate salt form for a basic drug.

4. Salt-Selection Timing

Morris et al. [34] pointed out that the selection of suitable chemical forms of new drug candidates, which includes salt selection, must be done at the early stage of drug development. This is because any later change in salt form may require repeating many of the developmental studies conducted prior to the change, with the consequent negative impact on the development time and cost. To prepare salts with good biopharmaceutical properties, certain attributes must be built into drug molecules. Therefore, the most appropriate time to start thinking about salt selection of any potential development candidate is in the drug discovery phase. Due to the pressure of bringing new drugs from discovery laboratories to the marketplace in the shortest possible time, the traditional discovery–development interface is getting blurred and more and more development scientists are participating in drug discovery working groups [35]. As a part of the overall developability assessment of new drug candidates, it is during this time that the developmental scientists should make assessment for the feasibility of salt formation. When a selection is made from among many potential candidates, some of the molecules may be more suitable for salt formation than the others. Also, when the medicinal chemists are still in the discovery mode, they might be able to make chemical modifications in molecules to facilitate salt formation.

Much of the assessment at the drug-discovery stage for the feasibility of salt formation can be done *in silico* based on physicochemical principles outlined in the present chapter, and any experimental work needed might be minimal. The actual synthesis and characterization of salts for the purpose of selecting an optimal form for development should preferably start as soon as a developmental candidate is identified. In many cases, the selection begins through prospective research before drug molecules are officially handed over to development groups. *Morris et al.* [34] noted that the salt selection can be removed from critical development path by completing the selection when the chemists are still involved with the scaling up of the synthetic process. According to them, a systematic salt selection may be completed in as little as 4–6 weeks.

5. Salt-Selection Team

The selection of optimal salt forms of new drug candidates involves a multi-disciplinary team approach. The team may even decide that a salt is not warranted for a particular drug, and a free acid or base form should be used instead. Since the ultimate use of a salt is in a dosage form, the formulation needs must carefully be addressed in the selection process. At the same time, a salt, as a drug substance, must be easily synthesized and manufactured. In addition, various analytical tools and techniques are required to characterize different salts prepared during the salt selection. For these reasons, in most pharmaceutical companies, representatives from pharmaceutics, chemical process development, and analytical research form core salt-selection team. Medicinal chemists from drug discovery make the original synthesis of drug molecules and can provide valuable input towards the synthesis of salts. Representatives from drug metabolism/pharmacokinetics address various bioavailability issues and, if necessary, conduct experimental work in animal models to compare absorption and bioavailability of different chemical and physical forms. Therefore, representatives from these two disciplines participate in the expanded salt-selection team. Inputs from drug safety and marketing are also necessary for the selection of certain salt forms.

6. Summary and Conclusions

In this chapter, a systematic strategy for the selection of optimal salt forms for acidic and basic drugs has been described. The selection of an optimal salt form for a drug involves the selection of both chemical and physical forms. At the end of a study, it might also be concluded that a salt form is not suitable for a particular drug, and the free acid or base form is preferred. Based on physicochemical principles described in this chapter, it is hoped that some of the 'trials and errors' usually associated with salt selection can be avoided, thus saving valuable time and resources in a drug-development program.

Several topics of experimental, physicochemical, and procedural nature as described in this chapter are summarized below. They should be regarded as essential building blocks of any effective salt-selection strategy.

1. The first consideration in any salt-selection program is to determine whether a compound is amenable to salt formation. The presence of an ionizable moiety for an acidic drug and a protonatable moiety for a basic drug does not necessarily mean that a salt would be formed. To form a salt, the pH of the aqueous solution (or suspension) of an acidic drug must be adjusted above its pH_{max} value, and, for a basic drug, the pH of the solution must be below its pH_{max}. Counter-ions used to form salts must be suitable to achieve such pH conditions. Otherwise, salts would not be formed. From this consideration, it can be determined whether the salt formation might be feasible for a particular compound, and, if so, which counter-ions should be tested.
2. The pH_{max} principles have been discussed in detail in *Chapt. 2* of this volume. The pH_{max} value for a particular drug can be determined experimentally from the pH–solubility study. It can also be estimated theoretically form a knowledge of pK_a and solubilities of free and salt forms of the compound. It is not necessary that pH–solubility profiles for a partic-

ular compound should be determined with all counter-ions considered for salt formation. A profile of the compound with only one suitable counter-ion can give a fairly good idea of its pH_{max} value. A reasonably good estimate of the pH_{max} value can also be obtained from a theoretical pH–solubility profile generated from S_0 and pK_a values, even without the solubility of a salt form.

3. Multiple pH_{max} values might exist for compounds with more than one ionizable or protonatable groups. pH–Solubility and pH_{max} principles are also applicable in determining whether such a compound would form a mono-salt or multi-salt (*e.g.*, disalt) with a particular counter-ion. Mono- or multi-salts may selectively be synthesized by using appropriate counter-ions.
4. It is granted that aqueous solutions alone are not always used to prepare salts, and mixtures of aqueous and organic solvents are often used. There are, however, conflicting effects of organic solvents on S_0, pK_a, and salt solubility, and, as a consequence, the pH_{max} may be positively or negatively impacted. The major advantage of using an organic solvent is to lower dielectric constant of the solvent system used, which generally decreases solubility of salts and thus facilitates their crystallization and isolation from solvents. In certain situations, a salt that would not normally exist in an aqueous medium might be formed in a cosolvent system due to a more favorable pH_{max} value. However, such a salt might disproportionate into its free unionized or nonprotonated form, when it contacts an aqueous medium. For these reasons, pH–solubility relationships of drugs in aqueous media remains the most useful tool in assessing the feasibility of salt formation.
5. In selecting counter-ions for salts, the fact should be considered that certain counter-ions can exert significantly more pronounced common-ion effects in aqueous solubilities than others. Salts formed with relatively stronger counter-ions (*e.g.*, hydrochloride salt, sodium salt, *etc.*) are relatively more affected by counter-ion than the salts formed with relatively weaker counter-ions (*e.g.*, salts with carboxylic acid, amine, *etc.*).
6. When several salts for a particular compound are synthesized, physicochemical tests to characterize solids can be conducted at different tiers with a 'Go/No Go' decision at the end of each tier of testing the salts. By a systematic multi-tier approach, many different salt forms can be screened for their physicochemical properties with the minimum of experimental effort.
7. Finally, the salt selection is a team approach with representatives from pharmaceutics, chemical process development, and analytical chemistry forming the core salt-selection team. Representatives from drug discovery, drug metabolism/pharmacokinetics, drug safety, and other disciplines

participate, as needed, in an expanded team. Through such teamwork and with proper planning, the salt selection can be removed from the critical development path, thus accelerating drug development.

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Chapter 7

A Procedure for Salt Selection and Optimization

by **Michael J. Bowker**

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1. Introduction

Until *ca.* 15 years ago the drug discovery processes adopted by pharmaceutical companies involved the screening of large numbers of compounds that had been synthesized by the company's research laboratories over many years. Alternative sources of compounds were also available to some companies from university laboratories, or as extracts from a multitude of natural sources. In the last 15 years, there has been a rapid change towards the use of combinatorial-chemistry techniques which are now being used routinely to prepare many thousands of compounds per year. As described in *Chapt. 6*, these compounds are generally dissolved in dimethyl sulfoxide (DMSO) to enable screening for activity in an enzyme- or receptor-based assay system. Initial screening usually involves a highly automated 'high throughput screen' (HTS). If the number of 'hits' found is large, the numbers are usually refined by a more involved and specific 'low throughput screen' (LTS) and other selection processes, until a manageable number of 'leads' is available. Often, several of these 'leads' show only moderate activity, and further structural refinement and optimization is invariably necessary, using a mixture of computational techniques and intuition by the chemistry team, until a smaller number (usually 1–5) of highly active potential 'candidates' remain.

These 'candidates' are usually relatively impure free bases, free acids, or neutral molecules, and are often amorphous. Because they are dissolved and stored in DMSO prior to being used in screening procedures, there is no need to ensure that they are crystalline. Also, the preparation of any salts of these compounds is rarely necessary as the neutral/covalent molecule usually exhibits better solubility in both DMSO and the assay system to be used by the pharmacology group. As can be seen readily, these new procedures favor lipophilic molecules, whereas the majority of marketed drug substances are hydrophilic. The need for water-soluble candidates for use in drug development and the vast majority of dosage forms has been recognized [1–4] for many years before the advent of 'combinatorial chemistry'.

Because drug substances are designed to bind with a receptor, enzyme, protein *etc.*, they normally possess several functional groups capable of hydrogen bonding. Some of these functional groups may give potential for salt formation and thus increased hydrophilicity. This salt formation also gives the pharmaceutical chemist and formulation scientist the opportunity to modify the physicochemical (*e.g.*, melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form *etc.*) and mechanical (*e.g.*, hardness, elasticity *etc.*) characteristics of the potential drug substance and to develop dosage forms with good bioavailability, stability, manufacturability, and patient compliance.

For weakly basic drug substances, salts of an inorganic acid (*e.g.*, hydrochloride, sulfate or phosphate), a sulfonic acid (mesylate, esylate, or isethionate), a carboxylic acid (acetate, maleate, or fumarate), a hydroxy acid (citrate or tartrate), or possibly an amino acid (arginine or lysine) could be considered. In the past, hydrochloride salts have often been the first choice for weakly basic drugs, since, as a consequence of the low counter-ion pK_a, salts can nearly always be formed, and recrystallization from organic solvents is normally straightforward. However, the potential disadvantages of hydrochloride salts include unacceptably high acidity in formulations (*e.g.*, parenteral products), the risk of corrosion of manufacturing plant and equipment, less than optimal solubility due to the risk of salting out, and the potential for poor stability, if the drug is acid labile and hygroscopic [2].

Historically, prior to the severe regulatory constraints that abound today, it had been possible to develop the neutral species (free acid or free base) together with one or more different salts. These different chemical forms were often used for specific purposes. An excellent example of this concerns the phenothiazine drug substance, prochlorperazine. The free base was used in suppositories, as it was the most lipophilic form, the mesylate salt was used in injections and in sachets for the preparation of an oral solution, whilst the less soluble maleate was used for the manufacture of tablets.

Occasionally, salts were also prepared in former times to decrease drug substance solubility for use in suspension formulations where very low solubility is necessary to prevent '*Ostwald* ripening', for taste masking (*e.g.*, dextropropoxyphene napsylate suspension), or to prepare an extended release product. Embonate salts have been used in suspension formulations to increase the duration of action (*e.g.*, chlorpromazine embonate). On some occasions, the selection of a salt with only modest aqueous solubility may be more suitable for use in tablet products prepared by wet granulation, since the use of highly soluble salts can be detrimental to the granulation process. Depending on the dose required, aqueous solubilities in the range of 0.1 – 1.0 mg/ml will normally be sufficient to satisfy the dissolution requirements for standard, solid, oral dosage forms of drugs with good-to-moderate potency. However, for parenteral solution products, higher solubilities, perhaps 10 mg/ml or greater, depending on the required dose and dose volume, may be required. For parenteral formulations, the pH of solution (normally within an acceptable range of 3 – 10 for intravenous solutions) should be monitored to help ensure that the formulation will be well tolerated.

Manipulation of drug substance solubility by selection of salts may also be employed to modify the pharmacokinetic profile of the drug (*e.g.*, benzathine penicillin and insulin zinc complexes used in parenteral formulations). Salt formation may be also advantageous where the melting point of the active moiety is low, and it is necessary to mill or micronize the active ingredient to achieve adequate homogeneity. A suitably stable salt may have a melting point that is 50 – 100 °C higher than that of the free acid or free base. Also, being more ionic, the crystals are likely to be less plastic and more easily deformed by brittle fracture.

Chapt. 6 describes some of the theoretical aspects behind salt formation. This chapter describes some of the procedures adopted by the *Preformulation* team at the *Aventis Pharma* (previously *Rhône-Poulenc Rorer*) *Dagenham Research Centre* (DRC). These procedures are similar to a systematic approach proposed by *Morris et al.* [3] but were devised empirically with one aim of how to obtain the maximum amount of information from the minimum amount of precious candidate batch. The outline of the process is shown in the *Figure*.

Where possible, we prepare a range of salts for each new candidate and compare their properties in our preformulation program, which is designed to give us the relative suitabilities of each one. Only one salt form is developed, and its properties should be appropriate to the primary route of administration and the intended dosage form proposed for initial marketing. The properties of the drug substance required for one dosage form may be quite different from those required for another. An understanding of the influence of drug substance, or its salt, properties on the finished product is essential to ensure selection of the optimum salt form. Some of these aspects are dealt with in more detail in *Chapt. 4*. The procedures demonstrated here are also described in outline form in [5].

2. Salt Formation – Is It Necessary, Is It Feasible?

Each new molecule synthesized within the *Discovery Chemistry* group has an entry prepared in the compound database. Among the first information added as an entry into this database for each compound is the calculated pK_a value of each ionizable group in the molecule [6 – 9]. Another early entry is the calculated log P value. Immediately, a small amount of material is made available, the values are determined experimentally on 1 – 2 mg of sample by potentiometric titration (*e.g.*, *Sirius Model GLpKa* apparatus, *Sirius Analytical Instruments* Ltd.), and the values determined experimental-

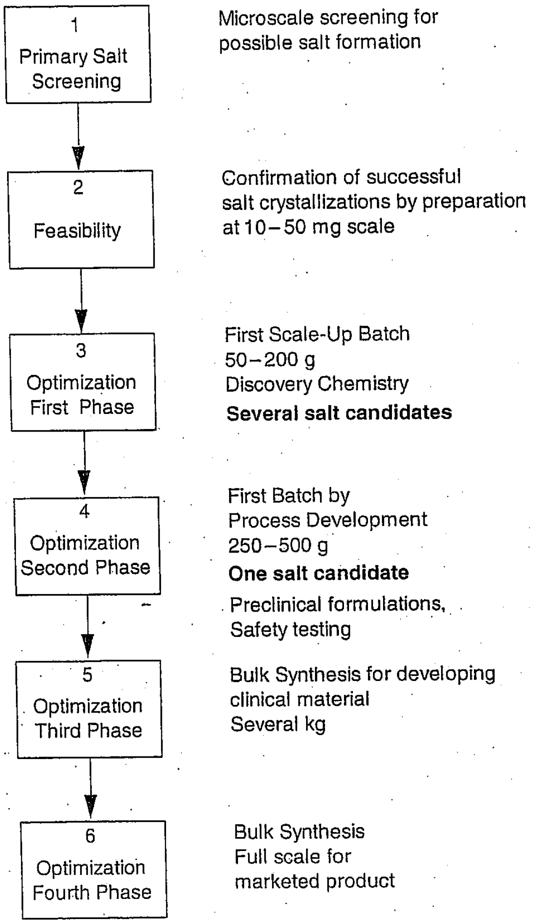
1
Primary Salt Screening
Microscale screening for possible salt formation
2
Feasibility
Confirmation of successful salt crystallizations by preparation at 10–50 mg scale
3
Optimization First Phase
First Scale-Up Batch
50–200 g
Discovery Chemistry
Several salt candidates
4
Optimization Second Phase
First Batch by Process Development
250–500 g
One salt candidate
Preclinical formulations, Safety testing
5
Optimization Third Phase
Bulk Synthesis for developing clinical material
Several kg
6
Optimization Fourth Phase
Bulk Synthesis
Full scale for marketed product

Figure. *Process of salt selection and optimization*

ly are again entered into the database. The $\log P$ value is usually determined concurrently by chromatography using an octanol-loaded HPLC column [10].

Synthesis of a working quantity of each new candidate is rarely undertaken at a scale that exceeds 5 g; the primary synthetic aim is to provide sufficient compound for activity screening in both cell and animal models. Once activity is confirmed in these screens, the material remaining from this first batch is usually further sub-divided across a small number of Departments. The amount of drug substance made available to *Physical Chemistry* and the *Preformulation* teams together rarely exceeds 1 g and is often less than 0.5 g.

With the pK_a value of each ionizable group in the molecule known, either by experimental determination or by calculation, a list of potential salt forming agents (counter-ions) can be selected, for each candidate, based on lists that are available in the literature [2] [11–13] (see also the tables in the *Appendix*). Based upon studies on numerous candidates over more than 10 years, it is our considered opinion that, for the formation of a stable salt, there should be a minimum difference of ca. three units between the pK_a value of the ionizable group and a possible counter-ion. This is especially so when the drug substance is a particularly weak acid or base where disproportionation back to the component parts often occurs in solution. This then results in precipitation of the free acid or free base. Occasionally, an exception may be found where a salt has an acceptable stability, despite there being a smaller difference in the pK_a values.

To maximize the amount of data obtained from small quantities of candidate drug substances, micro and semi-micro techniques have been developed and are used regularly within our groups. A microplate technique has been devised by the *Aventis Physical Chemistry* group for rapidly and qualitatively screening whether solid salts can be prepared. This involves dissolving *ca.* 50 mg of sample in a suitable, volatile solvent and adding a fixed volume of this solution, containing *ca.* 0.5 mg of sample, into each glass microplate well. Concentrated solutions of each potential counter-ion in equimolar proportion, or (if the molecule could form double or triple salts) other appropriate stoichiometric ratios, are prepared, and a few microlitres of each is added sequentially to each well. Thus, all the wells in line 1 ('*x*'-direction) will contain the same combination of sample and counter-ion 1; all the wells in line 2 contain the same combination of sample and counter-ion 2, *etc.* Different, potential crystallizing solvents can be investigated systematically in the '*y*'-direction. The wells are inspected using an inverted microscope (*Leica*, model *DMIRB*) at regular intervals for the appearance of crystals or solid. Occasionally, crystallization can be promoted by evaporation of any excess solvent in some wells using a slow stream of dry N_2 gas.

Once the possible combinations of counter-ion and solvent(s) are identified, studies at a slightly larger scale (usually 10–50 mg) can be initiated to confirm the formation of a crystalline salt or an amorphous solid and initiate a study of any polymorphism. These studies give a lead to the chemist and can help in the identification of future problems. Melting points are determined by hot-stage microscopy, and samples showing evidence of hygroscopicity can be evaluated using a dynamic vapor sorption (DVS) analyzer (Model *DVS-1*, *Surface Measurement Systems Ltd.*). There is usually sufficient material for a preliminary powder X-ray study using an environmental chamber (model *D8 Advance*, *Bruker Instruments*) to qualitatively determine the presence of crystalline or amorphous material. Frequently, these studies can also give information on the existence of solvates and hydrates, especially if differential scanning calorimetry (DSC; *Mettler Toledo DSC*, model *820*), thermal gravimetric analysis (TGA; *Mettler Toledo TGA*, model *850*), and hot-stage microscopy are also used in the evaluation process. Most of these studies can be accommodated, if care is taken, on 20 – 25 mg of sample.

