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21 ST EDITION

Remington

The Science and Practice of Pharmacy



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Preface to the Twenty-First Edition

For over 100 years and throughout 20 previous editions, *Remington: The Science and Practice of Pharmacy* has stood as the definitive text and reference source of all aspects of the science and practice of pharmacy. In this new edition, you will find a text that is practice-oriented while maintaining its traditionally reliable coverage of scientific aspects. The 21st edition keeps pace with the changes in pharmacy curriculum and professional pharmacy practice in general.

In the years since the first publication of *Remington's Pharmaceutical Sciences*, there have been many changes in the field of pharmacy and pharmacy practice. Although this edition of *Remington* maintains the general philosophy of previous editions, several changes have been made to present fresh and new information and to take advantage of the advances made in recent years. Each section of the book has been critically reviewed and revised to reflect the emerging trends in the field. The overall organization of the book is the same as the previous editions.

The biggest change in the 21st edition is in the *Pharmacy Practice* section. This section has been reorganized and expanded to reflect the changing realities of contemporary practice. The integration of new scientific information into clinical practice is often difficult, and one of the key purposes of this section is to help clinicians translate these scientific advances into clinical practice and care of patients. This section brings the reader up to date on the latest trends and approaches. New chapters have been added that cover the areas of:

- The application of ethical principles to practice dilemmas
- Statistics applied to pharmacy practice
- Technology and automation
- Professional communication
- Medication errors
- Re-engineering pharmacy practice
- Management of special risk medicines
- Specialization of pharmacy practice
- Disease state management
- Emergency patient care
- Wound care

The *Pharmaceutical and Medicinal Agents* section is the most very useful part of the book in terms of core drug information. For this edition, we've added more than 100 new drug monographs, and the previously existing material has been up-

dated. We realize that this is a section that is nearly impossible to keep current, and we've tried to include as many new drugs as possible. Because of space constraints, we were limited to the most important or most widely used drugs.

Another significant addition to this edition is the expansion of the *Pharmacodynamics and Pharmacokinetics* section to include the new, growing area of Pharmacogenomics. This chapter highlights many of the important advances including: practical applications and technological considerations, molecular diagnostics for optimizing drug therapy, and pharmacogenomics and drug development.

Many people were involved in creating this edition. I am grateful to all the Section Editors and authors for their skillful review of the literature and for incorporating their own unique perspectives and experience into their chapters. With this edition, we welcome five new Section Editors. They represent a wide geographic diversity and spectrum of experience. We also have approximately 100 new authors who represent over 32 universities as well as positions in governmental agencies and private industry.

I also gratefully acknowledge the extensive contributions of the authors and Section Editors of previous editions of *Remington* for laying the foundation for the current volume. I recognize that we all stand upon the shoulders of giants and are supported by those leaders who taught and inspired many previous generations.

I especially thank Alfonso R Gennaro, PhD for his continued support. Dr. Gennaro was *Remington* editor for the past four editions. No one is more familiar with *Remington* than he is. Dr. Gennaro has been instrumental in the creation and review of the drug monographs. Ensuring scientific accuracy is critical in a book such as *Remington*, and he has been very generous with his time and expertise in this area.

A heartfelt thanks also goes to Mr. John Hoover, author and indexer, who has been involved with *Remington* since the 1960s and has provided editorial guidance at every step of the process.

It is a pleasure and honor to work on a book with such a long and rich tradition.

Randy Hendrickson
Editor

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Property-Based Drug Design and Preformulation

Howard Y Ando, PhD
Galen W Radebaugh, PhD



The discovery and development of new chemical entities (NCEs) into stable, bioavailable, marketable drug products is a long, but rewarding process. Due to the tremendous cost of developing a NCE, and industry's need to enhance productivity, it is desirable to create NCEs that have suitable physical-chemical properties, rather than compensate for deficiencies solely by the formulation process. Hence, property-based design can enhance the likelihood a NCE will have the desired physical-chemical that will facilitate its ability to be developed into a stable, bioavailable dosage form. Even so, well-designed preformulation studies are necessary to fully characterize molecules during the discovery and development process so that NCEs have the appropriate properties, and there is an understanding of the deficiencies that must be overcome by the formulation process. This chapter provides guidance that will facilitate property-based design and the supporting preformulation studies necessary to direct formulation efforts to give NCEs the highest possibility of success.

EVOLUTION OF THE DRUG DISCOVERY PROCESS

The need for property-based design follows from the natural evolution of a research and development process that seeks to become more efficient. The growth and decline of markets and sectors is a natural process that applies to every life structure whether it is the universe, an individual, or a market sector. All have a sigmoidal curve with periods of vulnerability, growth, and decline. For the pharmaceutical new chemical entity (NCE) sector, this is shown in Figure 38-1 as NCE-1. Of course, the declining phase is of major concern and usually is seen only in retrospect. However, Charles Handy has pointed out that given enough foresight, organizations can renew themselves by changing their operational paradigm.¹ Ideally, they would initiate and build the basis for this change during the α phase (shown in Fig 38-1). If successful, they could then initiate the hypothetical second curve, labeled NCE-2 in Fig 38-1. What then are the causes for the aging of the NCE-1 cycle, and what will fuel the initiation and growth of the hypothetical NCE-2 cycle paradigm? The relevance of property-based design in this context is discussed below.

GROWTH CYCLE DETERMINANTS

NCE Paradigms

The first growth epoch for the pharmaceutical development was driven by the application of physical-chemical principles to the

design of dosage forms and delivery of NCEs. Physical chemistry provided scientists with a macroscopic, theoretical model, and as a young discipline, empirical experimentation predominated in the industrial design of dosage forms. Moreover, discovery and development phases occurred as separate and sequential phases. This was efficient and sufficient at the time, mainly because the targets were simpler. Evaluating the activity of new NCEs might involve bacterial cultures or perfused animal tissues. Testing for pharmacological activity in whole animals would then follow. Compounds that had poor development potential like limited aqueous solubility never showed any *in vivo* pharmacodynamic activity and were never advanced. In addition, indirect biomarkers were not needed because the physiological impact of an NCE could be readily measured and extrapolated from animals to humans (eg, blood pressure monitoring). However, new technological developments have caused the decline of this paradigm.

Advances in biotechnology fueled the second epoch starting in the 1980s because proteins could be synthesized from genetic information. Initially, bacteria and then mammalian cells were the source of these proteins. Such technology meant that these proteins could now be used as targets for discovery research. Individual receptors, enzymes, or transporters could now be synthesized in isolation from their parent tissue and could be used as surrogates for *in vivo* pharmacological activity. The banks of compounds that were accumulated during the first epoch, both in the academic and industrial setting, could now be screened for *in vitro* activity by high-speed robots.

The realization that a more integrated process of discovery was necessary became apparent only after a painful period. Early in this second epoch, a lot of energy was devoted to compounds that have been coined high affinity traps.² These are compounds that have very high *in vitro* activity but poor aqueous solubility. This occurred because of the needs of high throughput screening to automate the dispensing of compounds in a 96 well format. Because accurate and economical dispensing of powder is not possible, all reagents must be added as solutions. Liquid dispensing required a very general way to dissolve compounds. So the solution was to use small amounts of a very good, universal solvent, DMSO, that dissolved almost all organic compounds. The problem was that property-based factors like solubility and dissolution are not accounted for. Lipinski sounded the warning to the industry with his rule of five (RoF).³ Subsequently, developmental scientists have put into place a number of high throughput physical property screens that could be used during the discovery phase; hence the realization of a need for property-based design. However, there are signs that this epoch may be reaching the end of its growth phase. DiMasi⁴ has shown that the NCE-1 curve in Figure 38-1 for new INDs filings reached a plateau during the 1980s and has declined in the 1990s.

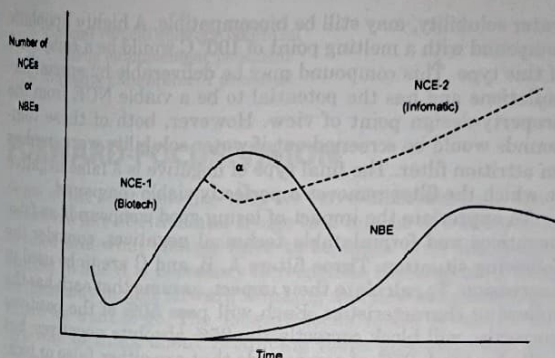


Figure 38-1. Charles Handy's sigmoidal growth curve. (From Handy C. *The Age of Paradox*. Cambridge, MA: Harvard Business School, 1995: 49-67. Copyright © 1995 by the Harvard Business School Publishing Corporation. All rights reserved.)

Because the biotechnology paradigm may now be reaching the limits of its efficiency, it is proposed that a new paradigm (Informatics) will begin to evolve, taking advantage of an increased molecular understanding of the crystalline state and advances in the computational sciences, especially machine learning. The α phase of Figure 38-1 may be upon us. This new paradigm, NCE-2, will be driven by both technological opportunities, especially informatics, and pharmaco-economic constraints.

Pharmaco-Economic Constraints

COST—In a recent white paper by IBM consultants, it was pointed out that the innovative driving force for drug development is rapidly shifting from the manufacturers and physicians to consumers, which in many cases are managed care organizations (MCO). One of the most important imperatives of this new consumer is the control of rising health care cost. With their control of formularies, MCOs will exert considerable influence in the future on the direction and limits of innovation.⁵

REGULATORY AND SAFETY—At the same time, regulatory agencies are requiring electronic filing requirements that in the short term considerably increase cost, but in the long term have the potential to speed review. In addition, because our understanding of side effects has increased substantially during the biotechnology epoch, self-imposed industry and regulatory requirements for NCEs have become much more stringent. For example, safety screens are now available for certain types of potentially fatal arrhythmias (torsades de pointes syndrome) that have been found to be associated with drug binding to potassium channels in the heart's conduction fibers. Chromosomal genotoxicity screens are also available that can detect a drug's interference with normal mitotic spindle and microtubule complex formations, or DNA strand breakage.⁶ All of these new insights increase what is expected for a new NCE before it can be introduced into the marketplace. How then can costs be reduced as NCE regulatory requirements increase?