In parallel with these studies, a preliminary HPLC method is developed within *ca.* one week, and, after completion of minimal validation, it is used to give an estimate of the purity of the original sample, whilst IR and other spectroscopic techniques may be used to define the salt and the stoichiometry. Knowledge of the approximate purity is important at this stage, as the presence of high levels of some impurities can often hinder crystallization by 'poisoning' crystal growth or promote the formation of a specific polymorphic form. Immediately after the development of this HPLC method for use in the assessment of the main manufacturing impurities, the analytical chemists turn their attention to the development of the corresponding stability-indicating method. The development and partial validation of this method involves the use of degraded solutions of the drug substance produced in accelerated stress studies. This method takes *ca.* three weeks to complete and can then be used in the early stability evaluation of salts, their solutions and, ultimately, simple formulations.

Thus, by carefully planned studies using a small quantity of drug substance, it is possible to identify quickly the possibilities for the chemist to investigate, once larger quantities of drug substance are made. These studies may point to a small group of potential salt formers for initial evaluation; they also give the chemist ideas on possible recrystallization solvents that can be tried.

3. The Salt-Optimization Process – First Phase

3.1. Choice of the Salt Former (Counter-Ion)

The choice of salt former (counter-ion) depends on several factors. Obviously the primary factor is that it should yield a crystalline salt. Crystallinity in a salt affords a means of purification and removal of unwanted impurities. Lack of crystallinity (*i.e.*, the salt is amorphous) normally would be expected to lead to severe problems and uncertainties, if the product intended to be developed is a solid, oral dosage form. The prospect of unexpected and uncontrolled crystallization at some stage with just one batch, creating a product recall, is something that the *Quality*, *Regulatory*, and *Marketing* groups could not live with. Absence of crystallinity is often less of a problem if the dosage form intended is a liquid.

The choice of salt is also governed largely by the acidity or basicity of the ionizable group, the safety of the counter-ion and the drug indications.

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Bilgi Merkezi

Table 1. *Classification of Common Pharmaceutical Salt Formers*

Salt Formers	**Examples**
Anions	
Inorganic acids	Hydrochloride, Hydrobromide, Sulfate, Nitrate, Phosphate
Sulfonic acids	Mesylate, Esylate, Isethionate, Tosylate, Napsylate, Besylate
Carboxylic acids	Acetate, Propionate, Maleate, Benzoate, Salicylate, Fumarate
Anionic amino acids	Glutamate, Aspartate
Hydroxy acids	Citrate, Lactate, Succinate, Tartrate, Glycolate
Fatty acids	Hexanoate, Octanoate, Decanoate, Oleate, Stearate
Acids for insoluble salts	Pamoate (= embonate), Resinate (*e.g.*, Polystyrene sulfonate)
Cations	
Metallic	Sodium, Potassium, Calcium, Magnesium, Zinc
Organic Amines	Triethylamine, Ethanolamine, Triethanolamine, Meglumine, Ethylene diamine, Choline
Cationic amino acids	Arginine, Lysine, Histidine
Bases for insoluble salts	Procaine, Benzathine

Toxicological and pharmacological implications of the selected salt former must be considered, as well as the effects of the parent drug. Salt formers can be subdivided into a number of categories depending upon their functionality and purpose. Some of the most frequently used examples are listed in *Table 1*.

3.2. Scaling Up the Preparation of Salts

In parallel with the preliminary evaluation of opportunities for the formation of crystalline salts, the *Process Chemistry* group start to investigate the possibilities for economic manufacturing routes for each of the candidates remaining (usually one or perhaps two at most). The manufacturing route may be the same as used by the *Discovery Chemistry* group, but usually is quite different as less expensive reagents with greater commercial availability start to be used. The aim is to manufacture rapidly 50 – 200 g of each candidate to permit their evaluation by teams from various departments, including *Toxicology*. A significant portion of this batch is destined for the preparation of 3 – 4-g of each of the salts that were considered viable from the early studies on the smaller batches. An equivalent portion of the free base/acid is also taken for comparison purposes. The combination of individual studies that are undertaken on each of these 3 – 4-g portions varies depending on the type(s) of dosage form required for initial clinical evaluation and also that ultimately required for marketing.

The most common route of administration for drug substances is orally. For the oral route, the dosage forms most commonly encountered during initial clinical investigations for the drug substances are highly dependent on company's philosophy. Some companies use simple oral solutions whenever the drug substance properties permit; they revert to capsules for less soluble candidates. Others prefer to develop tablets that would closely resemble a potential marketed formulation. The majority seem to adopt an intermediate strategy of using capsules for oral dosing, to be followed by tablets for marketing. In addition, an injection formulation is also invariably required for certain toxicology studies and at least a determination of the absolute bioavailability of the oral solid dosage form in humans. Obviously, if the candidate is required for the treatment of asthma, inhalation dosage forms would be developed, together with an injection formulation for limited studies.

To generate data that is an invaluable preliminary to the development process for the drug product(s), a basic 'checklist' has been devised. This list contains a reasonably comprehensive range of tests that give an initial database of properties to establish a firm basis for later decisions. The 4-g batches of each salt, plus the free acid or free base, are examined using each of these tests. Similar 'checklists' can be established for drug substances that are intended to be developed into a solution (injectable or oral) formulation or one intended to be delivered by the pulmonary route (solution metered dose inhaler (MDI), suspension metered dose inhaler, or dry powder inhaler (DPI)). Obviously, many of the tests give basic data that should be obtained irrespective of the type of formulation that is intended. In several cases, the test remains the same but the target value expected for the result may differ. An example of this would be aqueous solubility; the target value for a drug substance intended for use in a solid, oral dosage form would be around 1 mg/ml in a medium with a pH value within that found in the human gastro-intestinal system (a lower target solubility would be acceptable, if the candidate was shown to be highly potent). A similar candidate intended for use in an injectable formulation would have a target solubility value around

10 mg/ml, unless it was also exceptionally potent. Similarly, for a candidate intended to be developed into a solution MDI, it would be important to determine that the solubility in the new hydrofluoroalkanes (HFA 134a or HFA 227) was high enough to yield an acceptable dose from an actuator. The solubility would also be determined in these HFAs containing up to 5% ethanol. It is less important to determine it in aqueous-based solutions. Lack of adequate solubility in the pure HFAs or an ethanolic HFA solution implies that a suspension MDI should be considered. For a drug substance destined to be formulated as a suspension MDI, it should ideally be readily micronizable and also have a density similar to those of the HFAs to enable maintenance of a stable suspension.

A typical compilation of the main tests used for drug substances intended for solid, oral dosage forms is presented in *Table 2*; it shows the types of tests normally chosen and the information that these tests can yield. A more detailed tabulation of these tests and the amount of sample normally required is given in *Table 3*.

3.3. The Decision on What To Develop – Salt or Free Acid/Base?

The results obtained from each of the small batches of salt and the free acid or base form the initial '*Preformulation Database*'. The results are tabulated for comparison and the collated results discussed by all the scientists concerned in the project. The *Preformulation* scientists assess the relative merits of each form for use in the proposed clinical formulations, and whether the properties such as solubility are adequate to give the high concentrations required in the various pre-clinical formulations. *Process Chemistry* needs to assess the likely yield of each salt, as salt formation normally creates an additional step in the manufacturing process. Usually, the decision-making process results in the proposal of a single salt for further study, though, occasionally, it is seen that none of the salts has optimum properties, and two different salts can be proposed for further, in-depth study. It is occasionally found that the overall properties of the free acid/base are much better than any of the salts. This occurs more frequently where the candidate base has a low pK_a value (or a correspondingly high value, if the candidate is an acid), and the resulting salts are less stable than required, when the salts are particularly hygroscopic, or when they exhibit complex polymorphism/pseudopolymorphism (hydration or solvation).

These simple investigations give much useful information very quickly and with low usage of drug substance. It is important to realize, however, that the polymorphism study undertaken at this stage is very limited, and a much more detailed study is always undertaken later. This very early study uses a

Table 2. *Preformulation Studies That Are Normally Considered for Comparison of Salt Forms and Parent Compound for Oral Dosage Forms*

Test	**Suitable Techniques**	**Comments**
Dissociation constant	Potentiometry, solubility, UV spectrophotometry.	Determine pK_a for parent drug
Melting point	Capillary m.p., hot-stage microscopy, differential scanning calorimetry.	Perform on each salt and compare to parent.
Aqueous solubility	Overnight equilibration at 25 °C; analysis by UV spectrophotometry or HPLC.	Perform on each salt and compare to parent.
pH of solution		Examine pH of saturated solution if quantities permit.
Cosolvent solubility	Overnight equilibration at 25 °C, analysis by UV spectrophotometry or HPLC.	Determine solubilities in: ethanol, polyethylene glycol, propylene glycol, and glycerol (as a minimum) and compare to parent.
'Common-ion' effect on solubility	Overnight equilibration at 25 °C in suitable media and analysis by UV spectrophotometry or HPLC.	Compare solubility in demineralized water with 1.2% NaCl for salts and parent.
Hygroscopicity	Use DVS apparatus or expose to various humidity values and measure weight gain after one week.	Perform at 53%, 93% and 97% r.h., and other values of interest. Assign hygroscopicity classification to each salt [14].
Intrinsic dissolution rate (IDR)	Use *Wood*'s apparatus [15].	Compare dissolution rates at various pH values (can provide information on wettability). If appropriate, consider use of '*Dressman* buffers' [16].
Crystal shape and appearance	SEM or optical microscopy.	Compare crystal habits and levels of agglomeration.
Particle size	SEM and laser diffraction	Examine particle size distributions.
Polymorphism/ Pseudopolymorphism	Recrystallization from various solvents of differing polarities, HSM, DSC, TGA.	Preliminary exploration.
Powder properties	Bulk density measurement	Determine *Carr*'s Compressibility Index [17 – 19].
Stability	Various	Perform on parent drug and undertake preliminary tests on appropriate salts.

Table 3. *Tests To Be Considered for the Evaluation of Candidate Salts*

Test	**Amount required [mg]**
Elemental Analysis	10
Structural Analysis	
Mass spectrometry a)	1
^{1}H-NMR a)	5
^{13}C-NMR	25
IR	1
UV	1
Fluorescence spectrum a)	1
Physicochemical Properties	
Melting range	2
pK_a a)	5
C log$P$/log$P$ a)	5
Preliminary polymorphism study	200 – 500
X-Ray diffraction	20
Aqueous solubility b)	100
pH–Solubility profile	500
Cosolvent solubilities c)	300
Propellant solubility d)	500
Physical Properties	
Hygroscopicity	20
Microscopy (SEM/Optical)	10
Particle size (*Malvern*)	100
Size reduction (sonication)	300
Impurities (HPLC)	
Related substances a)	10
Degradation products a)	10
Chiral purity a)	10
Stability Studies	
Stability to hydrolysis (pH 2, 7, 10) a)	15
Stability to oxidation (peroxide/peracid) a)	15
Stability to photolysis a)	15

a) Determined on free acid/base only. b) Includes solubility in saline, 5% dextrose solution, and some buffers. c) Also solubilities in complexing agents/surfactant systems where appropriate. d) Propellants and propellant/cosolvent systems for inhalation dosage forms.

range of individual protic and aprotic solvents of widely differing polarity, mixtures of these solvents, and mixtures containing water. More often than not, it will enable detection of a 'stable' hydrate or solvate. If a relatively stable hydrate is detected in this early study, it is usually beneficial to prepare a small sample (1 – 2-g) and to repeat some of the tests such as solubility, intrinsic dissolution, thermal analysis *etc.*, as hydrates are invariably less soluble than anhydrates. Also, it is useful to know both the dehydration temperature and the polymorphic form produced upon dehydration.

Once we have completed these initial studies, a short document is drafted that gives a summary of what has been found, the likely effect on an initial clinical formulation (*i.e.*, do any of our findings impact heavily upon the choice of formulation or manufacturing process?). The recommendations of the collective group involved in these studies on whether to develop a specific salt, or the free acid or base are placed before senior management for ratification.

3.4. The Negative Aspects of Salt Formation

One of the negative aspects of salt formation is that the percentage of active content of the drug substance decreases markedly as counter-ions with higher molecular weights are used. If the free acid or base has only moderate or low activity, it may be necessary for the patient to be prescribed a relatively high dose for a clinical effect. It is quite common to have a situation where 20 – 50% of the weight of the drug substance is due to inactive counter-ion. Because most drug substances have flow properties that are non-ideal, it is necessary to formulate them with suitable excipients for encapsulation or tableting. The final powder mix, or granule, may require 40 – 70% of excipients to enable it to be filled successfully. Addition of the contribution made by the inactive counter-ion to that of the excipients may result in a very low percentage of active ingredient in the final mixture. This often creates a powder volume that is too great, even after granulation, to fill successfully into even the largest acceptable size of capsule shell. It may mean that the unit dose is more than one tablet or capsule, a situation that does not aid patient compliance.

Other problems that are frequently created, or exacerbated, by salt formation are an increased tendency for the existence or formation of hydrates and polymorphs. Hydrates may be produced slowly on storage in formulations by interaction with atmospheric water, water bound to excipients such as lactose monohydrate, or the water in capsule shells (gelatine capsule shells contain ca. 12% (*w/w*) loosely bound water) *etc.*

4. Recent Case Histories

To demonstrate how the decision-making process works in practice, three recent examples have been chosen from the many that have been studied over the last five years. These exemplify some of the principles involved.

4.1. RPR111423

RPR111423 contains a pyridine ring that is the only group capable of being ionized and a primary amide group; it has a single pK_a at 4.25 that is consistent with the presence of the pyridyl group. The log$P$ value was determined at 2.1. Thus, it is a very weak base and would be expected to form stable salts with only the strongest acids (mineral acids and sulfonic acids); it would not be expected to form a stable salt with any of the organic acids.

The free base was found to be a crystalline solid with a high melting range (241 – 244 °C). A screening of possible salts was undertaken and demonstrated that there were only two salts that could be isolated as crystalline solids; these were a hydrochloride (RPR111423A), with a melting point at 242 °C determined by DSC (model *DSC 820*, *Mettler Toledo Ltd.*, UK), and a mesylate (RPR111423B), with a melting point at 210 °C determined by DSC. We noted the similarity in melting points of the base and hydrochloride for later evaluation. It was decided that the free base should be taken through the initial evaluation process in comparison with these two salts and 4 – 5 g of each were prepared.

It was agreed that oral dosing was preferred, and it was hoped that capsules could be formulated from the drug substance form that remained to be selected; an injectable formulation would also be needed for some pre-clinical studies and for the determination of absolute bioavailability in man at a later stage in development. Because of its apparent high activity in screening studies, it became obvious that both of the above formulations could easily be very-low-dose products. For a low-dose capsule formulation, uniformity of active content may be an issue to be faced in the future. A determination of the particle-size distribution, perhaps linked with an assessment for size reduction by milling or micronization, thus became quite important.

4.1.1. *Basic Physicochemical Properties of RPR111423*

The free base crystallized in large laths, in the range of 10 – 100 µm which could be readily micronized, yielding material with a particle size range of 2 – 5 µm, without a change in polymorphic form. In addition to this information, numerous small-scale crystallization experiments all gave the same polymorphic form, with no evidence for the presence of amorphous material, hydrates, or solvates. Several experiments using both crystalline and micronized drug substance and either hygrostats, or a DVS apparatus (model *DVS-1*, *Surface Measurement Systems Ltd.*, UK) confirmed the material was non-hygroscopic.

As expected from the pK_a value and the chemical structure, the solubility profile was shown to be markedly dependant on pH (see *Table 4* for data). The intrinsic dissolution rate was determined using *Wood*'s apparatus [20] and was found to be 0.55, 0.085, and 0.017 mg/min/cm^2 into solution at pH 1.0, 2.0, and 4.0, respectively.

Preparation of a very simple capsule formulation containing 25 mg of the base, together with other common excipients and sodium dodecylsulfate as wetting agent, gave an acceptable dissolution profile when tested over the pH range 1.0–4.0 with $t_{70\%}$ values of *ca.* 12 min.

4.1.2. *Basic Physicochemical Properties of the Hydrochloride RPR111423A*

A similar investigation was undertaken on the hydrochloride. As noted earlier, the melting point was determined to be within the range found for the free base, and an investigation was undertaken using thermogravimetry (model *TGA 850, Mettler Toledo Ltd.*, UK). This technique clearly showed a weight loss, consistent with loss of HCl, between 110–120 °C and explained the similarity of melting range to that of the free base. The initial sample consisted of aggregates of micro-crystals, typically 1–2 µm, and further recrystallizations from a variety of solvents produced at least four different polymorphic forms. None was hydrated or solvated, and no evidence was found for the presence of an amorphous form. All these forms were shown to be metastable with respect to the form originally provided and reverted to that form on standing over a few days. Recrystallization from aqueous ethanol returned the free base. The original form was shown to be slightly hygroscopic when stored at 53% r.h. (2.0% weight gain) but gave a 22% increase in weight on storage at 97% r.h.

As with the free base, the solubility was markedly pH dependant at 37 °C (28 mg/ml at pH 1.0 and 4.6 mg/ml at pH 2.0). At higher pH values, any undissolved solid was shown to convert quantitatively to the free base, and, at pH values higher than 4, the free base precipitated from solution.