RISK MINIMIZATION—DiMasi has shown that the clinical approval rates from more recent IND filings has improved.⁷ Apparently, better preclinical screening has increased the success rate. Since filtering out poor clinical candidates during the preclinical screening stage should be much cheaper than having clinical candidates fail, highly efficient screening should be justified. On the other hand, even if current preclinical screening is efficient in increasing the clinical success rate, apparently it does not add to productivity as measured by the decline in IND filings in the 1990s.⁶ The substantial improvements that are needed to reduce both cost and risk and to initiate the simultaneous improvements of a number of informatic-based at point α .

Such improvements would include computational (a) activity-based design, (b) safety-based design, and (c) property-based design. If all of these elements could be highly accurate and applied at very early stages of discovery, fewer resources would be expended on nonproductive activities. In addition, if the number of potential opportunities both from the number of targets due to genomic opportunities and from increased property-based design possibilities can be achieved, then higher productivity should result.

Cost Reduction by Learning Before Doing

A model for the cost saving of such a paradigm has been carried out in the chemical development arena, but the concepts should hold for the property-design area as well. Today, when discovery chemists find a compound that has promising activity, additional amounts need to be made for further testing. Here the speed at which a chemical can be manufactured is critical. Usually, any route that will make the compound the quickest to synthesize on a small scale is chosen. If however, the compound continues to show potential, it has to be scaled up for even further testing. In his study, Pisano found that the two most important elements for reducing cost of manufacturing chemicals are: (a) the optimal synthetic route, and (b) telescoping successive unit operations. Of these two elements, finding the optimal synthetic route is the most important. If the company can effectively utilize its past experience to make the route determination earlier, then costs are reduced most effectively. Figure 38-2 shows the savings of this *learning before doing*.⁸ One can imagine sometime in the not too distant future discovery chemists making decisions on which compounds to move forward based on all of the discovery criteria previously discussed but also on chemical synthesis scalability and optimum route design. Not only would the speed for making NCEs benefit, but also the long-term cost and efficiency of the entire chemical development organization.

In summary, the development cost can in theory be drastically reduced if computational design of property, activity, and safety can be accomplished. Such savings have the potential to alter the pharmaceutical industry's focus on blockbuster NCEs to potentially smaller but still lucrative markets. Accomplishment of this goal would most likely initiate the NCE-2 curve of Figure 38-1. The biotechnology arena is a good model. In Figure 38-1, the new biologic entities (NBEs) are seen to be growing as the NCEs are shown to be flat or peaked.⁴

INTEGRATION OF DISCOVERY AND DEVELOPMENT

As discussed, the pharmaceutical industry has evolved from a sequential organization where problems were passed on from discovery to development (epoch 1) to one in which both drug activity and physical properties are considered very early in discovery (epoch 2). The RoF was one of the early movements to

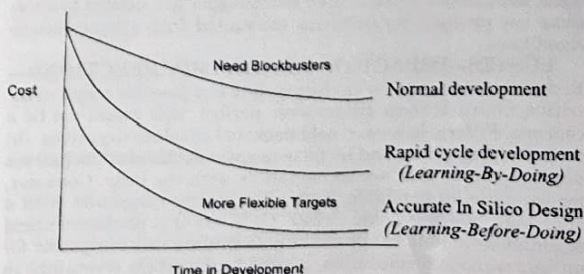


Figure 38-2. Cost savings by learning-before-doing.

Solvent-Mediated Transformations of Polymorphs: Water as a Transporter

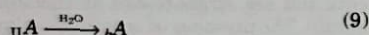
If two polymorphic forms can exist at a given temperature, the metastable polymorph will be more soluble (see *Salt Selection*). When this form is put in contact with water, the following solvent-mediated transformation can be promoted:



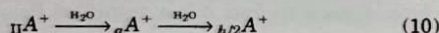
Water, in the vapor phase, has also been shown to be capable of mediating transformations between amorphous and crystalline forms in both directions.⁵³



Finally, transformations can occur that incorporate water into the crystal structure. Here, an anhydrous crystalline form is changed into the monohydrate,



and a salt is transformed into a hemihydrate after passing through the amorphous form:



Equations 7 to 10 emphasize solid-state changes. It is likely that most of these transformations may occur only after dissolving and forming a or a species forming a⁺.

DECISION-POINTS IN THE DISCOVERY AND DEVELOPMENT OF AN API

The term *active pharmaceutical ingredient* (API), also known as drug substance and bulk pharmaceutical chemical (BPC), highlights both a discovery and a development component. In this section, discovery Steps 1 to 4 will be introduced briefly. The focus will then shift to a detailed discussion of the developmental Steps 5 to 9. Using this background, the section Engineering in the Solid State will outline how early parallel integration of these activities can reduce the time from concept to market.

The term *expansion* is used when choices are being enlarged, and *selection* is used when choices are reduced by decision-making. Ultimately, the expansion and selection phases of discovery lead to a single choice, the best candidate for further development.

1. Library expansion refers to additions to a company's chemical library. Established pharmaceutical companies have amassed hundreds of thousands of compounds through previous discovery efforts. These collections are cataloged carefully and are used systematically in mass screens.
2. Series selection is a decision-making process in which the most active chemicals in the library are identified using a high-throughput biological assay. Typically, these assays are used to detect the ability of a small molecule to interact with a protein, *in vitro*. In the past, decisions regarding which leads will be pursued further were made based on activity, chemical diversity, patentability, and analog synthetic potential. Today, developmental potential increasingly is part of series selection decision-making.
3. Analog expansion is the increase in the number of compounds targeting a specific activity based on synthetic exploitation of the most promising leads.
4. Analog selection is the decision-making process in which the best new chemical entity is chosen for further development. In the past, *in vitro* activity alone was the dominating decision-maker; today, a blend of developmental issues is surfacing earlier.

Preformulation, as well as other areas of development such as metabolism, toxicology, and pharmacokinetics, will play an increasingly important role in Steps 1 to 4. Because a fundamental understanding of the solid state is essential for designing appropriate physical property methodologies for Steps 1 to 4, the remainder of this section will deal with how solid-state proper-

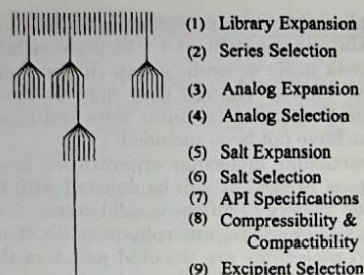


Figure 38-9. Typical API sequential decision-making: selection and expansion cycles.

ties affect absorption and consistency, the two major development issues for an API. Salt selection, which determines the character of *A'*, is the first critical solid-state decision for preformulation in the developmental arena.

Salt Expansion: Exploring the Molecular Possibilities of A'

The un-ionized (free) form of weak acids and bases, *A*⁰, may not be the ideal molecular form for development. During the salt expansion Step 5 of Figure 38-9, salts are prepared to explore whether one of them would make a more suitable API. Salts are formed by reacting *A*⁰ with an appropriate counter-acid or counter-base. In this discussion, *HAn* is used to represent a counter-acid that forms an anion *An*⁻. Common counter-acids like HCl and maleic acid are listed in Table 38-5. Similarly, *CnOH* is used to represent a mineral base of counter cation *Cn*⁺. Common mineral bases like NaOH and KOH are also shown in Table 38-5 along with organic counter-bases.

Table 38-5. Molecular Forms Marketed Worldwide Between 1983 and 1996

SALT FORM	FREQ	GROUP ^a	pK _a	CLOGP	MW
No salt form	390	0			
Hydrobromide	1	1	-8	0.45	80.91
Hydrochloride	102	1	-6.1	0.24	36.46
Sulfate	5	1	-3	-1.58	98.08
Nitrate	6	1	-1.44	2.09	63.01
Phosphate	2	1	2.15	-1.95	96.99
Glucuronate	1	1	3.22 ^b	-3.74	194.14
Acetate	8	1	4.76	-0.36	59.05
Maleate	3	2	1.92	-0.18	116.07
Fumarate	8	2	3.02	-0.18	116.07
Tartrate	1	2	3.03	-2.21	150.09
Citrate	1	2	3.13	-2.11	189.10
Succinate	2	2	4.21	-0.62	118.09
Mesylate	8	3	-1.20	-1.31	96.11
Acistrate	1	3	4.91 ^b	7.98	284.49
Besylate	2	4	-2.80 ^b	0.23	157.17
Tosylate	3	4	-1.34	0.88	171.20
Xinafoate	1	4	2.66 ^b	3.00	188.18
Potassium	1	1	16		39.10
Sodium	37	1	14.77		23.00
Tromethamine	2	1	8.07 ^c	-3.17	121.14
Bismuth	1	1	1.58		208.98
Bromide	6	5			79.90
Chloride	2	5			35.45

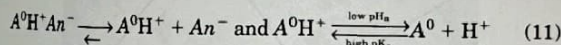
^a Groups: 0 = No salt, 1 = Polar, 2 = Multifunctional, 3 = Flexible aliphatics, 4 = Planar aromatics, 5 = Quaternary.

^b Calculated pK_a.

^c Data from CRC Handbook of Basic Tables for Chemical Analysis, page 469 From Serajuddin ATM, Sheen P, Augustine MA. To market, to market. In: Bristol J, ed. *Annu Rep Med Chem*. New York: Academic, 1983-1996.