4.1.3. *Basic Physicochemical Properties of the Mesylate RPR111423B*

The sample provided consisted of aggregates of fine laths, each *ca.* 1 µm × 7 µm, with a melting point at 210 °C. Hot-stage microscopy, DSC, and thermogravimetry demonstrated that the material is chemically stable upon melting. Small-scale recrystallization experiments from a range of solvents similar to those used for the hydrochloride resulted in the production of at least four new forms. Grinding and micronization each produced an additional form; all of these six new forms reverted back to the original one

Table 4. *Comparison of Some Basic Properties of RPR111423 and Two Salts*

Property	**Base** **RPR 111423**		**Hydrochloride** **RPR 111423A**		**Mesylate** **RPR 111423B**	
Appearance	Off-white to cream, crystalline powder		Pale yellow, highly agglomerated powder		Cream to pale yellow, highly agglomerated powder	
Particle size by microscopy [µm]	10 – 100 (large rhombic crystals)		2 × 1 (microcrystalline laths)		7 × 1 (microcrystalline laths)	
Melting range [°C]	241 – 244		242		210	
Polymorphism, preliminary results	No other form detected		At least 4 polymorphs detected; metastable forms revert to original on standing.		At least 6 polymorphs detected; phase changes detected on grinding or micronization. Reverts to original form on heating.	
Other thermal behavior	Nothing detected		Loss of HCl detected at 110 – 120 °C		Nothing detected	
Aqueous solubility [mg/ml]	At 25 °C	At 37 °C	At 25 °C	At 37 °C	At 25 °C	At 37 °C
– in 0.1M HCl (pH 1)	11.6	14.7	25.7	28.2	131.4	204.1
– in 0.01M HCl (pH 2)	0.71	0.89	2.51	4.58	6.11	8.91
– in acetate buffer (pH 4)	0.03	0.05	0.05	0.13	0.01	0.02
– in acetate buffer (pH 6)	0.01	0.02	0.01	0.02	0.03	0.34
– in acetate buffer (pH 6.8)	0.01	0.02	0.01	0.02	0.01	0.02
– in demineralized water	0.01	0.02	0.36	0.99	0.33	0.50
pH (saturated solution, water at 20 °C)	6.50		2.43		2.74	
Addition of water to concentrate						
– at pH 2	No changes detected		Some precipitation of free base		Some precipitation of free base	
– at pH 4	No changes detected		Extensive precipitation of free base		Extensive precipitation of free base	
Hygroscopicity (hygrostat for 14 days)	Non-hygroscopic <0.2% (*w*/*w*) water uptake at any r.h.		Slightly hygroscopic 2.3% (*w*/*w*) uptake at 53% r.h. 22% (*w*/*w*) uptake at 97% r.h.		Moderately hygroscopic 3.7% (*w*/*w*) uptake at 53% r.h. 32% (*w*/*w*) uptake at 97% r.h.	

upon standing within one week. As with the hydrochloride, recrystallization from aqueous ethanol returned the free base.

The material was slightly more hygroscopic than the hydrochloride with a 3.9% weight increase on storage at 53% r.h. and a 28% weight increase at 97% r.h. It was also more soluble than the hydrochloride but with an even more marked pH dependency (204 mg/ml at pH 1.0 and 8 mg/ml at pH 2.0). It suffered from exactly the same problems in aqueous solution with solid material converting to the free base at pH 2.0, and the free base precipitating from solution above pH 4.0.

4.1.4. *Discussion of Results*

The results from these preliminary studies are given in *Table 4*. The two salts clearly demonstrated the predictable problems associated with a relatively low pK_a value; the salts were quite weak and dissociated to liberate the free base in media with pH values around the pK_a value. The very low solubility of the free base resulted in immediate precipitation following dissociation. There was clear evidence for multiple polymorphism for each of the salts, and establishing the existence of a stable polymorph, or a suitable pseudopolymorph, may have been necessary before a decision could be made on which of the two salts could be developed further.

The corresponding results for the free base indicated that it appeared to be the better candidate; it showed no evidence of polymorphism, and it was not hygroscopic. The main area that required some additional investigation was whether it had sufficient solubility in gastro-intestinal media. Studies performed on samples of drug substance and on simple capsule formulations demonstrated that the dissolution rates of micronized free base were equivalent or superior to those of the salts under the same conditions. This was confirmed in a simple pharmacokinetic evaluation in individual dogs, where the stomach pH was controlled upon dosing capsules by the administration of citrate buffer at pH 4 and 7.4. Therefore, the free base was taken forward for further study in preference to either of the salts.

4.2. RPR127963

RPR127963 has been evaluated for the treatment of cardiovascular diseases; it is a crystalline, very weak base with a pK_a of 4.10 that is commensurate with the presence of an aromatic secondary amine. The log$P$ value was determined as 2.2. In common with most similar drug substances intended for the treatment of cardiovascular disease, it was considered that a high dose (up to 250 mg), solid, oral dosage form and a correspondingly high dose (up to 50 mg/ml) injection would be ultimately required. In line with our normal practice, a comprehensive evaluation of possible salts was undertaken, and this surprisingly demonstrated that five crystalline salts (a hydrochloride, a mesylate, a citrate, a tartrate, and a sulfate) could be readily produced. With regard to the low pK_a value, we expected successful salt formation with the two mineral acids and methanesulfonic acid, but not with the two organic acids. Nevertheless, it was decided to profile each of these five salts in comparison with the free base. The results of these studies are given in *Table 5*.

4.2.1. *Basic Physicochemical Properties of RPR127963*

When the properties of the anhydrous free base were evaluated, evidence for the existence of a mono-, di-, and trihydrate was found rapidly. It was shown that all these four forms could be interconverted under conditions that might be expected to be employed in granulation processes. The low melting range (119 – 123 °C) of the anhydrate was seen as a second potential problem. It was decided to do no further studies on the free base.

4.2.2. *Basic Physicochemical Properties of the Hydrochloride RPR127963A*

The hydrochloride salt exhibited complex melting behavior (see *Table 5*) that indicated the probable existence of different polymorphs. Recrystallization experiments produced two different monohydrates but no additional anhydrates as was suspected from the phase changes observed on melting. Solubility determinations indicated that it was unlikely to be a viable candidate because the solubility was lower than ideally required, especially for the formation of an injectable formulation. No further studies were undertaken.

4.2.3. *Basic Physicochemical Properties of the Mesylate RPR127963B*

The 4-g batch of the mesylate salt that was provided had a melting range (280.9 – 282.2 °C) that was significantly higher than either the citrate or the tartrate; it also melted cleanly, unlike the hydrochloride. Extensive crystallization studies failed to reveal additional polymorphs, hydrates, or solvates, and the material was found to be non-hygroscopic.

The solubility characteristics were much improved, and solutions containing more than 50 mg/ml drug substance could be achieved in water, 0.1M HCl, and in 5% (*w*/*v*) dextrose solution.

Table 5. *Comparison of Some Basic Properties of RPR127963 and Five Salts*

Property	**Base (RPR127963)**	**Hydrochloride (RPR127963A)**	**Mesylate (RPR127963B)**	**Citrate (RPR127963C)**	**Tartrate (RPR127963D)**	**Sulfate (RPR127963E)**
Appearance	Yellow, crystalline powder	Yellow, crystalline powder	Yellow, crystalline powder	Yellow, crystalline powder	Yellow, crystalline powder	Yellow, crystalline powder
Particle size (microscopy)	1 – 3 µm (agglomerates of microcrystals)	1 – 3 µm (agglomerates of microcrystals)	Tightly packed spherulites of agglomerated microcrystals 18 µm diameter.	Microcrystals (2 – 3 µm) with some aggregates (70 µm)	Rounded agglomerates of microcrystals in domains (70 µm)	Aggregates of microcrystals (10 – 15 µm)
Melting range [°C]	119 – 123	166 – 191 (regrows at *ca.* 166, recrystallizes at 191, then melts at *ca.* 275	280.9 – 282.2	130.2 – 134.3	198.5 – 201.6	305.7 – 308.9
Polymorphism (preliminary study)	Several hydrates detected	Two monohydrates and one anhydrate	No evidence of polymorphs	Stable hemihydrate detected	Unstable anhydrate	No evidence of polymorphs
Aqueous solubility (25 °C), [mg/ml]						
– in demineralized water	Not determined	3.92	108	0.83	0.89	*ca.* 50
– in 0.1M HCl	Not determined	5.2	50.4	Not determined	Not determined	5.9
– in 0.1M NaOH	0.020	0.019	0.022	Not determined	Not determined	0.018
– in dextrose 5% (*w/v*)	Not determined	2.84	90	Not determined	Not determined	*ca.* 40
pH of saturated solution	Not determined	2.33	1.76	2.49	2.56	1.32
Hygroscopicity	Not determined	Non-hygroscopic	Non-hygroscopic	Non-hygroscopic	Very hygroscopic	Non-hygroscopic

4.2.4. *Basic Physicochemical Properties of the Citrate RPR127963C*

Preliminary studies showed that the citrate salt readily formed as a low-melting and apparently stable hemi-hydrate. The aqueous solubility (0.83 mg/ml) was significantly less than that of the hydrochloride salt, salt A. As one of the main reasons for rejecting the hydrochloride was its low aqueous solubility, the citrate was subjected to only limited study before being also rejected.

4.2.5. *Basic Physicochemical Properties of the Tartrate RPR127963D*

The tartrate salt was shown to suffer from the same solubility problem as the citrate, with the added disadvantages of being a very hygroscopic, unstable anhydrate. It was immediately abandoned.

4.2.6. *Basic Physicochemical Properties of the Sulfate Salt RPR127963E*

The 4-g batch of the sulfate salt had a melting range (305.7 – 308.9 °C) that was the highest of all the different forms. Extensive crystallization studies failed to reveal additional polymorphs, hydrates, or solvates. The material was found to be non-hygroscopic.

The solubility characteristics were less impressive than those of the mesylate salt but were considered sufficient to warrant additional study of this salt. Solutions containing more than 40 mg/ml drug substance could be achieved in water and in 5% (*w*/*v*) dextrose solution. However, the solubility in 0.1M HCl was surprisingly low at *ca.* 6 mg/ml, *i.e.*, about the same order of magnitude as that of the hydrochloride.

4.2.7. *Discussion of Results*

For the reasons given above, the mesylate and the sulfate were the only salts with properties that would permit the manufacture of the high-dose formulations that were being considered. The free base still remained a possible candidate especially if a stable hydrate could be found. It was, therefore, decided to undertake some additional evaluations on these three forms; the results from these are presented in *Table 6*.

These additional results were considered to give a slight advantage in favor of the sulfate salt because of its better solubility in cosolvents, giving the formulator the opportunity of achieving a higher dose in an injectable for-

Table 6. *Comparison of Additional Properties of the Free Base Anhydrate, Mesylate, and Sulfate Salts of RPR 127963*

Test	**Base anhydrate RPR127963**	**Mesylate salt RPR127963B**	**Sulfate salt RPR127963E**
Solubility in co-solvents at 25 °C [mg/ml]			
Ethanol	190	0.6	0.2
Propylene glycol	35.4	0.7	1.7
Polyethylene glycol 400	188	0.2	0.2
Dimethyl sulfoxide	> 500	14	110
N-Methylpyrrolidone	> 400	4.4	8.5
Glycerol	42	Not determined	2.7
Peanut oil	0.18	None detected	None detected
Intrinsic dissolution rate [mg·min^{-1}·cm^{-2}]			
– in water	0.01	Not determined	Not determined
– in 0.01M HCl	0.35	7.3	7.7
Powder flow properties	Not determined	Good, but becomes much worse with increasing humidity	Sticks slightly

mulation. The sulfate salt was thus proposed as the form for further development with the mesylate, or the free base (if a suitably stable hydrate could be found), as a possible back-up, should unforeseen problems arise.

4.3. RPR200765

RPR200765 is a candidate drug substance proposed for the treatment of rheumatoid arthritis. It is another crystalline, weak base containing a substituted pyridine ring system with a pK_a of 5.3 and log$P$ of 2.5. It was expected that doses of 100 – 125 mg of RPR200765 in capsules would be required for initial clinical studies.

4.3.1. *Basic Physicochemical Properties of RPR200765*

Early studies suggested that RPR200765 free base was unacceptable for use in solid, oral dosage forms due to a very poor aqueous solubility of *ca.* 10 µg/ml and a low dissolution rate into acidic media. As was expected from these data, a preliminary absorption study in animals resulted in poor bioavailability of the free base. However, it did form a mesylate, a camphorsulfonate, a hydrochloride, and a hydrobromide each of which was crystalline. Aqueous solubility, particle size and shape, powder properties, and polymorphism profile were considered to be the key properties to permit a choice of salt to be made.

4.3.2. *Basic Physicochemical Properties of the Mesylate RPR200765A*

The mesylate salt was a free-flowing powder with a particle size and shape that was potentially ideal for the manufacture of tablets and capsules; the melting point was 214 °C. It was highly soluble (39 mg/ml), and this resulted in an enhanced dissolution rate from hand-filled capsules (equivalent to 50 mg free base) compared to the other salts. This was undertaken because intrinsic dissolution rate studies on compressed discs could not be carried out, as good compact could not be obtained for most of the salts.

The mesylate salt was shown to be a rather stable monohydrate that lost moisture at very low humidity (< 10% r.h.) but rapidly re-equilibrated to reform the monohydrate, when the humidity was raised. These results suggested that this salt probably would be amenable to solid-dose formulation, and there was little risk of changes in the hydration state on processing or storage under normal conditions.

4.3.3. *Basic Physicochemical Properties of the Camphorsulfonate RPR200765C*

The camphorsulfonate was again a free-flowing solid with a high solubility (*ca.* 20 mg/ml), though significantly less than the mesylate. It was a non-hygroscopic anhydrate with a high melting range of 265 – 267 °C. The only disadvantage when compared with the mesylate was the increased molecular weight due to the larger counter-ion. It was considered that this could create problems with capsule or tablet size and weight later in development.

4.3.4. *Basic Physicochemical Properties of the Hydrochloride RPR200765D*

The hydrochloride was also a free-flowing powder with a solubility that was close to that of the camphorsulfonate. It had a melting range of 245 – 248 °C. Studies demonstrated that it was very hygroscopic on exposure to humidity, resulting in the formation of multiple hydrates. Dissolution from hand-filled capsules was quite fast, but not as rapid as either of the sulfonates.

4.3.5. *Basic Physicochemical Properties of the Hydrobromide RPR200765E*

The hydrobromide had the lowest solubility and the slowest dissolution rate of all the salts and was particularly hygroscopic, resulting in the formation of multiple hydrated forms. It had the highest melting range of all the salts of 276 – 277 °C. With these problems and the disadvantageous pharmacological activity of the bromide ion, no further studies were undertaken.

4.3.6. *Discussion of Results*

The results of these studies are outlined in *Table 7*; in this case, very little comparative work was undertaken on the free base due to the poor solubility and bioavailability. Overall, the studies suggested that the mesylate salt was the form to be favored on the basis of its low hygroscopicity, clean polymorphic profile in the preliminary screen, high solubility, and rapid dissolution rates. Another favorable factor supporting the selection of the mesylate salt proved to be the good flow properties, which later allowed very satisfactory prototype capsule and tablet formulations to be developed.

5. Optimization – Second Phase: Drug-Substance Form for Preclinical Development

The initial studies described above require *ca.* 3 – 4 g of the free base and a similar quantity of each of the salts. The data for the free acid or base, and each of the different salt forms normally can be generated in *ca.* 4 – 6 weeks if the samples are available for simultaneous analysis. Having evaluated several possible alternatives in the three cases above, using a range of relatively simple tests, the choice of the form has been narrowed down to one candidate that should be suitable for further development. The next step is to build upon the initial database by employing a more comprehensive range of tests, which require more material. Within three months of receipt of the next batch of drug substance, it should be possible to define with some certainty whether this chosen form is suitable. A series of tests, analogous to those in *Table 2*, are used in this evaluation; these tests are listed in *Table 8*. Upon completion of this second battery of tests, the *Preformulation* team will have generated much additional, solid-state information to add to the database and

Table 7. *Comparison of Physicochemical Properties of RPR200765 Salts*

Property	**Mesylate salt RPR200765A**	**Camphorsulfonate salt RPR200765C**	**Hydrochloride RPR200765D**	**Hydrobromide RPR200765E**
Appearance	Off-white to cream, free flowing powder	White to off-white, crystalline, free flowing powder	White, free flowing powder	White to off-white, crystalline, free flowing powder
M_r	566.61	684.79	524.98	569.43
Melting Range [°C]	214	265 – 267	245 – 248	276 – 277
Crystal habit and appearance	Individual plate-like crystals with some agglomeration.	Clusters of highly aggregated, plate-like crystals	Plate-like crystals; individual crystals contain stress lines	Loosely agglomerated, flaky material
Particle size (by microscopy)	*ca.* 45 – 200 µm in agglomerates of 200 – 350 µm	Crystals *ca.* 20 – 50 µm, clusters *ca.* 80 – 200 µm, some larger clusters up to 500 µm	*ca.* 30 – 100-µm particles	10 – 40-µm particles
Maximum aqueous solubility at 25 °C [mg/ml]	39	19.95	16.68	3.29
pH of saturated solution in demineralized water at 20 °C [mg/ml]	1.93	2.22	2.16	2.63
Hygroscopicity (using DVS apparatus)	Non-hygroscopic with a stable, monohydrate form	Non-hygroscopic	Hygroscopic with multiply hydrated forms	Hygroscopic with multiply hydrated forms
Dissolution rate at pH 2 [$t_{80\%}$, min]	2.0	6.0	7.4	3.9
% Released into citrate buffer, pH 4	> 60	> 60	> 60	14

developed all the different dosage forms required for initial preclinical evaluation. Each of these formulations will have a defined manufacturing process, analytical methods, stability data, a set of defined storage conditions, and a shelf-life.

Even at this early stage, the *Process Chemistry* group will have started a thorough evaluation of the possible manufacturing routes to the chosen molecule and a batch of 250 – 500 g is normally made available within 1 – 3 months, depending on the complexity of synthetic route, for study across a wide range of departments. The recrystallization solvent normally employed would be that used for the preparation of the 4 – 5-g batch in an attempt to keep the physical form the same. The particle size may differ, however, because of different cooling rates. One of the key activities for the *Preformulation Scientist* and the *Process Chemist* is to start investigations into which other polymorphic or pseudopolymorphic forms exist. In the short development phase where initial preclinical administration occurs, it is rarely necessary to undertake these 'sighting studies' to *Good Laboratory Practice* (GLP) standards. Only a preliminary screening of these different forms is considered necessary, as it is possible that the compound will be found too toxic for further development. Our team undertakes this screening on *ca.* 0.5 – 1-g of sample; small portions are recrystallized from anhydrous and hydrated solvents of differing polarity. Any crystalline product recovered is examined by a variety of techniques in order to determine how many different forms are produced, and whether any of them are hydrates or solvates. Preliminary information on the inter-relationships between the different forms can often be found, even at this early stage.

The remainder of the tests are designed for two main purposes:

1. To define the various preclinical formulations that are required, to devise analytical methods for these, to determine their stability, establish storage conditions, and to propose shelf-lives.
2. To establish a database for the chosen form and to give an indication of the possibilities for clinical formulations.

To accomplish this, it is normal to request a minimum of 20 g of drug substance. More will be needed, if the drug substance is intended for inhalation, and there are difficulties with micronization.

6. Optimization – Third Phase: Drug-Substance Form for Clinical Development

Once the drug substance has successfully passed through the initial battery of safety studies, the main requirement is for the preparation of batches of drug substance manufactured using *Good Manufacturing Practice* (GMP) for use in the various safety studies undertaken to GLP standards. Also, at this stage, work can begin on the definition of a suitable series of clinical formulations. For this, we normally expect to have a reasonably clear picture of the interrelationships between the different solid-state forms of the drug substance and should have started to define the most stable form. As *Process Chemistry* produces more batches at increasing scale, they are also examined using some of the key tests (see *Table 8*) to add information to the database. Also, with the

Table 8. *Tests To Be Considered for the Second and Third Phases for Compounds Intended for Use in Oral, Injection, and Inhalation Products*

Test	**Amount required**	
	Second Phase	**Third Phase**
Physicochemical properties		
Melting range	50 mg	50 mg
Optical Rotation	–	1 g
Polymorphism	500 mg	25 – 50 g
X-Ray diffraction	20 mg	20 mg
Intrinsic aqueous solubility	400 mg	–
Cosolvent solubilities[a])	500 mg	2 g
Propellant solubility[b])	–	2 g
Physical properties		
Hygroscopicity	800 mg	–
Microscopy (SEM/Optical)	100 mg	100 mg
Particle size (Laser)	200 mg	200 mg
Micronization	5 g	–
Specific surface area	2 g (R)[c])	4 g (R)[c])
True density	200 mg (R)[c])	200 mg (R)[c])
Bulk-powder density	2.5 g (R)[c])	10 g (R)[c])
Wettability	–	1 g
Impurities (HPLC)		
Related substances	10 mg	10 mg
Degradation products	10 mg	10 mg
Chiral purity	10 mg	10 mg
Electrophoresis, TLC	10 mg	–
Stability studies		
Hydrolytic profile (identify degradants)	100 mg	–
Bulk-drug powder	–	2 g
Excipient compatibility (analyzed with HPLC, XRPD, and DSC)	50 mg	250 mg
Compression properties (for dry powder inhaler only)	–	5 g

Table 8 (cont.)

PRECLINICAL FORMULATION DEVELOPMENT		
Intra-tracheal suspensions	2 g	–
Oral solutions/suspensions	2 g	–
Solutions for nebulization	2 g	–
Intravenous solutions	2 g	–
Other routes (*i.p.*; *s.c.*)	1 g	–
CLINICAL FORMULATION DEVELOPMENT	Predict suitable dosage forms 3 g	Phase I – IIa[d]) 250 – 1200 g
Microbiological Controls		(?)[c])
TOTAL SUBSTANCE REQUIREMENT	20 – 25 g	Depends on dosage and form

[a]) Also solubilities in complexing agents/surfactant systems where appropriate. [b]) Propellants and propellant/cosolvent systems for inhalation dosage forms. [c]) (R): possible to recover drug substance for certain other tests; (?): Depends on supply of sample material. [d]) Develop and specify Phase-I formulation – commence stability/compatibility studies.

increased availability of drug substance, it is possible to finalize the definition of the solid-state form using *ca.* 50 g of drug substance for the initiation of 'maturation studies' [14] as an additional technique to assist in the definition of polymorphism. This experimental technique involves the preparation of suspensions of each of the available polymorphic forms in a variety of different solvents. These suspensions are then stored under a suitable range of temperatures for *ca.* one month. At the end of this storage, the solid material is isolated and the solid-state form evaluated. Much useful information on the relative stabilities of each form can be obtained using this technique.

If the structure of the drug substance has been determined by single-crystal X-ray study, under certain circumstances it may be possible at this stage to initiate the theoretical search for other polymorphic forms. This is achieved, with care, using the *Polymorph Predictor* software (*Molecular Simulations Inc.*, Cambridge). This software has been used successfully [20] on several small molecules (molecular weight <500) and predicts theoretical crystal structures and their relative energies. The most stable form has the lowest energy; increasing energy signifies lower stabilities. The purpose of these *ab initio* predictions is to gain knowledge on potential polymorphic forms that could theoretically exist to attempt to minimize setbacks in development due to the unexpected appearance of a previously unencountered form part way into development or marketing. If one, or more, forms are found with comparative energies and structural characteristics to the forms already produced, an urgent and extensive search is initiated to discover conditions for their formation.

As larger quantities of drug substance and samples from different batches become available, it is imperative that the variations in basic physical and solid-state properties (*e.g.*, crystal size and shape, specific surface area, powder flow properties, bulk and tapped density *etc.*) are studied and documented for each batch. By close liaison with *Process Chemistry*, it is normally possible to gradually modify the recrystallization conditions such that greater batch-to-batch uniformity of these physical characteristics can be achieved.

7. Optimization – Fourth Phase: Drug-Substance Form for Marketing

If the candidate passes through initial clinical evaluation (Phases Ia and Ib), additional characterization and refinement of the drug substance form should continue, and each batch of drug substance produced should be characterized physically. The *Process Chemistry* group normally continues to make minor adjustments to the manufacturing process and recrystallization conditions to improve the yield, purity, or particle size. It is imperative that samples of each batch produced are examined to ensure that the polymorphic form remains constant, until such time as it becomes necessary to 'lock' the *Process*. Close liaison and teamwork between the *Process Chemist* and the *Development Scientist* in an exploration of the various possible recrystallization solvents can often result in further refinement of the crystal properties.

An excellent scheme for the final characterization of solid drug substances, prior to the final regulatory submission, has been described recently by *Byrn et al.* [22]. The aim of both the *Development* and *Process Chemistry* teams is to finalize definition of all the characteristics of the drug substance in readiness for the initiation of Phase IIb.

The author would like to thank colleagues, especially *Anthony Argent*, *Richard Bastin*, *Attia Hasnain*, *Bruce Lithgow*, *Franck Leveiller*, *Derek Mills*, *Bryan Slater*, and *Michel Veillard* at *Aventis Pharma* for their continuously stimulating scientific discussions. Without these discussions, this chapter would not have been possible.

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Chapter 8

Large-Scale Aspects of Salt Formation: Processing of Intermediates and Final Products

by **Stanley Lee** and **Christian Hoff**

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1. Introduction

The life history of a new compound, from research to industrial production, involves many stages. The preparation of the crystallized solid begins with very small quantities at the chemical research level, but then quickly requires chemical-engineering problems to be solved as soon as the scale-up is initiated, to obtain quantities of the order of one kilogram, which are required for studies on safety and toxicity, pharmacokinetics, and stability studies; then it passes through *Process Development* for optimization of the synthetic route and the *Pilot Plant* for scaling up, and eventually it is transferred to the full-scale operation for the production of hundreds of kilograms or even tons.

Numerous synthetic organic compounds are produced on a large scale because of their desirable therapeutic effects. In every case, it is necessary that the compound is obtained in the physical form best suited for the intended use. Whilst there are examples of gases and liquids being produced on a large scale, the vast majority of synthetic organics are produced as solids. This is particularly true in the pharmaceutical field.

As made apparent within the context of industrial drug development and production, there are major reasons for the preference of solids:

i) The first reason is the *ease of handling*. Viscous oils and amorphous solids are very difficult to handle on a large scale. In the *Research Laboratory* countless compounds are generated and evaluated prior to the final choice for development. Usually, the material is isolated from the synthetic reaction by column chromatography and evaporation to dryness of the appropriate column fractions. This very often leaves the product as a sticky oil or amorphous solid. Nevertheless, it is usually suitable to be used in the various tests for biological activity. However, once the compound is selected for development and larger quantities of material are required, the limitations of this approach rapidly become apparent.

ii) The second reason is the *ease of purification*. Compounds intended for pharmaceutical use need to have a particularly high degree of purity. This is very difficult to achieve with a sticky oil, since separation from impurities is hardly possible, as it is likewise nearly impossible to remove the last traces of solvent. In the course of present-day development kg amounts of a drug candidate must be provided within a few weeks, to enable safety and biological studies to be conducted. In early phases, the chemistry is usually not yet optimized, hence the synthetic reactions employed frequently lead to reaction solutions that not only contain the desired product but also high levels of impurities. The formation of a solid is a valuable technique both to isolate and purify the desired product.

iii) *Stability:* Solids are much more stable to oxidation and hydrolysis than liquids. Therefore, solids are generally expected to have longer shelf life.

iv) Solid drug substances including drug salts are formulated into and manufactured as solid oral dosage forms, which are by far the most popular and widely used drug products.

However, there are also some negative aspects in handling solids:

i) The low bulk density of finely milled solids renders them bulky to store and difficult to handle for manufacturing dosage forms (insufficient flowability, problems with compressibility).

ii) Handling highly active solids requires high alertness and extensive engineering, and procedural measures for avoiding cross-contamination by airborne particles and for protecting operating personnel.

This chapter covers an overview of general techniques, concentrating on the physicochemistry and the chemical-engineering aspects of controlling the crystallization of solids and concludes with examples where salt formation has been successfully applied for intermediate steps within a synthetic route. It is appreciated that in no way are they exclusive. They are intended to convey an idea of the principles and issues involved.

2. Principal Techniques of Isolation and Purification

2.1. Crystallization

Crystallization is one of the most valuable and widely used technique for the isolation and purification of organic compounds both in the laboratory and on the manufacturing scale. It is a procedure that is reproducible and especially suited to use on a manufacturing-plant scale, since the results obtained in laboratory experiments often translate smoothly into large scale. Most other methods suffer from major disadvantages that make them less suitable for general use.

2.2. Chromatography

Chromatography is a superb technique for isolation of products in the research laboratory, and it has a high probability of success. However, it is a low-output procedure and requires large volumes of solvent and solid phase to achieve the desired separation. Typical loadings, for example, are *ca.* 20:1 solid phase/substrate and elution using *ca.* 1 l of solvent to elute *ca.* 1 g of product. The procedure can be difficult to scale up due to 'edge effects', which mean that there is no longer 'plug' flow down along wide columns resulting in poorer separations.

Great advances have been made recently in improved scale-up of chromatography, and now, for example, columns of 300-mm diameter or greater are available. Nevertheless, the procedure still remains as a low-output one and is only used on the large scale when most other procedures fail.

Chiral chromatography, in fact, chromatography on columns with chiral stationary phases, can also be performed on an industrial scale. It is frequently the technique of choice for the resolution of isomers, *i.e.*, the separation of the eutomer (the desired isomer) from the distomer (the unwanted isomer), and it is occasionally the only technique left where separation by fractional crystallization of diastereoisomeric salts is impossible.

2.3. Distillation

Distillation is an efficient high-throughput procedure for isolation and purification of volatile organic compounds. However, many compounds are not sufficiently volatile and stable for the technique to have universal applicability. Use of continuous-feed, short-path distillation can to some extent overcome some of those restrictions. In reality, distillation is confined to removal of reaction solvent and is used for purification of relatively few compounds only.

2.4. Other Techniques

Various specialized techniques are available which have advantages for purifying a particular material. These include zone refining (zone melting), freeze drying, ion exchange and counter-current extraction.

3. Fundamentals and Significance of Crystallization

Crystallization is one of the earliest recorded forms of molecular self-assembly. In its simplest form, it can be envisaged as deposition of molecules in an orderly fashion onto a template (unit cell of the crystal lattice). Only molecules that 'fit' are deposited onto the template. The driving force of the process is the release of energy due to formation of a stable crystal lattice. For the process to be effective, it is important that a selection process occurs at the surface of the growing crystal. In an ideal world, only the desired molecules are deposited, and all the impurities/by products remain in solution. A successful crystallization controls the parameters (solubility and supersaturation) that affect the rate of crystal growth. In general, the slower the rate of crystal growth, the more effective is the selection process and a purer crystalline product results. 'Crash cooling/crystallization' often leads to occlusion of impurities.

3.1. Quality Aspects of Crystallization

After the synthesis is completed, crystallization is the first step in the last phase of manufacturing the solid. It is intensively studied, usually over many months to obtain the best possible control, because most of the problems mentioned below depend on it. Specifically, the properties of the crystalline powder obtained can often be modified considerably by making only a minor change in the crystallization operating procedure. It is imperative in the current regulatory environment that the crystallization process is firmly established and validated as soon as possible, and that absolutely no variations are permitted to this process, except with full regulatory approval. The following considerations are thought as a reminder that strict requirements are indeed justified in order to safeguard high standards of quality and reliability of the final drug product.

3.1.1. *Steps Involved from the Solid to the Final Product*

From the time the crystals of drug substance are formed until that when the pharmaceutical product is manufactured in its commercial form, the solid undergoes many operations and the resulting tablet (or other dosage form) reflects, as it were, a 'history' of all the steps.
For a typical tablet product, these are essentially:

- crystallization,
- filtration,
- dehumidification and drying,
- milling and sieving,
- mixing with other powders (excipients),
- wet granulation with subsequent drying, or dry compaction,
- final compression yielding the tablet and packaging.

3.1.2. *Potential Problems Related to the History of the Solid*

For the same active substance and the same dosage form, variations related to the manufacture of the solid may involve:

- solubility and especially the dissolution rate [1];
- surface properties: adsorption, wettability, pore size, specific surface area;
- powder properties related to flow, angle of repose, cohesion, bulk density, mixing behavior, compressibility, generation of static electricity, minimum ignition energy,
- tablet properties: hardness, homogeneity, divisibility, friability, disintegration, stability in the presence of heat and humidity;
- other physical or chemical changes during each of the above operations and storage of the finished tablets in the packaging proposed for marketing.

As any or several of those parameters vary to an undue extent, the bioavailability of the active substance and the reliability of the drug product may be at stake.

4. Control of Industrial Crystallization

4.1. Choice of the Polymorphic Form of the Drug Substance

The first crystallization tests in the research stage are usually carried out with several grams or even milligrams of substance, under somewhat random conditions of temperature, stirring, and supersaturation. The first crystal forms obtained generally follow *Ostwald*'s rule [2], which stipulates that rapid crystallization initially involves the formation of the least stable polymorphs.

Historically and rather frequently, the first polymorph to crystallize is developed rapidly, taking into account the contemporary competitive situation, and the first kinetic tests are carried out on this crystal form. After several years of intense study, sometimes even leading to final industrialization and marketing, a newer polymorph occasionally appears that is more stable thermodynamically. Once this new structure exists, it is very difficult to reproduce the previous form, as the most stable seeds preferentially induce crystallization of this new structure.

At this point, tests must again be carried out on the bioequivalence of the two polymorphs, the pharmaceutical form, the analyses, stability tests, *etc.*, *i.e.*, practically the whole pharmaceutical dossier based on the first polymorph. Consequently, it is extremely important to carry out intensive screening of the different potential polymorphs as soon as possible (see *Chapt. 3*), at the risk of a sudden withdrawal of the product from the market, if it is no longer possible to manufacture the first polymorph registered. A recent example of this occurrence is with the antiviral, *Ritonavir*, reported in the world's press in August, 1998. The manufacturers (*Abbott*) had a potentially disastrous situation on their hands, when a different polymorphic form started to be routinely produced in their crystallization process, and it was reported that they had only one months supply of *Ritonavir* capsules remaining worldwide. The press reported 'the drug is forming a different crystalline structure which makes it less soluble, so the correct dose of drug is not released inside the patient's body'.

This research has now become a strategic issue for the large pharmaceutical companies, and there have been examples of individual polymorphs of some drug substances being patented. Another risk is the discovery of a new polymorph by a competitor, which can then be patented.

4.2. Choice of the Solvent

This is also an important parameter, for various reasons:

- the toxicity of trace levels of residual solvent in the dry product,
- the possibility of stable solvates or hydrates,
- the productivity of the process depending on solubilities varying with temperature,
- the crystallization yield depending on the solubility limit when cold,
- the definition of a crystal form, as the crystals can vary in terms of polymorphism and also habit, *i.e.*, the apparent form for the same crystal lattice, depending on the solvent.

4.3. Choice of Particle Size

Chemical and pharmaceutical production requirements are often quite different. However, to ensure reproducible bioavailability, it is crucial to develop a chemical production process that is consistent in terms of the final properties of the solid described above. Particle size is a key parameter that must be adapted to suit formulation difficulties. The control of particle size, to give consistency from one batch to another, is most critical for drugs with poor solubility and absorption characteristics. For low-dosed solid dosage forms, certain limits of particle size must not to be exceeded in order to comply with the requirement of content uniformity.

The problem is that there are practically no general definitions; each product is essentially a special case, which means that, at the beginning of development, powders with different characteristics must be prepared and formulation tests carried out so that the particle size can be chosen by *Pharmaceutical Development* scientists from among different samples provided by *Chemical Development* scientists.

Rather often, the tendency is for the *Pharmaceutical Development* scientists to request a very fine and uniform powder (typically with a median in the range 30 – 300 μm) for bioavailability requirements and for the *Chemical Development* scientists to prefer the formation of large crystals for ease of filtration and drying requirements. Compromises have to be found, and spherical agglomeration is a promising new approach.

For almost all drug substances, the final treatment is a mechanical comminution step: at least homogenizing for destroying agglomerates, and frequently milling for reducing the particle size.

5. Control of the Crystallization Process

5.1. Crystallization Steps

Generally, the final crystallization of a pharmaceutical active substance has two simultaneous objectives: to obtain the specified crystals and to purify the product so that traces of compounds resulting from the chemical synthesis are removed. This final crystallization is carried out either directly in the last synthetic step or more often on the 'crude' product. The crystallization steps are conventionally defined as follows:

- dissolution in a given solvent by raising the temperature, generally followed by filtration to eliminate foreign particles and decolorization on activated charcoal,
- nucleation after cooling, or seeding,
- crystal growth by programmed cooling,
- agglomeration of crystals (sometimes),
- attrition, due to particle collisions, which is proportional to the stirring speed.

What are the essential parameters?

To control crystallization, the following parameters must first be studied:

- supersaturation,
- seeding,
- cooling rate,
- stirring speed.

5.2. Supersaturation

This is the fundamental parameter, the driving force for the whole process. It is defined in different ways:

- by the difference between the concentration c of the solution and the concentration at equilibrium c^* (at the same temperature) (see *Fig. 1*).

$$\Delta c = c - c^* \tag{1}$$

- by the ratio of the two concentrations:

$$\mathrm{B} = c/c^* \tag{2}$$

- or relative supersaturation

$$c_{ss} = \frac{c - c^*}{c^*} \tag{12}$$

Thermodynamically, the driving force is the difference between the chemical potentials:

$$\Delta\mu = \mu - \mu^* = k \cdot T \cdot \ln c/c^* \tag{4}$$

where $k = 1.38 \cdot 10^{-23}$ J/K, the *Boltzmann* constant, and T the absolute temperature.