When A^0 is a weak base, the salt, $(A^0H)^+ An^-$, is composed of the protonated form of the base, $(A^0H)^+$ and the ionized form of the counter-acid HAn , An^- . For salt formation, A^0 must be sufficiently basic to remove the proton from HAn (see *Salt-Forming Reactivity Potential*).

Salts have different physical properties than their free forms. Salt selection explores whether a particular salt might have properties that are more appropriate for an API than its parent form. Improving oral absorption by increasing the dissolution rate is often a goal of the salt expansion step. Salts generally dissolve faster in water than their free forms because dissolution is enhanced by the rapid hydration of the ionized salt species with water. Salts of weak bases generally lower the pH of water; salts of weak acids elevate it. For the salt of a weak base in water, the initial dissociation of the salt into the two ions, A^0H^+ and An^- is relatively complete. On the other hand, the deprotonation of A^0H^+ depends on the pK_a of A^0 , as shown by these reactions:



It is the release of the H^+ in the second reaction by the salt that lowers the pH and increases the solubility (see *pH-Solubility Profiles*). Hydrochlorides are the most common salts of weak bases.

When A^0 is a weak acid, the salt that forms from a reaction with $CnOH$ is $A^- Cn^+$ (A^- represents A^0 minus a proton). The most common salts for weak acids are the sodium salts.

Even though salts increase aqueous solubility, they only alter the pH of the solution so that more of the ionized form is present in solution. Salts do not change the ionizable character of the free form; this is an intrinsic property of the free acid or free base and their associated $pK_a(s)$. pH-solubility profiles show the solubility relationship between salts and their free forms.

pH Solubility Profiles

For a weak base, a plot of solubility versus pH will show the highest solubility at low pH and the lowest solubility at high pH; for weak acids, the opposite is true. Such plots give a graphic view of the impact of ionization on solubility for an NCE. The pH range of the small intestine, where oral absorption generally occurs, is approximately 6.5 to 8. It is undesirable to have a compound totally charged or uncharged in this region. If it is entirely charged, there are no un-ionized species that can be transported across the GI membrane. If it is totally uncharged, there are no charged species to enhance solubility. For a monoprotic NCE, the pK_a denotes the pH where the number of charged and uncharged species in solution are equal. On the ionized side of the pK_a , the solubility of the salt limits the maximum solubility. The solubility decline at very low pHs is due to activity and solubility-product effects.⁵⁴⁻⁵⁶ On the un-ionized side, the solubility of A^0 (the intrinsic solubility) marks the lowest solubility. Salts promote a saturated solution to be formed at a pH that is on the ionized side of the pK_a . They cannot alter the pK_a or the intrinsic solubility. Using these parameters, a qualitative pH-solubility profile can be constructed. Figure 38-10 shows pH-solubility profiles for different counter-acid salts.

The synthesis of salts depends on

1. A proton-exchange reactivity between A^0 and the counter-acid/base
2. A long-range order that permits crystal formation.

The discussion that follows will focus on forming salts from weak bases, because they comprise the majority of the new drug candidates. Weak acids would be treated analogously.

Salt-Forming Reactivity Potential

In order for a salt to form, both the weak base, A^0 , and the counter-acid, HAn , must have sufficiently different pK_a values such that a Brønsted-Lowry proton transfer from HAn to A^0 can take place. Table 38-5 gives potential counter-ions and their pK_a values from a listing of all drugs approved worldwide from

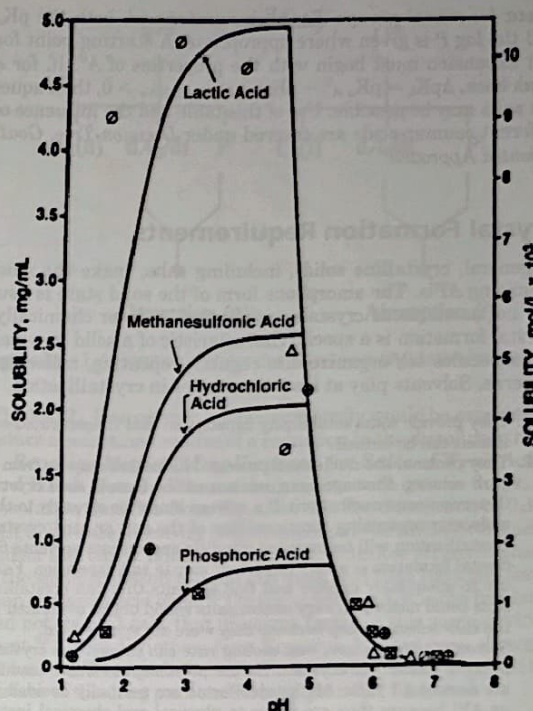
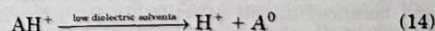
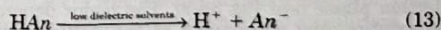


Figure 38-10. pH solubility profile of a weak base. (From Streng WH, et al. *J Pharm Sci* 1984;73:1679.)

1983 to 1996. An acid-base proton transfer should be possible as long as the pK_a of HAn is less than that of the weak base A^0 (recall that the pK_a of A^0 is referenced to its protonated form A^0H^+ ; see *Solid-State Character*). If ΔpK_a is defined as

$$\Delta pK_a = pK_a (\text{weak base}) - pK_a (HAn) \quad (12)$$

a salt-forming reaction should be possible as long as ΔpK_a is positive. For example, a succinate salt (pK_a 4.2) with doxyl amine (pK_a 4.4) is possible⁵⁷ where the ΔpK_a is 0.2. Nevertheless, the greater the ΔpK_a , the greater the probability that a salt can be formed. Because the pK_a values in Table 38-5 are calculated for an aqueous environment, this rule must be used only as a guide for salt-forming reactivity in organic solvents. In an organic solvent in which the dielectric constant is lower than water, the ionization equilibria would be shifted:



For acridine bases, 50:50 ethanol:water weakens the aqueous pK_a by 1.41 pH units. For the counter-acid, HAn , pK_a weakening is greater than for the protonated base, A^0H^+ , because of the greater solubility of HAn in the organic phase and the production of two charges upon ionization. The net effect of organic solvent weakening is to reduce the pK_a difference between the counter-acid and the weak base. This lowers the salt-forming reactivity potential. Therefore, in a given organic solvent, if salt formation fails to occur for a particular aqueous ΔpK_a , it is unlikely that salts can be formed in this organic solvent with a smaller aqueous ΔpK_a .

Varying Salt Properties Using Counter-Acid Groupings

For weak bases, salt-forming counter-acids can be used to alter an API's solubility, dissolution, hygroscopicity, stability, and processing.⁵⁷ Table 38-5 shows counter-acids organized into dif-

ferent functional groups. For each counter-acid, both the pK_a and the $\log P$ is given where appropriate. A starting point for salt expansion must begin with the properties of A^0 . If, for a weak base, $\Delta pK_a = pK_{a, A^0} - pK_{a, \text{counter-acid}} > 0$, then aqueous salts may be possible. Use of this table and the influence of different counter-acids are covered under *Decision-Tree, Goal-Oriented Approach*.

Crystal Formation Requirements

In general, crystalline solids, including salts, make the most promising APIs. The amorphous form of the solid state is usually not as stable as crystals, either physically or chemically. Crystal formation is a special characteristic of a solid in which the molecules self-organize into regular, repeating, molecular patterns. Solvents play at least three roles in crystallization.

1. They provide some solubilizing capacity so that concentrated solutions can be formed.
2. They promote the nucleation process. Nucleation may be from a pure solution (homogeneous nucleation) or from a seed crystal (heterogeneous nucleation). If a solvent binds too strongly to the molecular organizing functionalities of the salt or seed crystal, crystallization will be impeded. Finding appropriate solvents for crystal formation is a very important step in salt expansion. Failure to adequately explore and find solvents that can crystallize salts could mean that very usable salts would not be evaluated in the salt-selection step because they were not synthesized.
3. Solvents, temperature, and cooling rate can impact the crystal-packing pattern of crystals. Stable polymorphic forms usually are desired for APIs. Metastable forms are normally avoided in an API because they are prone to physical and chemical instability. Solvent conditions that promote metastable and stable crystal formations will be explored under *Metastable Polymorph Formation*.

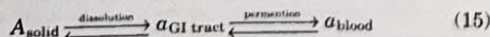
SALT SELECTION: CHOOSING THE "BEST" API

Salt selection is the first important API decision from the development perspective. Once a salt is chosen, time-consuming and lengthy toxicological studies are initiated that would have to be repeated if the salt form is changed. This decision involves choosing a solid-state phase, A , which balances potentially conflicting needs: increasing absorption versus maintaining an API that is consistent and can be manufactured in a market-image dosage form (see *Compressibility and Compactibility*). Figure 38-11 shows some of the factors involved in this decision.

Permeability, solubility (C_s), and pK_a are intrinsic properties of A^0 that have been already determined in the analog selection phase (see Fig 38-9). The major dependent variables, absorption and consistency of the API, can be manipulated and balanced in salt selection. In the following sections, the impact of dissolution and particle size on absorption will be explored. In addition, the consistency of the API solid state under the influence of environmental destabilizing factors—such as exposure time (t), ultraviolet light (UV), pH, moisture (H_2O), temperature (T), and pharmaceutical processing operations like milling, compression, and compaction—will be considered.

Absorption Assessment

Oral absorption is generally viewed as two-step, sequential process:



Either dissolution of solid drug, A_{solid} , after the dosage form disintegrates in the GI tract, or the permeation of the dissolved drug, $a_{\text{GI tract}}$, through the GI membrane could be the slowest process. The slower of these two steps determines the overall rate of absorption and is thus rate-limiting.