Industrially, supersaturation can be achieved by:

- evaporating the solvent (adiabatic crystallization),
- cooling the solution,
- adding an antisolvent to decrease solubility,
- chemical reaction: double decomposition of salts,

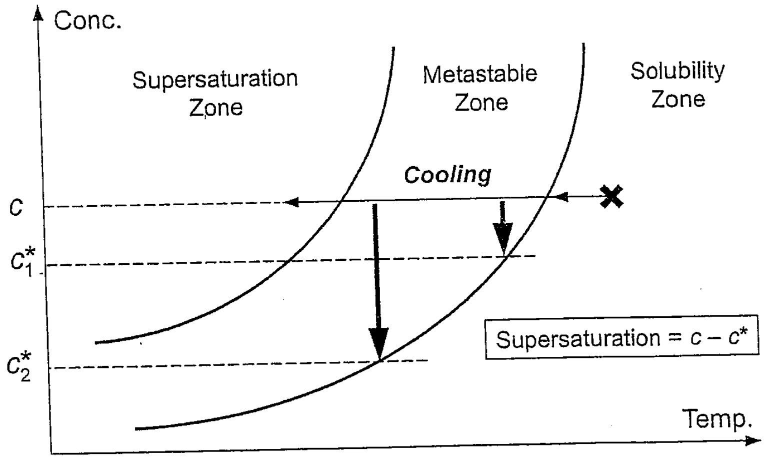

Fig. 1. *Supersaturation as the driving force in the crystallization process* (see text)

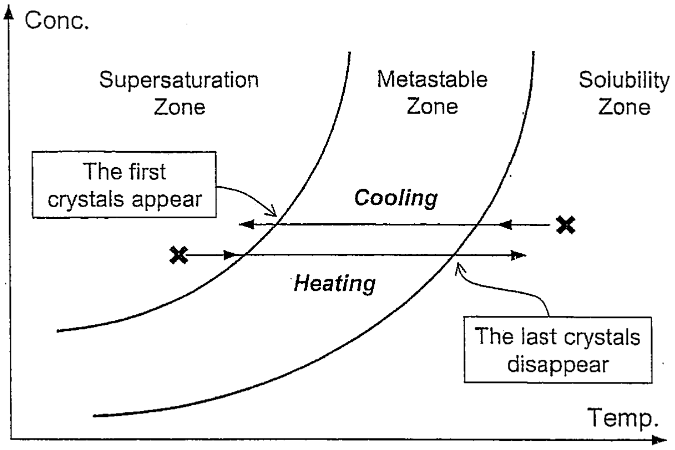

Fig. 2. *Definition of the metastable zone in crystallization from solution* (see text)

- changing the pH, which is a widely used process for crystallizing salts by adding acids to the active basic substance (or bases in the case of acid compounds) in solution.

When supersaturation increases, crystals spontaneously start appearing at a certain temperature, *i.e.*, primary nucleation occurs. By changing the concentration several times and repeating the operation, the supersaturation curve is obtained. By increasing the temperature, the crystals are dissolved (reverse process). This determination is repeated by varying the concentration to obtain the solubility curve. The two curves define three ranges (see *Fig. 2*):

- the total solubility range at high temperatures, where it is impossible to crystallize the solute,
- the metastable range between the solubility curve and the supersaturation curve, where crystallization may or may not occur, depending on the conditions,
- the supersaturation range at low temperatures, where there is necessarily excess solid.

The solubility curve is a thermodynamic limit, which depends only on the solvent/solute couple. The supersaturation curve is a kinetic limit, which essentially depends on the cooling rate but also on stirring and impurities (water content, other solvents present, particulate impurities in suspension, *etc.*).

5.3. Seeding

If the solution nucleates spontaneously, large numbers of nuclei are obtained, *i.e.*, there is the formation of very small crystals that are difficult to filter and dry, and that are difficult to control from one batch to another. In some cases, the whole mass in the vessel can crystallize, resulting in a substantial exothermic process. The phenomenon can be violent and cause problems both for process security (boiling solvent), and the equipment (damage to stirring system, *i.e.*, the impeller shaft, speed selector, electric motor).

Consequently, controlling the crystallization process by cooling often involves a seeding study.

The following points must be optimized:

- seeding temperature,
- seed quantity,
- seed quality,
- cooling rate.

Seeding Temperature. Seeding near the solubility curve (*Fig. 3*, *Case 1*) is carried out at low supersaturation. There is little secondary nucleation, crystal growth is slow and large crystals are obtained.

Seeding near the supersaturation curve (*Case 2*) is carried out at high supersaturation. It induces abundant secondary nucleation, crystal growth is rapid, and small crystals are thus obtained.

Seed Quantity. If the quantity of seeds is too small, secondary nucleation and growth will be insufficient to take up the supersaturation. In this case, a second nucleation phase may occur, which results in a heterogeneous population at the end of the process, consisting of large and small particles.

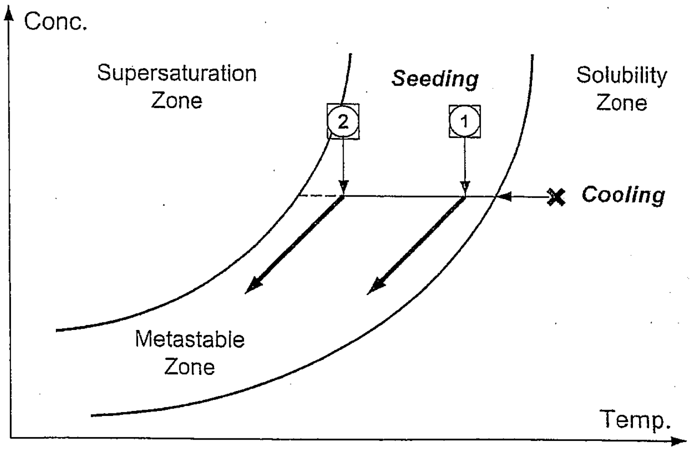

Fig. 3. *Effect of seeding on crystallization while system is within the metastable zone* (see text)

Seed Quality. To avoid the same phenomenon, it is useful to test different seed particle sizes, the effect of which is in fact to vary the specific surface area, on which secondary nucleation depends.

It is preferable first to obtain thermodynamic equilibrium by stirring in the same solvent rather than directly charging the crystallization vessel with dry powder.

The effect of the seed particle size on the final size is also a factor to take into account, especially if seeding is carried out at low supersaturation, *i.e.*, the larger the seed, the larger the final particles obtained, and inversely. Seeding in continuous crystallization processes is discussed in [3].

5.4. Cooling Rate

If seeding is carried out at a certain temperature in the metastable range (*Fig. 4*), two cases can arise:

- A slow cooling rate allows the nuclei to take up the supersaturation, and the course tends to approach the solubility curve (*Case 1*). In this case, rather large particles are obtained.
- If the cooling rate is rapid (*Case 2*), supersaturation continues to increase during cooling, and the course approaches the supersaturation curve. A second nucleation then occurs spontaneously, and the particle size distribution is bimodal, *i.e.*, the population consists of large particles due to seed growth, plus a large quantity of fines. Filtration of this type of population is always problematic, because the filter medium can clog, resulting in an unacceptably long filtration time, or the solid can even be lost

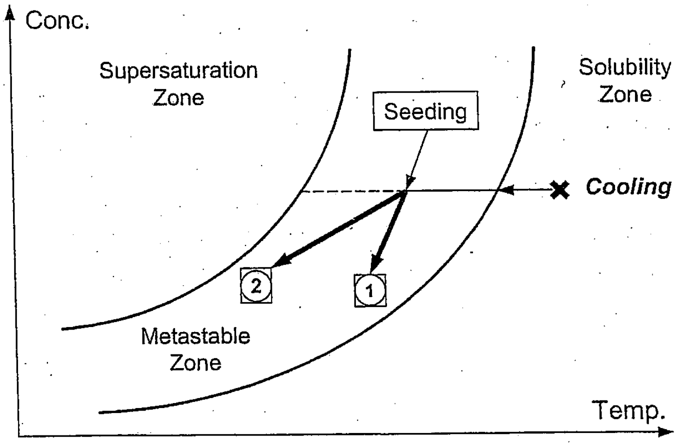

Fig. 4. *Effect of the cooling rate on the crystallization process* (see text)

in the mother liquors. A satisfactory operating procedure consists in maintaining the solution at an isotherm for a sufficient time after seeding to reduce supersaturation before cooling is started.

5.5. Stirring Rate

This is a typical chemical engineering parameter, which must be extrapolated carefully.

As a rule, rapid stirring favors nucleation by seed proliferation. Another effect is to favor attrition by increasing the number of collisions among particles or with the impeller.

Stirring can also enhance growth kinetics, especially if the volume is limited, *i.e.*, in a viscous mixture with less diffusion of the solute towards the growing crystal surface. When the process is transferred from the laboratory to the industrial scale, several rules of extrapolation can be used:

- maintain constant peripheral impeller speed,
- maintain constant turbulence (*Reynolds* number),
- maintain constant power input per unit volume,
- more empirically: increase the stirring rate to obtain a uniform suspension.

The most widely used rule is the extrapolation of the speed to maintain constant power per unit volume, P_V:

$$P_V = N_p \cdot \varrho \cdot N^3 \cdot d^5 / V \tag{5}$$

where N = stirring rate [s^{-1}],
N_p = the power number of the stirrer, a dimensionless coefficient,
ϱ = the density of the solution stirred [$kg \cdot m^{-3}$],
d = the diameter of the stirrer [m].

As an approximation, ϱ and N_p can be considered to be constant (k_s), and thus

$$N^3 \cdot d^5 / V = k_s \tag{6}$$

from which the relationship for the large-scale stirring rate can be derived:

$$N_{prod} = N_{lab} \cdot \sqrt[3]{\frac{V_{prod}}{V_{lab}} \cdot \left(\frac{d_{lab}}{d_{prod}}\right)^5} \tag{7}$$

where the indices lab and prod refer to the parameters valid for laboratory and industrial production scale, respectively.

This is valid only if the reactors are homothetic, *i.e.*, they have comparable geometry and identical stirring device. Various examples are explained in detail in [4].

6. Control of Crystallization by Measurement

The complexity of the crystallization process, *i.e.*, the need to control polymorphism, crystal habit, and particle-size distribution to guarantee consistent powder quality and thus consistent bioavailability, lead the industrial chemist or chemical engineer to use more and more powerful measuring instruments starting in laboratory development.

Temperature is of course the primary parameter to measure and adjust. The reactors must be equipped with precise sensors and a computerized measurement and control system to allow control of temperature gradients as well as isotherms.

Particle size during crystallization is traditionally monitored with a laser particle sizing apparatus, which involves sampling the medium for analysis and tends to alter the crystal population. A new method consists of using a laser probe introduced directly into the reactor during stirring [5].

Supersaturation can be monitored with a densitometer [6] in the liquid phase, with a conductivity meter, or *in-situ* IR spectroscopy. It should be noted, however, that the measurement is often disturbed by crystals depositing and growing on the sensors [7]. Another method that avoids this drawback is monitoring the heat released by crystallization with a reaction calorimeter. The crystal mass formed is proportional to the heat released and can be evaluated directly without sampling. Based on the mass of solute added, the supersaturation of the medium can be calculated by subtraction [8]. By coupling the laser probe in the medium with heat-flow measurements, the crystallization process can be monitored and optimized rather precisely (*Figs. 5* and *6*). This method can also be used to obtain solubility and supersaturation curves automatically, as the calorimetric reactor can be programmed.

The *particle size of the final powder* is obtained by various methods: sedimentation, specific flow resistance through a diaphragm, laser diffraction, sieving, *etc*. The error of the determination increases with the form factor:

$$f = \text{particle length} / \text{particle width}.$$

Conventional particle sizing gives a single value for crystal size, which is exact for cubic and spherical particles for which $f = 1$. As the form factor increases, the size can no longer be indicated by a single value. This is true for the acicular habit (needle shaped crystals), which requires an evaluation of length and width. This can be carried out with image analysis software coupled with microscopy. The method provides excellent digital results, which can be used to model crystallization conditions [9] [10].

Polymorphism is detected early, usually by microscopic examination of crystal appearance, which often shows differences. However, this is not al-

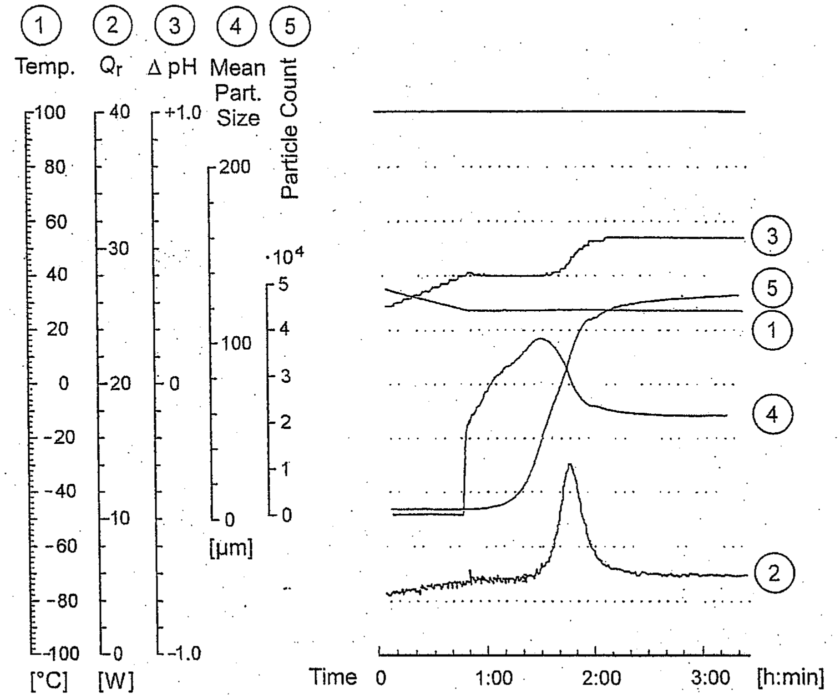

Fig. 5: *Multichannel stripchart recording of a typical batch crystallization process without seeding, isothermal mode.* Initiated by slow cooling (*Trace 1*), at time 0:50 h first crystals begin to appear (*Trace 4*), from which time on constant temperature is maintained. The number of particles rises slowly (beginning at 1:00 h, *Trace 5*). At 1:30 h, secondary nucleation occurs resulting in a increasing number of small particles thereby reducing the mean particle size (*Trace 4*). Between 1:30 and 2:00 h, massive nucleation and crystal growth run in parallel, thereby producing the exotherm (*Trace 2*), the area of which is proportional to the mass of solid generated. A slight and insignificant shift of the pH is also recorded during the process (*Trace 3*).

ways true. There are cases when different polymorphs may have identical appearance. Even the reverse can occur: the same polymorph may crystallize to yield crystals of different appearance. The microphotographs in *Fig. 7* present the same substance in three different shapes. Frame *a* shows crystals of one polymorph, while frames *b* and *c* show a second polymorph, which crystallized in two different habits, *i.e.*, with the same crystal lattice (X-ray diffraction pattern), but with quite different morphologies. The crystals in frame *b* were crystallized very rapidly at high supersaturation, and those in frame *c* were crystallized slowly at low supersaturation.

Bulk-density measurement provides also a very simple means of detecting a polymorph. A simple graduated test tube and a balance is all what is needed for this measurement.

The most widely used method is DSC (differential scanning calorimetry), which enables the determination of endothermic events on the DSC thermo-

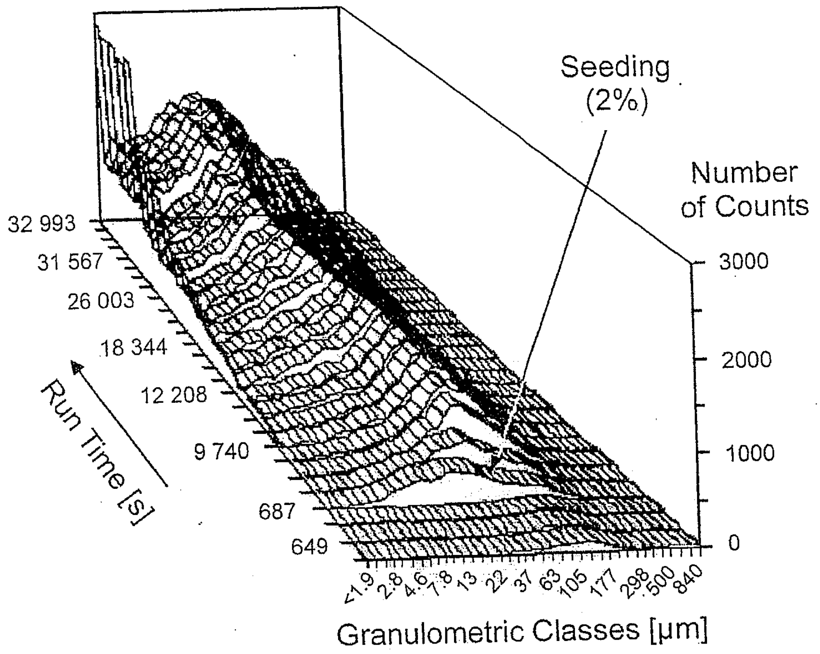

Fig. 6. *Time profile of particle size distribution during a batch crystallization process.* Crystallization was induced by seeding.

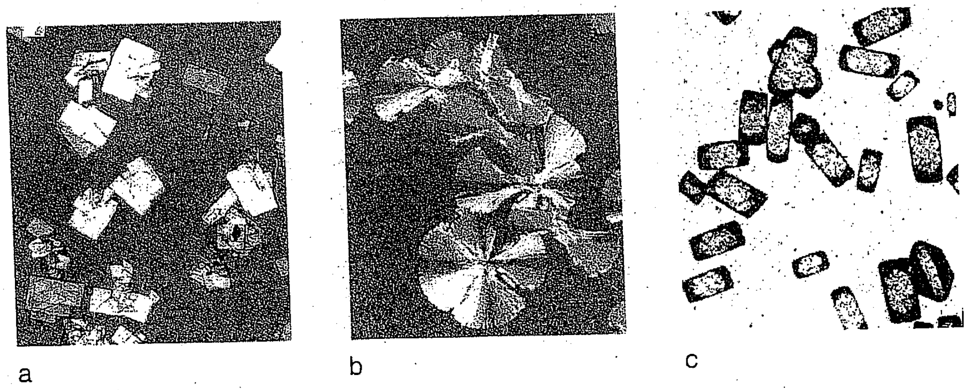

Fig. 7. *Microphotographs of three crystalline forms of a drug substance* (see text)

gram, corresponding to the fusion of each crystal variety and characterized by the values for temperature and enthalpy. It should be noted, however, that any measurement undertaken by DSC should ideally be complemented by a temperature scan of the X-ray powder diffraction (XRPD) on a temperature programmable hot-stage.