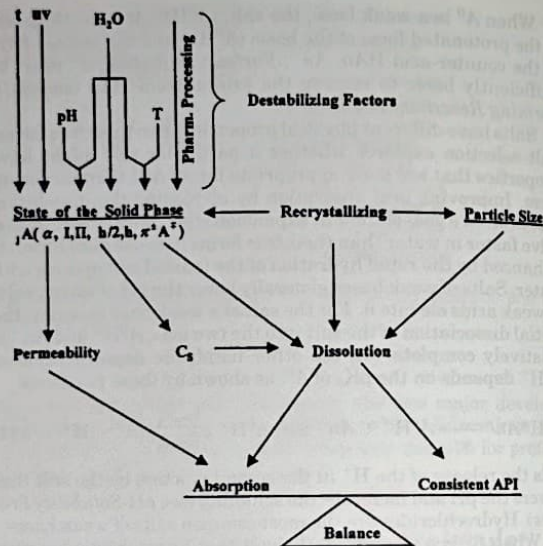


Figure 38-11. API salt selection decision: a balance between absorption and consistency

Dissolution-limited absorption occurs when the rate of appearance in the GI tract by dissolution (a_{GI}) is slower than the rate of appearance in the systemic system (a_{blood}); *permeation-limited* absorption occurs when the a_{blood} appearance is the slowest process. The impact of these two rate processes on *in vitro-in vivo* (IVIV) correlations will be discussed in the section *Biopharmaceutical Classification of API*. Dissolution-limited absorption will now be considered.

The rate of dissolution of a particle is given by the Noyes-Whitney equation,

$$dA/dt = k_d S_a [C_s - C_{\text{bulk}}] \quad (\text{non-sink conditions}) \quad (16)$$

where

A is the amount of drug dissolved.

dA/dt is the rate of dissolution (Q sometimes is used for this rate).

k_d is the intrinsic dissolution constant for the drug.

S_a is the total surface area of the dissolving particle.

C_s is the saturation solubility of the drug at the surface of the particle.

C_{bulk} is the concentration of the drug in the bulk solution.

Because the rate of dissolution depends on the concentration difference between C_s and C_{bulk} , the maximum rate of dissolution would occur if $C_{\text{bulk}} = 0$ (ie, if drug was removed from solution as fast as it dissolved). This would be analogous to a sink that could drain the water coming out of a water faucet as fast as it comes in so that the water level never built up. This analogy is the basis for referring to Equation 16 as nonsink conditions for dissolution, because drug does build up in the solution and the rate of dissolution is correspondingly reduced.

The expression for the maximum dissolution rate is found by setting C_{bulk} equal to 0⁶⁸:

$$dA/dt = k_d S_a C_s \quad (\text{sink conditions}) \quad (17)$$

This initial rate of the Noyes-Whitney equation is termed sink conditions for the dissolution rate.

PARTICLE-SIZE EFFECTS—For a spherical drug particle of radius r , amount m , and of density ρ , Equation 17 can be rewritten as:

$$dA/dt = (3k_d m / \rho) (1/r) C_s \quad (18)$$

This expression emphasizes the inverse relationship between the dissolution rate, dA/dt , and the particle size r , assuming no dissolution rate-reducing factors are present such as adsorbed air bubbles or aggregated particles.

Smaller particles dissolve faster than larger particles. Thus milling, a pharmaceutical unit-operation, increases dissolution because the API particle size is reduced. On the other hand, when drug particles are suspended in an aqueous solution, particles can increase in size due to recrystallization growth⁵⁹



FORM I
INITIAL SUSPENSION



FORM I
SUSPENSION AFTER 6 HOURS.

Figure 38-12. Photomicrographs showing change in crystal size for a suspension of Form I of an experimental drug.

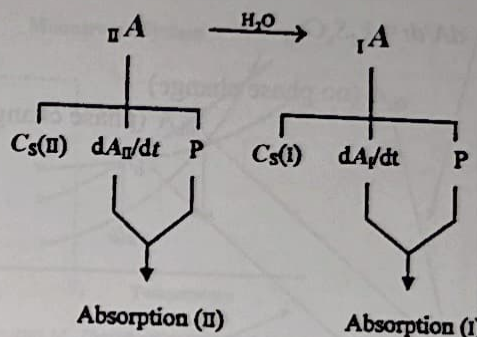


Figure 38-13. Absorption changes due to aqueous-phase transformations.

(Fig 38-12). Dosing such suspension orally would be expected to reduce absorption because of a reduction in the dissolution rate.

Reactive Media 1: Implications for Salts of Weak Acids and Weak Bases—When a drug reacts with gastric fluids, its dissolution deviates from Equation 17. For dissolution in 0.1 N HCl, acid-base reactivity is most important for salts of weak acids and for free bases. It has been found that the low pH environment of the stomach dissolves a salt of a weak acid 10 to 100 times faster than the weak acid itself.⁶⁰ On the other hand, it is the free base, and not its HCl salt, that dissolves faster in this same environment.⁶¹ These deviations from Equation 17 have been shown to be due to differences between bulk-solution pHs and the pH at the surface of the drug particle. Thus, Equation 17 becomes

$$dA/dt = k_d S_a C_{s,h=0} \quad (19)$$

where $C_{s,h=0}$ is the saturation solubility at the surface of the API.

For weak acid salts, the surface pH has been calculated to be 6.2 to 6.5 for sodium salicylate (pK_a 3.0) and 10.3 for sodium theophylline (pK_a 8.4) in bulk solutions having pHs of 1.10 and 2.1, respectively. On the other hand, the weak base phenazopyridine (pK_a 5.2) sees a surface pH of 3.3 to 3.6, while its HCl salt sees a surface pH of 1.2 for a bulk-solution pH of 1.10. If the solubility due to surface pH and not the pH of the bulk is considered, deviations from Equation 17 become understandable. For the HCl salt, the common-ion effect reduces its solubility from the maximum solubility of the pH-solubility profile at 3.45. Thus, the nonaggregated free base, in this situation, has a surface pH that is optimized to give the highest dissolution rate because it has the highest surface solubility.

Reactive Media 2: Implications for Anhydrides and Metastable Polymorphs—Aqueous-phase transformations are solid-state changes in which water acts as a mediator. During the transition from one form to another, dissolution behavior will reflect the switch from the dissolution rate of the initial solid state to that of the more stable state. Two types of aqueous-phase transformations were introduced in Equations 7 and 9: (1) a transformation from Polymorph II to Polymorph I and (2) a transformation from an anhydrous Form II to a hydrated form h. ⁶² In Figure 38-13, the transformation of Equation 7 is shown.

Because the permeability (P) of the dissolved drug is the same for the different crystalline forms, the impact on absorption will be due to differences in their solubilities (C_s) as defined in Equation 17 and thus will be reflected in the dissolution rates, dA_I/dt and dA_{II}/dt , being different.

When a solvent-mediated transformation like that shown in Equation 9 occurs, dissolution profiles become more complex. Figure 38-14 shows the biphasic dissolution characteristics for Equation 9. In this situation, an anhydrous substance, o_hA , becomes hydrated as it dissolves and forms a surface layer of hA . It is this latter layer that controls subsequent dissolution. The concentration versus time plot for the net reaction is o_hA (phase change). Note that initially the slope for o_hA (phase change) approaches that of the very steep slope o_hA (no phase change), and

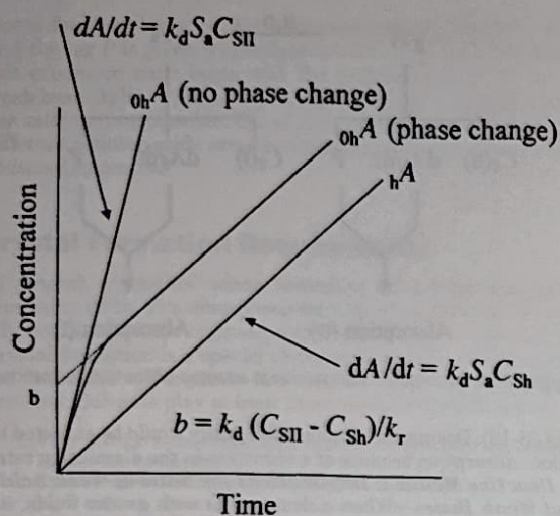


Figure 38-14. Biphasic dissolution of anhydrous to hydrous forms. (Data from Nogami H, Nagai T, Yotsuyanagi T. *Chem Pharm Bull* 1969;17:499.)

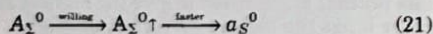
that the terminal slope approaches that of hA (no phase change), the hydrated form. Modifications of Equation 17 to take into account surface recrystallization of hA on ohA_s give the biphasic dissolution behavior,

$$dA/dt = k_d S_a [C_{sh} e^{-k_r t} + C_{sh} [1 - e^{-k_r t}]] \quad (20)$$

where k_r is the recrystallization rate constant for the second phase, k_d is the intrinsic dissolution constant, C_{SII} is the saturation concentration for the first phase, and C_{Sh} is the saturation concentration for the second hydrate phase.⁶³

ENHANCED AND RETARDED DISSOLUTION DUE TO SINKS AND PLUGS

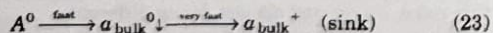
The increase in dissolution due to the particle-size reduction of an uncharged API, A^0 , can be estimated from Equation 18. Equation 21 shows the resulting surface area increase, Σ , and the corresponding dissolution enhancement.



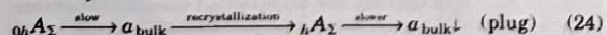
This enhancement, however, is assumed to be under sink conditions and is driven by $C_s = a_s^0$ in Equation 17. If the concentration of drug does build up, dissolution is reduced by and is given by Equation 16. This slower dissolution is diagrammed in Equation 22 where $a_{bulk}^{0\uparrow}$ indicates the buildup of the drug in the bulk solution.



An ionizable drug, on the other hand, reduces a_{bulk}^0 , which is indicated by $\downarrow$ in Equation 23 because it is rapidly converted to a_{bulk}^+ , the ionized form. Thus, the ionized form ($a_{bulk}^+ = a_{bulk}^{0H^+}$) acts as a sink to remove a_{bulk}^0 and promotes the dissolution of A^0 by driving the reaction to the right:



Reduction of dissolution, on the other hand, can occur for an anhydrous API when the hydrated form recrystallizes on the surface as in Figure 38-14. This effect is the opposite of the sink concept, hence the term plugging. Equation 24 shows the species involved in plugging. The subscript Σ emphasizes that this is a surface phenomenon.



ACCEPTANCE CRITERIA GUIDANCE

A simple model to assess the impact of particle size on dissolution and absorption of a non-ionized drug considers the intestine as a single compartment.⁶³ If the number of particles of uniform size at time t is

$$N(t) = N_0 e^{-Q/V} \quad (25)$$

where N_0 is the initial number of particles, Q is the flow rate out of the intestine, and V is the intestinal volume, then the surface area for spherical particles of uniform size, r , as a function of time can be given by

$$S_a = 4\pi r^2(t)N(t) \quad (26)$$

This expression can then be used in the non-sink dissolution expression of Equation 16, with certain assumptions including linear intestinal absorption, to approximate the fraction absorbed as

$$F \propto \frac{k_a X_d \hat{t}_r}{X_0} \quad (27)$$

where k_a is the absorption rate constant, X_0 is the administered dose, X_d is the amount of drug dissolved in the GI tract at $\hat{t}_r$, and $\hat{t}_r$ is the GI transit time. Further refinements to this model include accounting for polydispersed spherical powders and comparing cylindrical with spherical shape factors, with and without time-dependent diffusion layer thickness.

Finally, for poorly soluble drugs, simulated dose absorption studies have been carried out over different ranges of solubility, absorption rate constants, doses, and particle sizes. Table 38-6 shows the percent of drug absorbed for a drug that has a solubility of 10 $\mu\text{g/mL}$ with a k_a of 0.01 min^{-1} . Note that, even though particle-size reduction from 100 to 10 μm increases the percent absorbed, as the dose increases, the impact of this reduction decreases dramatically.

Consistency Assessment

POLYMORPHIC STABILITY: IMPORTANCE OF THE TRANSITION POINT

Polymorphic systems, in which different crystalline forms of the same molecular composition can exist, vary in their ability to interconvert at different temperatures. The enantiotropic/monotropic classification is based on the observation that some systems can reversibly interconvert and some cannot. In enantiotropic systems, reversible interconversion between the different forms is possible. For monotropic polymorphic systems, interconversion is only possible in one direction, from a metastable form to a more stable form.

For enantiotropic systems, a critical temperature exists, the transition point, T_p , at which the rate of conversion from one form to another is equal. At temperatures below T_p , one form is more stable; at temperatures above T_p , another form is more stable (see the section *Solid-State Character*; the convention of designating Form I as the most stable polymorph breaks down for such systems because Form I cannot be the most stable form both above and below T_p).

Figure 38-15 shows a solubility versus temperature diagram for an enantiotropic polymorphic system.^{64,65} For the enan-

Table 38-6. Reduced Absorption with Increasing Particle Size for a Poorly Soluble Drug

DOSE		PERCENT OF DOSE ABSORBED			
10 μm	25 μm	50 μm	100 μm		
1	91.3	66.9	38.5		17.5
10	70.0	50.0	30.7		15.4
100	9.0	8.7	8.0		6.3
250	3.6	3.6	3.4		3.1

Data from Johnson KC, Swindell AC. *Pharm Res* 1996; 13:1795.

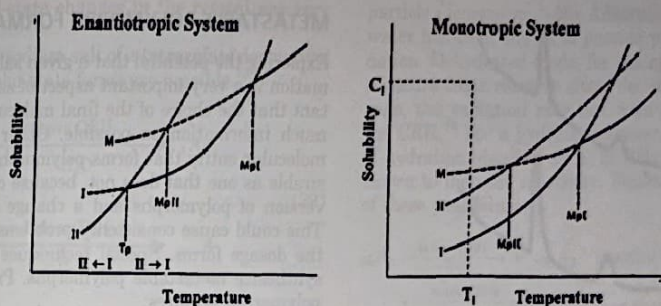


Figure 38-15. Thermal stability of polymorphic systems. (Data from Kuhnert-Bradstatter M. *Thermomicroscopy in the Analysis of Pharmaceuticals*. New York: Pergamon, 1971; and Heleblan J, McCrone W. *J Pharm Sci* 1969;58:911)

otropic system on the left, at constant pressure, there are three solubility versus temperature curves: Form II is the lowest, Form I is the next higher, and the melting curve is M. The critical temperature, T_p , occurs at the intersection of the Form II and I curves. At this point the solubilities of Form II and Form I are equal and the interconversion rate in any direction is zero.⁶⁵ Below the T_p , Form I interconverts to Form II; above the T_p , Form II converts to Form I. The melting point of Form I occurs at the intersection of the Form I curve and the melting curve M.

Because enantiotropic forms show a change in relative physical stability as temperature is changed, it is important to anticipate the impact of temperature on stability. An early warning sign that one is dealing with an enantiotropic system can be found by relating solubilities with thermal parameters. The higher melting Form I has a smaller heat of fusion. Equation 28 gives the relationship between the solubilities,

$$\ln \left[\frac{S_I(T)}{S_{II}(T)} \right] = \left[\frac{\Delta H_{II} - \Delta H_I}{RT} \right] \left[\frac{T_m - T}{T_m} \right] \quad (28)$$

where S_I and S_{II} are the solubilities and ΔH_I and ΔH_{II} are the heats of fusion of Forms I and II, respectively.⁶⁶ The more stable form at a given temperature will have lower solubility at that temperature.

Enantiotropism exists only when the transition point is below the melting point of Form I (see Fig 38-15). However, if a transition point is not found below the melting point of Form I, it does not mean that the system is monotropic.⁶⁵ The transition point, for example, could be below the lowest temperature studied.

For monotropic systems, interconversion is always from the metastable Form II to Form I. The solubility curve of Form II is always above that of Form I, and a transition point does not exist because a crystal cannot be heated above its melting point (see Fig 38-15). Oswald's Law of Stages dictates that if a system is supersaturated with respect to Form II at concentration C_i and T_i , the metastable Phase II will be the first solid phase that appears.⁶⁷ As Form II continues to crystallize, the supersaturation is reduced until it reaches its solubility. At this point, although there is no longer a driving force to crystallize more Form II, the solution continues to be supersaturated with respect to Form I. Thus, crystallization of Form I occurs at the expense of the dissolution of Form II.

POLYMORPHIC SOLUBILITY: DIFFERENCE BETWEEN EQUILIBRIUM AND DISSOLUTION-BASED SOLUBILITY

Assume Polymorphs I and II are possible for an NCE. Oswald's Law of Stages tells us that a supersaturated solution will first crystallize out as Form II and then ultimately Form I. Thus, the thermodynamic equilibrium solubility will be limited by the solubility of Form I. However, because the rate of nucleation of II and I is a function of a wide variety of vari-

ables, equilibrium solubility is not an especially useful parameter in estimating the impact of a polymorph form on the absorption of drug from a dosage form. A dissolution-based solubility definition is more useful in this regard. How might such a solubility be defined?

Because the metastable state Form II has a faster dissolution rate, $dA/dt_{II} > dA/dt_I$, where it is assumed that dissolution is carried out under sink conditions of Equation 17. Because $dA/dt = k_d S_a C_s$, we can conclude that $C_s(II) > C_s(I)$ if we assume that S_a and k_d are the same for both polymorphs. Thus, Equation 17 provides a working definition for the solubility differences between Polymorph II and Polymorph I, and it provides a method for measuring them from dissolution experiments. More precisely, it provides the solubility at the surface of the API, which is the solubility that is most relevant for dissolution (see the section *Reactive Media 1*).

POLYMORPH CHARACTERIZATION TECHNIQUES

At a given temperature, a fluid-phase transformation can cause a metastable polymorph to change into a more stable, less soluble polymorph. Using a hot-stage microscope, fluid-phase transformations as a function of temperature can be observed.⁶⁵ As the temperature is varied, the more soluble polymorph dissolves and the less soluble one grows. If a temperature can be found at which both polymorphs have the same solubility, then the system is enantiotropic, and the temperature is the transition point, T_p . Plots similar to Figure 38-15 can be constructed qualitatively in which the intersection is the measured transition point. These plots are important because they tell which form is most stable at low temperatures, and whether the system is enantiotropic.

Differential scanning calorimetry (DSC) is another characterization tool that is commonly used. It measures heat changes that occur when a solid undergoes phase transitions. Melting of a solid into a fluid, for example, requires an influx of heat into the crystal. Two techniques are useful for detecting polymorphic systems using DSC: scanning-rate variation and temperature cycling.

Scanning-rate variation has been shown to detect some reversible polymorphic systems. In Figure 38-16, crystallization of the more stable polymorph shows up as exothermic depressions as the scanning-rate increases.⁶⁸ Hot-stage microscopy can be used to confirm these thermal changes.