Infrared (IR) spectroscopy can be used to distinguish polymorphs, on condition that the interactions in the solid differ enough to shift some bands.

Near IR spectroscopy is a promising new method in this field, particular for online monitoring. The difficulty is that a large number of factors can affect the data and thus many calibrations are required to obtain reliable results.

X-Ray analysis always provides ultimate proof of polymorphism, as the spectra depend directly on the crystal structure. Ideally a monocrystal is prepared, which provides very precise information on the crystal lattice and makes it possible to index the crystal faces with a goniometer. With a synchrotron, the crystal lattice can now be determined with powder spectra.

Lattice modelling can be then carried out on a computer. There are many applications: determining the absolute density of the solid, representing the surface atoms on each face, lacunae, *etc.* It is possible to deduce the hydrophobic or hydrophilic properties, the faces where growth can be predicted to be slow, or those faces where it could be predicted to be fast, the possibilities for 'poisoning' the growth on certain faces by the use of additives ('crystal engineering'), *etc.* [11] [12].

7. Filtration and Drying

When the crystallization process finally yields the desired crystals in terms of polymorphs and particle size, they must then be suitably separated from the mother liquors and dried. Often too frequently, chemists tend to focus in depth on the development of organic synthesis and the reduction of the cost per kilogram of the final drug substance. Crystallization is considered to be a secondary matter, with filtration and drying receiving even less attention. However, the successful final preparation of a medicinal product is highly dependent on these two steps.

7.1. Avoiding Contamination

The resulting drug substance powder must be as pure as possible, of course, with only limited concentrations of impurities arising from the synthetic route and very low residual levels of any catalysts used. It must also be free of cross-contamination by other active substances that are manufactured in the same equipment or stored on the same site, as manufacturing campaigns are often carried out simultaneously. Most of the processing and handling of the powder tends to be undertaken in closed vessels to reduce the risk of contamination by air borne, sub-micrometer dust particles that can remain in the atmosphere for some time and settle very slowly.

7.2. Stability of the Moist Product

Moist powder can be the site of many transformations, for example agglomeration, settling, partial recrystallization, and polymorphic conversion.

The methods that are used for filtration and drying include the following:

- The most conventional method involves the *Büchner* filter and tray drying. This system is clearly more susceptible to cross-contamination because of the many handling steps it requires and exposure to the air is high. It is still used, however, for small quantities.
- For larger batch sizes, the double-cone spin-dryer or conical dryer with an epicycloid screw is very effective. However, this is intended for large manufacturing operations dedicated to a single product.
- The use of sealed filter dryers with stirrers is now more widespread (see *Fig. 8*). In this type of apparatus, it is possible to filter, dewater the cake, smooth the surface to avoid cracking (preferential route), wash it, take up the cake again in a solvent, filter it again, and dry it with inert gas or in a vacuum by heating the walls and stirring moderately.

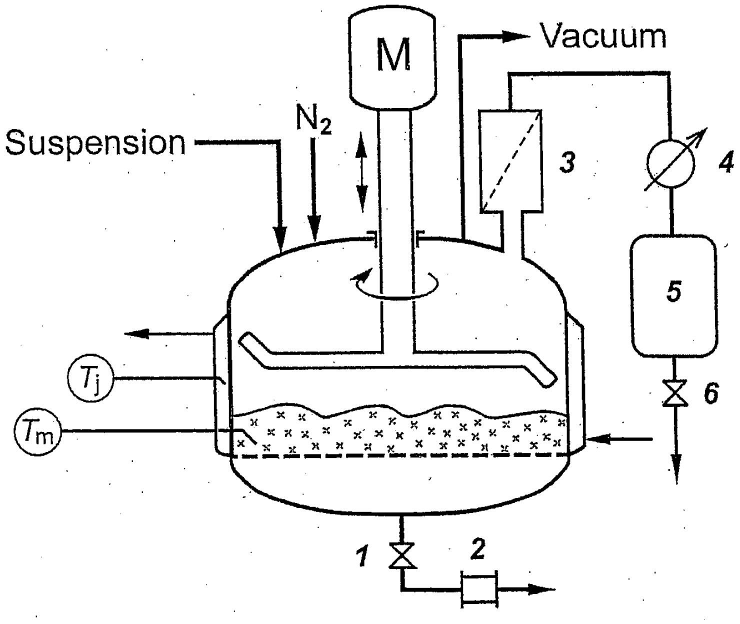

Fig. 8. *Schematic representation of a filter dryer.* M, stirring motor; T_j, jacket temperature, T_m, temperature of product mass; *1*, suction valve for filtrate withdrawal; *2*, viewing glass; *3*, dust filter; *4*, condenser for evaporated solvent; *5*, solvent receiver; *6*, solvent withdrawal valve.

The dry powder is discharged directly into drums. Thus, filter dryers are suitable for pharmaceutical chemistry, as they allow to perform operations without contact to the open air. However, they have some limitations due to their design and operation characteristics:

- a small filter surface;
- a small heat exchange surface between the wall and the powder;
- strong stirring, causing crystal attrition, and agglomeration of the moist powder; product degradation can even occur due to frictional heating, if the stirring is too intense;
- occasionally static electricity is generated due to rubbing against the stirrer.

7.3. Optimizing the Filtration Process

To avoid filtration difficulties, the specific flow resistance of the cake must be measured on a filter cell. This is a cylinder that can be pressurized, and the filter cloth can be fixed to its base. The suspension to be filtered is added, and the time-course of the filtrate volume is recorded. The following relation is obtained by applying *Darcy*'s law:

$$t/V = R_{\mathrm{fm}} \cdot \eta/A \cdot \Delta P + (\alpha \cdot m \cdot \eta/2A^2 \cdot \Delta P) \cdot V \qquad (8)$$

where:
t = the filtration time [s]
R_{fm} = resistance of the filter medium [m^{-2}]
A = filter surface area [m^2]
α = specific resistance of the cake [$\mathrm{m} \cdot \mathrm{kg}^{-1}$]
m = mass of the solid per unit volume of filtrate [$\mathrm{kg} \cdot \mathrm{m}^{-3}$]
η = viscosity of the liquid [$\mathrm{Pa} \cdot \mathrm{s}$]
ΔP = filtration pressure [Pa]
V = filtration volume [m^3]

In fact, it is sufficient to plot t/V *vs.* V (see *Fig. 9*):

The y-intercept is: $R_{\mathrm{fm}} \cdot \eta/A \cdot \Delta P$

and the slope is: $\alpha \cdot m \cdot \eta/2\mathrm{A}^2 \cdot \Delta P$

Thus, the resistance of the filter medium (R_{fm}) is obtained very easily, which makes it possible to optimize the choice of material (cloth, metal, or frit filter), as well as the specific resistance of the cake α, which can be used to optimize the operating procedure for crystallization. Values of α below $10^9\ \mathrm{m} \cdot \mathrm{kg}^{-1}$ provide very easy filtration, values between 10^9 and $10^{11}\ \mathrm{m} \cdot \mathrm{kg}^{-1}$ give moderately rapid filtration, and above 10^{11} to $10^{12}\ \mathrm{m} \cdot \mathrm{kg}^{-1}$ filtration is rather difficult, especially with a sealed filter dryer.

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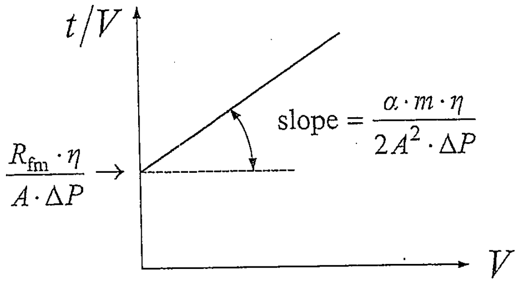


Fig. 9. *Obtaining relevant filtration characteristics from plot according to* Darcy*'s law*

By plotting the curve $\ln \alpha = f(\ln \Delta P)$, the cake compressibility is obtained from the slope n:

If $n = 0$, the cake is incompressible.
If $n > 1$, the cake is very compressible.

The use of a sealed filter dryer requires crystals with a specific resistance of *ca.* 10^8 to 10^{10} $m \cdot kg^{-1}$ to obtain reasonable process times (from several hours to *ca.* 48 h). Beyond this, a centrifuge is preferable.

7.3.1. *Change of Temperature*

The solubility of most materials is lower in cold solvent than in hot solvent. This is the typical principle applied in traditional crystallization. The material to be crystallized is dissolved in hot solvent, and the resulting solution is cooled. Nucleation (initial deposit of solid material) occurs, when the concentration in solution exceeds the supersaturation threshold at the given temperature. Control of the cooling rate controls the rate of change of solubility and hence the rate of crystal growth.

7.3.2. *Change in Polarity/Solvent Composition*

Many materials have high solubility in one solvent and low solubility in a second solvent. Advantage can be taken of this difference by dissolution in the high-solubility solvent and addition of the low-solubility solvent either in a controlled manner at constant temperature or in combination with a change in temperature.

7.3.3. *Supersaturation and Seeding*

When a solution of a solid is cooled in absence of particulate matter, often no crystals are deposited even though the equilibrium solubility at a given temperature has been exceeded. This phenomenon is known as supersaturation. Control of supersaturation is vitally important in achieving a controlled crystallization, as poor control often leads to the material 'crashing out' of solution in a poor physical form and impure state.

One common way that the supersaturation can be reduced is by seeding. This has a twofold effect. First, it provides a template of the correct shape for the new material to be deposited onto and promotes additional nucleation. Second, once the crystallization has been induced, the material being deposited as a solid is continually reducing the solution supersaturation concentration. This leads to a more uniform product quality.

7.3.4. *Control of Polymorph*

The topic of polymorphism is dealt with in *Chapt. 3*. For most pharmaceutical purposes, it is preferable to use the most stable polymorphic form. Control of crystallization parameters is vital in large scale manufacture to ensure a reproducible product. In general, a rapid crystallization at low temperatures can lead to the 'kinetic' crystalline product that may be a less stable (metastable) polymorph. Crystallization at a higher temperature and over a longer period of time will lead to the thermodynamically stable product, ideally, the most stable polymorph.

7.3.5. *Salt Formation*

As exemplified in detail later, salt formation essentially lowers the equilibrium solubility of organic bases and acids in the organic processing solvent, because the salt formed is a new species, which is typically less soluble in such solvents. The driving force for the process is again the energy released by formation of the stable crystal lattice.

8. Acids and Bases for Salts

Focussing here on chemical-technical properties, the more common acids and bases which have been used on both the laboratory and plant-manufacturing scale are briefly described in the following sections (for other descriptions see the monographs, *Chapt. 12*).

8.1. Acids for Salts of Organic Bases

8.1.1. *Hydrochloric Acid*

This acid is the most widely used acid for formation of salts both for the isolation of synthetic intermediates and for the final pharmaceutical dosage form. It is a very strong acid and so forms salts with most bases. However, loss of the volatile HCl can give rise to long-term stability concerns with very weak bases.

Chlorides and hydrochloric acid can cause stress corrosion/pitting in stainless steel equipment particularly at low pH. On a large scale, this necessitates use of glass lined vessels or equipment such as centrifuges and pressure filters being fabricated from special resistant alloys (*e.g.*, Hastelloy).

Hydrochloric acid is conveniently used as the 36% (*w/w*) solution in water. If, however, water interferes with the formation and isolation of a solid crystalline product, it is possible to use the anhydrous gas from cylinders.

8.1.2. *Sulfuric Acid*

This strong acid has also been widely used both for isolation of intermediates and as the final pharmaceutical salt form. The dibasic acid can give either neutral (*i.e.*, two moles of base to one mole of sulfuric acid) or acid salts. It is important, therefore, to ensure that the correct stoichiometry is used in the formation of a sulfate salt.

8.1.3. *Hydrobromic Acid*

Retrospectively, hydrobromic acid is the third most frequently used acid for final pharmaceutical products, but, because of the potential of adverse reactions to bromide ions, it is becoming less favored for new products.

It is still widely used for isolation of intermediates, since hydrobromides are often of lower solubility and better crystallinity than the corresponding hydrochlorides.

Hydrobromic acid is also volatile and attacks stainless steel. It is used both as the anhydrous gas and as a 48% (*w/w*) solution in water.

8.1.4. *Maleic Acid*

Many pharmaceutical final products are isolated as maleates because of high crystallinity of the salts. Its two carboxyl groups may form both neutral and acid salts. A potential disadvantage is that it can isomerize to the thermodynamically more stable (*E*)-isomer, fumaric acid. For this reason, high temperatures must be avoided.

The solid-state nature of maleic acid requires it to be dissolved in a suitable solvent when used for salt formation reactions.

8.1.5. *Methanesulfonic Acid*

This is a strong acid and so forms stable salts with many weak bases. It is frequently used for the salt form of the final pharmaceutical product. In addition, it finds considerable utility for isolation of synthetic intermediates. Operationally, it is very convenient to use on a large scale, since it is a liquid containing no water.

8.1.6. *Phosphoric Acid*

Phosphoric acid is especially used to enhance water solubility of final products. It is an involatile acid and so tends to form thermally stable salts. There is, however, a tendency to form hydrates.

Stainless steel processing equipment is relatively inert to attack from phosphoric acid. Anhydrous phosphoric acid is very viscous liquid and so is operationally difficult to use.

8.1.7. para-*Toluenesulfonic Acid*

This strong acid is relatively cheap. Because of its high molecular weight, it forms insoluble salts with many organic bases. For this reason, it is widely used to isolate and purify synthetic intermediates. It is occasionally also used as a salt of a pharmaceutical product.

8.1.8. *Carbonic Acid*

This is a very weak acid and only forms salts with the strongest of organic bases such as guanidines. This special property can be used to separate guanidines from weaker bases.

8.1.9. *Other Organic Acids*

These include tartaric, citric, fumaric, succinic, acetic, formic, lactic, malic, malonic, and many other acids. The primary choice of salt is often made on the empirical basis of laboratory studies. This takes into account issues such as the stability, bioavailability, pharmaceutical acceptability, and ease of manufacture. Readily crystallizing salts with a high degree of crystallinity are preferred from a manufacturing viewpoint, since they offer good purification and chemical stability properties.

8.2. Bases for Salts of Organic Acids

8.2.1. *Sodium*

This is the most commonly used base both for final pharmaceutical products and for intermediates. Sodium salts are often crystalline, but often have a tendency to form hydrates of variable water content. Some of the salts are very hygroscopic, which can give rise to handling issues. Those may be prone to support microbial growth because of the water content, and special precautions are needed to ensure freedom from contamination.

There are several techniques used for formation of sodium salts on a large scale. The simplest way is to neutralize an aqueous solution of the acid with sodium hydroxide or sodium carbonate/bicarbonate. The water is then removed by distillation or freeze-drying, or the sodium salt can be precipitated by addition of a miscible organic solvent such as acetone. If the acid is insoluble in water, methanol can be used as solvent and one equivalent of sodium methoxide is used to form the sodium salt, followed by a suitable workup.

8.2.2. *Potassium*

The comments about sodium salts referred to above are in general equally applicable to potassium salts.

8.2.3. *Calcium*

The simplest method of formation is by addition of an aqueous solution of calcium hydroxide to a solution of the acid in water, followed by evaporation/concentration.

Another technique is stirring the organic acid and a stoichiometric excess of calcium carbonate in water, producing a water-soluble calcium salt. The excess insoluble calcium carbonate is filtered off, and the aqueous filtrate is either concentrated and freeze-dried, or the calcium salt is isolated by addition of a miscible solvent such as acetone or methanol.

8.2.4. *Magnesium*

Most of the comments about calcium salts are equally applicable to magnesium salts.

8.2.5. *Lysine*

The naturally occurring basic amino acid L-lysine has been used extensively to form crystalline salts of acids. Most salts are produced in an aqueous solution, but occasionally methanol has been used.

L-Lysine is an optically active base, and the chiral purity of the material used is important. Care is needed with racemic acids to ensure that preferential crystallization of one of the enantiomers does not occur, thus shifting the ratio of enantiomers in the final product.

8.2.6. *Arginine*

Bearing a guanidine group, L-arginine is a very strong organic base. For this reason, it is able form stable salts with many of the weaker organic acids. Because of its chirality so the comments for lysine apply likewise to arginine.

8.2.7. *Other Organic Bases*

These include various types of amines (triethylamine, diethylamine, ethanolamine, diethanolamine, triethanolamine, piperazine, morpholine, meglumine, imidazole, ethylenediamine) and quaternary ammonium bases (choline). Each of these has found occasional use to form salts for pharmaceutical products. There is much debate about the pharmaceutical acceptability of several of these bases. This is dealt with in *Chapt. 5*.

These bases have also found use in the isolation and purification of synthetic intermediates. The organic base is removed later during the further course of the synthesis and so the pharmaceutical acceptability concerns are not applicable.

8.3. Diastereoisomeric Salts

With chiral drug substances, the biological activity of a synthetic racemate compound is frequently more pronounced or even fully resides in one of the two enantiomers. It is thus highly desirable to produce and develop a single enantiomer – the desirable *eutomer* rather than the undesirable *distomer* – since this leads to a more active and potentially less toxic product. Several synthetic techniques are available to produce single enantiomers. They include starting out from homochiral compounds, stereospecific introduction of a chiral center (*e.g.*, chiral hydrogenation) or separation of the enantiomers from the synthetic racemate.

Optically active acids and bases are widely used as resolving agents to separate the desired active enantiomer. Their salts formed with racemic bases and acids, respectively, are mixtures of diastereoisomeric salts, which can be separated due to their different physical properties, in particular, by fractionated crystallization due to different solubility. After formation and crystallization of the desired diastereoisomeric salt, the eutomer is recovered from the salt as well as the optically active acid (or base) used for resolution. Examples of the procedure are described below.

8.3.1. *Agents for Chiral Separations*

There are more chiral acids and bases that have been used on a large scale for separation of enantiomers. In every case, the formation of a salt of high crystallinity is essential for success of the procedure.

The topic of chiral separations is dealt with in much greater detail in [13].

8.3.2. *α-Methylbenzylamine*

This strong base is readily available as both the (+)- and (–)-isomers. Because of its high basicity, it forms stable salts with many organic acids, which often have a high degree of crystallinity, which aids the separation.

In practice, the procedure followed is to dissolve the (±)-racemic acid in a suitable solvent and to add 0.5 to 1.0 equivalents of for example (+)-α-methylbenzylamine. Two different salts are possible: (+)-acid · (+)-base and (–)-acid · (+)-base. These salts usually have different solubilities, and only one of the salts preferentially crystallizes from the system. The crystalline diastereoisomeric salt is filtered off leaving the other enantiomer in solution in the filtrate. Separation into the two single enantiomers has thus been achieved. The crystalline salt separated by filtration is then treated with aqueous hydrochloric acid, and the regenerated pure enantiomer acid is extracted into a suitable solvent. Sometimes, it is necessary to recrystallize the salt to ensure high chiral purity.

Since both the (+)- and the (–)-isomers of this base are readily available, it is usual to choose the benzylamine isomer, which forms a less soluble and, therefore, preferentially crystallizing salt with the eutomer, since this gives overall a much more efficient separation.

8.3.3. *Brucine and Strychnine*

These alkaloids have been widely used for resolution due to the highly crystalline nature of the salts. Both alkaloids are toxic, for which reason it is obvious to ensure complete removal of the resolving agent once the separation has been achieved.

The alkaloids are obtained from natural sources, and so only one isomer is readily available. This can be a limitation, since, in general, it is easier to obtain an optically pure product from the crystalline solid rather than from the residual filtrates.

8.3.4. *Camphorsulfonic Acid*

This strong acid forms stable salts with many organic bases and so has found extensive use. As it is derived from natural camphor, only one isomer is readily available.

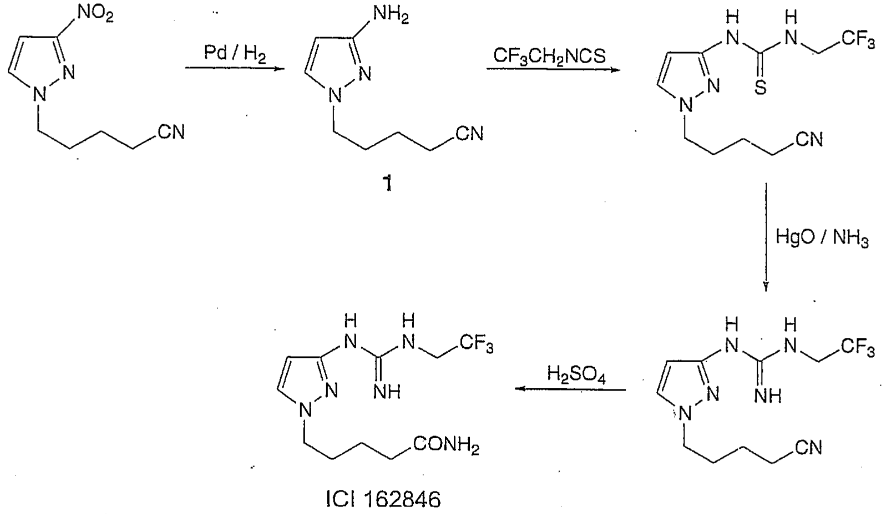
8.3.5. *Dibenzoyltartaric Acid*

This is prepared from tartaric acid. It is a relatively weak carboxylic acid, but does form stable salts with many organic bases.

9. Example: Using Salts to Isolate Products and Intermediates

The various applications of salt formation and crystallization will be illustrated by examples from the ICI 162846 synthesis. The compound under-

Scheme 1



went evaluation as a potential histamine H2 blocker. The initial synthetic route is indicated in *Scheme 1.*

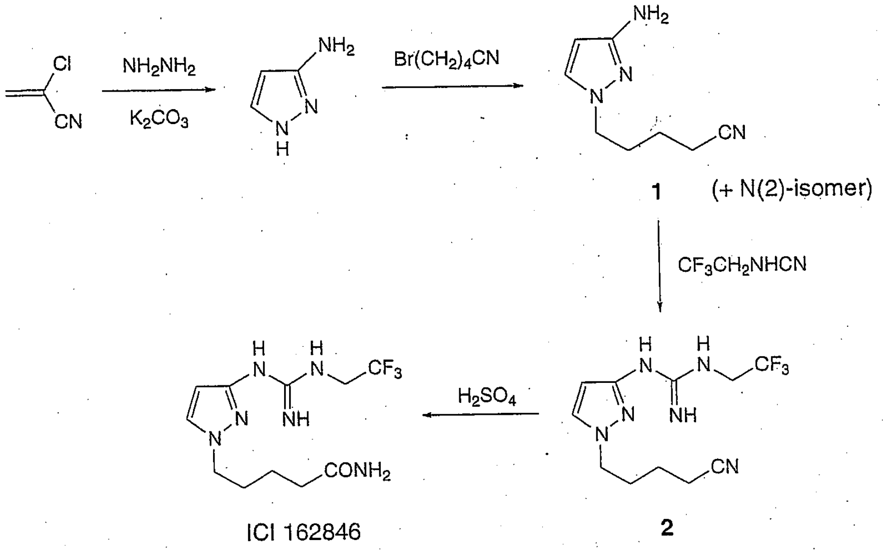
The initial four-step route gave rise to many impurities which prevented crystallization of the final product ICI 162846 as the free base. Advantage was taken of a highly crystalline hydrogen maleate salt to isolate ICI 162846 from the crude reaction mixture. It was considered preferable to develop ICI 162846 as the free base. This was easily achieved by treatment of the maleate salt with sodium hydroxide, extraction into ethyl acetate, and crystallization. The maleate salt had thus been successfully served to avoid a large scale chromatographic separation.

The above route sufficed to enable development quantities to be made. It was, however, unsuitable for large-scale use due to the potentially explosive nature of nitropyrazoles and the toxicity and availability of the reagents used. Moreover, there was the potential of mercury contamination of the final ICI 162846 Pure.

To avoid various problems associated with the initial synthesis, an alternative route was developed for large-scale manufacture. This route used salt formation at various points to enable hundreds of kilograms to be made.

The alkylation of 3-aminopyrazole with 5-bromovaleronitrile gave rise to a mixture containing *ca.* 20% of the unwanted N(2)-isomer (*Scheme 2*). A modest separation could be achieved by crystallization of the free base, but substantial losses occurred, since it was necessary to recrystallize the N(1)-isomer **1** for removing the last traces of the N(2)-impurity.

Scheme 2



A superior technique relied on the salt formation with toluene-4-sulfonic acid to isolate the desired N(1)-isomer as its highly crystalline tosylate salt. This gave better separation of the isomers, and the crystallized product was free from contamination with the unwanted N(2)-isomer.

The reaction of amino nitrile **1** with 2,2,2-trifluoroethylcyanamide formed guanidinenitrile **2** in good yield, but this required separation from the other reactants, which also had basic properties. Guanidines are strongly basic and form stable carbonate and bicarbonate salts. The other bases in the reaction (aminopyrazole and 2,2,2-trifluoroethylamine) are very weak and do not form crystalline salts with carbonic acid. Separation of the desired guanidine was very easily achieved by isolation as its highly crystalline bicarbonate salt.

It was possible to isolate ICI 162846 pure as the crystalline free base directly from the hydrolysis stage. With the increase in purity at the intermediate stages, it was no longer necessary to use the maleate salt as an intermediate purification step.

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Chapter 11

Selected Procedures for the Preparation of Pharmaceutically Acceptable Salts

by **Camille G. Wermuth*** and **P. Heinrich Stahl**

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1. Introduction

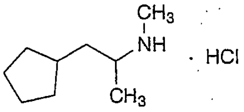
The preparation of pharmaceutical salts is usually not a matter of university teaching, and most of the organic chemists are not trained to prepare salts. For this reason, it appeared useful to the authors to collect some preparation methods from the literature and to present them in this chapter as possible models. Most of the 'recipes' stem from the patent literature and, therefore, are not optimized. Nevertheless they illustrate the state of the art and sometimes propose several variants for the preparation of a given salt form.

2. Preparation of Salts of Basic Drug Substances

2.1. Hydrochlorides

Hydrochlorides do sometimes require strictly anhydrous conditions to be prepared (*e.g.*, HCl gas in anhydrous diethyl ether (Et_2O)), at other times they require stoichiometric amounts of H_2O to be present in order to yield hydrated crystals. A typical procedure is to dissolve the organic base in the minimal amount of hot isopropanol (i-PrOH) and to add the calculated volume of concentrated HCl (85 ml ≈ 1 mol). If, after cooling, crystallization does not occur, it can be induced by progressive additions of Et_2O. Only if both procedures fail, salt formers other than HCl should be envisaged.

Cyclopentamine Hydrochloride
Clopane® (*Lilly*)
Procedure [1]

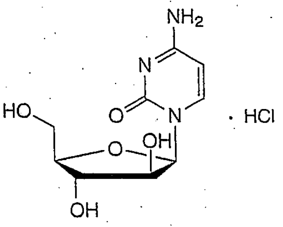


Dissolve 141 g (1 mol) of 3-cyclopentyl-*N*-methylpropan-2-amine in 500 ml of dry Et_2O, and pass dry HCl into the solution, until the weight of the mixture and container has increased by 36 g. During the addition of the HCl, the HCl salt of 3-cyclopentyl-*N*-methylpropan-2-amine precipitates as a white powder. The salt is filtered off and washed with dry Et_2O. 3-cyclopentyl-*N*-methylpropan-2-amine hydrochloride thus prepared melts at *ca.* 113 – 115 °C. The yield is practically quantitative.

Caution!

When this procedure is performed on a small scale, it is often observed that the initially formed hydrochloride re-dissolves. This is due to the fact that an excess of gaseous HCl in anhydrous Et_2O produces the very polar diethyloxonium chloride, which solubilizes the initially precipitated hydrochloride.

Cytarabine Hydrochloride
Cytosar® (*Upjohn*)

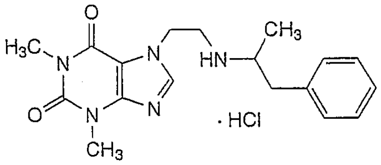


Procedure [2]

A solution of 250 mg D-1-β-arabinofuranosylcytosine in absolute methanol (MeOH) was warmed and stirred with decolorizing charcoal. The mixture was filtered through a bed of filter aid, and the filter bed was washed repeatedly with absolute MeOH. The combined filtrate and washings were pale yellow. The solution was diluted to faint cloudiness with anhydrous Et_2O, and an excess of anhydrous HCl was introduced. Crystallization began at *ca.* 25 °C and further crystallization was induced by chilling at 0 °C for 14 hours. The crystalline product was collected on a filter, washed with anhydrous Et_2O, and dried in air. There was thus obtained 180 mg of pale yellow D-1-β-arabinofuranosylcytosine hydrochloride melting at 186 to 189 °C.

The pale yellow product was dissolved in warm, absolute MeOH, and after treatment with decolorizing charcoal the solution was filtered through a bed of filter aid. The filter bed was washed with warm absolute MeOH, and the combined methanolic filtrate and washings were warmed and diluted with anhydrous Et_2O to incipient crystallization. The MeOH/Et_2O mixture was kept at *ca.* 25 °C for *ca.* 1 hour and then chilled, first at 0 °C, and then at –20 °C. The resulting colorless needles were collected on a filter, washed with anhydrous Et_2O, and dried at 85 °C, yielding 100 mg of D-1-β-arabinofuranosylcytosine hydrochloride with a melting point of 186 – 188 °C.

Fendiline Hydrochloride
Sensit® (*Thiemann*)

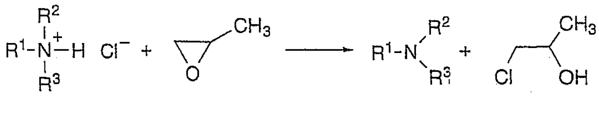


Procedure [3]

The freshly distilled base, 25.38 g of 1,7-dihydro-1,3-dimethyl-7-{2-[(1-methyl-2-phenylethyl)amino]ethyl}-2*H*,6*H*-purine-2,6-dione is dissolved in 134 ml of 96% EtOH, whereupon 26.8 ml of concentrated HCl and 201 ml of hot H_2O are added while cooling with ice-water. The precipitate is filtered off and dried *in vacuo* at 100 °C: 22.98 g of hydrochloride salt are obtained. M.p. 200 – 201 °C. On recrystallization from 285 ml of a 2:1 mixture of H_2O and 96% EtOH the melting point remains unchanged.

Conversion of a Hydrochloride to the Free Base

The usual way to prepare free bases from hydrochlorides and, more generally from salts, consists in adding an inorganic base (NaOH, K_2CO_3) and extracting the free base by means of a water-immiscible organic solvent. However, under some circumstances it may be desirable to work under anhydrous conditions. This can be achieved for example in bringing the hydrochloride to react with an HCl scavenger such as propylene oxide, according to the reaction below:



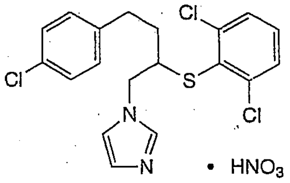
The 1-chloropropan-2-ol formed can be easily removed under reduced pressure. One of the interesting applications of this procedure is the transition from hydrobromides, the usual product of demethylation reactions, to the corresponding hydrochlorides, *via* the free base.

Procedure [4]

To a solution of 3.3 g (13.3 mmol) of L-3-hydroxy-4-methoxyphenylalanine hydrochloride in 150 ml of EtOH are added portionwise over 3 hours 12,5 ml propylene oxide. The mixture is allowed to stand 20 hours at ambient temperature (*ca.* 25 °C). The precipitated crystals are collected and purified by dissolution in 40 ml of absolute EtOH and inducing the crystallization by adding some drops of H_2O. The yield is 2.15 g of colorless crystals of L-3-hydroxy-4-methoxyphenylalanine melting at 251 – 252 °C.

2.2. Nitrates

Butoconazole Nitrate
Femstat® (*Syntex*)



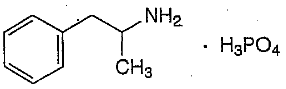
Procedure [5]

To a solution of 10 g (*ca.* 0.025 mol) of butoconazole (= 1-{4-(4-chlorophenyl)-2-[(2,6-dichlorophenyl)sulfanyl]butyl}-1*H*-imidazole) base in 300 ml of dry Et_2O, 70% HNO_3 ($d = 1.42$) is added dropwise until the precipitation is complete (*ca.* 2.2 ml). The resulting nitrate salt is recrystallized from acetone/AcOEt to give butoconazole nitrate as colorless blades; yield: 9.6 g corresponding to *ca.* 80%.

2.3. Phosphates

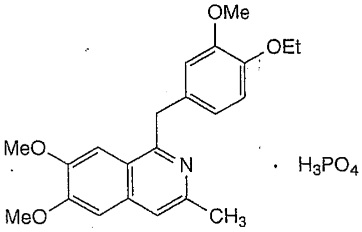
Amphetamine Phosphate

Procedure [6]



Amphetamine (= α-methylbenzeneethanamine; 135 g, 1 mol) is stirred into 300 ml of acetone in a stainless-steel vessel. To the resultant solution, 115.3 g of 85% H_3PO_4 (containing 1 mol of H_3PO_4) are added under constant agitation, care being taken to avoid any sudden rise in temperature or local overheating due to the considerable amount of heat that is evolved. During the addition of the H_3PO_4, a fine, white, flocculent precipitate appears, which becomes more and more dense and abundant, as the quantity of added acid increases. When the entire quantity of the H_3PO_4 has been added, agitation of the mixture is continued for *ca.* ½ hour or more to insure complete conversion. The precipitate is then allowed to settle, the supernatant liquid is discarded, and the residue is filtered. The precipitate thus separated may, if desired, be washed with acetone and is then dried by evaporation to constant weight, providing a fine, white, impalpable powder, which consists of pure monobasic amphetamine phosphate.

Dioxyline Phosphate
Paveril® (Lilly)



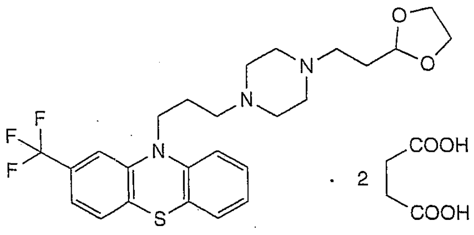
Procedure [7]

A solution of 5 g of 6,7-dimethoxy-3-methyl-1-(4-ethoxy-3-methoxybenzyl)isoquinoline in 100 ml of EtOH is treated with a solution of 1.5 g of H_3PO_4 in 10 ml of EtOH. Thereafter, 10 ml of H_2O are added to effect complete solution, and the reaction mixture is then cooled, and Et_2O is added, until precipitation of the salt is complete. The precipitate of 6,7-dimethoxy-3-methyl-1-(4-ethoxy-3-methoxybenzyl)isoquinoline phosphate is filtered off and recrystallized from 85% EtOH by the addition of 2 volumes of Et_2O.

2.4. Succinates

Oxaflumazine Succinate
Oxaflumine® (Diamant)

Procedure [8]

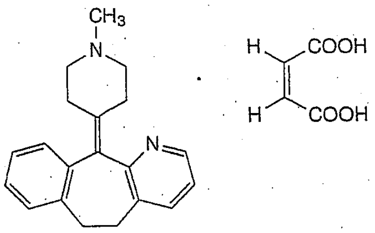


A solution of 257 g oxaflumazine (= 10-(3-{4-[2-(1,3-dioxan-2-yl)ethyl]-piperazin-1-yl}propyl)-2-(trifluoromethyl)-10*H*-phenothiazine) base in 500 ml of acetone is added with stirring to a solution of 118 g of succinic acid in 4000 ml of acetone. The agitation is continued at room temperature until the desired salt crystallizes. The mixture is allowed to stand overnight at 0 °C. The weight of the collected crystals is 256 g (yield, 70%). After recrystallization in 1000 ml of acetonitrile (MeCN) the acid disuccinate melts at 136–138 °C.

2.5. Maleates

Azatadine Maleate
Optimine® (Schering)

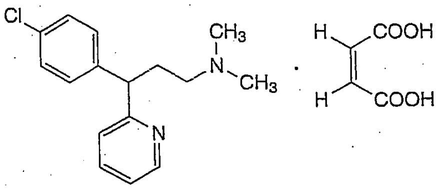
Procedure [9]



To a solution containing 4.3 g of 6,11-dihydro-11-(1-methylpiperidin-4-ylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine in 55 ml of AcOEt, add a solution of 3.45 g of maleic acid dissolved in AcOEt. Filter the resulting precipitate and recrystallize the desired product from an AcOEt/MeOH mixture to yield the dimaleate salt. M.p. 152–154 °C.