Temperature cycling using DSC also can be used to study the relative interconvertibility of crystalline forms. A loss of the metastable, lower melting point polymorph of metoclopramide base was found after heating, cooling, and then reheating.⁶⁹ The more stable polymorph can often be observed as exotherms due to crystallization after heat-cool cycles.⁷⁰ In addition, storage of a metastable polymorph below the melting point of either polymorph can result in the formation of the more stable polymorph. For gepirone hydrochloride, this occurred after a heat treatment of 3 hours at 150° C.⁶⁸

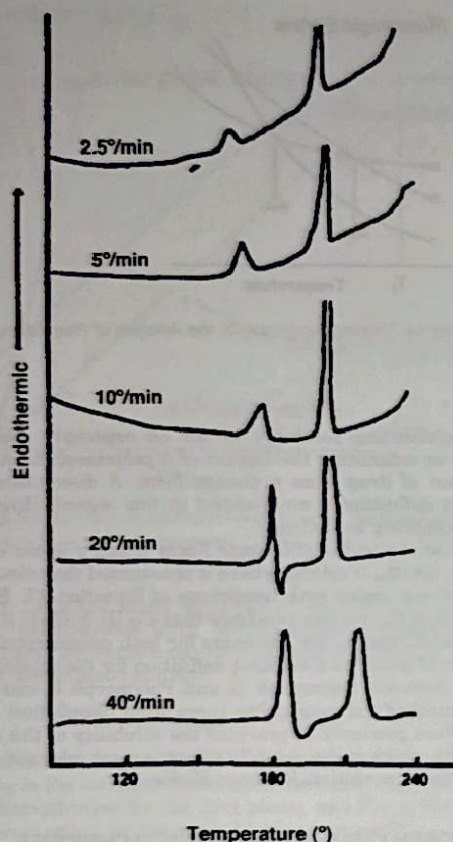


Figure 38-16. Detection of polymorphs by varying the DSC scanning rate.

Powder x-ray diffraction is the most powerful method for detecting polymorphs. Because different polymorphs have different crystal structures, the packing patterns of their atoms are different. Powder x-ray diffraction detects these packing differences as differences in diffraction patterns. Comparisons of diffraction scans between different polymorphs show characteristic differences that can be used for identification (fingerprinting) purposes.

Single-crystal x-ray diffraction is the most definitive characterization tool because the exact relative locations of atoms in the molecular crystal can be determined. However, most often, high-quality crystals for this type of analysis are not available from the bulk API (especially if the material was milled). Recrystallization of suitable crystals from saturated solutions may be possible. If the single-crystal x-ray diffraction problem can be solved, programs are now available that can convert single-crystal diffraction data to a powder x-ray diffraction pattern. This is necessary to ensure that the recrystallization process has not grown a new polymorph.

Solid-state nuclear magnetic resonance (NMR) is also a powerful technique for studying polymorphic systems. In this technique, a powder sample must be rotated at a special angle (the *magic angle*) with respect to the magnetic field so that preferential orientations of the powder particles are averaged. Microcalorimetry also has been used to characterize the thermodynamic properties of different polymorphs. Finally, diffuse reflectance infrared Fourier-transform spectroscopy recently has been used to quantify binary mixtures of polymorphs using the partial least-squares method for spectral analysis.⁷¹

METASTABLE POLYMORPH FORMATION

Exploring the potential that a given salt has for polymorph formation is a very important aspect of salt selection. It is important that the choice of the final molecular form be based on as much information as possible. Other factors being equal, a molecular entity that forms polymorphs is generally not as desirable as one that does not, because of the potential interconversion of polymorphs and a change in an API's dissolution. This could cause consistency problems both in the API and in the dosage forms. Special techniques are used to attempt to synthesize metastable polymorphs. Preparation of metastable polymorphs requires:

1. Supersaturating conditions for the metastable form, II A.
2. Crystallization of the metastable state before the stable polymorph forms.
3. Stable conditions for the metastable polymorph so that conversion to the stable I A form is prevented.

These steps are shown in Figure 38-17.

For a monotropic system, the metastable state can only change to the stable state; for an enantiotropic system, the transition point is critical for interconversion. Therefore, the formation temperature should be as far above the transition point as practical.

The ideal solution conditions to prevent II A from converting to I A are such that the solution phase, α , should be highly supersaturated, of a small volume, and in a relatively poor solvent. Rapid cooling is the method of choice for maintaining supersaturation with respect to II A. To help ensure that the rate of metastable crystallization is much greater than the rate of thermodynamic equilibration, small volumes and poor solvents for I A are used. The use of dry ice for rapid cooling with alcohol or acetone is common for these purposes. Once crystallization from the saturated solution phase, α , has occurred, it is important to filter and dry the precipitate as quickly as possible to prevent a fluid-phase transformation to the stable polymorph. Alternatively, if I A can be melted without degradation, complete melting and rapid cooling of the melt is another method of forming metastable forms. This avoids two major problems of solution-phase metastable polymorph formation—filtration and drying, both of which can promote interconversion.

HYDRATE STABILITY: IMPORTANCE OF THE CRITICAL RELATIVE HUMIDITY

Relative humidity (RH) is the percentage of the maximum amount of moisture that air can hold. A substance is hygroscopic when it takes up this moisture from air. For a drug substance, the RH that is in equilibrium with a saturated aqueous solution of a solute is termed the critical relative humidity (CRH).⁷² It is a key parameter that can influence the physical stability of solid-state hydrates. A number of studies have shown that the gain or loss of water from a hydrate can center on the CRH. Because water in organic crystals is never a passive entity (see Hy-

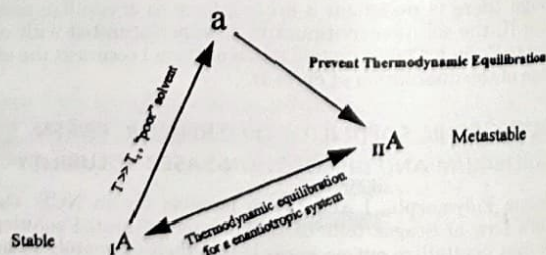
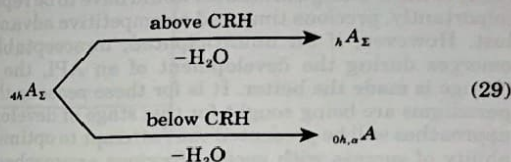


Figure 38-17. Formation of a metastable polymorph in a monotropic system.

hydrate Formation), solid-state changes in the crystal are very likely to follow.

For the tetrahydrate sodium salt of a tetrazolate derivative, a number of different solid-state forms are possible.⁷³



The conversion of ${}_{4h}\text{A}$ to ${}_h\text{A}$ requires elevated temperature and a RH above the CRH. Water's plasticizing action in reducing the intermolecular H-bonding between adjacent molecules is believed to be the mechanism that facilitates the solid-state transformation to the more stable ${}_h\text{A}$ crystal form.⁷⁴ Similarly, elevation of both temperature and RH were required to convert the ${}_{0h}\text{A}$ form of paroxetine HCl to the ${}_{0.5h}\text{A}$ form.⁷⁵ Water also promoted a solid-state transformation of the αA form to the ${}_{0h}\text{A}$ form of a disodium leukotriene antagonist. The amorphous form initially picked up a small amount of water (2%) and then slowly released this water as the anhydrous form was formed. Conversely, the humidity-mediated conversion from ${}_h\text{A}$ to αA has been observed for another leukotriene antagonist.⁷⁶ Difficult hydrate situations have been dealt with by carefully defining the RH ranges of different species and setting specifications consistent with typical manufacturing environments.⁷⁷

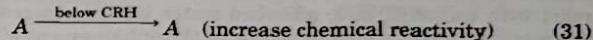
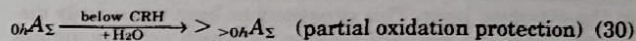
In general, hydrates that are more closely packed tend to be more physically stable with respect to moisture loss. The ideal solid state is one that is stable over a wide range of RH, such as the ${}_{0.5h}\text{A}$ form of paroxetine HCl.⁷⁵ For the sodium salt of the tetrazolate derivative shown in Equations 29 and 30, the denser ${}_h\text{A}$ structure is physically more stable than the ${}_{4h}\text{A}$ structure. The latter loses four water molecules from crystal channels at a significantly lower temperature than the one water molecule of the ${}_h\text{A}$ form, which is integrated into the crystal structure in a more cohesive manner.⁷³ In the sections *H-Bonding Networks*, and *Hydrate Formation*, hydrate formation is discussed from a molecular point of view. Crystal formation involves two mutually opposing principles: (1) satisfying the molecule's intermolecular H-bonding needs and (2) packing the atoms in the crystal as closely as possible. Hemi- ($h/2$) and monohydrates (h) evidently satisfy both close packing and H-bonding needs more efficiently than hydrates that contain water in channels.

Hysteresis is a general term that is used when a material's response to a second exposure of a stress differs from a prior response. This has been observed in the moisture uptake of an API as a function of RH. A number of instruments are now available that can monitor a sample's weight as RH is cycled from 0% to 95%. The noncoincidence of the weight as the sample is back cycled from 95% to 0% indicates hysteresis. One explanation of this type of behavior is that surface-initiated changes occurred in the solid state below or above the sample's CRH. Dehydration of the surface below the CRH, as in Equation 29, with the formation of an amorphous coat of ${}_{0h,\alpha}\text{A}$ means that any subsequent water vapor will encounter a more hygroscopic surface than ${}_{4h}\text{A}$ and thus a different hydration kinetic behavior. On the other hand, conversion of ${}_{4h}\text{A}$ to ${}_h\text{A}$ above the CRH, as in Equation 30, will produce a different kinetic behavior upon rehydration. Thus, RH hysteresis may result from changes in both the kinetic and equilibrium behavior of the surface of the particle.