Dexchlorpheniramine Maleate
Polaramine® (Schering)

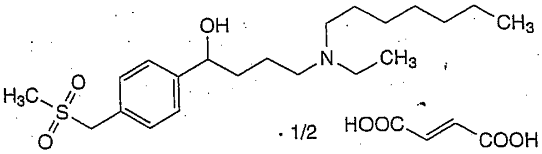
Procedure [10]



(+)-Dexchlorpheniramine (= γ-(4-chlorophenyl)-*N*,*N*-dimethylpyridine-2-propanamine) (4.3 g) and maleic acid (1.8 g) are dissolved in 20 ml of isopropyl acetate (AcO(i-Pr)) and kept at room temperature until crystallization is complete. The crystals are filtered, washed with AcOEt and recrystallized from 15 ml of this solvent in the same manner. The crystalline maleate salt so formed is filtered off and dried. M.p. 113 – 115 °C.

Ibutilide Fumarate
Corvert® (*Pharmacia & Upjohn*)

Procedure [11]

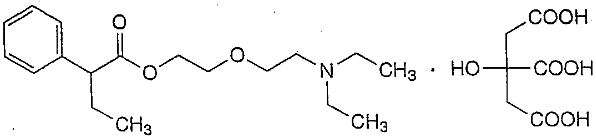


Ibutilide (= {3-[(ethyl)(heptyl)amino]propyl}{4-[(methylsulfonyl)methyl]-phenyl}methanol; 31.9 g, 0.0829 mol) is dissolved in 135 ml of absolute EtOH and mixed with a solution of fumaric acid (4.3 g, 0.037 mol) in absolute EtOH (203 ml). The solution was concentrated under reduced pressure, and the residue was dissolved in hot acetone and allowed to crystallize. Recrystallization from acetone gave a solid that was dried under reduced pressure for 4 days at 60 °C to give 31.4 g of the (*E*)-but-2-enoate salt of ibutilide (2:1). M.p. 117 – 119 °C.

2.6. Citrates

Butamirate Citrate
Sinecod® (*Hommel*)

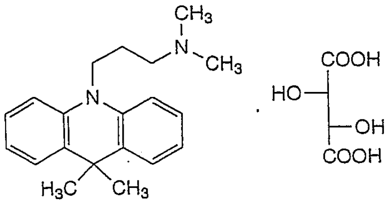
Procedure [12]



To 10 g of high-vacuum distilled 2-[2-(diethylamino)ethoxy]ethyl α-ethylbenzeneacetate is added a solution of 7 g of citric acid in 30 ml of warm acetone. After standing for some time, the citrate crystallizes out. After suction filtration and washing with acetone, the citrate is recrystallized from acetone. M.p. 75 °C.

2.7. Tartrates

Dimetacrine Tartrate
Isotonil® (*Siegfried*)

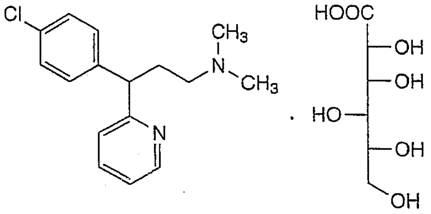


Procedure [13]

N,N,9,9-Tetramethyl-9H-acridine-10-propanamine (43 g) is dissolved in 229 ml of 1N aqueous (+)-tartaric acid, and the clear solution obtained is evaporated to dryness under reduced pressure. The residue is dissolved in 150 ml of 90% EtOH. The solution gives after cooling, the corresponding tartrate as white needles. The salt contains 1 mol of tartaric acid per mol of the base and is easily soluble in cold H_2O. M.p. 155 – 156 °C.

2.8. Gluconates

Dexchlorpheniramine Gluconate
Polaramine® [Gluconate] (Schering)

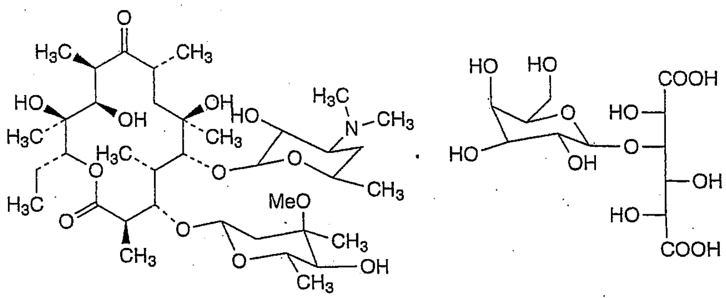


Procedure [10]

D-γ-(4-Chlorophenyl)-N,N-dimethylpyridine-2-propanamine (10 g) and 6.5 g of D-gluconolactone are mixed in 50 ml of 50% aqueous EtOH and kept at 50 °C for 2 hours. The solvent is then removed under reduced pressure to leave the desired salt as viscous colorless oil.

2.9. Lactobionates

Erythromycin Lactobionate
Erythrocin lactobionate® (Abbott)

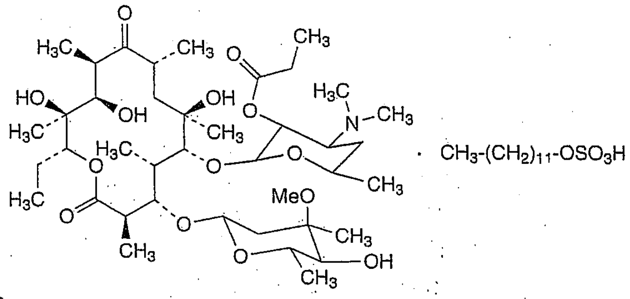


Procedure [14]

A solution of erythromycin base is prepared by dissolving 8.0 g of erythromycin in 25 ml of acetone. One the other hand, a solution of 4.0 g of δ-lactobionolactone is dissolved in 25 ml of H_2O, providing the free lactobionic acid (= 4-O-β-D-galactopyranosyl-D-gluconic acid). The two solutions are mixed and evaporated to a gummy residue, which is dissolved in 60 ml of H_2O, and the resulting solution is frozen and dried *in vacuo* by lyophilization. The dried residue of erythromycin lactobionate (11.7 g) is a white amorphous powder with solubility in H_2O of *ca.* 200 mg/ml. M.p. 145 – 150 °C.

2.10. Lauryl Sulfate Salts

Erythromycin Estolate (*Erythromycin Propionate Laurylsulfate*)
Ilosone® (*Dista*)

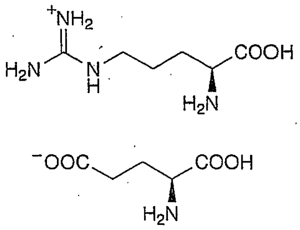


Procedure [15]

Monopropionylerythromycin (16.7 g) is dissolved in 50 ml of warm acetone. To the solution is added sodium lauryl sulfate (6.4 g), dissolved in 50 ml of distilled H_2O containing 2 ml of glacial AcOH. The white crystalline precipitate of monopropionylerythromycin lauryl sulfate separated is filtered off and dried. M.p. *ca.* 135 – 137 °C.

2.11. Glutamates

Arginine Glutamate
Modamate® (*Abbott*)



Procedure [16]

This water-soluble salt may be prepared by mixing L-arginine with L-glutamic acid in H_2O and crystallizing the resulting salt by the addition of a polar water-miscible organic solvent. For instance, when 17.2 g of L-arginine and 14.5 g of L-glutamic acid are dissolved in 155 g of H_2O, a clear homogeneous solution results, which has a pH of 5.3. After filtration, this solution is concentrated at 50 °C under reduced pressure to a solid content of *ca.* 45%. Absolute MeOH (220 g) is added, and this mixture is cooled to 5 °C for 1 hour. The resulting solid salt is removed by filtration and washed with absolute MeOH. The salt is left to become air-dry and is then further dried in a vacuum oven at 60 °C for 3 hours. Thus, 30 g (94.6% of the theoretical yield based on the amounts of

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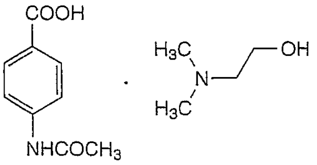
L-arginine and L-glutamic acid employed) of the L-arginine L-glutamate salt are obtained. M.p. 193 – 194.5 °C with decomposition.

2.12. Acetamidobenzoates

Deanol Acetamidobenzoate
Deaner® (Riker)



Procedure [17]

4-(Acetylamino)benzoic acid (*ca.* 40 g, 0.223 mol) is dissolved in 600 ml of absolute MeOH, and the solution is heated to reflux temperature. Heating is discontinued, and, under mechanical stirring, 2-(dimethylamino)ethanol (19.9 g, 0.223 mol) is added through a dropping funnel as fast as the exothermic nature of the reaction permits. The reaction mixture is allowed to cool to room temperature (2.5 – 3 hours) under mechanical agitation, and the solution is suction-filtered through *Celite* filter aid. The filtrate is poured into 500 ml of anhydrous Et_2O and seeded with a few crystals of 2-(dimethylamino)ethanol 4-(acetylamino)benzoate. The seeding crystals are previously obtained by introducing 3 to 6 drops of the filtered reaction mixture into a test tube containing 10 ml of anhydrous Et_2O. The contents of the test tube are thoroughly shaken and allowed to stand at room temperature. The salt crystallizes within not more than 10 – 15 minutes.

The crude product (48.4 g, 80.9% yield) is recrystallized from an absolute EtOH/AcOEt mixture by suspending the salt in boiling anhydrous AcOEt. Just enough absolute EtOH is gradually added to effect solution, then the solution is concentrated to *ca.* ⅔ of the original volume on the steam bath, treated with charcoal, and suction-filtered through *Celite* filter aid. The white crystals of 2-(dimethylamino)ethanol 4-(acetylamino)benzoate obtained are dried at room temperature at a pressure of 0.08 mm Hg for 15 hours. M.p. 159.0 – 161.5 °C.

3. Preparation of Salts of Acidic Drug Substances

3.1. Potassium and Sodium Salts

These salts can be prepared by means of sodium or potassium hydroxide, carbonate, or alkoxide. The preferred preparations make use of rather anhydrous sodium or potassium carboxylates, which are well soluble in polar organic solvents.

Traditional Procedure with NaOH

A stirred solution of 111 g (0.43 mol) of (2-amino-3-benzoylphenyl)acetic acid in 777 ml of tetrahydrofuran is treated with 31.3 g (0.39 mol) of 50% NaOH. After cooling the solution at 0 °C for 3 hours, the solid, which precipitates, is collected by filtration to yield 64 g (56%) of the expected sodium salt. M.p. 245 – 252 °C. An analytical sample is obtained by dissolving 1.0 g of the crude salt in 10 ml of 95% EtOH and treating the solution with 5 ml of $(i\text{-}Pr)_2O$. The pure sodium salt precipitates slowly to yield 0.9 g of yellow solid. M.p. 254 – 255.5 °C [18].

Procedure with Anhydrous Alkali Acetates

The following procedure is used for the industrial preparation of the sodium or potassium salts of penicillins.

The carboxylic acid is dissolved in cold MeOH or EtOH (do not heat in order to avoid esterification!). An equimolar amount of anhydrous potassium or sodium acetate is added, dissolved in the minimum volume of MeOH, EtOH, or AcOH. The mixture is allowed to stand and cooled at + 4 °C. The crystals are collected and recrystallized in a polar solvent, if necessary.

Solubility of the alkali acetates:

AcOK:	1 g dissolves in: 0.5 ml H_2O; 0.2 ml boiling H_2O; 2.9 ml EtOH.
AcONa:	1 g dissolves in: 0.8 ml H_2O; 0.6 ml boiling H_2O; 19 ml EtOH.

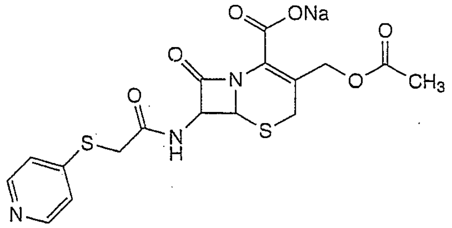
Procedure with 2-Ethylhexanoates

The carboxylic acid, dissolved in a polar organic solvent (MeOH, EtOH, i-PrOH, CH_2Cl_2) is neutralized by an equimolar amount of Et_3N. If necessary, the resulting solution is treated with decolorizing charcoal for 15 minutes and filtered. A solution of sodium 2-ethylhexanoate (concentration *ca.* 25%) in $BuOH/CH_2Cl_2$ mixture is added to the filtrate under stirring. Crystallization is induced by adding acetone or Et_2O.

Sodium 2-ethylhexanoate is an inexpensive reagent that can easily be prepared from sodium hydride with 2-ethylhexanoic acid and is also readily available commercially at less than US $ 10 from several sources [19].

Example

Cephapirin Sodium
Cefadyl® (*Bristol Myers*)



Procedure [20]

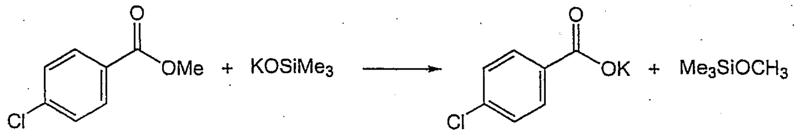
CH_2Cl_2 (5 l) is added to a clean dry vessel equipped with stirrer. 3-[(Acetyloxy)methyl]-8-oxo-7-{[(pyridin-4-ylthio)acetyl]amino}-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (1,000 g) is added to the vessel, followed by 350 ml of Et_3N. The resulting solution is treated with decolorizing charcoal for 15 minutes and filtered. A solution of sodium 2-ethylhexanoate (27.3%) in BuOH/CH_2Cl_2 is added to the filtrate under stirring. Acetone (7500 ml) is added. Crystallization occurs while stirring is continued for several hours under dry conditions. The crystals are collected by filtration, washed with large volumes of acetone, and then dried *in vacuo* at 50 °C to yield *ca.* 950 g of the title compound.

Procedure with Metal Silanolates

This procedure allows the direct transformation of a methyl ester, in anhydrous medium, into the corresponding sodium or potassium salt by means of sodium or potassium trimethylsilanolates. The silanolates are commercially available, they have appreciable solubility in organic solvents (Et_2O, tetrahydrofuran, toluene, CH_2Cl_2) and the Si–O bond can be easily cleaved [21].

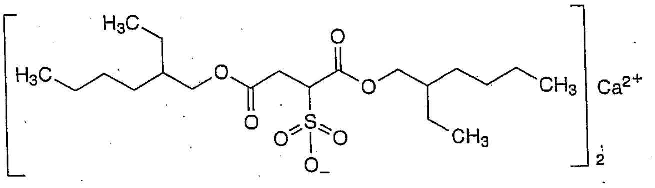
Example

Methyl 4-chlorobenzoate (13.65 g, 80 mmol) is added in one portion to a stirred slurry of potassium trimethylsilanolate (10.26 g, 80 mmol) in dry Et_2O (500 ml) at ambient temperature under N_2. The reaction mixture is stirred for 4 hours. The white solid is filtered under N_2, washed with Et_2O, and dried under a stream of N_2 to afford analytically pure potassium 4-chlorobenzoate (13.1 g, 84%) [21].



3.2. Calcium Salts

Docusate Calcium
Surfak® *(Hoechst)*

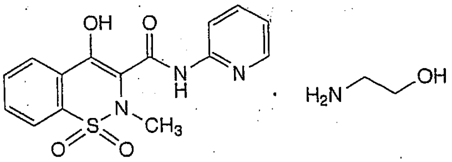


Procedure [22]

1,4-Bis(2-ethylhexyl)sulfobutanedioate sodium (88 g) is dissolved in i-PrOH (100 ml), and another solution of $CaCl_2$ (25 g) in MeOH (50 ml) is prepared. Both solutions are mixed and stirred for *ca.* 3 hours and then cooled with ice. The NaCl, which precipitates from the cold mixture, is removed by filtration, and most of the alcohol is evaporated from the resulting filtrate with heat. The remaining liquor is poured into 88 ml of H_2O, and the resulting precipitate is washed with H_2O to free from chloride ion. The calcium salt is then dried.

3.3. 2-Aminoethanol Salts

Benzothiazine Dioxide 2-Aminoethanol

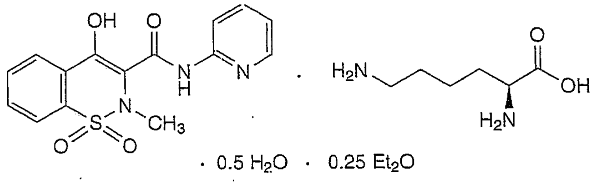


Procedure [23]

In a 2-l, three-necked round bottomed reaction flask equipped with magnetic stirrer, dropping funnel (250 ml), and thermometer, a filtered solution of 55.0 g (0.166 mol) 4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-1,2-2*H*-benzothiazine-3-carboxamide 1,1-dioxide dissolved in 660 ml of CH_2Cl_2 is placed. The solution, which also contained 0.1 g of the mono(2-aminoethanol) salt of 4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-1,2-2*H*-benzothiazine-3-carboxamide 1,1-dioxide as seed, is initially prepared by first dissolving the solid material in 610 ml of CH_2Cl_2 in an *Erlenmeyer* flask at 25 °C under gentle magnetic stirring. The remaining 50 ml of CH_2Cl_2 is then used for washing during the transfer of the solution to the aforementioned reaction flask. At this point, the latter flask and its contents are heated to 27 °C with the aid of a steam bath, and the entire system was subjected to constant and vigorous agitation, while a solution consisting of 10.7 g (0.175 mole) of 2-aminoethanol dissolved in 110 ml of fresh CH_2Cl_2 is slowly added during 50 minutes. Upon completion of this step, the reaction mixture was stirred at 27 °C for 1 hour and then filtered on a *Büchner* funnel to afford the crystalline salt, which is dried in a vacuum oven at 35 °C. Yield: 63 g of the pure mono(2-aminoethanol) salt. M.p. 171 – 174 °C.

3.4. Lysine Salts

Benzothiazine Dioxide Lysine Salt



Procedure [24]

In a 1000-ml *Erlenmeyer* flask equipped with magnetic stirrer and reflux condenser, a filtered solution of 3.5 g (0.0106 mol) of 4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-1,2-2*H*-benzothiazine-3-carboxamide 1,1-dioxide, 1,54 g (0.0106 mol) of L-lysine, and 700 ml of EtOH is placed to form a yellow suspension. This suspension is then heated to reflux and treated with 10 ml of H_2O added slowly at the reflux point. The resulting yellow solution was then cooled to room temperature (*ca.* 25 °C) and evaporated to near dryness under reduced pressure to afford a yellow foam. This foam is subsequently treated with 400 ml of Et_2O by slurrying overnight and then filtered to give a fine yellow solid. Yield: 4,5 g (89%) of the pure amorphous L-lysine salt as the hemihydrate with 0.25 mol of Et_2O.

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