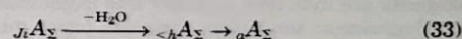
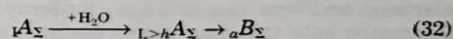
CHEMICAL STABILITY: COMMON DEGRADATION SEQUENCES—BELOW CRH

ABSORPTION/DESORPTION OF SURFACE WATER—If an anhydrous form of A is exposed to an RH below the CRH, water molecules will slowly adsorb onto the surface of the drug

particle (denoted as $>0h$). Adsorption of up to a monolayer of water has been shown to provide partial protection from oxidation. Dehydrated foods, for example, are more stable when moisture coats reactive sites. For the anhydrous phenylbutazone, the oxidation rate has been shown to be lower below the CRH.⁷⁸ For a hydrate, however, the loss of surface water of hydration (denoted as h) at RHs below the CRH has been shown to increase reactivity. Equations 30 and 31 show both of these possibilities.

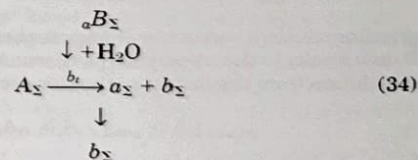


FORMATION OF AN AMORPHOUS (A) SURFACE—A water enriched/depleted surface, ($>h/<h$), is prone to further solid-state changes shown in Equations 32 and 33. For the water-enriched surface, a chemical reaction is shown in which the crystalline form of A ($j = I$) reacts to form the product αB_Σ , which is amorphous. This type of surface hydrolysis at RHs below the CRH was shown to occur for meclufenoxate HCl decomposition⁷⁹ and for propantheline bromide hydrolysis.⁸⁰ For the latter, a lag time occurred that was attributed to the amount of time that was necessary to form a monolayer. For the water-depleted hydrate ($j = h$), the loss of water initiated the formation of an amorphous surface layer, αA_Σ . The consequences of these amorphous surfaces will now be explored.

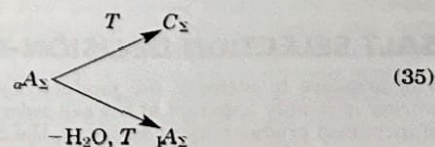


TRANSFORMATION OF AMORPHOUS SURFACES

Because amorphous layers are more prone to be hygroscopic than crystalline solids, the chemical transformation of ${}_I\text{A}_\Sigma$ to αB_Σ in Equation 32 is significant because the latter can attract more water to the surface. Dissolution of αB_Σ shown in the first downward reaction of Equation 34 will then form a surface coated with b_Σ , as shown in Figure 38-8. The reaction of meclufenoxate HCl below the CRH to form amorphous dimethylaminoethanol HCl (see Eq 32) is a good example of this.⁷⁹ Next, the water adsorbed to the surface due to the dissolved form of B on the surface, b_Σ , promotes the dissolution of the surface of A, A_Σ , to form a surface coated also with αA_Σ , the dissolved form of A on the surface, which then undergoes further decomposition to b_Σ . This is shown in the horizontal and final downward reactions of Equation 34.

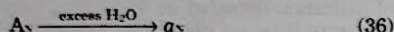


In Equation 35, two possible solid-state changes for αA_Σ are shown. First, the reactive amorphous surface can undergo a degradation reaction to form C_Σ . Second, the surface can continue to lose water below the CRH so that the subsurface ${}_h\text{A}$ undergoes a solid phase transformation to a crystalline phase, ${}_I\text{A}$. The dehydration changes for cefixime trihydrate are examples of these reactions.⁸¹ The partially dehydrated form of this compound was more unstable than the fully hydrated or the completely dehydrated crystalline forms.



CHEMICAL STABILITY: COMMON DEGRADATION SEQUENCES—ABOVE CRH

When water is adsorbed to the surface of the particle above the CRH, the drug particle becomes coated with a dissolved drug layer, a_z , which is assumed to be saturated⁵²:

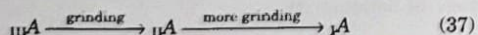


Degradation under these conditions is assumed to occur solely in the dissolved layer. This situation has been extensively discussed.⁵² For the Maillard reaction, in which primary amines react with carbohydrates, adsorbed water initially increases the reaction rate to a maximum due to the enhancement of reactant mobility. Greater amounts of water then decrease the reaction rate due to dilution of the reactive species. Similarly, for free-radical auto-oxidation of unsaturated groups, reactivity increases above the CRH because of accelerated reactant mobility. Below the CRH, oxidation decreases due to the immobilization of hydrogen peroxides and trace metal catalysts and the protective effects of a monolayer of water that is insufficient to increase reactant mobility.

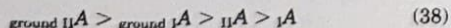
INFLUENCE OF SALT FORM ON HYGROSCOPICITY—Table 38-2 shows that the non-salt forms, including free bases, free acids, and nonelectrolytes, are the most popular molecular forms on the market. In general, these forms would be expected to be less hygroscopic than salt forms due to their un-ionized character. Although the sodium salt is the most popular weak acid form, this form has a tendency to be hygroscopic. Alternative salts that have proven useful in overcoming hygroscopicity are hydrogen sulfate⁵² and tromethamine.^{53,54}

Hygroscopic tendencies for weak bases might be overcome by using aromatic counter-ions. Aryl sulfonic acids were shown to provide moisture protection without decreasing dissolution for the sparingly soluble weak base, Xiobam.⁵⁵ The free-base form of this drug (pK_a 6.1) was hydrolyzed at 40°C/80% RH. On the other hand, one weak base (pK_a 3.67) was chosen for development because it was less reactive to moisture exposure than the HCl salt. The latter showed chemical instability with moisture and heat and was the only salt that could be formed.⁵⁶ Stronger bases like pelrinone (pK_a 4.71) can form stable and nonhygroscopic HCl salts.⁵⁷

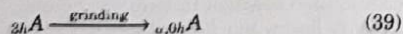
GRINDING IMPACT—Processing of solids can have a major impact on dissolution due to solid-solid phase changes. Grinding is one process that has been shown to cause changes in both polymorphs and hydrates. For the III A polymorph (Form C) of chloramphenicol palmitate,⁵⁸



grinding causes a successive change to the II A polymorph (Form B) and finally to the I A polymorph (Form A).⁵⁹ Correspondingly, dissolution from the fastest to the slowest is in the order



For hydrates, similar solid-state changes have been observed. When cefixime trihydrate is ground, a solid-phase transformation takes place:



Water in this situation plays an essential role in crystal formation. Its removal causes a collapse of the crystal lattice.⁶⁰ Other pharmaceutical processing operations and their impact on crystals have been reviewed.⁵¹

SALT SELECTION DECISION-MAKING

The pressure to increase the productivity of the knowledge worker is readily apparent at the salt-selection stage. Because of increased productivity in discovery, the cascading impact on

development to choose rapidly the best molecular form is readily apparent; toxicological and bioavailability studies cannot proceed until the salt is chosen. Once these studies are initiated, it becomes very costly to change the molecular form because many of these biological studies would have to be repeated. More importantly, precious time and a competitive advantage will be lost. However, if an unanticipated, unacceptable property emerges during the development of an API, the sooner the change is made the better. It is for these reasons that efficient paradigms are being sought for this stage of development. Two approaches will be presented that attempt to optimize the probability of success with speed. Previous approaches were criticized for excessive characterization of poor candidates and for a lack of clear go/no-go decision-making.⁹² As a practical consideration, it is essential that NCEs have high purity, and that salts be crystallized. In the following discussion, weak bases that are to be absorbed orally are used. Similar approaches can be developed for intravenous NCEs and for weak acids.

Multi-Tiered Selection Approach

One approach in which different critical parameters are used to filter a salt candidate's progression to the next stage has recently been proposed.⁹² Crystalline salts are successively sorted by a three-tier system in the following way:

- Tier 1. Hygroscopicity
- Tier 2. Thermal analysis and x-ray diffraction
- Tier 3. Accelerated solid-state stability

Tier 1 eliminates any form with excessive moisture sorption/desorption characteristics. Only the survivors progress to Tier 2. In this second tier, changes in crystal structure are examined under extremes of moisture conditions by using thermal analysis and powder x-ray diffraction to detect desolvation and aqueous-phase transformation problems. In addition, aqueous solubility is determined to address potential dissolution problems. The best candidates for formulation and manufacturing are considered here and survivors proceed onto Tier 3. In this third tier, accelerated thermal and photo-stability testing is carried out. This is considered to be the most time-consuming step so the limiting of candidates saves time and effort. Selected excipient compatibility testing may also occur at this stage. If Tier 2 eliminates all of the candidates, additional salts or free acid/bases are considered before reevaluating any salt that was dropped in an earlier tier.

Several comments can be made regarding this approach.

1. The HCl salt of ranitidine, due to its hygroscopicity,⁹³ probably would not have been a final candidate in the multi-tiered approach. Yet this is one of the most successful drugs ever marketed. This emphasizes a need for prioritizing the salt selection process so that as wide a range of development issues are addressed as early as possible and that they all are put in perspective. If a hydrochloride salt has much better absorption properties than the free base but is hygroscopic, it would be very prudent for development to see if it can deal with this problem. Otherwise, bioavailability may be compromised by a single-minded emphasis on API consistency.
2. The free base is not considered in the multi-tiered approach unless all alternatives have failed despite its potentially favorable dissolution in gastric fluids and its sensitivity to particle size reduction with a reactive sink.

The decision-tree, goal-oriented approach discussed below addresses some of these issues.

Decision-Tree, Goal-Oriented Approach

An alternative approach to the multi-tiered go/no-go selection approach is one based on a decision-tree using statistical probabilities and functional grouping of counter-ions to seek prioritized physical properties. In Figure 38-18, prioritized problems are shown, absorption being the highest priority.

Blending studies have shown the potential benefits of using sodium lauryl sulfate to offset these types of effects.⁹⁷

Finally, manufacturing for a global market has forced a reevaluation of excipients that are used in formulations so that manufacturing can be carried out with internationally acceptable components. The European Economic Community has recently focused the pharmaceutical industry on eliminating excipients that have the potential for transmissible spongiform encephalopathies, replacing ingredients like stearic acid, magnesium stearate, polysorbate 80, and simethicone with vegetable grade sources.

API SPECIFICATIONS: MEETING PRODUCT AND REGULATORY REQUIREMENTS

Polymorphic Forms and Hydrates Decision Trees

A major portion of this chapter has been devoted to characterizing the solid state, jA . The left side of Figure 38-19^{98,99} summarizes some of the potential solid states that can exist for the unionized form of A ; if a salt form was chosen for the API, the same states also would be possible. Previous sections have discussed the impact on API consistency and dissolution for the different solid states. The critical relative humidity (CRH) and the transition point (T_p) for enantiotropic polymorphic systems are especially important intrinsic physical parameters that control solid-state consistency and potential solid-state interconversion. Moisture and temperature, as we have discussed, are the major environmental variables that can promote these changes. Rapid methods, therefore, are needed to characterize potential solid-state forms and their physical properties. The decision-tree on the right side of Figure 38-19 summarizes when specifications need to be set to maintain API consistency. If the physical properties of the solid states differ, assessments need to determine the impact this will have on a formulated API. Specifications need to be set to ensure a consistent product.

Particle-Size Acceptance Criterion

Once the solid state, jA , has been characterized, the potential impact of particle size on absorption can be assessed. Figure 38-20 shows a decision-tree approach, suggested by the Interna-

tional Committee on Harmonization, for determining whether a particle-size acceptance criterion is needed.¹⁰⁰ Previous sections in this chapter have discussed nearly every aspect of this tree. Although dissolution-limited absorption is a major concern, Figure 38-20 also includes dosage form issues such as content uniformity.

Biopharmaceutical Classification of API

Although it is possible to alter the solid state, jA , such that dissolution and absorption can be enhanced, solubility and passive permeability are, in general, intrinsic properties of the NCE. Thus, even though the amorphous state, αA , in some situations can be stabilized to enhance dissolution, the equilibrium solubility will be determined by the least soluble solid state. A classification has been proposed to segregate situations when *in vitro* and *in vivo* correlations (IVIV) are expected. Such designations may be used as a guide for determining when bioequivalent studies may need to be carried out. Table 38-7 shows the four major classes based on solubility and passive permeability.

CONCLUSION: APPLICATION OF KNOWLEDGE

"The actual product of the pharmaceutical industry is knowledge; pills and prescriptions ointments are no more than packaging for knowledge."¹⁰¹ The introduction of methods to probe and exploit human and animal genomics has had a cascading impact on the industry. These new concepts had a number of qualities that ensured adaptation. The systematic use of mechanism-based reagents was a tangibly better solution for finding new therapeutic entities than the more serendipitous methods of the past. Such high-throughput screens were compatible with increasing use of robotics whose advantages could easily be understood by all in the pharmaceutical industry. Each company was able to hold trial runs to test the utility of such screens and in the end obtain observable results. Today, the recombinant DNA innovations of the 1980s still provide the driving force for other innovations in the pharmaceutical industry: miniaturization, customizing, and artificial intelligence.

Miniaturization began in earnest with the micronization of the transistor concept onto silicone chips. In the pharmaceutical industry, mass screening, the demand for higher and higher

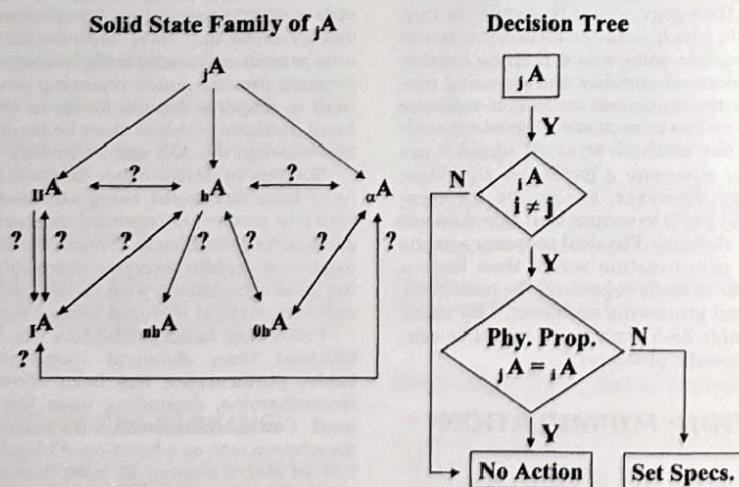


Figure 38-19. Solid-state forms and specification setting. (Data from Byrn S et al. *Pharm Res* 1995;9:84; and Byrn S et al. *Gold Sheet* 1996;30(6):1)

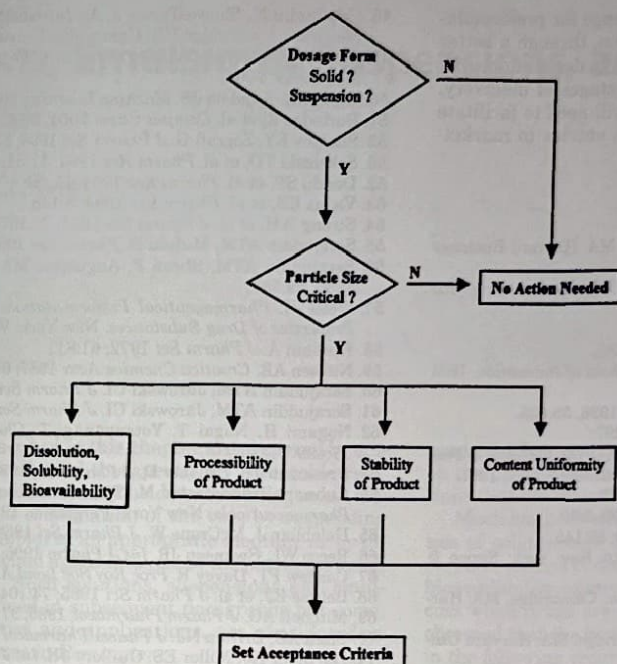


Figure 38-20. Decision-tree for drug substance particle-size distribution. (From Byrn S et al. Specifications for new drug substances and products: Chemical Substances, ICH4, Fourth International Conference on Harmonization. Brussels, July 1997.)

throughput, and the need to conserve chemical libraries have accelerated analytical and synthetic nanotechnology. This latter need is extremely important because chemical libraries are expendable resources that are not easily replaced. Old library entries were synthesized in gram quantities, and newer entries in milligrams. Conservation of this resource will require a combination of nanotechnology along with a host of regeneration technologies including combinatorial synthesis, high-throughput purification, and promotion of an increasingly diverse molecular library for mass screening. In addition, chromatographic columns, HPLCs, and electrophoresis on the nanoscale hold promise for extremely high resolution with extremely low material consumption. On this scale, area can efficiently be converted to a linear dimension. Thus a chip 10×10 mm can be converted easily to an electrophoretic path of 9.5 cm. The potential for massive parallel processing is evident when one con-

templates the possibilities of 100 nanolaboratories on a single chip.

Customization at low cost also will be possible with new technology. DNA probes located on biochips will permit the individualization of a treatment course depending on a person's ability to metabolize a given drug. Such innovations likely will cause a cascading demand on development to individualize dosage forms. Finally, the rapid and parallel demands placed on preformulation will force more decisions to be made using artificial intelligence. High-throughput determinations of physical properties will result in high quality databases, which can in turn be systematically exploited by expert systems. Highly accurate predictions of solubility, permeability, and dissolution will be possible in the 21st century.

Although artificial intelligence is still in its infancy, the benefits of its applications can be appreciated from a consideration of the differences between knowledge and information. A chemical reaction database, for example, stores information on particular reactions. However, it cannot apply this information to new molecules. Expert systems, on the other hand, so codify knowledge that they can be applied to entirely new situations. Knowledge differs from information in that information is random and miscellaneous, and it tends to expand too rapidly and overwhelm us. Knowledge, on the other hand, requires that the structure of a subject be understood in a way that permits other things to be related to it in a meaningful way; it permits intuitive heuristic procedures to be developed to solve problems when no algorithms are available. Such applications of artificial intelligence, however, are still in the early-stage knowledge revolution, in which knowledge is applied to produce results. In the postcapitalist society, knowledge will be applied toward systematic innovation: "It will be applied systematically and purposefully to define what new knowledge is needed, whether it is feasible, and what has to be done to make knowledge more effective."

Knowledge and the productive application of knowledge are anticipated to be the sole factors that will drive the postcapitalist society into the 21st century. In the pharmaceutical industry, massive diffusion of innovations from discovery into de-

Table 38-7. *In Vitro/In Vivo* Correlation Expectations for Immediate-Release Products Based on Biopharmaceutics Class for Passive Absorption

CLASS	SOLUBILITY	PERMEABILITY	IVIV CORRELATION EXPECTATION
I	High	High	IVIV correlation if dissolution rate is slower than gastric emptying rate. Otherwise limited or no correlation.
II	Low	High	IVIV correlation expected if <i>in vitro</i> dissolution rate is similar to <i>in vivo</i> dissolution rate (unless dose is very high).
III	High	Low	Absorption (permeability) is rate-determining and limited or no IVIV correlation with dissolution rate.
IV	Low	Low	Limited or no IVIV correlation expected.

From Amidon GL, et al. *Pharm Res* 1995; 12:413.

velopment will pose an accelerating challenge for preformulation. To meet this challenge, preformulation, through a better understanding of the solid state, must seek to design improved characteristics into APIs at the earliest stages of discovery. This will be the edge that any company will need to facilitate the rapid movement of new therapeutics entries to market-place. The patient is waiting!

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